Schlossberg's

CLINICAL INFECTIOUS DISEASE

Third Edition

Edited by

Cheston B. Cunha

OXFORD

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David Schlossberg edited the first two editions of this textbook. When he died on February 28, 2019, the infectious diseases community lost one of its most accomplished and admired members.

As a Yale undergraduate, David majored in English literature and excelled as both a scholar and a wrestler. He was an AOA graduate of Tufts University School of Medicine. While a student at Tufts, David encountered the legendary Louis Weinstein, one of the giants of infectious diseases. David asked Dr. Weinstein if he could follow him around for a month. Dr. Weinstein agreed, and David enjoyed what was probably the very first student elective in infectious diseases in the United States. David was a medicine resident at Mount Sinai in New York and an infectious diseases fellow at Emory University in Atlanta.

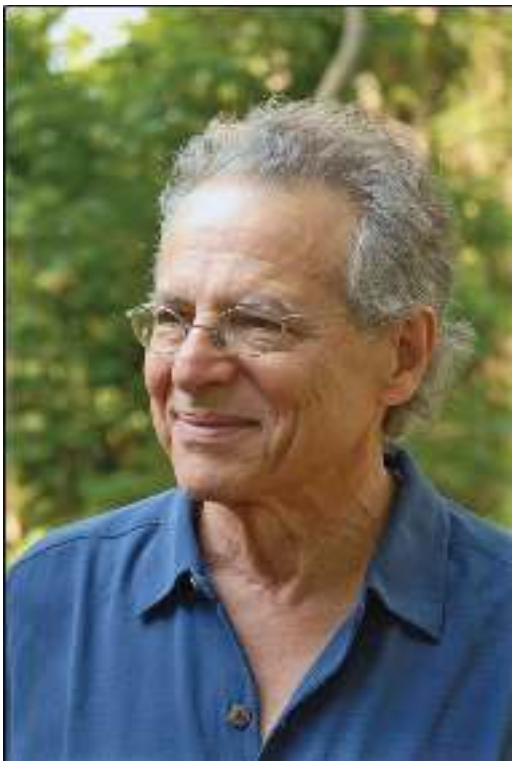
David served for 2 years in the US Navy as Chief of Infectious Diseases at the Naval Regional Medical Center in Portsmouth, Virginia. After his Navy service he became Chair of the Department of Medicine at the Polyclinic Medical Center in Harrisburg, Pennsylvania, following which he served for 16 years as Chair of the Department of Medicine and Head of Infectious Diseases at Episcopal Hospital in Philadelphia. Later he became Director of Medical Services at Merck and most recently served as the Head of the TB control program for the City of Philadelphia. He held adjunct faculty positions at Temple University, Jefferson University, and the University of Pennsylvania, and for almost 20 years made rounds each Monday with the Temple infectious diseases consult team.

David was a consummate clinician and educator and a true polymath. He edited or authored 28 textbooks—not 28 editions of books: 28 individual titles. He was a martial arts expert and a Talmudic scholar. He spoke about 10 languages including Yiddish, Chinese, and Polish. He could sing the words to every major Broadway show tune. He read widely and deeply, and he knew a good single malt whisky.

After the death of his father, David became the patriarch of the Schlossberg clan. Family was of paramount importance to David, and, along with Yuan Mirow, his dear partner of 25 years, he gathered together his siblings, children, and grandchildren each Thanksgiving and Passover and each summer for a week at the New Jersey shore. Attendance at these family events was mandatory, no excuses. While at the shore, David arose early each morning to buy newspapers and a special crumb cake that all the Schlossbergs loved.

David Schlossberg was smart, warm, kind, and generous with his time. He was everyone's friend. He had a genuine interest in people and had a way of making you feel that you had his full attention. He loved a good story and could tell one. He had a strong handshake, a ready smile, and looked you directly in the eye when you spoke with him. He was a loyal friend. He was honest and forthright, a man of the finest character, a mensch. The world has lost a very good man. This third edition of Clinical Infectious Diseases is dedicated to his memory.

—Bennett Lorber, MD, MACP



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Preface

I was not expecting Dr. Schlossberg's call asking me to be co-editor for the next edition of *Clinical Infectious Disease.* Previously, in the second edition, I felt most fortunate to have been a contributor. Needless to say, I was surprised, delighted, and honored to be asked by David to be co-editor of *Clinical Infectious Disease*, his clinically oriented infectious disease textbook for practitioners. *Clinical Infectious Disease* remains the only single-volume, easy-to-use, handy, clinically based infectious disease desktop reference. Subsequently, we had many conversations regarding plans for the third edition of *Clinical Infectious Disease* to be published by Oxford University Press. David was, as usual, confident, enthusiastic, and happy. His great sense of humor was always part of our discussions about *Clinical Infectious Disease*, the practice of infectious diseases, and about life. David was at the peak of his distinguished career.

All was progressing as planned when the unthinkable happened. I learned that David had passed away at the end of February. This sweet man of substance, religion, experience, empathy, and kindness had, without warning, left us. David was an incomparable clinician, teacher, and educator. Prolific and accomplished, he wrote or edited more books on infectious diseases than anyone, some 28 in total. Early on, he was greatly influenced by the clinical approach of Dr. Louis Weinstein. Throughout his career, David's main focus was always on the clinical aspects of infectious disease, which is evident in his *Clinical Infectious Disease.* Dr. Bennett Lorber was a lifelong colleague and friend of David's and has kindly written the Dedication to David and provides a personal perspective on David's life.

Under these circumstances, I assumed the duties as editor of *Clinical Infectious Disease* (3rd edn.). I was determined to continue in the tradition of David's *Clinical Infectious Disease* emphasis on clinical diagnosis and management. To honor him, I had the book, in its third edition, renamed *Schlossberg's Clinical Infectious Disease*. *Schlossberg's Clinical Infectious Disease* (3rd edn.) perspective and organization remains the same.

It has been difficult, given the severity and duration of the global covid-19 pandemic, for contributors with their primary responsibilities to patients during the pandemic to update or complete their chapters. I am pleased that *Schlossberg's Clinical Infectious Disease* is completed, and there have been two new, timely chapters added, one on COVID-19 and the other on antimicrobial stewardship.

David's memory and professional perspective as an infectious disease clinician and educator par excellence are reflected in the pages of *Schlossberg's Clinical Infectious Disease* (3rd edn.). I am humbled and honored that David entrusted me with his *magnum opus,* and I hope that he is pleased that his work continues to provide infectious disease clinicians with a single-volume, easy-to-use desktop reference.

—Cheston B. Cunha

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Section 1

Clinical syndromes: General

1

Fever of unknown origin

Cheston B. Cunha and Burke A. Cunha

Overview

Fever of unknown origin (FUO) describes prolonged fevers >38°C/101°F lasting for 3 or more weeks that remain undiagnosed after a focused FUO outpatient/inpatient workup. The causes of FUO include infectious and noninfectious disorders. A variety of infectious, malignant, and rheumatic/inflammatory disorders may be associated with prolonged fevers, but relatively few persist undiagnosed for sufficient duration to be classified as FUOs.

Causes of FUO

The distribution of disorders causing FUOs is dependent on age, demographics, family history, zoonotic exposures, and previous/current conditions (e.g., malignancies, rheumatic/inflammatory disorders, cirrhosis). Each category of FUO may also be approached by subgroups (e.g., elderly, immunosuppressed, transplants, febrile neutropenia, zoonoses, HIV, nosocomial, returning travelers). The differential diagnosis in each subgroup reflects the relative distribution of disorders within the subgroup and the geographic distribution of endemic diseases. The relative distribution of causes of FUO has changed over time, but, with few exceptions, the disorders responsible for FUOs have remained relatively constant over time (Table 1.1).

Diagnostic approach to FUOs

In patients presenting with prolonged fevers, the clinician should first determine if the patient indeed has an FUO. Because there are many causes of FUO, there is no "cookbook" or algorithmic approach for diagnosing FUOs. In medicine, the history provides important initial diagnostic clues and a general sense of the likely FUO category (e.g., weight loss with early anorexia suggests malignancy, arthralgias/myalgias suggest a rheumatic/inflammatory disorder, and fever with chills suggests an infectious etiology).

After an FUO category is suggested by historical clues, the physical examination should focus on history-relevant findings in the differential diagnosis. The physical examination should not be comprehensive but, more importantly, should be carefully focused on demonstrating the presence or absence of key findings in the differential diagnosis (e.g., a complete neurologic exam is unhelpful in an FUO patient with probable adult Still's disease). On physical examination particular attention should be given to eye findings, liver, spleen, lymph nodes, joint findings, and skin lesions (Table 1.2). At this point, based on the presence or absence of history and physical examination clues, the initial FUO diagnostic workup (e.g., nonspecific laboratory tests) should also be focused on ruling in or ruling out the most likely diagnostic possibilities. Since the patient has already been seen by one or more physicians prior to presentation, routine laboratory tests have already been done (e.g., CBC, liver function test [LFTs],

TABLE 1.1 **CLASSIC CAUSES OF FEVER OF UNKNOWN ORIGIN (FUO)**

Type of disorder	Common	Uncommon	Rare
Malignancy/neoplastic disorders	Lymphoma[a] Hypernephromas/ renal cell carcinoma (RCC)	Pre-leukemias (AML)[a] Myeloproliferative disorders (MPDs)	Atrial myxomas Multiple myeloma Colon carcinoma Pancreatic carcinoma CNS metastases Hepatomas Liver metastases
Infectious diseases	Miliary TB SBE Brucellosis[a] Q fever[a]	Intra-abdominal/pelvic abscess Intra/perinephric abscess Typhoid fever/enteric fevers[a] Toxoplasmosis Cat-scratch disease (CSD)[a] EBV CMV HIV Extrapulmonary TB (renal TB, CNS TB)	Periapical dental abscess Chronic sinusitis/mastoiditis Subacute vertebral osteomyelitis Aortoenteric fistula Relapsing fever[a] Rat-bite fever[a] Leptospirosis[a] Histoplasmosis Coccidiomycosis Visceral leishmaniasis (kala-azar) LGV Whipple's disease[a] Castleman's disease[a] (MCD) Malaria Babesiosis Ehrlichiosis
Rheumatologic/ inflammatory disorders	Adult Still's disease[a] Giant cell arteritis (GCA)/temporal arteritis (TA)[a]	PAN/MPA[a] Late-onset rheumatoid arthritis (LORA)[a] SLE[a]	Takayasu's arteritis[a] Kikuchi's disease[a] Sarcoidosis (CNS) Felty's syndrome Gaucher's disease Polyarticular gout[a] Pseudogout[a] Schnitzler's syndrome[a] Behçet's disease[a] FAPA syndrome[a] (Marshall's syndrome)
Miscellaneous disorders	Drug fever[a] Alcoholic cirrhosis[a]	Subacute thyroiditis[a] Regional enteritis (Crohn's disease)[a]	Pulmonary emboli (small/multiple) Pseudolymphomas Kikuchi's disease[a] Rosai–Dorman disease[a] Erdheim–Chester disease (ECD)[a] Cyclic neutropenia[a] Familial periodic fever syndromes[a] • FMF • Hyper IgD syndrome[a] • TNF receptor-1-associated periodic syndrome (TRAPS) • Muckle–Wells syndrome Systemic mastocytosis Hypothalamic dysfunction Hypertriglyceridemia Factitious fever[a]

[a]Also cause of recurrent FUOs.

Disorders with FUO potential include any not easily diagnosed disorder with prolonged fevers, travel-related infections with prolonged fevers presenting in nonendemic areas, any relapsing/recurrent disorder with prolonged fevers, or any disorder with prolonged fevers with unusual clinical findings.

AML, acute myelogenous leukemia; CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein–Barr virus; FAPA, fever, aphthous ulcers, pharyngitis, adenitis; FMF, familial Mediterranean fever; HIV, human immunodeficiency virus; LGV, lymphogranuloma venereum; MCD, multicentric Castleman's disease; MPA, microscopic polyangiitis; PAN, periarteritis nodosa; SBE, subacute bacterial endocarditis; SLE, systemic lupus erythematosus; TB, tuberculosis; TNF, tumor necrosis factor.

Adapted from: Cunha BA. Fever of unknown origin (FUO). In: Gorbach SL, Bartlett JB, Blacklow NR (eds.) *Infectious Diseases in Medicine and Surgery*, 3rd ed., Philadelphia: WB Saunders, 2004; pp. 1568–1577 and Cunha BA. Overview. In: Cunha BA (ed.) *Fever of Unknown Origin*. New York: Informa Healthcare; 2007; pp. 1–16.

TABLE 1.2 **HISTORY AND PHYSICAL EXAMINATION CLUES TO FEVER OF UNKNOWN ORIGIN (FUO) CATEGORIES**

	Historical features	Clues from the history	Physical examination findings	Clues from the physical examination
Malignant/ neoplastic disorders	• PMH/FMH malignancy	• Possibility of same disease likely	• Fever pattern: Relative bradycardia Hectic/septic fevers (Pel-Ebstein)	
	• HA/mental confusion	• CNS metastases, lymphomas, multiple myeloma, atrial myxoma (CNS emboli)		• CNS, malignancies, lymphomas • Lymphomas
	• Weight loss (with early decreased appetite)	• Any malignant/neoplastic disorder	• Cranial nerve palsies	• CNS lymphomas, CNS neoplasms
	• Early satiety	• Lymphomas, any malignant/ neoplastic disorder causing splenomegaly	• Fundi: Roth spots • Fundi: cytoid bodies (cotton wool spots)	• Lymphomas, atrial myxoma • Atrial myxoma
	• Pruritus (post hot shower/ bath)	• Lymphoma, MPDs	• Fundi: retinal hemorrhages	• Pre-leukemia (AML)
	• Night sweats	• Any malignant/neoplastic disorder	• Adenopathy	• Lymphoma, Kikuchi's disease, Rosai–Dorfman disease
	• Abdominal discomfort/ pain	• Hypernephroma, hepatoma, liver metastases, colon carcinoma, pancreatic carcinoma	• Sternal tenderness • Heart murmur	• Pre-leukemia (AML), MPDs • Marantic endocarditis, atrial myxoma
	• Testicular pain	• Lymphoma	• Hepatomegaly	• Hepatoma, hypernephroma, liver metastases
	• Bone pain	• Multiple myeloma, any malignant/neoplastic disorder with bone involvement	• Splenomegaly • Splinter hemorrhages • Epididymitis	• Lymphomas, MPDs • Atrial myxoma • Lymphomas
Infectious diseases	• PMH/FMH of infections	• Possibility of same disease high	• Fever pattern: Relative bradycardia	
	• HA/mental confusion	• Brucellosis, CSD, ehrlichiosis, Q fever, malaria, leptospirosis, Whipple's disease, typhoid fever/enteric fevers, rat-bite fever, relapsing fever, CNS TB, HIV, LGV		• Typhoid fever/enteric fevers, leptospirosis, Q fever, malaria, babesiosis, ehrlichiosis
			Double quotidian fever	• Visceral leishmaniasis (kala-azar)
			Camelback fever curve	• Ehrlichiosis, leptospirosis, brucellosis, rat-bite fever (*S. minus*)
	• Recent/similar illness exposure	• Possibility of same disease high	Morning temperature spikes	• Miliary TB, typhoid fever/ enteric fevers
	• Surgical/invasive procedures	• Abscess, SBE		
	• Aortic aneurysm/repair	• Q fever, enteric fever	Relapsing fevers	• Brucellosis, malaria, rat-bite fever (*S. moniliformis*)
	• STD history	• LGV	• Abducens (CN VI) palsy	• CNS TB
	• Recent travel	• Typhoid/enteric fevers, leptospirosis, malaria, visceral leishmaniasis (kala-azar), brucellosis, Q fever	• Conjunctival suffusion • Conjunctival hemorrhages	• Trichinosis, relapsing fever, leptospirosis • SBE
	• Insect exposure	• Malaria, ehrlichiosis, babesiosis, visceral leishmaniasis (kala-azar), relapsing fever	• Chorioretinitis • Choroid tubercles	• Toxoplasmosis, TB, histoplasmosis • Miliary TB
	• Pet/animal contact	• Q fever, CSD, toxoplasmosis, rat-bite fever, relapsing fever, leptospirosis, brucellosis	• Roth spots • Palatal petechiae	• SBE • EBV, CMV, toxoplasmosis
	• Unpasteurized milk/cheese consumption	• Q fever, brucellosis	• Tongue ulcer • Adenopathy	• Histoplasmosis • CSD, EBV, CMV

(continued)

TABLE 1.2 CONTINUED

	Historical features	Clues from the history	Physical examination findings	Clues from the physical examination
	• Undercooked meat consumption	• Toxoplasmosis, trichinosis	• Heart murmur • Spinal tenderness	• SBE • Subacute vertebral osteomyelitis, typhoid fever/enteric fever, skeletal TB, brucellosis
	• Blood transfusions	• Malaria, babesiosis, ehrlichiosis, CMV, HIV	• Hepatomegaly	• Q fever, typhoid fever/ enteric fevers, brucellosis, visceral leishmaniasis (kala-azar), rat-bite fever, relapsing fever
	• Poor dentition	• SBE, apical root abscess		
	• Sleep disturbances	• Brucellosis, relapsing fever, leptospirosis	• Splenomegaly	• Miliary TB, EBV, CMV, typhoid fever/enteric fevers, brucellosis, histoplasmosis, ehrlichiosis, malaria, Q fever, SBE, CSD Rat-bite fever, relapsing fever
	• Early satiety	• EBV, CMV, Q fever, brucellosis, SBE, miliary TB		
	• Arthralgias	• Rat-bite fever, LGV, Whipple's disease, brucellosis	• Splinter hemorrhages • Ostler's nodes/Janeway lesions	• SBE • SBE
	• Myalgias	• Q fever, leptospirosis, relapsing fever, trichinosis	• Skin hyperpigmentation	• Visceral leishmaniasis (kala-azar), Whipple's disease
	• Sinusitis	• Chronic sinusitis		
	• Night sweats	• Miliary TB, histoplasmosis	• Epididymitis	• EBV, renal TB, brucellosis
	• Weight loss	• Miliary TB, histoplasmosis		
	• Tongue pain	• Histoplasmosis, relapsing fever		
	• Neck pain	• Subacute vertebral osteomyelitis, chronic mastoiditis		
	• Tender finger tips	• SBE		
	• Abdominal pain	• Relapsing fever, leptospirosis, typhoid fever/enteric fevers, trichinosis		
	• Back pain	• Subacute vertebral osteomyelitis, brucellosis, SBE		
	• Testicular pain	• EBV		
Rheumatic/ inflammatory disorders	• PMH/FMH of rheumatic disorders	• Possibility of the same disease likely	• Fever pattern:	
	• HA/mental confusion	• GCA/TA, CNS sarcoidosis, adult Still's disease	Double quotidian fever Morning temperature spikes	• Adult Still's disease • PAN
	• Transient facial edema	• Takayasu's arteritis		
	• Hearing loss	• PAN	• Lacrimal gland enlargement	• LORA, sarcoidosis, SLE
	• Nasal stuffiness	• Sarcoidosis	• Parotid gland enlargement	• Sarcoidosis
	• Joint pain/swelling	• SLE, LORA, sarcoidosis, adult Still's disease	• Rash	• Sarcoidosis, SLE, adult Still's disease
			• Unequal pulses	• Takayasu's arteritis
	• Eye symptoms	• PAN, sarcoidosis	• Conjunctival nodules	• Sarcoidosis
	• Transient blindness	• PAN, SLE, GCA/TA, Takayasu's arteritis	• Dry eyes	• Sarcoidosis
	• Neck/jaw pain	• GCA/TA, Takayasu's arteritis	• Watery eyes	• PAN
	• Sore throat	• SLE, adult Still's disease	• Argyll-Robertson or Adies' pupils	• Sarcoidosis
	• Tongue tenderness	• GCA/TA	• Band keratopathy	• Adult Still's disease, sarcoidosis
	• Mouth ulcers	• SLE	• Episcleritis	• GCA/TA, LORA, PAN
	• Night sweats	• Takayasu's arteritis	• Scleritis	• SLE
	• Rash	• Adult Still's disease, SLE, sarcoidosis	• Iritis	• Adult Still's disease, SLE, sarcoidosis

TABLE 1.2 **CONTINUED**

	Historical features	Clues from the history	Physical examination findings	Clues from the physical examination
	• Dry cough	• Sarcoidosis, GCA/TA	• Uveitis	• Adult Still's disease, SLE, LORA, sarcoidosis
	• Acalculous cholecystitis	• SLE	• Fundi: optic neuritis with "macular star"	• PAN
	• Intermittent abdominal pain	• SLE, PAN, adult Still's disease		
	• Tender finger tips	• SLE, PAN		
	• Testicular pain	• PAN, SLE	• Fundi: cytoid bodies (cotton wool spots)	• SLE, GCA/TA, PAN, adult Still's disease
			• Fundi: "candlewax drippings"	• Sarcoidosis
			• Fundi: Roth spots	• SLE, PAN
			• Fundi: central/branch retinal artery occlusion	• SLE, GCA/TA, Takayasu's arteritis
			• Fundi: central retinal vein occlusion	• SLE, sarcoidosis
			• Oral ulcers	• SLE, Behçet's disease, FAPA syndrome
			• Tongue ulcers	• GCA/TA
			• Adenopathy	• SLE, LORA, sarcoidosis
			• Splenomegaly	• Felty's syndrome, SLE, adult Still's disease, sarcoidosis
			• Heart murmur	• SLE (Libman–Sacks)
			• Arthritis/joint effusion	• Any rheumatic/ inflammatory disorder
			• Epididymitis	• PAN, SLE, sarcoidosis
Miscellaneous disorders	• Negative HPI/PMH for infectious, inflammatory, rheumatic/malignant/ neoplastic disorders	• Non-miscellaneous disorders unlikely	• Fever pattern: Relative bradycardia	• Drug fever, factitious fever
	• PMH of periodic fevers (FMF, hyper IgD syndrome, TRAPS, Muckle– Wells syndrome)	• Possibility of same disease likely	• Periorbital edema • Parotid enlargement • Episcleritis	• TRAPS • Alcoholic cirrhosis • Regional enteritis (Crohn's disease)
	• Drugs/medications • Fume exposure • Alcoholism	• Drug fever, pseudolymphoma • Fume fever • Alcoholic cirrhosis	• Fundi: lipemia retinalis • Oral ulcers • Adenopathy	• Hypertriglyceridemia • Hyper IgD syndrome • Pseudolymphoma, hyper IgD syndrome (cervical), Schnitzler's syndrome (axillary/inguinal)
	• Regional enteritis (Crohn's disease)	• Abscess	• Signs of alcoholic cirrhosis	• Alcoholic cirrhosis
	• Thyroid disease • Hyperlipidemia • Medical personnel • Sore throat	• Subacute thyroiditis • Hypertriglyceridemia • Factitious fever • Subacute thyroiditis, hyper IgD syndrome	• Hepatomegaly • Splenomegaly	• Schnitzler's syndrome, hyper IgD syndrome • Regional enteritis (Crohn's disease), alcoholic cirrhosis, FMF, hyper IgD syndrome, Muckle–Wells syndrome, Schnitzler's syndrome
	• Neck/jaw pain • Intermittent abdominal pain	• Subacute thyroiditis • Regional enteritis (Crohn's disease), FMF, Muckle–Wells syndrome	• Epididymitis • Perirectal fistula	• FMF, TRAPS • Regional enteritis (Crohn's disease)

Historical features	Clues from the history	Physical examination findings	Clues from the physical examination
• Arthralgias/joint pains	• FMF, hyper IgD syndrome, TRAPS, Muckle–Wells syndrome, cyclic neutropenia, Schnitzler's syndrome		
• Testicular pain	• FMF, TRAPS		
• Bone pain	• Schnitzler's syndrome		
• Intermittent urticaria	• Schnitzler's syndrome Hyper IgD syndrome		

AML, acute monocytic leukemia; CMV, cytomegalovirus; CN VI, cranial nerve VI; CNS, central nervous system; CSD, cat scratch disease; EBV, Epstein–Barr virus; ESR, erythrocyte sedimentation rate; FAPA, fever, aphthous ulcers, pharyngitis, adenitis; FMF, familial Mediterranean fever; FMH, family medical history; GCA, giant cell arteritis; HA, headache; HIV, human immunodeficiency virus; LGV, lymphogranuloma venereum; LORA, late-onset rheumatoid arthritis; MPA, microscopic polyangiitis; MPDs, myeloproliferative disorders; PAN, periarteritis nodosa; PMH, past medical history; RCC, renal cell carcinoma; SBE, subacute bacterial endocarditis; SLE, systemic lupus erythematosus; STD, sexually transmitted disease; TA, temporal arteritis; TB, tuberculosis; TRAPS, tartrate-resistant acid phosphatase.

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urinalysis [UA]), but these tests should be carefully re-reviewed for diagnostic clues (e.g., relative lymphopenia).

The "shotgun" approach to laboratory testing for FUOs should be avoided. Since the number of FUO causes are legion, it is not clinically or cost effective to test for every cause of FUO. When asked why he robbed banks, Willy Sutton replied, "Because that's where the money is!" Similarly, a focused FUO workup should be directed at the most likely—not all—diagnostic possibilities as suggested by the history, physical, and nonspecific laboratory tests. Nondirected testing often provides misleading information. It makes no sense to obtain thyroid function tests (TFTs) in FUOs with joint symptoms; neither should TFTs be obtained in FUOs likely due to adult Still's disease, giant cell arteritis/temporal arteritis (GCA/TA), or periarteritis nodosa (PAN).

Blood cultures should not be obtained in all cases of FUO. If the FUO differential diagnosis includes adult Still's disease, subacute thyroiditis, or GCA/TA, blood cultures make little sense. Even if an infectious etiology is likely, blood cultures should not always be obtained (e.g., Epstein–Barr virus [EBV], cytomegalovirus [CMV], HIV). Blood cultures are ordered to rule out subacute bacterial endocarditis (SBE). The diagnosis of SBE is based on an otherwise unexplained high-grade/continuous bacteremia (with a known endocarditis pathogen) *plus* a cardiac vegetation. The diagnosis of culture-negative endocarditis (CNE) is not based on the presence of negative blood cultures and a vegetation. Rather, the diagnosis of CNE is based on three essential key findings: a cardiac vegetation, negative blood cultures, *plus* peripheral signs of SBE. The differential diagnosis of CNE includes marantic endocarditis (usually due to a malignancy). The diagnosis of marantic endocarditis is based on the size/shape of vegetation (different from SBE vegetations). Alternately, if an infectious etiology of CNE is suspected, then serologic tests for brucella and Q fever should be obtained. While brucella SBE vegetations are easily seen, Q fever SBE vegetations may be small or undetectable.

Because the appropriateness of therapy is based on a correct diagnosis, the main focus of the clinical approach to FUOs is diagnostic rather than therapeutic. The diagnostic workup should be focused based on signs, symptoms, and nonspecific laboratory abnormalities that may either enhance or diminish particular diagnostic possibilities. Nonspecific laboratory tests often provide important, albeit often subtle, clues in the FUO workup. By definition nonspecific laboratory tests are nonspecific, but when considered in concert often are helpful in narrowing diagnostic possibilities and in prompting specific diagnostic testing to rule in or rule out the most likely diagnoses being considered. Importantly, the diagnostic workup should not be excessive and should not include every conceivable cause of FUO. Focused diagnostic testing should be based on the pertinent aspects of the history, the presence or absence of characteristic physical findings, and a presumptive syndromic diagnosis based on combining key nonspecific laboratory findings.

Nonspecific laboratory test clues

Nonspecific laboratory clues are important in focusing the FUO diagnostic workup. In addition to the initial history and physical examination, selected nonspecific laboratory tests are helpful. If malignancy is a likely cause of an FUO, highly elevated ferritin, LDH, or B_{12} levels often point to an occult malignancy. Serum protein electrophoresis (SPEP) is helpful in demonstrating monoclonal or polyclonal gammopathy, which may be a clue to specific disorders. As with all laboratory tests, nonspecific findings should be interpreted in the appropriate clinical context (e.g., an FUO with polyclonal gammopathy, heart murmur, negative blood cultures, and peripheral signs of endocarditis) and should suggest an atrial myxoma. In an adult with FUO, otherwise unexplained highly elevated serum ferritin levels should suggest either a neoplasm/malignancy, myeloproliferative disorder (MPD), or a rheumatic/inflammatory disorder. Elevated serum ferritin levels are also present in systemic lupus erythematosus (SLE) flares, adult Still's disease, and GCA/TA. Elevated ferritin levels also have exclusionary diagnostic importance in FUOs; for example, malignancy is less likely with unelevated/minimally elevated serum ferritin levels (Box 1.1, Tables 1.3 and 1.4).

BOX 1.1

Fever of unknown origin (FUO) nonspecific: laboratory tests

Nonspecific tests for FUOs

- CBC
- ESR
- LFTs
- Ferritin
- SPEP
- UA

CBC

- Leukocytosis[a] → malignant/neoplastic and infectious focused workup
- Leukopenia[a] → malignant/neoplastic, infectious, and rheumatic inflammatory focused workup
- Anemia[a] → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup
- Myelocytes/metamyelocytes[a] → malignant/neoplastic focused workup
- Lymphocytosis[a] → malignant/neoplastic and infectious focused workup
- Lymphopenia[a] → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup
- Atypical lymphocytes[a] → infectious and malignant/neoplastic focused workup
- Eosinophilia[a] → malignant/neoplastic, rheumatic/inflammatory, and infectious focused workup
- Basophilia[a] → malignant/neoplastic focused workup
- Thrombocytosis[a] → malignant/neoplastic, infectious, and rheumatic inflammatory focused workup
- Thrombocytopenia[a] → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup

ESR

- Highly elevated[a] → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup

LFTs

- Elevated SGOT/SGPT[a] → infectious and rheumatic/inflammatory focused workup
- Elevated alkaline phosphatase[a] → malignant/neoplastic and rheumatic/inflammatory focused workup

Ferritin

- Highly elevated[a] → malignant/neoplastic, rheumatic/inflammatory, and miscellaneous disorders focused workup

SPEP

- Monoclonal gammopathy → malignant/neoplastic and miscellaneous disorders workup
- Polyclonal gammopathy → infectious rheumatic/inflammatory and miscellaneous disorders focused workup

UA

- Microscopic hematuria → malignant/neoplastic, infectious, and rheumatic/inflammatory focused workup[a]

[a]See Table 1.4.

CBC, complete blood count; ESR, erythrocyte sedimentation rate; LFTs, liver function tests; RD, rheumatic disease; SGOT/SGPT, serum glutamic-oxaloacetic transaminase/serum glutamic pyruvate transaminase; SPEP, serum protein electrophoresis; UA, urine analysis.

Adapted from Cunha BA. A focused diagnostic approach. In: Cunha BA (ed.) *Fever of Unknown Origin*. New York. Informa Healthcare; 2007; pp. 9–16 and Cunha BA. Fever of unknown origin: Focused diagnostic approach based on clinical clues from the history, physical examination, and laboratory tests. *Infect Dis Clin North Am* 2007;21:1137–1187.

Therapeutic considerations

The clinical approach to FUO is based on making a correct diagnosis. Empiric therapy is rarely justifiable unless a potentially treatable life-threatening disease is a definite/highly probable diagnosis. Antipyretics should be used only under unusual circumstances. Fever, per se, should not be treated because treatment eliminates a potentially important diagnostic sign (i.e., the fever curve). Temperature–pulse relationships may also have important diagnostic implications (i.e., relative bradycardia). With an FUO, if the differential diagnosis is between malignancy and infection, the Naprosyn test (naproxen 375 mg orally q12h × 3 days) is useful for *diagnostic* purposes. During the 3 days of Naprosyn little/no decrease in temperature points to an infectious disorder (a *negative*

TABLE 1.3 FEVER OF UNKNOWN ORIGIN (FUO): NONSPECIFIC LABORATORY CLUES

Leukopenia
- Miliary TB
- Lymphomas
- Pre-leukemia (AML)
- Typhoid fever/enteric fevers
- Felty's syndrome
- Gaucher's disease

Monocytosis
- Miliary TB
- Histoplasmosis
- PAN/MPA
- GCA/TA
- LORA
- SLE
- Sarcoidosi s
- CMV
- Brucellosis
- SBE
- Lymphomas
- Carcinomas
- MPDs
- Regional enteritis (Crohn's disease)
- Gaucher's disease

Eosinophilia
- Trichinosis
- Lymphomas
- Hypernephroma (RCC)
- PAN/MPA
- Kikuchi's disease
- Drug fever

Basophilia
- Carcinomas
- Lymphomas
- Pre-leukemia (AML)
- MPDs

Atypical lymphocytes
- Malaria
- Babesiosis
- Ehrlichiosis
- EBV
- CMV
- Toxoplasmosis
- Brucellosis
- Kikuchi's disease
- Drug fever

Thrombocytosis
- SBE
- Q fever
- Miliary TB
- Histoplasmosis
- Subacute vertebral osteomyelitis
- Carcinomas
- Lymphomas
- Hypernephroma (RCC)
- MPDs
- PAN/MPA
- GCA/TA

Thrombocytopenia
- Leukemias
- Lymphomas
- MPDs
- Multiple myeloma
- EBV
- CMV
- Alcoholic cirrhosis
- Drug fever
- PAN/MPA
- SLE
- Malaria
- Babesiosis
- Ehrlichiosis
- Brucellosis
- Relapsing fever
- Miliary TB
- Histoplasmosis
- Visceral leishmaniasis (kala-azar)
- Ehrlichiosis

ESR (>100 mm/h)
- SBE
- Abscesses
- Subacute vertebral osteomyelitis
- Hypernephroma (RCC)
- Carcinomas
- Lymphomas
- MPDs
- Atrial myxoma
- PAN/MPA
- Takayasu's arteritis
- Hyper IgD syndrome
- Erdheim–Chester disease (ECD)
- Rosai–Dorman disease
- Kikuchi's disease
- Schnitzler's syndrome
- Castleman's disease (MCD)
- Adult Still's disease
- GCA/TA
- LORA
- Drug fever

SPEP

Polyclonal gammopathy
- HIV
- CMV
- Alcoholic cirrhosis
- Castleman's disease (MCD)

Monoclonal gammopathy
- Multiple myeloma
- Hyper IgD syndrome
- Schnitzler's syndrome (IgM > IgG)
- Castleman's disease (MCD)

Elevated α_1/α_2 globulins
- Lymphoma
- SLE

TABLE 1.2 **CONTINUED**

Lymphocytosis
- Miliary TB
- Histoplasmosis
- Typhoid fever/enteric fevers
- Brucellosis
- EBV
- CMV
- Toxoplasmosis
- Visceral leishmaniasis (kala-azar)
- Lymphomas

Relative lymphopenia
- Q fever
- Brucellosis
- Whipple's disease
- Miliary TB
- Histoplasmosis
- Malaria
- Babesiosis
- Ehrlichiosis
- EBV
- CMV
- SLE
- Lymphomas
- Multiple myeloma
- Alcoholic cirrhosis
- LORA
- Whipple's disease
- Typhoid fever/enteric fevers

Rheumatoid factors
- SBE
- Visceral leishmaniasis (kala-azar)
- LORA
- Sarcoidosis
- SLE
- Alcoholic cirrhosis

Elevated alkaline phosphatase
- PAN
- Miliary TB
- Lymphomas
- GCA/TA
- Gaucher's disease
- Systemic mastocytosis
- Schnitzler's syndrome
- Erdheim–Chester disease (ECD)
- Adult Still's disease
- GCA/TA
- PAN/MPA
- Hypernephroma (RCC)
- Liver metastases
- Subacute thyroiditis

Elevated serum ferritin
- Malignancies
- Pre-leukemia (AML)
- MPDs
- Rosai–Dorfman disease
- Erdheim–Chester disease (ECD)
- SLE (flare)
- GCA/TA
- LORA
- Adult Still's disease
- Subacute thyroiditis

Elevated serum transaminases
- EBV
- CMV
- Typhoid fever/enteric fevers
- Brucellosis
- Q fever
- Malaria
- Babesiosis
- Ehrlichiosis
- Adult Still's disease
- Kikuchi's disease
- Drug fever

Microscopic hematuria
- SBE
- Renal TB
- Brucellosis
- PAN/MPA
- Lymphomas
- Hypernephroma (RCC)

AML, acute monocytic leukemia; CMV, cytomegalovirus; EBV, Epstein–Barr virus; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; HIV, human immunodeficiency virus; LORA, late-onset rheumatoid arthritis; MCD, multicentric Castleman's disease; MPA, microscopic polyangiitis; MPDs, myeloproliferative disorders; PAN, periarteritis nodosa; RCC, renal cell carcinoma; SBE, subacute bacterial endocarditis; SLE, systemic lupus erythematosus; TA, temporal arteritis; TB, tuberculosis.

Adapted from Cunha CB. Infectious disease differential diagnosis. In Cunha CB, Cunha BA, eds. *Antibiotic Essentials*, 17th ed. New Delhi: Jaypee Publishing; 2020: pp. 475–506; and Cunha BA. Nonspecific tests in the diagnosis of fever of unknown origin. In: Cunha BA (ed.) *Fever of Unknown Origin*. New York: Informa Healthcare; 2007: pp. 151–158.

TABLE 1.4 **FEVER OF UNKNOWN ORIGIN (FUO): SIGN AND SYMPTOM FOCUSED TESTING**

FUO infectious disease tests	FUO neoplastic disease tests	FUO rheumatic/inflammatory tests	Miscellaneous other tests
Blood tests (if suspected by history and physical examination)			
• Q fever IgM/IgG titers • Brucella IgM/IgG titers • Bartonella IgM/IgG titers • Salmonella IgM/IgG titers • EBV IgM/IgG titers • CMV IgM/IgG titers • HHV-8 IgM/IgG titers • **Blood cultures** If PVE suspected or if peripheral signs of SBE present *and* TTE/TEE shows a vegetation **Culture-negative endocarditis (CNE)** TTE shows a vegetation *Plus* Negative blood cultures *Plus* Peripheral signs of SBE present **Infectious CNE** If vegetation on TTE/TEE *and* blood cultures are negative, *and* peripheral signs of SBE present → proceed with *infectious CNE workup* (Q fever, etc.) **Noninfectious CNE (marantic endocarditis)** If *infectious CNE workup negative* → proceed with marantic endocarditis workup (malignancy, lymphoma, etc.)	• Ferritin • LDH • B_{12} levels • β-2 microglobulin levels • ACE† • SPEP	• RF • ANA • DsDNA • Ferritin • CPK • ACE • Anti-CCP • Antiphospholipid antibodies • SPEP	• **TFTs** (thyroid function tests) and **ATAs** (anti-thyroid antibody tests) If subacute thyroiditis suspected • **GGTP** • **B_{12} levels** If alcoholic cirrhosis suspected • **MEFV gene studies** If FMF suspected
Radiologic tests (if suspected by history, physical examination, or nonspecific tests)			
• **TTE** If **SBE suspected with a** murmur *plus* peripheral signs of SBE If **marantic endocarditis** suspected, *negative* BCs *plus* peripheral signs of SBE ± signs of extracardiac malignancy • **TEE** If **PVE suspected or** if **TTE equivocal** (can't exclude vegetation) • **CT/MRI abdomen/pelvis**[a] If intra-abdominal/pelvic infection suspected • **Gallium/indium scan** If occult infection suspected • **Panorex film of jaws** If apical root abscess suspected • **Abdominal PET/CT scan** If infected graft/focal vascular infection suspected • **BM biopsy/culture** If miliary TB, SBE, brucellosis, Q fevers suspected fever, typhoid/enteric fevers suspected	• **CT/MRI abdomen/pelvis** If intra-abdominal/pelvic neoplasm suspected • **Gallium/indium scan** If neoplasm suspected • **PET/CT scan** If occult neoplasm likely	• **CT/MRI abdomen** If hepatomegaly/splenomegaly or peritoneal adenopathy suspected	• **Abdominal CT scan** • **Gallium/indium scan** If regional enteritis (Crohn's disease) suspected • **Chest CT (pulmonary embolus protocol)** If pulmonary emboli suspected • **Abdominal CT/PET scan** If Erdheim–Chester disease suspected (periaortic fibrosis or "coated aorta")

TABLE 1.4 **CONTINUED**

FUO infectious disease tests	FUO neoplastic disease tests	FUO rheumatic/inflammatory tests	Miscellaneous other tests
Other tests (if suspected by history, physical examination, or nonspecific tests)			
• **Naprosyn test** If infection or malignancy suspected • **Anergy panel/PPD and T-spot** If TB suspected	• **Naprosyn test** If infection or malignancy suspected • **BM biopsy** If myelophthisic anemia/ abnormal RBCs/WBCs • **TTE** If atrial myoma or marantic endocarditis suspected • **β-2 microglobulins** If lymphoma suspected	• **Temporal artery biopsy** If GCA/TA suspected • **Low-dose steroids** If PMR suspected, prednisone 10 mg/d diagnostic/therapeutic for PMR	

[a]Chest/head CT/MRI (if head/chest infectious etiology suspected).
ACE, angiotensin converting enzyme; ANA, antinuclear antibody; ATAs, anti-thyroid antibody tests; BM, bone marrow; CBs, blood cultures; CCP, cyclic citrullinated peptide antibody; CMV, cytomegalovirus; CPK, creatinine phosphokinase; CPK, creatinine phosphokinase; EBV, Epstein–Barr virus; FMF, familial Mediterranean fever; GCA, giant cell arteritis; GGTP, gamma-glutamyl transpeptidase; HHV-8, human herpesvirus-8; LDH, lactic acid dehydrogenase; PMR, polymyalgia rheumatica; PVE, prosthetic valve endocarditis; RF, rheumatoid factor; SBE, subacute bacterial endocarditis; SPEP, serum protein electrophoresis; TA, temporal arteritis; TEE, transesophageal echocardiogram; TFTs, thyroid function tests; TTE, transthoracic echocardiogram.

Adapted from Cunha CB. Infectious disease differential diagnosis. In Cunha CB, Cunha BA, eds. Antibiotic Essentials, 17th ed. New Delhi: Jaypee Publishing; 2020. pp. 475–506; and Cunha BA. A focused diagnostic approach and non-specific tests in the diagnosis of FUO. In: Cunha BA (ed.) *Fever of Unknown Origin*. New York: Informa Healthcare; 2007: pp. 9–16, 151–158.

Naprosyn test), whereas a sustained decrease in the febrile response points to a malignancy (*positive* Naprosyn test). The Naprosyn test should not be used and is not interpretable if a rheumatic/inflammatory or miscellaneous cause of FUO is suspected.

If an FUO is likely due to miliary tuberculosis (TB), empiric anti-TB therapy may be life-saving. Among rheumatic/inflammatory disorders, empiric therapy of polymyalgia rheumatica (PMR) with low-dose prednisone (5–10 mg/d orally) is both diagnostic and therapeutic. Patients with FUO due to GCA/TA may develop acute unilateral visual impairment, and blindness may be prevented with high-dose steroid therapy (prednisone 60–80 mg/d).

Once the cause of the FUO has been determined, specific therapy, if available, may be given. Therapy may also involve removal of the underlying cause of the FUO (e.g., discontinuing the drug causing drug fever, abscess drainage, specific therapy of treatable infections and rheumatic/inflammatory disorders).

Suggested reading

Brusch JL, Weinstein L. Fever of unknown origin. *Med Clin North Am*. 1988;72:1247–1261.

Chang JC, Gross HM. Utility of naproxen in the differential diagnosis of fever of undetermined origin in patients with cancer. *Am J Med*. 1984;76:597–607.

Cunha BA. Fever of unknown origin. In Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases*, 3rd ed. New York: Lippincott Williams & Wilkins; 2004:1568–1577.

Cunha BA. Fever of unknown origin: Clinical overview of classic and current concepts. *Infect Dis Clin North Am*. 2007;21:867–915.

Cunha BA. Fever of unknown origin: Focused diagnostic approach based on clinical clues from the history, physical examination, and laboratory tests. *Infect Dis Clin North Am*. 2007;21:1137–1187.

Cunha BA. Fever of unknown origin (FUO): Diagnostic serum ferritin levels. *Scand J Infect Dis*. 2007;39:651–652.

Cunha BA, eds. Antibiotic Essentials, 17th ed. New Delhi: Jaypee Publishing; 2020.

Cunha BA, Bouyarden M, Hamid NS. Fever of unknown origin (FUO) caused by multiple myeloma: The diagnostic value of the Naprosyn test. *Heart Lung*. 2006;35:358–362.

Cunha BA, Petelin A. Fever of unknown origin (FUO) due to large B-cell lymphoma: The diagnostic significance of highly elevated alkaline phosphatase and serum ferritin levels. *Heart Lung*. 2013;42:67–71.

Cunha CB. Diagnostic tests in infectious diseases. In Cunha CB, Cunha BA, eds. *Antibiotic Essentials*, 17th ed. New Delhi: Jaypee Publishing; 2020:474–506.

Knockaert DC. Recurrent fevers of unknown origin. *Infect Dis Clin North Am*. 2007;21:1189–1211.

Murray HW. Fever of Unknown Origin, Informa Healthcare, NY, 1983.

2

Sepsis

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Introduction

Sepsis is a complex syndrome that results from the host's dysregulated immune response to infection. It is regarded as one of the most complex and challenging syndromes described in medicine. Historically, Hippocrates described sepsis as the process by which "flesh rots, swamps generate foul air and wounds fester," Later, with the introduction of germ theory, sepsis was described as "blood poisoning" and considered the invasion of pathogens into the bloodstream. To this day, old terms such as "septicemia" persist. Since the 1930s, in the era of antibiotic treatment for serious infections, it has become clear that patients with sepsis die of complications of the sepsis syndrome and not from the microbes responsible for that syndrome.

The International Consensus Panel in 1992 redefined sepsis as the *systemic inflammatory response syndrome* (SIRS) rising from infection. Clinically, SIRS is identified by the presence of at least two of the following: fever or hypothermia, tachycardia, tachypnea, and leukocytosis or leukopenia. *Severe sepsis* is sepsis with acute organ dysfunction or tissue hypoperfusion. *Septic shock* is sepsis with hypotension refractory to fluid resuscitation, often in the setting of hyperlactatemia due to decreased tissue perfusion.

Definitions and key concepts

Sepsis can be thought of as life-threatening organ dysfunction resulting from dysregulated host responses due to infection. Septic shock is a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are profound enough to substantially increase the rate of mortality.

Severity of organ dysfunction has been assessed with various scoring systems that quantify abnormalities according to clinical findings, laboratory data, or therapeutic interventions (Table 2.1). There are two scoring systems available: the sequential organ failure assessment (SOFA) (Table 2.2) and SIRS. Differences in the definitions of the scoring systems have led to inconsistencies in estimates of the incidence of sepsis as well as debates as to which system is "better."

Using the SOFA score, the historical categories of sepsis, severe sepsis, and septic shock have been changed to infection (in the absence of sepsis), sepsis, and septic shock. Thus, sepsis has been redefined as the presence of an infection combined with an acute change in SOFA score of 2 points or more (baseline assumed to be zero in patients not known to have preexisting organ dysfunction).

A simplified scoring system based on using just three criteria and identified from a large retrospective analysis of large databases was termed *quick SOFA* (qSOFA). Patients were considered "high risk" if they met at least two of the following criteria: alteration in mental status, systolic blood pressure of <100 mm Hg, or a respiratory rate of >22 breaths per minute (Table 2.3). High risk is defined as having a mortality risk of >10%.

TABLE 2.1 **SEPSIS-RELATED TERMINOLOGY AND DEFINITIONS**

Infection	A pathologic process caused by invasion of normally sterile host tissue by pathogenic microorganisms
Bacteremia	The presence of viable bacteria in blood
SIRS	The systemic inflammatory response to a wide range of infectious and noninfectious conditions. Currently used criteria include two or more of the following: temperature >38°C/100°F or <36°C/97°F heart rate >90 beats/minute: respiratory rate >20 breaths/ minute, or $PaCO_2$ <32 mm Hg: WBC >12,000 cells/mm^3 or <4,000 cells/mm^3, or >10% immature (band) forms
SOFA	The sequential organ failure assessment score: A system that assesses the status of several organ systems in the body (neurologic, blood, liver, kidney, and blood pressure/hemodynamics). A score is assigned based on the data from each category. The higher the SOFA score, the higher the mortality rate.
Septic shock	Pre 2016: Systolic blood pressure (SBP) <90 mm Hg or mean arterial pressure (MAP) <70 mm Hg or a SBP decrease >40 mm Hg or a SBP less than two standard deviations below normal for age in the absence of other causes of hypotension Current: Persistent hypotension after fluid resuscitation requiring vasopressors to maintain MAP >65 mm Hg or a serum lactate level of >2 mmol/L
MODS	Multiple organ dysfunction syndrome: The presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention. Primary MODS occurs early and can be directly attributable to an insult itself (such as trauma or neoplasia); secondary MODS develops as consequence of a host response and is identified in the context of SIRS

In patients with suspected sepsis who eventually required admission to the ICU, the qSOFA score was found to be marginally superior to SIRS criteria in predicting mortality risk and ICU-free days in the high-risk group. qSOFA does not require laboratory tests and can be assessed quickly and repeatedly. From a practical standpoint, based on the qSOFA score, clinicians can decide to order additional studies to assess organ dysfunction, initiate or escalate therapy as appropriate, and consider referral to a critical care unit or increase the frequency of monitoring. Positive qSOFA criteria should prompt consideration of possible infection in patients not previously recognized as infected.

The main limitation of using SIRS criteria for identifying individuals with suspected sepsis is that it has a lower specificity compared to SOFA. However, SIRS is more sensitive than SOFA in identifying patients with suspected sepsis. Thus, it remains in place at many medical centers, often incorporated in the electronic medical record (EMR) as a "sepsis alert" or warning.

Epidemiology

The true incidence of sepsis probably is underestimated or unknown. The methods to record the incidence depend on clinician reporting and coding in the EMR, which is not standardized across the country.

TABLE 2.2 **SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORING SYSTEM**

Organ system	SOFA score 1	SOFA score 2	SOFA score 3	SOFA score 4
Respiration PaO_2/FiO_2	<400	<300	<200	<100
Coagulation Platelet count (number per mL)	<150,000	<100,000	<50,000	<20,000
Liver Bilirubin mg/dL	1.2–1.9	2.0–5.9	6.0–11.9	>12
Cardiovascular Hypotension; vasoactive dosing as micrograms per kg per minute	MAP <70 mm Hg	Dopamine ≤5; or dobutamine (any amount)	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
CNS Glasgow Coma Scale	13–14	10–12	6–9	<6
Renal Creatinine mg/dL	1.2–1.9	2.0–3.4	3.5–4.9	>5.0

TABLE 2.3 **QUICK SEQUENTIAL ORGAN FAILURE ASSESSMENT (QSOFA) SCORING**

Quick SOFA (qSOFA) criteria	Points
Respiratory rate >22/min	1
Change in mental status	1
Systolic blood pressure <100 mm Hg	1

A retrospective analysis of more than 2.9 million adults admitted to 409 US hospitals in 2014 found that sepsis was present in 6% of hospitalized patients, of whom 21% died in the hospital or were discharged to hospice. Sepsis was present in 35% of all hospitalizations that culminated in death. Sepsis incidence rates using clinical data were stable from 2009 to 2014; in-hospital mortality rates declined, but there was no significant change in the combined outcome of death or discharge to hospice. There likely is significant underreporting of the incidence of sepsis, especially in older populations where other comorbidities exist. Often, it is the final event in patients with comorbidities such as malignancy or kidney injury listed as the discharge diagnosis in the EMR.

Pathogenesis

The clinical manifestations of the sepsis syndrome are caused by the host's response to infection when a microbial pathogen-associated molecular pattern is recognized by pattern recognition receptors (PRRs) on the surface of the host immune cells. These receptors are key components of the innate immune system that recognize "danger signals" on invading bacteria and other pathogens. Conserved motifs expressed by pathogens (pathogen-associated molecular patterns or PAMPs) include lipopolysaccharide (LPS), peptidoglycan, lipopeptides, lipoteichoic acid (gram-positive bacteria), and flagellin (a motility factor for bacteria). PRRs also can recognize endogenous "danger signals," called alarmins or danger-associated molecular patterns (DAMPs), which are released during the inflammatory insult. Toll-like receptors express leucine-rich repeats that mediate the recognition of PAMPs. Ten TLRs have been identified in humans; they can be expressed on the cell surface or intracellularly.

Peptidoglycan of gram-positive bacteria is recognized by TLR2; LPS of gram-negative bacteria is recognized by TLR4. The involvement of TLRs elicits a signaling cascade via the cytosolic nuclear factor-kappa b (NF-κB). Activated NF-κB moves from the cytoplasm to the nucleus, binds to the transcription sites and induces activation of a large set of pro-inflammatory cytokines (e.g., tumor necrosis factor [TNF]-α; interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10). This activation occurs within minutes to hours after macrophages have been activated. TNF-α is the most important cytokine in sepsis. IL-1β has similar effects. The two stimulate the release of stress hormones, other cytokines (e.g., IL-2, IL-6, IL-8, IL-10), and other inflammatory mediators of sepsis (e.g., nitric oxide, lipoxygenase and cyclooxygenase metabolites, platelet activating factor, interferon-γ, and adhesion molecules). All of these interact in a complex fashion to effect various changes to multiple organ systems.

The resulting sepsis, multiorgan system failure, and death were previously believed to be solely from an exaggerated, uncontrolled inflammatory response known as a "cytokine storm." But it is now thought that they also arise from subsequent immunosuppression—the result of an "injured" adaptive immune response. This state includes the alteration of neutrophil migration at multiple stages, as these cells become more rigid and sequestered in organs (limiting blood flow, causing tissue ischemia and multiorgan failure), as well as suppressed activity because of reduced TLR expression and signaling. Nitric oxide blocks neutrophil migration and the interaction between leukocytes and endothelial cells. Likewise, peroxisome proliferator-activated receptor (PPAR)-γ contributes to neutrophil chemotaxis suppression. There also is evidence that gene expression of TNF-α and interferon-β stops with continued insult, necrosis, and infection. The initial release of and exposure to high levels of chemoattractants "desensitizes" G-protein-coupled receptor (GPCR) responsiveness, resulting in downregulation of GPCR cell surface expression. All of these effects show that the innate immune system seems unable to respond to continuous inflammatory

TABLE 2.4 **SOME PRO-INFLAMMATORY AND ANTI-INFLAMMATORY CYTOKINES IN SEPSIS**

Cytokine	Cell origin	Function	Role in sepsis
Pro-inflammatory			
IL-6	T-cells, macrophages, endothelial cells	Cell growth, differentiation, cytokine production	Disease severity, mortality, biomarker
IL-8	Macrophages, epithelial cells endothelial cells	Chemotaxis, angiogenesis	Mortality, biomarker
IL-18	Macrophages, monocytes, dendritic cells	IFN-γ production, antimicrobial immunity	Disease severity, biomarker
TNFα	Macrophages, T cells, NK cells	Cytokine production, cell proliferation, apoptosis, anti-infection, tumor necrosis	Disease severity, survival, biomarker
Anti-inflammatory			
IL-10	Th2 cells, B cells, monocytes	Potent inhibitor of pro inflammatory cytokine production	Disease severity, mortality

stimuli, progressing to a dysfunctional stage and ending in an irreversible phase of sepsis and end-organ injury. Table 2.4 summarizes the role of some of these cytokines in sepsis.

Excessive "cross-talk" exists between coagulation and inflammation during sepsis, characterized by inflammation-induced activation of coagulation with concurrent impairment of anticoagulant systems, fibrinolysis, and endothelial function. Furthermore, during sepsis, inflammation-induced coagulation contributes to further inflammation. The intensity of both the pro-inflammatory and immunosuppressive phases of sepsis likely depends on multiple factors, including genetics and comorbidities (host factors), and the type, virulence, and burden of invading pathogen (organism factors). Various single nucleotide polymorphisms (SNPs) are associated with increased susceptibility to infection and to poor outcome. SNPs are used as genetic markers. They include SNPs of genes that encode cytokines, cell surface receptors, lipopolysaccharide ligands, mannose binding lectin, heat shock protein 70, angiotensin 1 converting enzyme, plasminogen activator inhibitor, and caspase-12.

The role of the complement system in sepsis is complex. Mice lacking C3, the central component of the complement system, have increased sepsis-related mortality. Complement is activated in many ways. For instance, C1 can bind to antigen-antibody complexes as well as to DAMPs. C1 also can bind to C-reactive protein (CRP) and serum amyloid protein, both of which recognize PAMPs. On the other hand, inhibition of C5a signaling improves survival of animals in experimentally induced sepsis. Thus, it now is believed that, early in sepsis, activation of the complement system improves survival by its role in decreasing inflammation and vascular permeability. Later in sepsis, increased C5a activity contributes to the development of multiorgan dysfunction.

Other systemic effects of sepsis

Tissue ischemia occurs secondary to microcirculatory dysfunction. Microcirculatory dysfunction is associated with worse outcomes. Tissue ischemia can occur due to a systemic or local mismatch between oxygen delivery and tissue demand. Mitochondrial dysfunction occurs during sepsis and contributes to failure of tissue oxygen extraction despite sufficient oxygen delivery (cytopathic hypoxia). Mitochondrial dysfunction, tissue hypoxia, and apoptosis (programmed cell death) are important mediators of organ dysfunction during sepsis. Coagulopathies seen in sepsis range from microthrombosis to massive thromboembolism and hemorrhage (disseminated intravascular coagulation or DIC).

During microbial attack and invasion of the host cells, microbial pathogen associated molecular pattern (PAMPs) is recognized by Pattern Recognition Receptors (PRRs) situated on the surface of the host immune cells. Some of the bacteria undergo phagocytosis in optimal conditions (Figure 2.1). The pro-inflammatory responses lead to cellular or tissue damage and anti-inflammatory response leads to immune system impairment. The inflammatory changes occur secondary to release of cytokines and protease, complement activation, B and T cell impairment, leukocyte activation, and activation of coagulation cascade. The release of stress hormones, cytokines, and inflammatory mediators of sepsis interact in a complex fashion to cause multi-organ dysfunction and subsequent failure. This is facilitated by genetic factors, advanced age, nutritional deficiencies, diabetes, immunosuppression, and recent surgeries. Multiple organ dysfunction manifests as altered mental status, circulatory collapse, tachycardia, renal failure, respiratory failure, liver failure, and GI dysfunction.

Etiology

Historically, antibiotic recommendations for therapy of sepsis and septic shock were based on coverage of gram-negative organisms. However, sepsis caused by gram-positive organisms is clinically identical to sepsis caused by gram-negatives. After 1987, gram-positive bacteria became the predominant pathogens in most areas. In recent studies, 47% to 55% of sepsis cases were due to gram-positives (e.g., *Staphylococcus aureus*, coagulase-negative staphylococci, *Streptococcus pneumoniae,* and enterococci), while gram-negatives made up 38% to 51%. *Escherichia coli* has remained the most common gram-negative pathogen in community and nosocomial infections. *Staphylococcus epidermidis* has become the most common cause of nosocomial bacteremias, followed by *S. aureus*, enterococci, and *Candida* species. Infections caused by vancomycin resistant enterococci (VRE), particularly *Enterococcus faecium* (resistant to ampicillin and aminoglycosides) and non-albicans *Candida* species have become more common. Gram-negative bacteria, including multidrug-resistant (MDR) *Pseudomonas aeruginosa,* extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, *Enterobacter* species and other plasmid-mediated AmpC β-lactamase producing bacteria, and *Acinetobacter* species, are increasing and becoming resistant to multiple antibiotics. Sepsis caused by anaerobic organisms is uncommon, perhaps because anaerobic gram-negative anaerobes lack lipid A (endotoxin), a potent trigger of the sepsis cascade.

Diagnosis

Diagnosis starts with a thorough history and physical examination. The history should focus on symptoms, recent surgery, underlying disease(s), recent antibiotic use, travel. and known risk factors such as the presence of indwelling catheters and other devices.

Physical examination includes vital signs. While fever is the most common manifestation of sepsis, hypoxia and/or hypotension are present in approximately 30% to 40%. Absence of fever is more likely in individuals with extremes of age or those in debilitated condition.

Table 2.5 lists the diagnostic criteria for sepsis (SIRS-based).

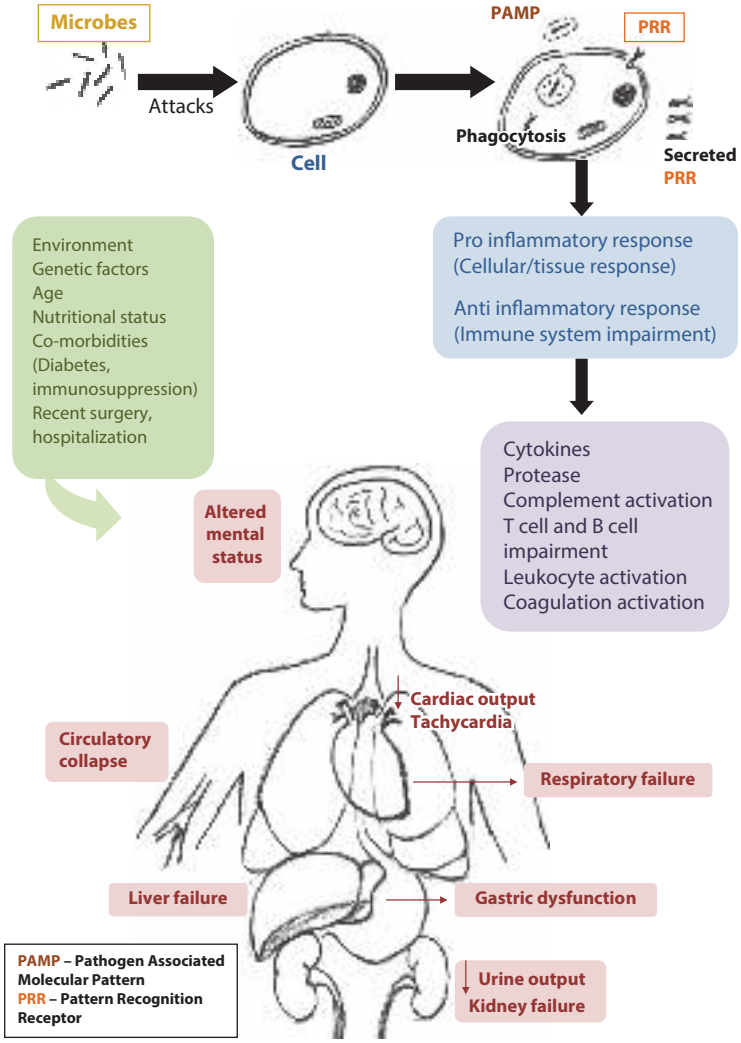

FIGURE 2.1 The pathogenesis of sepsis.

TABLE 2.5 DIAGNOSTIC CRITERIA FOR SEPSIS

Infection (documented or suspected) and some of the following parameters must be present:

General parameters	(1) Fever (>38°C/100°F), (2) hypothermia (core temperature <36°C/97°F), (3) heart rate >90 beats/min or greater than two SDs above the normal value, (4) tachypnea, (5) altered mental status, (6) significant edema or positive fluid balance (>20 mL/kg over 24 hours), (7) hyperglycemia (plasma glucose>140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory parameters	(1) Leukocytosis (white blood cell count >12 000/μL), (2) leukopenia (white blood cell count <4,000/μL), (3) normal white blood cell count with >10% immature forms, (4) plasma C-reactive protein (CRP) greater than two SDs above the normal limit, (5) plasma procalcitonin greater than two SDs above the normal limit
Hemodynamic parameter	(1) Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg, or an SBP decrease of >40 mm Hg in adults or greater than two SDs below normal for age
Organ dysfunction parameters	(1) Arterial hypoxemia (PaO_2/FiO_2 <300), (2) acute oliguria (urine output <0.5 mL/kg/h for at least 2 hours despite adequate fluid resuscitation), (3) creatinine increase >0.5 mg/dL or 44.2 μmol/L, (4) coagulation abnormalities (INR >1.5 or aPTT >60 s), (5) ileus (absent bowel sounds), (6) thrombocytopenia (platelet count <100 000/μL), (7) hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 μmol/L)
Tissue perfusion parameters	(1) Hyperlactatemia (>1 mmol/L), (2) decreased capillary refill or mottling

Abbreviations: SBP = systolic blood pressure; MAP = mean arterial pressure; SD = standard deviation; INR = international normalized ratio; aPTT = activated partial thromboplastin time.
In the pediatric population, the diagnostic criteria for sepsis are (1) signs and symptoms of inflammation plus (2) infection with (3) hyper- or hypothermia (rectal temperature >38.5°C/101°F or <35°C/95°F), (4) tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ dysfunction: (a) altered mental status, (b) hypoxemia, (c) increased serum lactate level, or (d) bounding pulses.

Recommended investigations include a CBC with differential, basic metabolic panel, hepatic function panel, coagulation studies, lactate level, and urinalysis. Clinically suspected respiratory infections should be assessed with a chest x-ray and arterial blood gas analysis (evaluation of hypoxemia and acid–base abnormalities).

Multiple cultures from suspected infected sites need to be obtained. All cultures should be delivered promptly to the microbiology laboratory. Gram staining should be done and read as soon as possible on specimens submitted for cultures. Ideally, cultures should be obtained before starting antibiotics. For clinically and hemodynamically unstable patients, antibiotics should be given as early as possible and certainly within 3 hours of presentation.

At least two sets of cultures from different sites should be obtained from all sepsis suspects. Each blood culture set consists of one aerobic and one anaerobic bottle. Typically, 6 to 10 mL of blood needs to be injected into each bottle to increase the likelihood of culturing pathogens. If an indwelling venous or arterial catheter is present, it is important to obtain additional cultures through each one of the ports, unless the device is recently placed (within 48 hours). DNA probes (polymerase chain reaction [PCR]-based) have become increasingly common for more rapid detection of certain pathogens (e.g., methicillin-resistant *S. aureus* [MRSA]).

Sputum for culture can be spontaneously expectorated or induced by 3% saline nebulization or obtained by nasotracheal, endotracheal, or transtracheal techniques. Specimens should have >25 polymorphonuclear cells and <10 squamous epithelial cells per low-power microscopic field to decrease the chance that the specimen is contaminated with upper airway flora. Semi-quantitative or quantitative cultures may be used for ventilator-associated pneumonia (VAP) diagnosis. Nasotracheal swabs (DNA probes) are particularly useful for detecting viral pathogens as well as bacteria such as *Legionella* species.

Urine for culture should be obtained in most cases. Urine also should be sent for legionella and pneumococcal antigens as part of the determination of bacterial causes of pneumonia. Stool for detection of *Clostridium difficile* toxins A and B should be obtained from individuals presenting with diarrhea and recent antibiotic use. Enzyme immunoassay (EIA) testing for toxins A and B is faster but less sensitive than cell-based cytotoxin assays. The two-step method, starting with EIA to detect glutamate dehydrogenase followed by the cell-based assay, increases sensitivity. In our institution, we use *C. difficile* PCR to detect the toxins, which is much more sensitive and specific than EIA testing. Testing should be done only on symptomatic patients since many are colonized with *C. difficile*.

When suspecting fungal causes of sepsis, fungal blood cultures and/or histopathologic evidence are considered gold standards. Other diagnostic tests also are available. These include the 1,3 β-D glucan assay (Fungitell), which is helpful for diagnosing certain invasive fungal infections such as those caused by candida and aspergillus species. The galactomannan enzyme immunoassay provides a presumptive diagnosis for invasive aspergillosis. The serum capsular antigen for cryptococcus species and urine polysaccharide cell wall antigen for histoplasmosis and blastomycosis species are useful in certain circumstances. Invasive pulmonary aspergillosis may be diagnosed using galactomannan antigen detection in bronchoalveolar lavage fluid. It is important to recognize that not all fungal infections will produce a positive Fungitell. Furthermore, clinicians must consider the possibility of a false-positive result which may occur in patients who recently received β-lactam antibiotics or due to the use of cellulose filters in hemodialysis. The galactomannan assay also may be falsely positive in patients who received fluids containing gluconate or citric acid, as occurs in platelet transfusions or total parental nutrition.

Depending on clinical suspicion, other lab tests may be useful. Rapid influenza antigen testing should be done during influenza season. In our institution, we prefer Influenza A and B plus respiratory syncytial (RSV) PCR because processing time is only 6 hours, and the sensitivity and specificity of the test are excellent. PCR-based respiratory pathogen panels, as well as PCR testing for SARS-CoV-2, can be very useful when patients present with a respiratory source for sepsis.

A CT scan of the abdomen may reveal previously overlooked fluid collections that may be accessible by needle aspiration. Certain infections prevalent in intravenous (IV) drug users, such as epidural abscesses and psoas muscle abscesses, may be diagnosed by MRI. Ultrasonography is useful for detecting ascites and biliary and pancreatic pathologic conditions. A portable (bedside) ultrasound can be obtained for critically ill patients who are too unstable to be transported to the radiology department. Echocardiography is recommended for the diagnosis of infective endocarditis and should be performed in patients with murmurs or suspected IV drug use.

A lumbar puncture for cell count, protein, glucose, bacterial and viral antigens, fungal studies (e.g., cryptococcal antigen), Gram stain, and culture should be performed on septic patients with unexplained altered mentation and on patients with suspected meningitis.

Despite the widespread availability of sensitive and specific diagnostic tests, recognizing sepsis still is not optimal. Studies have estimated that physicians correctly diagnosed sepsis between 73% and 77% of the time. This unsatisfactory rate of diagnosis is why numerous biomarkers (e.g., IL-6) have been under investigation. The hope is to discover a marker that will assist clinicians in reliably distinguishing sepsis from other inflammatory conditions and early enough to improve clinical outcomes.

Management of sepsis

Early goal-directed therapy (EGDT) emphasizes a timely (within the first 3–6 hours of presentation) and coordinated approach to sepsis management, with a significant mortality benefit when efforts are made for early diagnosis, risk stratification, fluid resuscitation, early administration of antimicrobials, control of the source of infection, and hemodynamic optimization utilizing vasoactive drugs.

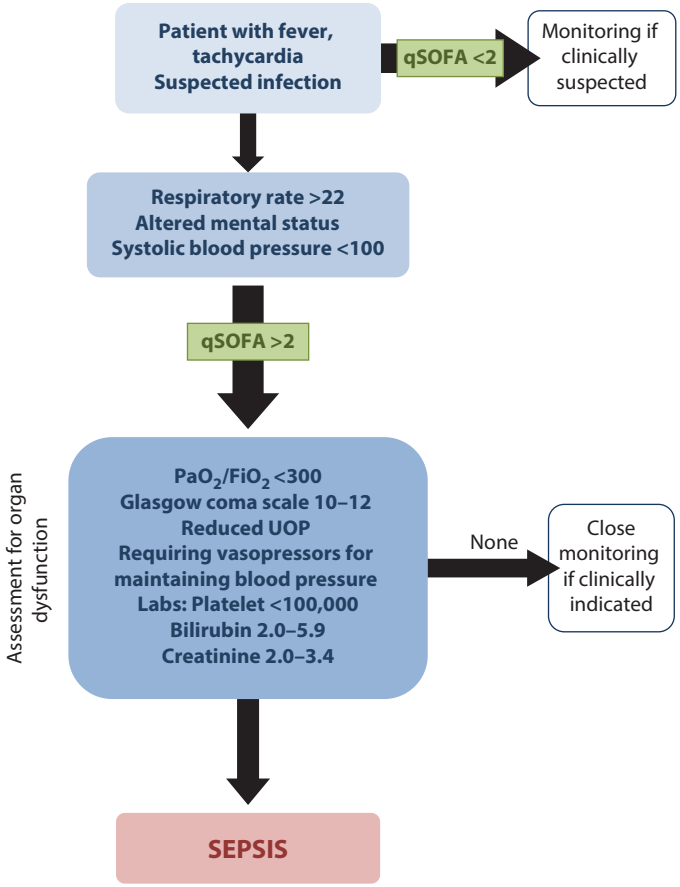

FIGURE 2.2 Assessment of patient in the emergency department.

Effective treatment should focus on timely intervention, including the removal of sources of infection. Aggressive assessment for an unrecognized source or undrained abscess through appropriate initial evaluation, laboratory testing, and diagnostic imaging is critical. Early initiation of appropriate antimicrobial therapy, restoration of tissue perfusion via fluid resuscitation, and advanced interventions guided by assessment of the adequacy of the efforts at resolution of organ dysfunction should be part of initial and ongoing sepsis management.

Broad-spectrum antibiotics need to be administered within the first 3 hours of presentation. Begin rapid administration of 30 mL/kg of crystalloid fluids or balanced crystalloid fluids (e.g., Ringer's lactate or Hartmann's solution) for hypotension or in those with serum lactate levels of >4 mmol/L. Initiate vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain a mean arterial pressure (MAP) of ≥65 mm Hg.

Source control should be done early, keeping in mind the risks and benefits of both surgical and medical intervention. Observational data have shown that inadequate source control is associated with an increase in 28-day all-cause mortality from 26.7% to 42.9%.

Figures 2.2 and 2.3 illustrate a management approach for patients starting with presentation to the emergency department (ED).

Table 2.6 lists some specific organisms to consider in certain clinical situations.

Antimicrobial therapy: Selection and duration

The initial empiric antibiotic regimen (AR) should include coverage for common gram-positive and gram-negative aerobes. As soon as the pathogen is isolated or drug sensitivities are known, the antibiotic spectrum may be narrowed. De-escalation (narrowing the spectrum) of the AR should be considered daily based on the clinical course of the patient.

Giving effective antimicrobials within the first 3 hours of admission to the hospital increases survival to hospital discharge in adults with septic shock. Delayed antimicrobial therapy is associated with increased mortality in severe infections that have the potential to progress to septic shock. The choice of antimicrobials should be based on the patient's history (e.g., recent antibiotics, previous organisms if known), comorbidities (e.g., diabetes), immunodeficiencies (e.g., HIV), clinical context (i.e., community- or hospital-acquired), suspected site of infection, presence of invasive devices, Gram stain data, and local prevalence and resistance patterns.

The antimicrobial choice should be tailored to each individual patient. A few principles are worth emphasizing. Patients with septic shock should receive combination therapy with at least two antimicrobials from different classes depending on the organisms which are considered likely pathogens and local antibiotic

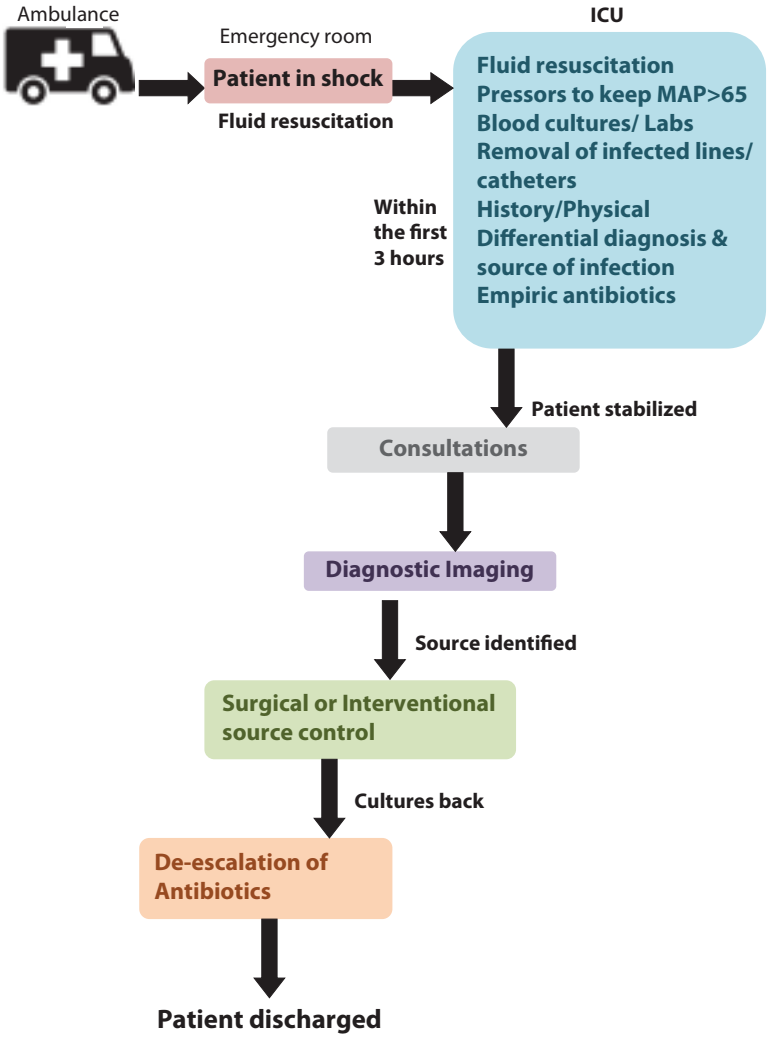

FIGURE 2.3 Management algorithm.

susceptibilities. Anti-pseudomonal agents should be used for empiric therapy for nosocomial infections. Antibiotic dosages should be optimized for the site of infection, usually the highest allowable dosage adjusted for organ dysfunction. Intravenously administered antibiotics often result in higher serum and tissue levels than oral antibiotics. Orally administered antibiotics should not be used for patients with compromised gut absorption. Community-acquired infections are likely to be caused by organisms different from those in the hospital. For example, *Pseudomonas aeruginosa* is unlikely in community-acquired infections, with few exceptions (e.g., IV drug users): consequently, anti-pseudomonal coverage is not warranted routinely for community-acquired infections. In contrast, *Streptococcus pneumoniae* is one of the most common causes of community-acquired sepsis and should be covered adequately.

TABLE 2.6 SPECIAL CIRCUMSTANCES AND PATHOGENS

Circumstances	Possible pathogens
Splenectomy	Encapsulated organisms; *Streptococcus pneumoniae, Hemophilus influenzae,* and *Neisseria meningitidis*
Neutropenia	Gram negatives such as *Pseudomonas*. Gram positives (*Staphylococcus aureus*) and fungi
Hypogammaglobulinemia	*Streptococcus pneumoniae, Eschericia coli*
Burns	MRSA, *Pseudomonas aeruginosa*, resistant gram-negatives and *Candida* species
AIDS	*Salmonella* species, *Staphylococcus aureus*, and *Pneumocystis jirovecci*
Intravascular devices	*Staphylococcus aureus* and *Staphylococcus epidermidis*
Nosocomial infections	*Staphylococcus aureus* (especially MRSA), *Enterococcus* species, resistant gram-negatives, and *Candida* species

Antibiotics need to achieve therapeutic drug levels in infected tissues and fluid throughout the dosing interval. Achieving adequate levels in lung parenchyma can be challenging with the aminoglycosides and daptomycin; achieving adequate cerebrospinal fluid levels typically requires the inclusion of a third-generation cephalosporin or a carbapenem.

Aminoglycosides offer rapid killing of gram-negative aerobic bacteria in a concentration-dependent manner. The risk of nephrotoxicity and ototoxicity, the poor penetration of aminoglycosides into abscesses and lung parenchyma, and the lack of data to indicate that the addition of aminoglycosides affects outcomes in sepsis call for their judicious use. We suggest aminoglycosides be used as follows: (1) large single daily doses (e.g., 5 mg/kg) when used for synergy against streptococcal and enterococcal infections and (2) use only for the first few days for empiric coverage of aerobic gram-negative bacteria, especially *P. aeruginosa*. Note that the potential advantages of using two antibiotics, each with activity against the same likely pathogen include (1) a higher probability that the infecting pathogen will be covered by at least one of the antimicrobials, (2) a potential synergistic killing effect, and (3) possibly preventing the emergence of bacterial resistance.

Clinicians need to be cognizant of underlying medical conditions (e.g., avoidance of trimethoprim-sulfamethoxazole in patients with renal failure, and imipenem in patients with seizure disorders). It also is prudent to consider suspected organisms and target them appropriately. For example, carbapenems are preferred for infections caused by ESBL-producing bacteria, as well as Amp C β-lactamase-producing bacteria (the "SPICE" organisms: *Serratia*, *Providencia*, indole-positive bacteria such as Proteus, Citrobacter, and Enterobacter species). Cephalosporins should be avoided in organisms that tend to become constitutive producers of β-lactamases, such as *Enterobacter* species)

The incidence of nosocomial β-lactam-resistant gram-positive organisms has been increasing, as has the incidence community-acquired MRSA infections. The inclusion of an anti-MRSA antibiotic (e.g., vancomycin, linezolid, or daptomycin) in the AR is recommended when the prevalence of MRSA in the community exceeds 10% to 20% of all *S. aureus* isolates. Physicians need to be aware of the pattern of antimicrobial resistance in their places of practice and surrounding communities.

Fungi account for only 5% of all cases of severe sepsis or septic shock. Therefore, routine antifungal therapy is not recommended in sepsis unless the patient is at higher risk of fungal infections (e.g., neutropenic or post bone marrow transplant, undergoing chemotherapy, or receiving total parental nutrition).

Macronodular skin lesions with biopsies consistent with *Candida* infection and candida endophthalmitis are each synonymous with dissemination. Since only a fraction of patients with systemic candidiasis have positive blood cultures, a number of approaches have been developed to estimate the risk of systemic fungal infection in hospitalized patients. In general, when *Candida* species are isolated from three or more non-blood sites, the risk of subsequent infection of the blood by these colonizing fungi increases. Initiating AR therapy in such situations depends on the total clinical picture, but most physicians would add an antifungal agent to the AR if fever or other signs of infection were present. In any case, the efficacy of the azole antifungals (e.g., fluconazole) and their favorable toxicity profiles have made their empiric use more acceptable, especially in non-neutropenic patients. Nevertheless, a non-azole antifungal (e.g., micafungin) is preferred initially at institutions with high rates of azole resistance, especially for the moderately severe to severely ill individual. Micafungin or another antifungal from the echinocandin class also is used in places with high rates of glabrata and krusei species of candida. These organisms have high rates of resistance to the azoles.

Duration of antibiotic therapy depends on the clinical response and, occasionally, the infecting pathogen. Bacteremia typically is treated with 10 to 14 days of therapy, although shorter courses may be possible if improvement is rapid. If bacteremia with *S. aureus* is prolonged (>48 hours), therapy is given for at least 4 weeks, although during some percentage of that time the antibiotic may be given orally. Endocarditis and osteomyelitis, regardless of pathogen, typically are treated for 6 weeks.

Antibiotic decisions should be re-evaluated at least daily. Changes need to be considered as culture and susceptibility results become available or as the clinical course dictates. A patient who has not responded or who has relapsed after an initial improvement needs to be re-evaluated thoroughly. Additional diagnostic studies may be indicated, and repeat cultures should be obtained to search for new or resistant pathogens. If the clinical syndrome is determined to be noninfectious, antibiotics should be stopped.

The persistently febrile neutropenic patient presents an especially challenging problem. Empiric antifungal therapy should be started (and testing for invasive fungal infections should be done) if fever persists or is recurrent despite broad-spectrum antibiotic coverage for more than 4 to 7 days, as well as for febrile neutropenia expected to last for more than 7 to 10 days.

Poor decisions about antibiotic use have potential immediate and future negative consequences. Long-term antibiotics will not protect patients from infection; rather this approach will cause emergence of multidrug-resistant organisms. The best way to avoid widespread resistance is to continuously re-evaluate the need for antibiotic therapy and to de-escalate when microbial susceptibility panels become available. In addition, side effects, such as cumulative antibiotic toxicity and superinfection with multidrug-resistant pathogens and *C. difficile*, are much more common after long courses of multiple antibiotics. Antibiotic stewardship has been shown to reduce the incidence of infection with multidrug-resistant organisms.

Table 2.7 lists some antibiotic combinations to consider based on selected clinical circumstances.

Source control

Source control remains an important aspect of treatment in patients with sepsis and septic shock. Source control entails rapidly identifying the anatomical site involved, followed by the removal of the infected material (e.g., drainage of abscesses). For the skin and

TABLE 2.7 **SELECTED EMPIRICAL ANTIMICROBIAL THERAPY**

Diagnosis	Suspected pathogen	Empiric therapy
Bacteremia, catheter associated	**Staphylococci, Enterococci, Enterobactereciae**	Vancomycin + Piperacillin/tazobactam Hemodialysis patients Cefepime + vancomycin Critically ill or neutropenic patients Cefepime + vancomycin + tobramycin Severe β-lactam allergy Aztreonam + tobramycin + vancomycin
Meningitis	***S. pneumoniae*, *N. meningitidis*, *Listeria monocytogenes* (EtOH use, age >50)**	Ceftriaxone + vancomycin (add ampicillin if risk factors for *Listeria* present)
Intra-abdominal infection	**Enterobacteriaceae, *Bacteroides* sp. Enterococci, Streptococci, *P. aeruginosa*, Staphylococci**	Cefepime + Metronidazole Piperacillin/tazobactam Meropenem especially with a prior history of ESBL-producing organisms in the past 12 months) Severe β-lactam allergy: Aztreonam + metronidazole + vancomycin
Pneumonia: Hospital-acquired/ ventilator-associated	**Enterobactereiacea, *P. aeruginosa*, *Staphylococcus aureus***	Cefepime (or piperacillin/tazobactam) + vancomycin (or linezolid in ICU patients only) ± tobramycin Piperacillin/tazobactam + Severe beta lactic allergy: Aztreonam + vancomycin (or (linezolid in ICU patients only) ± tobramycin Add azithromycin for patients presenting from the community who are at risk for Legionella species
Pneumonia: Community-acquired	***S. pneumoniae*, *H. influenzae*, *Legionella* species**	Azithromycin + Ceftriaxone Severe β-lactam allergy: Moxifloxacin For ICU patients with suspected MRS, add vancomycin or linezolid
Urinary tract infection, healthcare-associated	**Enterobacteriaceae, Enterococci, *P. aeruginosa***	Cefepime + vancomycin ± tobramycin

soft tissue infections, it includes actions such as wound care, incision and drainage, debridement, and, in some cases, amputation. All infected devices should be removed promptly.

In intra-abdominal infections, the appropriate interventions to determine the adequacy of the source control are dictated by the clinical scenarios. High-risk patients with compromised hemodynamic status benefit from minimally invasive procedures, including percutaneous or endoscopic procedures. Recent recommendations on source control and peritonitis use "damage control" surgery (i.e., more limited surgery) for critically ill patients. If patients with intra-abdominal infections are stable, source control measures include surgical incision and drainage of abscesses, debridement of infected necrotic tissues, removal of potentially infected devices, and extensive intra-abdominal irrigation to decrease the peritoneal inoculum.

Similarly, empyemas need to be drained, and obstructive pyelonephritis needs to include surgical involvement. Failure to adequately control the source, regardless of the severity of the illness, typically results in poor survival rates and additional complications in those who do survive.

Supportive therapy

After initial fluid resuscitation, the fluid responsiveness should be assessed in patients with continued hemodynamic instability. All currently available methods for assessing fluid responsiveness have limitations. Dynamic methods such as responsiveness to stroke volume and cardiac output to passive leg raise are helpful, although they may be practically challenging at the bedside.

Crystalloids are the recommended fluid for initial resuscitation. Among crystalloids, there is increasing interest in the comparison between using balanced crystalloid solutions (Ringer's lactate and Hartmann's solution) with normal saline. No consensus exists at present. There is emerging evidence that a chloride-restrictive

resuscitation strategy is associated with reduced incidence of both acute kidney injury and the need for renal replacement therapy.

Monitoring central venous oxygen saturation ($SVCO_2$) and blood lactate levels, though controversial, seem to have improved the outcomes of sepsis.

Patients who fail to maintain a MAP of >65 require vasopressor support. Norepinephrine is the preferred first-line vasopressor due to its increased potency and reduced risk for arrhythmias. Vasopressin administration allows for reduction of the dose of catecholamine vasopressors, but does not appear to independently improve patient mortality. The US Food and Drug Administration recently approved angiotensin II as a new vasopressor for the treatment of septic shock. However, this approval was not based on any mortality benefit as the study (ATHOS-3) was not designed to detect such differences. In addition, limited safety data exist. Note that angiotensin II has pro-inflammatory properties, can increase IL-6 levels, and also is pro-thrombotic.

Contrary to previous recommendations to tightly control glucose levels, the current consensus is to simply maintain serum glucose at <180 mg/dL. Many controversies continue to exist in nutritional support regarding the timing and route of administration. Several trials have failed to show benefits of enteral feeding compared with the parenteral route.

The role of corticosteroids in patients with sepsis remains controversial. There are some data to suggest that there is some benefit in using corticosteroids in the subset of patients with shock. There also is some evidence to suggest that corticosteroids are associated with ICU-acquired weakness. Multiple clinical trials with different doses of corticosteroids have failed to show a 30-day survival benefit. Two recent clinical trials using an endpoint of 90-day survival came to opposite conclusions, with one trial (APROCHSS) showing a benefit and the other (ADRENAL) showing no benefit.

Mesenchymal stem cells for treatment of the acute respiratory distress syndrome (ARDS) have shown some promise. Interferon-β also is being studied in patients with moderate to severe ARDS. Endotoxin removal via polymyxin B hemoperfusion is a novel therapeutic approach for patients with septic shock and is under investigation. Activated protein C (drotrecogin) was withdrawn from the market after multiple subsequent trials could not replicate the findings of benefit in 30-day survival found in the initial trial.

Sepsis is a clinical syndrome rather than a disease. It is associated with high mortality and long-term morbidity. Many survivors of sepsis are admitted to long-term care facilities, and readmissions to hospitals are frequent. Many sepsis survivors report a decreased quality of life and substantial cognitive impairment in addition to functional disability. Continued effort is required to improve the long-term outcomes of patients with sepsis and septic shock.

Suggested reading

Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369:840–851.

Bernhard M, Lichenstern C, et al. The early antibiotic therapy in septic patients: Milestone or sticking point? *Crit Care*. 2014;18;671.

Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286:1754–1758.

Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589–1596.

Lagunes L, Encina B, Ramirez-Estrada S. Current understanding in source control management in septic shock patients: A review. *Ann Transl Med*. 2016;4:330 (1–5).

Liu VX, Fielding-Singh V, et al. The timing of early antibiotics and hospital mortality in sepsis. *Am J Respir Crit Care Med*. 2017;196:856–863.

MacArthur RD, Miller M, Albertson T, et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: Experience from the MONARCS trial. *Clin Infect Dis*. 2004;38:284–288.

Markiewski M, DeAngelis RA, Lambris JD. Complexity of complement activation in sepsis. *J Cell Mol Med*. 2008;12:2245–2254.

Ndukka OO, Parillo JE. The pathophysiology of septic shock. *Crit Care Clin*. 2009;25:677–702.

Paul M, Shani V, Muchtar E, et al. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother*. 2010;54:4851–4863.

Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45:486–552.

Singer M, Duetschman CS, Seymour CW, et al. Septic shock (Sepsis-3). *JAMA*. 2016;315:801–810.

Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358:111–124.

Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell*. 2010: 140;805–820.

3

Chronic fatigue syndrome

Stephen J. Gluckman

Introduction: Nature of the syndrome

Chronic fatigue syndrome (CFS) is a syndrome of subjective complaints most prominently featuring profound and prolonged physical exhaustion. Many experts suggest that this syndrome is the late-twentieth-century formulation of an illness that has been described under various designations in medical literature for centuries, such as *febricula* ("little fevers") in the eighteenth century, *neurasthenia* in the nineteenth century, and *myalgic encephalomyelitis* (ME) in Great Britain and Canada or *chronic fatigue and immune dysfunction syndrome* (CFIDS) in the United States during the late twentieth century. The designation *chronic fatigue syndrome* was adopted by the US Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) because this name does not assume a direct role for infection, inflammation, or immune system dysfunction in the genesis of the symptoms. Indeed, an abundance of research has failed to attribute the syndrome to any specific infection or immunologic disturbance. Patients may complain of neurologic, cardiac, gastrointestinal, rheumatologic, psychiatric, and endocrine symptoms. CFS concerns infectious disease physicians because it is frequently ascribed to an active infection or a sequel of infection (i.e., as postviral or postinfectious fatigue).

The association of chronic fatigue and infection was first examined systematically in a study of chronic brucellosis. In a 1951 study, Wesley Spink found that 20% of patients with serologic evidence of brucellosis went on to develop persistent fatigue, muscle weakness, myalgia, mental confusion, and depression without evidence of ongoing infection with *Brucella*. He suggested that the symptoms of chronic brucellosis depended on both a previous *Brucella* infection and a psychological predisposition. Evidence for this theory was provided by investigators from Johns Hopkins during the Asian influenza pandemic of 1957–1958. During that epidemic season, these investigators conducted a retrospective cohort analysis of military personnel and their dependents who had completed the Minnesota Multiphasic Personality Inventory (MMPI) prior to the epidemic. Prolonged convalescence after influenza was associated with unfavorable scores on the test. Moreover, the MMPI profiles of subjects with prolonged postinfluenza symptoms were nearly identical to MMPI profiles of the previously studied patients with chronic brucellosis. This observation implies that the persistent fatigue and associated symptoms may reflect a programmed response to a variety of different infections in predisposed subjects.

Acute mononucleosis has also long been postulated to be a precipitant of prolonged postinfectious fatigue. Consequently, when two large studies in 1985 reported an association between chronic fatigue and elevated titers of Epstein–Barr virus (EBV) antibodies, EBV became a leading candidate as the etiologic agent, and "chronic mononucleosis" became a popular designation for fatigue syndrome. As with other attempts to link CFS to a specific infectious agent, the association between active EBV and CFS was not confirmed by subsequent virologic studies. EBV infection is now best understood as one of the infectious precipitants of the syndrome rather than as a chronic active infection that is a direct cause of the persistent symptoms. A recent prospective study of 301 adolescents diagnosed with infectious mononucleosis found that 13%, 7%, and 4% met criteria for pediatric CFS 6, 12, and 24 months after the onset

BOX 3.1

Case definition of chronic fatigue syndrome

All three of the following:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for >6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest.
2. Post-exertional malaise: Physical, psychological, or emotional exertion
3. Unrefreshing sleep

Plus, one or two of the following:
One of the following:

1. Cognitive impairment
2. Orthostatic intolerance

Institute of Medicine. http://iom.nationalacademies.org/Reports/2015/ME-CFS.aspx

of symptoms, respectively, regardless of whether steroids were used during the acute illness. Similarly, infections with enteroviruses, cytomegalovirus, Ross River virus, parvovirus, human herpesvirus 6, *Borrelia burgdorferi*, *Coxiella burnetii*, *Candida albicans*, and *Giardia lamblia* have also been cited as potential triggering events. The notion that CFS is a direct consequence of chronic active infection with any of these agents is not supported by existing evidence. Studies are either inconclusive or definitively negative. Making a distinction between infection as an acute precipitant and as a chronic persistent cause of the syndrome is critical. It explains why attempts to treat the syndrome with antibiotics, antivirals, and antifungals have been uniformly disappointing. Further, it has been suggested that non-infectious life stresses can also initiate CFS.

In the absence of a simple etiology or a uniformly applicable diagnostic test for CFS, the NIH and the CDC proposed a consensus definition of the syndrome intended to serve as a standard for future studies. In 2015, the Institute of Medicine proposed a simplified case definition as noted in Box 3.1. Because fatigue is one of the most common complaints encountered in general medicine, the definition excluded patients with trivial or medically explainable fatigue states and captured those with illnesses that were characteristic of the syndrome. However, there are problems with both specificity and sensitivity of a case definition of this kind. Clinical case definitions of a disease where there is no definitive diagnostic test should be used with caution when applied to a specific patient. They are more appropriately considered epidemiologic or research tools. Thus, rigid application of the CFS criteria (e.g., requiring 6 symptomatic months) may exclude patients who might profit from an early intervention.

Epidemiology

Idiopathic chronic fatigue is very common (5–10% of patients in general medical practice), but very few (≤1%) can be diagnosed with CFS using the proposed criteria. The US national prevalence of CFS was estimated by the CDC through a network of physicians in four American cities. The prevalence ranged from 3 to 11 per 100 000 population, and the gender and age distribution were similar in all four sites. Most patients were female (7:1) in the fourth and fifth decades of life. Estimates from clinic-based studies in Australia and the United Kingdom yield similar results. However, a population-based survey in San Francisco and other community-based studies elsewhere suggest a prevalence of about 0.2%, with a larger proportion of males, ethnic minorities, and those of lower socioeconomic classes. The discrepancy between community- and clinic-based studies is attributable to the greater utilization of clinical services by middle- and upper-class women. It belies the notion of a "yuppie flu," a pejorative term applied to this disorder in the past.

Illnesses consistent with CFS also occasionally occur in epidemic fashion. In some instances, the outbreaks may be associated with an infectious event; however, in others, the distribution of illness among the populations at risk clearly does not resemble the spread of an infection. Examples of the latter type include the large hospital-based outbreaks in Los Angeles, California, and London, that affected the hospital professional staff but not the hospitalized patients or nonprofessional staff.

Pathophysiology

The majority of patients have an acute onset of the syndrome. A small proportion can be traced to a diagnosed infectious disease. CFS may also follow other physically and psychologically stressful events, such as surgeries, accidents, deaths, and divorces. A smaller number of patients have an insidious onset with no definite precipitating event. Regardless of the onset, the majority of patients have past or current psychiatric disorders, but a large minority has no active or past psychiatric symptoms.

Numerous infections have been associated with CFS, but evidence that the syndrome is not associated with any specific infectious agent is of three main types. First, there is no single infectious agent that is detectable in all cases of CFS; the disorder may occur even in the absence of the most common agents, such as EBV. Second, the development of the same syndrome occurs during convalescence after infections with non-overlapping geographic distribution (e.g., Ross River virus, Q fever, or Lyme disease). Third, attempts to treat CFS with anti-infectives have been uniformly disappointing. It may be true that only a specific type of infection with prolonged duration or severity is necessary to precipitate CFS. Indeed, patients seen in general practice for common, simple infections do not have an increased frequency of prolonged fatigue relative to patients seen for other medical problems. However, postinfectious cases and those with no apparent precipitant are clinically indistinguishable with respect to symptoms and psychosocial features once the defining

criteria are met. These observations lead to the conclusion that the syndrome is a nonspecific sequel to a variety of infections or other precipitants. The inability to determine a single cause may be frustrated by the fact that there is, in reality, no single cause but rather a number of triggers. Whether patients who have CFS will reactivate latent viruses more frequently than well individuals is an unsettled issue, but no correlation between viral reactivation (e.g., EBV) and the expression of symptoms has been demonstrated.

From time to time, sensational reports appear linking a persistent infectious agent with the syndrome, as in 1985 with EBV. The latest of these events occurred in late 2010, when an article appeared in *Science* reporting the presence of a xenotropic murine retrovirus (XMRV) in two-thirds of a panel of CFS patients and only approximately 4% of controls. The putative presence of this virus was later shown to be due to contamination of samples with mouse DNA, and the original article supporting the claim was subsequently retracted. Clinicians should maintain skepticism about claims of this kind since the attribution of CFS to a single transmissible agent is not easy to reconcile with the clinical and epidemiologic features described earlier.

In addition to a quest to find an infectious etiology, attention has been focused on immunologic, endocrine, and neuropsychiatric causes. Subtle alterations have been noted but the findings are inconsistent, minor, and do not correlate with disease severity. The hypothesis that the central nervous system is the principal site of the pathophysiology in CFS has gained support in recent years. This hypothesis is bolstered by the presence of neuropsychological symptoms in the active syndrome, the observation of prior or pre-existing psychiatric disorders in a large proportion of patients, and subtle alterations of hormones regulated at the hypothalamic level. Previous or concurrent depression is frequently present in CFS. When patients in general practice are evaluated for "viral" illnesses, the psychiatric morbidity and the patient's belief structure concerning the illness are better predictors of subsequent chronic fatigue than are the severity of symptoms at the time of presentation. More objective evidence of central nervous system involvement includes the observed disruption of the hypothalamic-pituitary-adrenal (HPA) axis. As a group, patients with CFS appear to have lower HPA axis activity than age- and gender-matched controls. Most evidence points to the hypothalamus as the affected element of the axis; however, it is not known whether any of these findings are primary or secondary to inactivity, sleep disruption, or continuing stress accompanying CFS. Nevertheless, the decreased HPA activity in CFS contrasts with the increased activity of the HPA axis observed in patients with major depressive disorder. It is more consistent with findings in posttraumatic stress disorder (PTSD), suggesting that CFS may represent a dysfunctional capacity to respond to both physical and psychological stress, either acquired or genetic or both.

Some evidence for a genetic predisposition to CFS has been generated by twin studies. Studies in the United States, Australia, and Great Britain have shown an increased concordance in monozygotic, rather than dizygotic, twins. However, a microarray analysis of the transcriptome of monozygotic twins who are discordant for CFS failed to show any significant differences. These observations and the other findings mentioned earlier support a pathophysiologic theory of CFS that depends on a predisposition involving genetic or environmental factors or both. In the presence of an acute provocation, such as an infection, the stress response system fails and results in both the production and perpetuation of subjective symptoms (i.e., fatigue, pain, disrupted sleep, poor cognition) and detectable immune alterations.

Diagnosis

CFS is a clinical diagnosis that depends almost entirely on the history and the patient's report of symptoms. There are no characteristic clinical signs. There are no laboratory tests that can be used with any reliability to rule in or rule out the diagnosis. The purpose of the physical examination and basic laboratory testing is to confirm that there is not another medically definable condition that may be causing the symptoms. In the absence of any confounding medical conditions, the diagnosis of CFS may be guided by the published consensus criteria. For reasons explained earlier, the clinician should not apply these criteria stringently for individual patients.

In postinfectious fatigue, the chronic symptoms may appear to be an extension of the inciting infection. Most often, there is no identifiable precipitating event, and the same flu-like symptoms develop gradually. They include sore throat, low-grade fever, tender cervical lymphadenopathy, generalized myalgia or arthralgia, headache, sleep disturbances, and a perception of impaired cognition. Objective physical findings accompanying these symptoms (e.g., pharyngeal erythema or exudate, fever >38°C/100°F, muscle weakness, signs of arthritis, or enlarged lymph nodes) are rare. The presence of any of these signs should raise suspicion of an alternative diagnosis and be evaluated accordingly.

The cardinal symptom of the syndrome is persistent and disabling fatigue, and the fatigue has several characteristic qualities. Most importantly, it is unrelenting and of long duration. It is not improved by rest but worsens after physical or emotional exertion. Postexertional malaise may persist for hours to days after even a modest expenditure of effort. Many patients perceive a limited allotment of energy to expend each day, and, once it is used, they cannot function.

Most patients describe impaired concentration and poor short-term memory. Standard neuropsychological testing typically shows no evidence of an organic syndrome and need not be ordered unless there is objective evidence for cognitive or memory deficit on physical examination. This problem may be the most alarming for the patient who fears a loss of intellectual function; however, such patients can be reassured that the "mental fog" that they experience will lift as the physical symptoms improve.

Most patients will also report either insomnia or excessive sleep. A thorough sleep history is important because many primary sleep disorders present with chronic fatigue as the chief complaint. If there is a suspicion of sleep apnea or a nocturnal movement disorder, a formal polysomnography is indicated. Understandably, many patients will have symptoms of depression or anxiety. Their pre-CFS life has been restricted. The clinician must determine whether these symptoms are reactive to CFS, or primary,

accounting for all of the patient's symptoms. If all of the symptoms can be attributed to major depression or anxiety, then a diagnosis of CFS is excluded.

A limited laboratory evaluation should be done to exclude unrecognized medical conditions. All patients should have a CBC, a chemistry profile, urinalysis, and thyroid function testing. Additional testing may be ordered to rule out other specific medical conditions if the history or physical examination is suggestive. However additional testing should be done judiciously and only if there is a suggestion in the history or physical. Testing when there is a low pre-test probability for a specific disease runs a high risk for false-positive results and potentially additional unnecessary testing and treatments. For example, 15–54% of patients may have a low-titer antinuclear antibody test. This is usually nonspecific, and anti-DNA antibodies and antibodies to extractable nuclear antigens are typically absent. Lupus and other such inflammatory disorders have objective physical findings. Patients with CFS are more likely than healthy controls to have small areas of increased single intensity by brain MRI. These are usually nonspecific and easily distinguished from plaques of demyelinating disease. Urinary free cortisol levels may be relatively low in CFS, but this finding is not reliable enough to be of any diagnostic value. Hormonal testing, other than thyroid-stimulating hormone, should be ordered only when a particular disorder is suspected. Similarly, measurement of the 2′,5′-oligoadenylate synthetase pathway can be ordered from some commercial laboratories. Although opinions differ about the value of these tests, this author finds them insufficiently sensitive and specific to be useful. EBV, Babesia, Lyme disease, and CMV serologies are uninformative both for diagnosis and follow-up of CFS. The clinical syndrome of CFS does not overlap with these disorders. Finding antibodies to these agents may result in unnecessary and occasionally harmful treatments.

CFS often overlaps or coexists with other common idiopathic disorders. Patients with CFS may also meet diagnostic criteria for fibromyalgia, irritable bowel syndrome, interstitial cystitis, premenstrual syndrome, migraine, restless leg syndrome, neurally mediated hypotension or postural orthostatic tachycardia, atypical depression, or spastic dysphonia. The pathophysiologic relationship between these entities and CFS is unclear, but it is important to identify these coexisting disorders because they often respond to treatments that are not necessarily appropriate for use in CFS alone.

Treatment

Guiding principles

At present, the pathophysiology of CFS is not sufficiently understood to inform specific therapy. Consequently, specific medical or psychiatric therapy is indicated only when there is an alternate or coexisting diagnosis. There is no rationale for treating infectious agents. Antivirals and other anti-infective agents are not of value in treating the symptoms of CFS.

In the absence of specific therapy for CFS, treatment should be focused on the remediation of symptoms, nonpharmacologic interventions, and physical rehabilitation. There are only a few treatment modalities that can be recommended based on consistent efficacy demonstrated in well-designed, controlled studies (Table 3.1). Because evidence-based information is inconclusive, clinicians must use their own judgment when using empirical, symptomatic therapies based on the patient's complaints and their own comfort when prescribing the medications. Several other treatments have been proposed, but a preponderance of studies suggests that they are unhelpful or potentially harmful (Table 3.1). Clinicians should also be aware that there is typically a robust placebo effect in trials with CFS patients; therefore, treatment trials that lack appropriate control groups are uninterpretable.

When initiating treatment, it is useful to objectify the symptoms as much as possible. Patients should be asked to rate their symptoms and to keep personal logs so that their response to any treatment can be assessed. This approach is consistent with the principles of one of the possibly effective treatments, cognitive-behavioral therapy (CBT). Therapeutic interventions should be initiated sequentially so that their positive and negative effects can be assessed. In addition, it is especially important to document unconventional or alternative therapies because many patients may resort to using these products. Polypharmacy, including alternative treatments, may confuse the patient's ability to assess their response to any particular treatment that may be prescribed. In general, both the empirical use of allopathic medications and the patient's experimentation with alternative therapies should be guided by concerns for safety and cost, and empirical trials of treatment should be undertaken systematically in a manner that allows the patient and the doctor to assess the value of the intervention.

Critically important aspects of treatment

The most important components of treatment include giving the patient enough time; making it clear to the patient that this is not a new disease; making it clear to the patient that their symptoms are valid; and reviewing with the patient that it is not unusual for them to have had the response from their family, employers, friends, and other healthcare providers that their symptoms were not legitimate. They have a disabling illness that is not their fault, they cannot wish away, and is chronic. Their disability does not allow them to function at a level that they were functioning prior to the development of CFS. Like any other person with a disability they will need to learn a new reality to be able to get the most they can out of their situation.

Empirical treatment of symptoms

Certain medications may be useful for symptomatic therapy in selected patients. Non-narcotic pain relievers for myalgia, arthralgia, or headache may be helpful. Some combination of nonsteroidal anti-inflammatory medications, acetaminophen, and tramadol may improve symptoms in some patients with prominent pain symptoms. Pregabalin, gabapentin, Cymbalta have all been used with some benefit in some patients.

TABLE 3.1 **TREATMENTS FOR CHRONIC FATIGUE SYNDROME**

Critical therapeutic strategies: Educating the patient: 1. This is not a new disease, just a new diagnosis. Therefore, we know a lot about it 2. Symptoms are completely valid and often disabling, though because they are not "visible" and testing is normal patients often have to defend the legitimacy (see IOM paper). These people are suffering. They want their pre-CFS lives back. They are not malingering.	
Therapies supported by several randomized controlled trials:	None
Empiric, symptomatic treatments	Nonnarcotic pain relievers: Cymbalta, pregabalin, gabapentin, amitriptyline Antidepressants Sleep hygiene Sleep aids
Controversial treatments supported by some studies but not by others:	Graded exercise program Cognitive-behavioral therapy
Inappropriate treatments without out clinical support or proved ineffective in controlled trials: Antibiotics, antivirals, antifungals Hydrocortisone Galantamine Fludrocortisone Dehydroepiandrosterone (DHEA) IV immunoglobulin Interferons Vitamins Nutritional supplements Restrictive diets	

Although studies conflict on the value of antidepressant therapy, there are two rationales for their use in selected patients: (1) certain antidepressants are generally considered effective treatment (e.g., for mood disturbances, anxiety, insomnia, pain, poor concentration), and (2) it is expected that chronic illness and disability will result in some degree of depression. Treating depression will help them cope better with their disability, and (3) CFS and fibromyalgia frequently coexist or have substantial symptom overlap, and a benefit of tricyclic antidepressants and similar medications has been demonstrated in fibromyalgia. It should be noted that studies that show benefit of these agents in CFS generally report relief of the associated symptoms noted earlier rather than the cardinal symptom of fatigue. Therefore, a particular antidepressant may be favored for a given patient depending on the intensity of these symptoms. The remarkable safety profile of antidepressants makes them a reasonable choice for an empirical trial.

Many CFS patients also suffer from sleep disturbances. Pharmacologic sleep aids (e.g., eszopiclone, zolpidem, clonazepam) may be helpful short term but risk creating dependency. Various antidepressants (e.g., low-dose trazodone or amitriptyline) may be better suited for long-term use. Melatonin is a popular over-the-counter sleep remedy, but CFS patients have normal levels and timing of endogenous melatonin secretion. A trial of high-dose melatonin improved CFS symptoms in patients with delayed melatonin secretion; however, the trial used historical controls and must be interpreted with caution.

Perhaps as important as pharmacologic agents is some attention to sleep hygiene. All patients should be instructed to keep regular sleep hours. Patients who are sleeping excessively should be encouraged to reduce their hours of sleep gradually. Those with insomnia should be encouraged to reduce daytime napping to <1 hour a day.

Controversial therapies

While some studies have demonstrated that graded aerobic exercise is helpful in reducing the symptoms of CFS, others have not. If undertaken they must be done cautiously because of the characteristic exacerbation of symptoms by exercise. A program of exercise tailored to the individual patient's tolerance should be a part of any treatment effort. The form of exercise should be aerobic and quantifiable. An approach that targets a specified exercise duration is likely to give the best results. This is best done under the supervision of an experienced physical therapist. Adherence to such a program usually requires substantial oversight by the physician and physiotherapist, especially among patients who experience serious post-exertional fatigue. In contrast, there is no evidence to support the prescription of bed rest and some suggestion that continuous inactivity may both reinforce illness behavior and lead to complicating myofascial pain syndromes.

CBT is can be helpful for symptom control in a variety of organic diseases, so it is not surprising that it also benefits some CFS patients. CBT involves a restructuring of the patient's beliefs about the illness and encourages objective assessment of the symptoms and disabilities. One innovative approach developed by a Dutch research group used an internet-based CBT program for treating adolescents and found it more effective for increasing school attendance than a treatment program based in a tertiary care center. Unfortunately, CBT is not universally available; however, the physician can integrate some of the principles into routine medical care. Educating the patient about the causes and manifestations of CFS is critical, particularly when there are misconceptions that may lead to counterproductive behaviors. Having the patient objectify their symptoms and identify factors that exacerbate or relieve them may also be helpful in management. A rational and sympathetic approach to the patient is essential. Challenging the reality of symptoms or attributing them to some other cause (e.g., depression in the absence of standard criteria) is distinctly unhelpful because these ideas will not be consistent with the patient's own experience and beliefs. Similarly, classical insight-oriented psychotherapy should be reserved for those patients who have significant emotional stress.

Contraindicated therapies

Several specific therapies for CFS have been tried based on a particular pathophysiologic hypothesis. Until now, none of these therapies has been shown to have meaningful benefit. For instance, a carefully conducted trial of anti-herpesvirus therapy with acyclovir to test the hypothesis that EBV replication is associated with ongoing symptoms failed to show any benefit over placebo (both showed some benefit). Similarly, a randomized therapeutic trial of oral nystatin was conducted to assess the effect on CFS-like symptoms in patients who claimed to have yeast hypersensitivity. The only benefit was a slight reduction in *Candida* vaginitis in the treatment group.

The finding of depressed HPA axis activity prompted a trial of low-dose hydrocortisone and subsequently a trial of galantamine (to stimulate HPA axis activity centrally). Investigators judged that the bone mineral loss and prolonged suppression of the HPA axis that resulted from hydrocortisone therapy was not justified by the minimal benefit gained by treatment. The study of galantamine showed no substantial benefit. Another neuroendocrine hypothesis involves the hormone dehydroepiandrosterone (DHEA). DHEA supplementation in CFS has reportedly improved fatigue and other symptoms in patients with depressed levels of this enzyme at baseline; however, there has been no controlled trial of this treatment, and it should be regarded skeptically. A study connecting neurally mediated hypotension (diagnosed by a 45-minute tilt table protocol) with CFS prompted therapeutic trials of volume expansion with fludrocortisone. Two independent studies showed no significant benefit of this approach.

Using a model of immune dysfunction as a key factor in the production of CFS symptoms, immune modulation with immunoglobulins and interferons has been studied. In particular, patients should be cautioned about unproved, costly, inconvenient, and potentially dangerous treatments. Other therapies that have been ineffective or conflicted in randomized controlled trials include the thiamine precursor sibutramine, growth hormone, homeopathic preparations, and essential fatty acids.

Occasionally, patients report relief of symptoms with specialized dietary alterations. A common example is the restrictive diet recommended to reduce intestinal "yeast." There is no experimental evidence to support these diet therapies in CFS, and highly restrictive diets may impair nutrition and general health. Trials of nutritional supplements (e.g., vitamins, liver extract) have also been discouraging.

Physicians and patients should be aware that there is a lucrative internet market catering to desperate patients with CFS whose primary care physicians are dismissive. Most of the online sales involve unproved supplements and remedies. Many are very expensive (such as replacement of all amalgam dental fillings) and some may be hazardous (such as various hormones and ephedra). Some patients with CFS are motivated to take risks and spend abundantly from their personal resources to achieve relief from their suffering. Sympathetic physicians should not be judgmental but rather attempt to guide patients through this morass of "treatments" to protect them from financial exploitation or harm.

One final caveat: it is important to evaluate each new symptom in a patient with CFS before ascribing it to CFS. Patients with CFS are, of course, are at risk for any additional disease. Before assuming this is just another manifestation of CFS, consideration must be given to an alternative and potentially specifically treatable cause.

Conclusion

CFS may occur spontaneously or as a result of an acute stressor, such as an infection. However, there is no evidence that a chronic infection is the cause of the chronic symptoms. Diagnostic criteria have been established by expert consensus in an attempt to standardize research on this disorder. Diagnosis based on the patient's subjective report, physical examination, and laboratory tests is useful only to rule out confounding medical conditions. Medical treatments directed at specific symptoms may be helpful in individual patients. Treatments based on a pathophysiologic hypothesis of the disorder have been uniformly disappointing. Consequently, the most important elements of care include (1) educating the patient with restructuring of beliefs and perceptions of the illness, (2) evaluating symptomatic treatments, and (3) protecting the patient from physical or financial harm associated with unproved therapies.

Suggested reading

Institute of Medicine. Beyond myalgic encephalomyelitis/chronic fatigue syndrome. Full Report. http://iom.nationalacademies.org/Reports/2015/ME-CFS.aspx

Fukuda K, Straus S, Hickie I, et al. The chronic fatigue syndrome: A comprehensive approach to its definition and study. International

Chronic Fatigue Syndrome Study Group. *Ann Intern Med*. 1994; 121:953–959.

Holgate ST, Komaroff AL, Mangan D, Wessely S. Chronic fatigue syndrome: Understanding a complex illness. *Nat Rev Neurosci*. 2011;12(9):539–544.

Imboden JB, Canter A, Cluff LE. Convalescence from influenza: A study of the psychological and clinical determinants. *Arch Intern Med*. 1961;108:393–399.

Nijhof SL, Bleijenberg G, Uiterwaal CS, et al. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): A randomised controlled trial. *Lancet*. 2012;379(9824):1412–1418.

Van Cauwenbergh D, De Kooning M, Ickmans K, Nijs J. How to exercise people with chronic fatigue syndrome: Evidence-based practice guidelines. *Eur J Clin Invest*. 2012;42(10):1136–1144.

White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): A randomised trial. *Lancet*. 2011;377(9768): 823–836.

Section 2

Clinical syndromes: Head and neck

4

Pharyngotonsillitis

Itzhak Brook

Pharyngotonsillitis (PT) is an inflammation of the pharynx and tonsils characterized by the presence of increased pharyngeal and tonsillar redness and finding of an exudate, ulceration, or a membrane covering the tonsils. Because the pharynx is served by lymphoid tissues of the Waldeyer ring, an infection can spread to include various parts of the ring such as the nasopharynx, uvula, soft palate, tonsils, adenoids, and the cervical lymph glands. Based on the extent of the infection, it can be described as pharyngitis, tonsillitis, tonsillopharyngitis, or nasopharyngitis. The duration of any of these illnesses can be acute, subacute, chronic, or recurrent.

Etiology

The diagnosis of PT generally requires the consideration of group A β-hemolytic streptococci (GABHS) infection. However, other bacteria, viruses, and other infections and noninfectious causes should be considered. Recognition of the cause and choice of appropriate therapy are of utmost importance in assuring rapid recovery and preventing complications.

Table 4.1 lists the different causative agents and their characteristic clinical features. The occurrence of a certain etiologic agent depends on multiple variables that include environmental conditions (season, geographic location, exposure) and individual variables (age, host resistance, and immunity). The most prevalent agents accounting for PT are GABHS, adenovirus, influenza virus, parainfluenza virus, Epstein–Barr virus (EBV), and enterovirus. However, the exact etiology is generally not determined, and the role of some potential pathogens is not certain.

Interactions between various organisms, including GABHS, other aerobic and anaerobic bacteria, and viruses, may occur during PT. Some of these interactions may be synergistic (i.e., between EBV and anaerobic bacteria), thus enhancing the virulence of some pathogens, whereas others may be antagonistic (i.e., between GABHS and certain "interfering" α-hemolytic streptococci). Furthermore, β-lactamase-producing bacteria (BLPB) can protect themselves and other bacteria from β-lactam antibiotics. Bacterial biofilms may be a causative factor in the pathogenesis of chronic tonsillitis. Bacterial biofilms are recalcitrant to antibiotic therapies and immune clearance due to biochemical factors, molecular mechanisms, and altered host environment.

Aerobic bacteria

Because of the potential of serious suppurative and nonsuppurative sequelae, GABHS are the best known cause of sore throat. Occasionally non-B groups, large colony C, and G β-hemolytic streptococci are responsible. However, the other groups are generally not associated with acute rheumatic fever due to biochemical factors, molecular mechanisms, and altered host environment fever.

The clinical presentation of PT is generally identical for all groups and is characterized by exudation, palatal petechiae, follicles, tender cervical adenitis, and scarlet fever rash. What are generally absent are the

TABLE 4.1 **INFECTIOUS AGENTS OF PHARYNGOTONSILLITIS**

I. Bacteria	Clinical lesions	Clinical frequency
Aerobic		
Groups A, B, C, and G streptococci	F, Er, Ex, P	A
Streptococcus pneumoniae	E	C
Staphylococcus aureus	F, ER, Ex	C
Neisseria gonorrhoeae	Er, Ex	C
Neisseria meningitidis	Er, Ex	C
Corynebacterium diphtheriae	Er, Ex	C
Arcanobacterium hemolyticum	Er, Ex	C
Bordetella pertussis	Er, Er	C
Haemophilus influenzae	Er, Ex	C
Haemophilus parainfluenzae	Er, Ex	C
Salmonella typhi	Er	C
Francisella tularensis	Er, Ex	C
Yersinia pseudotuberculosis	Er	C
Treponema pallidum	F, Er	C
Mycobacterium spp.	Er	C
Anaerobic		
Peptostreptococcus spp.	Er, E	C
Actinomyces spp.	Er, U	C
Pigmented *Prevotella* and *Porphyromonas* spp.	Er, Ex, U	B
Bacteroides spp.	Er, Ex, U	C
Fusobacterium spp.	Er, Ex, U	C
II. Mycoplasma		
Mycoplasma pneumoniae	F, Er, Ex	B
Mycoplasma hominis	Er, ex	C
III. Viruses and Chlamydia		
Adenovirus	F, Er, Ex	A
Enteroviruses (Polio, Echo, Coxsackie)	Er, Ex, U	A
Parainfluenzae 1–4	Er	A
Epstein–Barr	F, Er, Ex	B
Herpes hominis	Er, Ex, U	C
Human immunodeficiency virus	F, Er, Ex	C
Respiratory syncytial	Er	C
Influenzae A and B	Er	A
Cytomegalovirus	Er	C
Reovirus	Er	C
Measles	Er, P	C
Rubella	P	C
Rhinovirus	Er	C
Chlamydia trachomitis	Er	C
IV. Fungi		
Candida spp.	Er, Ex	B
V. Parasites		
Toxoplasma gondii	Er	C
VI. Rickettsia		
Coxiella burnetii	Er	C

Abbreviations: Clinical lesions: F = Follicular, Er = Erythematous, Ex = Exudative, U = Ulcerative, P = Petechial; Frequency: A = most frequent (>66% of cases), B = frequent (between 66% and 33% of cases), C = uncommon (<33% of cases).

classical signs of viral infections such as cough, rhinitis, conjunctivitis, and diarrhea.

There is no symptom or single sign that reliably identifies GABHS pharyngitis. Symptoms in children younger than 3 years of age are atypical and include nasal congestion and discharge, low-grade fever, and tender anterior cervical lymph nodes. GABHS should be suspected in the presence of abrupt onset of fever in a child older than 3 years (with or without "sore throat"), higher temperature, ill appearance, headache, neck muscle pain, tenderness, abdominal pain, nausea, or vomiting, flushed cheeks, circumoral pallor, palatal "petechiae" and semicircular red marks, early strawberry tongue and/or scarlatiniform rash, a history of exposure to the organism, winter season, and the presence of a peculiar, sour-sweet, yeasty breath odor.

The isolation rate of GABHS varies with patient age, with the highest prevalence in school years (15–30% of all PT). The isolation rate of non-GABHS is higher in adults than in children.

There was a marked decrease in the incidence of acute rheumatic fever in the United States over the past 50 years that is correlated with the replacement of rheumatogenic types by non-rheumatogenic types. However, streptococcal tonsillitis is still a potential serious illness because rheumatic fever still occurs, and GABHS is manifesting increased virulence. More cases of invasive disease such as sepsis, necrotizing fasciitis, pneumonia, and toxic shock syndrome due to streptococci have been observed in recent years. Streptococci can be involved in suppurative complications of tonsillitis such as peritonsillar and retropharyngeal abscesses.

Streptococcus pneumoniae can also be involved in PT that can either subside or spread to other sites.

Corynebacterium diphtheriae can cause a "bull neck," as can *Arcanobacterium hemolyticum*, and both can cause an early exudative PT with a grayish-green thick membrane that may be difficult to dislodge and often leaves a bleeding surface when torn off. The infection can spread to the throat, palate, and larynx. It is rare in developed countries where children are vaccinated against it.

Arcanobacterium hemolyticum produces a lethal systemic exotoxin. *A. hemolyticum* incidence of causing PT is 2.5% to 10%, occurs mostly in 15- to 18-year-old individuals, and about half of the patients have a scarlatiniform rash.

Neisseria gonorrhoeae is common in homosexual males and can be detected in sexually active adolescents with pharyngitis. The infection is often asymptomatic but can exhibit ulcerative or exudative pharyngitis, may result in bacteremia, and can persist after treatment. *Neisseria meningitidis* can cause symptomatic or asymptomatic PT that can be a prodrome for septicemia or meningitis.

Nontypeable *Haemophilus influenzae* and *H. parainfluenzae* can be recovered from inflamed tonsils. These organisms can cause invasive disease in infants and elderly persons, as well as acute epiglottitis, otitis media, and sinusitis.

Staphylococcus aureus is often recovered from chronically inflamed tonsils and peritonsillar abscesses. Methicillin-resistant *S. aureus* (MRSA) was isolated from 16% of recurrently infected tonsils. It can produce the enzyme β-lactamase that may interfere with the eradication of GABHS. High tissue concentration of *H. influenzae*, *S. aureus*, and GABHS correlates with recurrent infection and hyperplasia of the tonsils.

Francisella tularensis infection (tularemia) is rare and should be considered in patients unresponsive to penicillin. It can be contracted by ingestion of contaminated water as well as in poorly cooked wild

animal meat. Clinical presentation of PT includes fever, painful ulcerative-exudative pharyngitis, and cervical lymphadenitis.

Other rare causes of PT are *Treponema pallidum*, *Mycobacterium* spp., and *Toxoplasma gondii*.

Anaerobic bacteria

The anaerobic species that have been implicated in PT are *Actinomyces* spp., *Peptostreptococcus* spp., *Fusobacterium* spp., and pigmented *Prevotella* and *Porphyromonas* spp.

The role of anaerobes is supported by their predominance in tonsillar or retropharyngeal abscesses and Vincent's angina (*Fusobacterium* spp. and spirochetes). Furthermore, patients with non-GABHS tonsillitis as well as infectious mononucleosis respond to antibiotics directed only against anaerobes (metronidazole), and elevated serum levels of antibodies to *Prevotella intermedia* and *Fusobacterium nucleatum* were found in patients with acute and recurrent non-GABHS tonsillitis and peritonsillar cellulitis and abscess.

Fusobacterium necrophorum has been recovered in recent studies from the United Kingdom and Denmark of adolescents and young adults with streptococcal as well as non-streptococcal PT. Other studies also suggest a role for *F. necrophorum* in recurrent or persistent sore throat. It is also the etiology of most cases of Lemierre's syndrome, which generally occurs in previously healthy adolescents and young adults. The syndrome includes necrotizing tonsillopharyngitis associated with *Fusobacterium* bacteremia, septic internal jugular vein thrombophlebitis, and metastatic pulmonary infection. Clinical findings include fever (>39°C/102°F), rigors, respiratory symptoms, and unilateral neck pain and/or swelling.

Mycoplasma

Mycoplasma pneumoniae and *Mycoplasma hominis* can cause PT usually as a manifestation of a generalized infection. Mycoplasma accounts for 5% to 15% of cases of PT, and most cases occur in those older than 6 years.

Chlamydia

Chlamydia pneumoniae may cause PT in young adults, often accompanying pneumonia or bronchitis.

Viruses

Viral PT is generally characterized by the absence of an exudate, the presence of ulcerative lesions, minor nontender adenopathy, enanthems, cough, rhinitis, hoarseness, conjunctivitis, or diarrhea.

The viruses known to cause PT are adenovirus (concomitant conjunctivitis), Coxsackie A virus, influenza and parainfluenza viruses (seasonal with high fever, cough, headache, and myalgias), coronavirus, enteroviruses (posterior pharyngeal vesicles or ulcers, vesicles on palms and soles in summer), Epstein–Barr virus (exudative pharyngitis, liver and spleen enlargement, cervical adenopathy), herpes simplex (HSV; most caused by HSV-1, anterior oral and lip ulcers, fever), rhinovirus, respiratory syncytial virus (RSV), rubeola (oral erythema and Koplik spots prior to exanthema), and cytomegalovirus (CMV).

Primary HIV infection may cause an acute retroviral syndrome which is similar to infectious mononucleosis. The symptoms usually occur within days to weeks after exposure, and infection includes fever, weight loss, rash, lymphadenopathy, and splenomegaly.

Mixed infections

PT can be caused by multiple pathogens. Mixed viral/bacterial pathogens were found in 26 of 127 patients (20.5%) and none of the controls ($p < 0.0001$). Combined pathogens included double bacterial infection with GABHS plus *C. pneumoniae* or *M. pneumoniae* plus *C. pneumoniae* with *M. pneumoniae*; and viral and bacterial infection with GABHS plus RSV, adeno and influenza B and parainfluenza type 1 viruses, *C. pneumoniae* plus RSV or adeno virus, and *M. pneumoniae* plus adeno virus.

A concomitant GABHS and influenza A virus PT, as evident by increased antistreptolysin O (ASO) and anti-DNase B titers, was found in 4 of 12 (33%) patients who had both of these organisms isolated in their upper airways.

Clinical findings

PT has generally a sudden onset, with fever and sore throat, nausea, vomiting, headache, and rarely abdominal pain. At an early stage, redness of throat and tonsils is observed, and the cervical lymph glands become enlarged. The clinical manifestations may vary by causative agent (see earlier discussion and also Table 4.1) but are rarely specific. Erythema is common to most agents; however, the occurrence of ulceration, petechiae, exudation, or follicles varies. The common features are exudative pharyngitis in GABHS infection, ulcerative lesions in enteroviruses, and membranous pharyngitis in *C. diphtheriae*. Petechiae can often be seen in GABHS, Epstein–Barr, measles, and rubella viruses infections.

Viral disease is generally self-limited, lasts 4 to 10 days, and is generally associated with the presence of nasal secretions. Bacterial illness lasts longer if untreated. The most unique features of anaerobic tonsillitis or PT are enlargement and ulceration of the tonsils associated with fetid or foul odor and the presence of fusiform bacilli, spirochetes, and other organisms on Gram stain.

Diagnosis

Determining if GABHS is the cause of the PT is very important because early antimicrobial therapy shortens the illness, prevents suppurative and nonsuppurative complications, reduces transmission of the pathogen, and prevents misuse of antimicrobials.

GABHS PT can be diagnosed by either a positive throat culture or rapid test. Culture is obtained when microbiologic isolation is needed. Throat culture should be obtained before initiation of antimicrobial therapy. Vigorous swabbing of both tonsillar surfaces and the posterior pharyngeal wall, and plating the specimen on sheep blood agar media is the standard. Incubation in anaerobic condition and use of selective media can increase the recovery rate of GABHS. More than 10 colonies of GABHS per plate are considered to represent a true infection rather than colonization. However, using the number of colonies of GABHS in the plate as an indicator for the presence of true infection is difficult to implement because there is overlap between carriers and infected individuals. A single throat culture has the sensitivity of 90% to 95% in detection of GABHS in the pharynx. False-negative results can occur in patients who received antibiotics. Throat cultures that generally identify GABHS by direct growth may take 24 to 48 hours. Re-examination of plates at 48 hours is advisable. The use of a bacitracin disk provides presumptive identification. Attempts to identify β-hemolytic streptococci, other than group A, may be worthwhile in older individuals. Commercial kits containing group-specific antisera are available for identifying the specific streptococcal group.

Rapid methods for detection of GABHS that take 10 to 60 minutes are available. They are more expensive than the routine culture but allow for rapid administration of therapy and reduction of morbidity. Antigen tests depend on the detection of the surface Lancefield group A carbohydrate. Newer tests use nucleic acid (DNA) probes and polymerase chain reaction (PCR) with greater sensitivity and identify more pathogenic serotypes of GABHS. Early kits showed low sensitivity, but the currently available ones have 85% to 90% sensitivity but are still associated with 5% to 15% false-negative results. It is therefore recommended that a bacterial culture be performed in instances where the rapid streptococcal test is negative. Unfortunately, neither rapid test nor throat culture can differentiate patients with PT due to GABHS from viral infection in a GABHS carrier.

A rise in antistreptococcal antibody titers (e.g., antistreptolysin O, antideoxyribonuclease B, streptokinase, hyaluronidase, or nicotinic acid dehydrogenase) after 3 to 6 weeks can provide retrospective evidence for GABHS infection and assist in differentiating between the carrier state and infection.

Other less common pathogens should be identified in specific situations when no GABHS is found or when a search of other organisms is warranted. Because many of the other potential pathogens are part of the normal pharyngeal flora, interpretation of these data can be difficult. When tularemia is suspected serologic testing is advisable. Pharyngeal cultures for *N. gonorrhoeae* require special media (Thayer–Martin agar). Attempts to identify corynebacteria should be made whenever a membrane is present in the throat. Cultures should be obtained from beneath the membrane using special moisture-reducing transport media. A Loeffler slant, a tellurite plate, and a blood agar plate should be inoculated. Identification by fluorescent antibody technique is possible. *Arcanobacterium haemolyticum* grows slowly on sheep blood agar plates and produces a tiny zone of β-hemolysis after at least 3 days of incubation.

Viral cultures or rapid tests for some viruses (i.e., influenza, respiratory syncytial and herpes simplex viruses) are available. A heterophile slide test or other rapid tests for infectious mononucleosis can also provide a specific diagnosis. Laboratory features of primary HIV infection may include lymphopenia and increased transaminase levels. HIV viral load and HIV antibodies tests may be helpful.

Therapy

Many antibiotics are available for the treatment of PT caused by GABHS. However, the recommended optimal treatment for GABHS infection is penicillin administered three times a day for 10 days (Table 4.2). Oral penicillin VK is used more often than intramuscular (IM) benzathine penicillin G. However, IM penicillin can be given as initial therapy in those who cannot tolerate oral medication or to ensure compliance. An alternative medication is amoxicillin, which is as active against GABHS, but its absorption is more reliable, blood levels are higher, plasma half-life is longer, and protein binding is lower, giving it theoretical advantages. Furthermore, oral amoxicillin has better compliance (better taste). Amoxicillin should not be used, however, in patients suspected of infectious mononucleosis, where it can produce a skin rash.

The frequently reported inability of penicillin to eradicate GABHS from patients with PT despite its excellent in vitro efficacy

TABLE 4.2 **ORAL ANTIBIOTICS FOR 10-DAY COURSE OF TREATMENT OF ACUTE GABHS PHARYNGOTONSILLITIS**

	Dosage (in mg)		
Generic name	**Pediatric (mg/kg/d)**	**Adult**	**Frequency**
Penicillin-V	25–50	250	q6–8h
Amoxicillin	40	250	q8h
Cephalexin[a]	25–50	250	q6–8h
Cefadroxyl[a]	30	1000	q12h
Cefaclor[a]	40	250	q8h
Cefuroxime-axetil[a]	30	250	q12h
Cefpodoxime-proxetil[a]	30	500	q12h
Cefdinir[a,d]	7 mg 14 mg	300 600	q12h q 24h
Cefprozil[a]	30	250	q12h
Cefditoren	NA	200	q12h
Azithromycin[d]	12	250[c]	q24h
Clarythromycin	7.5	250	q12h
Cefixime	8	400	q24h
Ceftibuten	9	400	q24h
Erythromycin estolate	40	250	q8–12h
Amoxicillin-calvulanate[b]	45	875	q12h
Clindamycin[b]	20–30	150	q6–8h

[a] Effective also against aerobic β-lactamase-producing bacteria (BLPB).
[b] Effective also against aerobic and anaerobic BLPB.
[c] First day dose is 500 mg.
[d] Duration of therapy 5 days.
Abbreviations: NA = not approved for children younger than 12 years.

TABLE 4.3 **ORAL ANTIMICROBIALS IN TREATMENT OF GABHS TONSILLITIS**

Acute	Recurrent/Chronic	Carrier state
Penicillin (amoxicillin)	Clindamycin, amoxicillin-clavulanate	Clindamycin
Cephalosporins[b]	Metronidazole plus macrolide	Penicillin plus rifampin
Clindamycin	Penicillin plus rifampin	
Amoxicillin-clavulanate		
Macrolides[a]		

[a] GABHS may be resistant.
[b] All generations.
For dosages and length of therapy, see Table 4.2.

is of concern. Although about half of the patients who harbor GABHS following therapy may be carriers, the rest may still show signs of infection and represent true clinical failure. Studies have shown that the recommended doses of either oral penicillin V or IM penicillin failed to eradicate GABHS in acute-onset pharyngitis in 35% of patients treated with oral penicillin V and 37% of those treated with IM penicillin.

Penicillin failure in eradicating GABHS tonsillitis has several explanations (Table 4.3). These include noncompliance with the 10-day course of therapy, carrier state, reinfection from another person or object, and penicillin tolerance. Some postulate that bacterial interactions between GABHS and members of the pharyngotonsillar bacterial flora can explain these failures. These explanations include the "shielding" of GABHS from penicillins by BLPB that colonize the pharynx and tonsils, the absence of normal flora organisms that interfere with the growth of GABHS, and the coaggregation between *Moraxella catarrhalis* and GABHS. Repeated penicillin administration can induce many of these changes. It can result in a shift in the oral microflora with selection of β-lactamase-producing strains of *S. aureus*, *Haemophilus* spp., *M. catarrhalis*, *Fusobacterium* spp., pigmented *Prevotella* and *Porphyromonas* spp., and *Bacteroides* spp.

It is possible that BLPB can protect the GABHS from penicillin by inactivating the antibiotic. Such organisms in a localized soft-tissue infection may degrade penicillin in the area of the infection, protecting not only themselves but also penicillin-susceptible pathogens such as GABHS. Thus, penicillin therapy directed against a susceptible pathogen can be rendered ineffective. An increase in in vitro resistance of GABHS to penicillin was observed when GABHS was inoculated with *S. aureus*, *Haemophilus* spp., and pigmented *Prevotella* and *Porphyromonas* spp. *Bacteroides* spp. protected a penicillin-sensitive GABHS from penicillin therapy in mice. Both clindamycin and the combination of penicillin and clavulanic acid (a β-lactamase inhibitor), which are active against both GABHS and *Bacteroides* spp., eradicated the infection.

Penicillin therapy can also reduce the number of aerobic and anaerobic bacteria that can interfere with the growth of GABHS. The oropharyngeal flora of >85% of individuals who are not tonsillitis-prone contains numerous types of organisms that are capable of interfering with the in vitro growth of potential pathogens. In contrast, only 25% to 30% of children who suffer from recurrent tonsillitis harbor interfering organisms.

Acute pharyngotonsillitis

Oral penicillin given for 10 days is still recommended as the antibiotic of choice given its proved efficacy, safety, narrow spectrum, and low cost. Other effective antibiotics included cephalosporins, lincomycin, clindamycin, macrolides, and amoxicillin-clavulanate. Some of these agents were more effective than penicillin in acute (cephalosporins, macrolides) and others in recurrent (lincomycin, clindamycin, and amoxicillin-clavulanate) GABHS PT.

There are patients in whom more effective antimicrobials that are less likely to fail to eradicate GABHS should be considered. Individual medical, economical, and social issues should be considered in each patient prior to selecting an antimicrobial for the treatment of GABHS PT (Box 4.1). These include the existence of a high probability for the presence in the pharyngotonsillar area of BLPB and the absence of interfering organisms, the recent failure of penicillin therapy, or a history of recurrent GABHS PT.

The macrolides are also an alternative choice in therapy of PT. Compliance with the newer macrolides (clarithromycin and azithromycin) is better compared with erythromycin because of their longer half-life and reduced adverse gastrointestinal side effects. However, the increased use of macrolides for the treatment of various respiratory and other infections has been associated with increased GABHS resistance to these agents. Resistance of GABHS to macrolides has reached 70% in Finland, Italy, Japan, and Turkey.

BOX 4.1

Possible reasons for antibiotic failure or relapse in GABHS tonsillitis

Bacterial interactions

- The presence of β-lactamase-producing organisms that "protect" GABHS from penicillins
- Co-aggregation between GABHS and *Moraxella catarrhalis*
- Absence of members of the oral bacterial flora capable of interfering with the growth of GABHS (through production of bacteriocins and/or competition on nutrients)
- Presence of bacterial biofilm that causes resistance to antimicrobial due to biochemical factors, molecular mechanisms, and altered host environment

Internalization of GABHS (survives within epithelial cells, thus escaping eradication by penicillins)
Resistance (i.e., erythromycin) or tolerance (i.e., penicillin) to the antibiotic used
Inappropriate dose, duration of therapy, or choice of antibiotic
Poor compliance with taking medication
Reacquisition of GABHS from a contact or an object (i.e., toothbrush, dental retainer, or dental braces)
Carrier state, not disease

Of concern is the significant increase of such resistance in the United States that reached 48% in specific populations. The current resistance of GABHS to macrolides in the United States is 5% to 16%. It is therefore advisable to avoid the routine use of macrolides for GABHS PT and save these agents for those patients who are type I penicillin allergic.

The success rate of treatment of acute GABHS tonsillitis was consistently found to be higher with cephalosporins than with penicillin. The cephalosporins' increased efficacy may be due to their activity against aerobic BLPB such as *S. aureus*, *Haemophilus* spp., and *M. catarrhalis*. Another possible reason is that the nonpathogenic interfering aerobic and anaerobic bacteria that compete with GABHS and help to eliminate them are less susceptible to cephalosporins than to penicillin. These organisms are therefore more likely to survive cephalosporin therapy.

The length of therapy of acute tonsillitis with medication other than penicillin has not been determined by large comparative controlled studies. However, certain new agents have been administered in shorter courses of ≥5 days (Table 4.2). Early initiation of antimicrobial therapy results in faster resolution of signs and symptoms. However, spontaneous disappearance of fever and other symptoms generally occurs within 3 to 4 days, even without antimicrobials. Furthermore, acute rheumatic fever can be prevented even when therapy is postponed up to 9 days.

Prevention of recurrent tonsillitis due to GABHS by prophylactic administration of daily oral or monthly benzathine penicillin should be attempted in patients who suffered from rheumatic fever. American Heart Committee guidelines on the prevention of rheumatic fever should be followed, and if any family members are carrying GABHS, the disease should be eradicated and the carrier state monitored.

Macrolides are the drugs of choice for *A. haemolyticum* that is unresponsive to penicillin. When *C. diphtheriae* infection is suspected, erythromycin is the drug of choice, and penicillin or rifampin are alternatives. Supportive therapy of PT includes antipyretics and analgesics, such as aspirin or acetaminophen, and attention to proper hydration.

Pharyngeal *N. gonorrhoeae* infection appears to be more difficult to treat and can serve as an important reservoir of infection. The recommended treatment is a single injection of ceftriaxone (250 mg IM) plus azithromycin (1 g PO). Doxycycline (100 mg PO BID for 7 days) is an alternate therapeutic option as a second agent to administer with ceftriaxone. HSV infection is treated with acyclovir.

Antiviral therapy may be provided to those with influenza virus if the diagnosis is made early in the course of illness and the symptoms are severe.

Recurrent and chronic pharyngotonsillitis

Penicillin failure in treatment of recurrent and chronic tonsillitis is even higher than the failure of therapy of acute infection. Several clinical studies demonstrated the superiority of lincomycin, clindamycin, and amoxicillin-clavulanate over penicillin. These antimicrobial agents are effective against aerobic as well as anaerobic BLPB and GABHS in eradicating recurrent tonsillar infection.

BOX 4.2

Indications for the use of antimicrobials other than a penicillin for GABHS tonsillitis

- Presence of β-lactamase-producing bacteria (recent antibiotic exposure, winter, region)
- Absence of "interfering flora" (recent antibiotic therapy)
- Recurrent GABHS tonsillitis
- Past failures to eradicate GABHS
- High failures of penicillins in the community
- Comorbidities
- When failure is a medical, economical, or social hardship
- Penicillin allergy (non-type I)

Clindamycin also provides coverage against many MRSA that can resist other antimicrobials such as amoxicillin-clavulanate. However, no studies showed them to be superior to penicillin in treatment of acute tonsillitis. Other drugs that may also be effective in the therapy of recurrent or chronic tonsillitis are penicillin plus rifampin and a macrolide (e.g., erythromycin) plus metronidazole (see Box 4.2). Referral of a patient for tonsillectomy should be considered only after these medical therapeutic modalities have failed.

Suggested reading

Bisno AL, Gerber MA, Gwaltney JM Jr, Kaplan EL, Schwartz RH. Diagnosis and management of group A streptococcal pharyngitis: A practice guideline. Infectious Diseases Society of America. *Clin Infect Dis*. 1997;25:574–583.

Brook I. The role of anaerobic bacteria in tonsillitis. *Int J Pediatr Otorhinolaryngol*. 2005;69:9–19.

Brook I. The role of bacterial interference in otitis, sinusitis and tonsillitis. *Otolaryngol Head Neck Surg*. 2005;133:139–146.

Brook I, Foote PA Jr. Isolation of methicillin resistant Staphylococcus aureus from the surface and core of tonsils in children. *Int J Pediatr Otorhinolaryngol*. 2006;70:2099–2102.

Brook I, Gober AE. Persistence of group A beta-hemolytic streptococci in toothbrushes and removable orthodontic appliances following treatment of pharyngotonsillitis. *Arch Otolaryngol Head Neck Surg*. 1998;124: 993–995.

Brook I, Gober AE. Concurrent influenza A and group A beta-hemolytic streptococcal pharyngotonsillitis. *Ann Otol Rhinol Laryngol*. 2008;117:310–312.

Esposito S, Blasi F, Bosis S, et al. Aetiology of acute pharyngitis: the role of atypical bacteria. *J Med Microbiol*. 2004;53: 645–651.

Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: A scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2009;119:1541–1551.

Holm K, Bank S, Nielsen H, et al. The role of Fusobacterium necrophorum in pharyngotonsillitis: A review. *Anaerobe*. 2016;42:89–97.

Jensen A, Hagelskjaer Kristensen L, Prag J. Detection of Fusobacterium necrophorum subsp. funduliforme in tonsillitis in young adults by real-time PCR. *Clin Microbiol Infect*. 2007;13:695–701.

Kaplan EL, Johnson DR. Unexplained reduced microbiological efficacy of intramuscular benzathine penicillin G and of oral penicillin V in eradication of group A streptococci from children with acute pharyngitis. *Pediatrics*. 2001;108:1180–1186.

Lean WL, Arnup S, Danchin M. Rapid diagnostic tests for group A streptococcal pharyngitis: a meta-analysis. *Pediatrics*. 2014;134:771–781.

Lindroos R. Bacteriology of the tonsil core in recurrent tonsillitis and tonsillar hyperplasia: A short review. *Acta Otolaryngol Suppl*. 2000;543:206–208.

Nouri S, Newburger JW, Hutto C, et al. Prevention of bacterial endocarditis: Recommendations by the American Heart Association. *Clin Infect Dis*. 1997;25: 1448–1458.

Richter SS, Heilmann KP, Beekmann SE, et al. Macrolide-resistant Streptococcus pyogenes in the United States, 2002–2003. *Clin Infect Dis*. 2005;41:599–608.

Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012; 55:e86–102.

Shulman ST, Stollerman G, Beall B, Dale JB, Tanz RR. Temporal changes in streptococcal M protein types and the near-disappearance of acute rheumatic fever in the United States. *Clin Infect Dis*. 2006;42:441–447.

Weinstock H, Workowski KA. Pharyngeal gonorrhea: An important reservoir of infection? *Clin Infect Dis*. 2009;49:1798–1800.

Zaoutis T, Attia M, Gross R, Klein J. The role of group C and group G streptococci in acute pharyngitis in children. *Clin Microbi Infect*. 2004;10:37–40.

5

Infectious thyroiditis

Jeanne Carey and Stephen G. Baum

Introduction

Acute suppurative thyroiditis (AST) is a rare but potentially life-threatening infection. AST is usually bacterial in etiology, although fungal, parasitic, and mycobacterial organisms have also been documented causes. The routes of infection are predominantly hematogenous or lymphatic; however, thyroid infections may also be the result of direct spread from an adjacent deep fascial space infection, an infected thyroglossal fistula, or anterior perforation of the esophagus. Thus, infectious thyroiditis may occur either as a local infection or as part of a disseminated systemic infection. Because prognosis depends on prompt diagnosis and treatment, it is important to differentiate AST from the noninfectious inflammatory conditions of the thyroid and other inflammations in the neck that it may closely resemble.

Pathogenesis

The thyroid gland is rarely infected, and several protective factors have been postulated to explain why the gland is relatively resistant to infection. First, there is a rich blood supply to and extensive lymphatic drainage from the thyroid. Second, the high iodine content of the gland may be bactericidal; however, there are no data to show that the concentration of iodine present in the thyroid would be enough to inhibit the growth of microorganisms. Third, in addition to being surrounded by a complete fibrous capsule, the thyroid is separated from the other structures of the neck by fascial planes.

Primary infections of the thyroid are most likely to occur in individuals with preexisting thyroid disease or with certain congenital anomalies. Goiters, Hashimoto's thyroiditis (chronic lymphocytic thyroiditis), or thyroid cancer have been present in up to two-thirds of women and one-half of men with infectious thyroiditis. With respect to congenital anomalies, which are associated with AST more frequently in children than in adults, transmission of infective organisms via a pyriform sinus fistula is the most common direct route of thyroid infection (Figure 5.1). The fistula arises from the apex of the pyriform recess and often ends in or near the thyroid gland, allowing bacterial infection to develop in or around the thyroid.

Episodes of AST are often preceded by an upper respiratory infection or another factor (e.g., injury or obstruction of the fistula by food or foreign bodies) that may induce inflammation of a pyriform fistula and thus facilitate transmission of pathogens to the thyroid. Particularly in children, the left lobe is more commonly involved, reflecting the observation that pyriform sinus fistulas predominantly occur on the left.

Infected embryonic cysts of the third and fourth branchial pouches have also been identified as causes of AST. Infectious organisms may also spread directly to the thyroid via a patent thyroglossal duct fistula (Figure 5.2). AST may be caused by spread of microbes from adjacent sites of infection, such as the oropharynx and middle ear, although this occurs infrequently, presumably because the thyroid is encapsulated within its fibrous sheath. Perforation of the esophagus may also result in direct spread of infection to the thyroid gland.

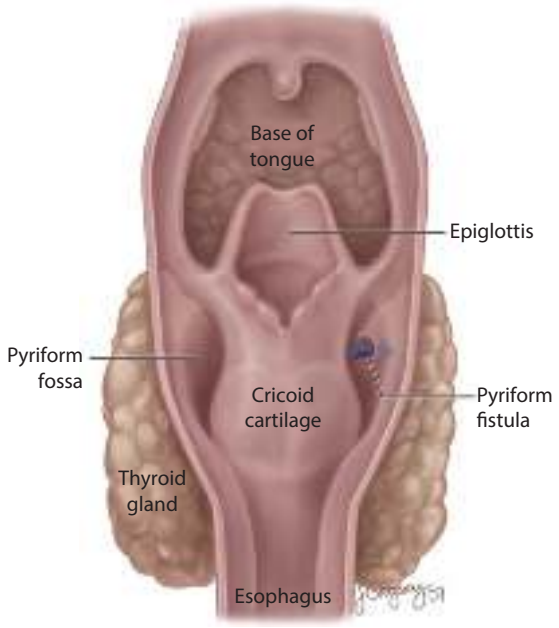

FIGURE 5.1 Anatomy of the thyroid gland and oropharynx, demonstrating the relationship to a pyriform fistula, anterior view.

Bacterial AST may also result from trauma to the anterior neck. One of us (SGB) has seen a single case of direct spread of infection to the thyroid from a neck wound. The patient was a mechanic who scraped his anterior neck while working on his back underneath an automobile. The wound appeared superficial, but infection spread to the thyroid with abscess formation. The offending organism was a staphylococcus. Even fine-needle aspiration (FNA) of thyroid nodules has resulted in thyroid infection.

Immunosuppressed patients, such as those with HIV infection or hematologic malignancies, as well as patients with autoimmune diseases or organ transplants treated with immunosuppressive agents, are at risk for suppurative thyroiditis, which can occur as part of a disseminated infectious process. These infections arise when pathogens reach the thyroid hematogenously or through the lymphatic system.

Microbiology

Gram-positive organisms are the most common etiologic pathogens in AST, although a wide variety of bacteria have been isolated as causative agents in case reports (Box 5.1). In a review of 224 cases of thyroid infections reported between 1900 and 1980, staphylococci, found in 23 of 66 (35%) of culture-positive specimens, were the most frequently identified organisms; *Staphylococcus aureus* was the predominant species. *Streptococcus pyogenes*, presumably acquired after a recent pharyngeal infection or colonization; *Streptococcus pneumoniae*; and other streptococci were also commonly recovered. In a subsequent review of an additional 191 cases of AST reported between 1980 and 1997, in which 130 microorganisms were isolated, Yu et al. found that the most common bacterial isolates were gram-positive aerobes (39%), gram-negative aerobes (25%), and anaerobes (12%, mostly in mixed culture). More recently, the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasing.

When anaerobic bacteria are isolated from the infected thyroid, they are usually members of the oropharyngeal flora. The true involvement of anaerobic bacteria in AST is unknown because past studies have not used uniform methods for the recovery

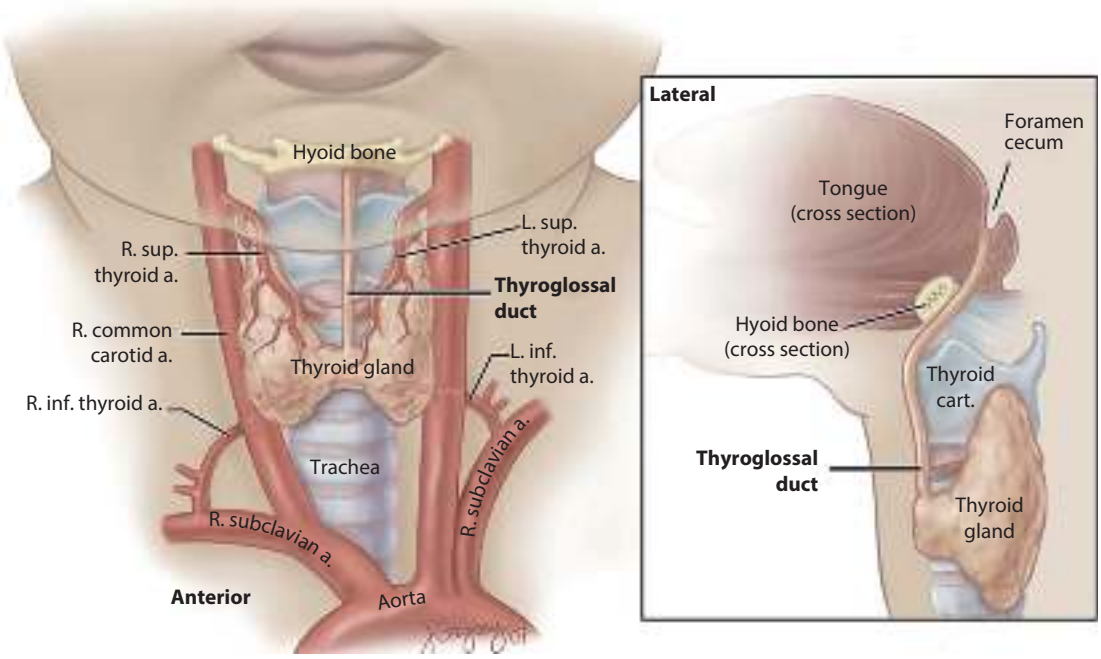

FIGURE 5.2 Anatomy of the thyroid gland and neck. A thyroglossal duct fistula is shown in frontal and lateral views.

BOX 5.1

Microbiology of infectious thyroiditis

Nonimmunocompromised host

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pyogenes
Other streptococcal species
Klebsiella species, especially in diabetic patients
Other Enterobacteriaceae
Anaerobic oral flora (foul smell on needle aspiration may give hint of this)
Other gram-negative bacteria free-living in water secondary to upper respiratory tract infection
Mycobacterium tuberculosis
Mycobacterium bovis
Actinomyces spp.

Immunocompromised host

Mycobacterium avium-intracellulare
Nocardia spp.
Pneumocystis jirovecii

Modified from Shah and Baum, 2000.

of anaerobes. Because anaerobes are more difficult to isolate, it is possible that culture-negative cases of AST may represent purely anaerobic or mixed infections, an important consideration when choosing empiric therapy for AST.

The bacterial pathogens implicated in AST in children are similar to those found in adults. *S. aureus, S. pyogenes, Staphylococcus epidermidis*, and *Streptococcus pneumoniae* are the most commonly isolated organisms in pediatric cases of AST.

Following bacteria, fungi are the second most common microorganisms to infect the thyroid, representing 15% of cases of AST in the review by Yu and colleagues. Fungal thyroiditis most commonly occurs in immunocompromised patients, such as those with leukemia, lymphoma, and autoimmune diseases and in organ transplant patients on immunosuppressive therapy. In a review of 41 fungal thyroiditis cases published between 1970 and 2005, Goldani et al. found that *Aspergillus* species (spp.) were the most commonly reported cause of fungal thyroid infection. Thyroid involvement by *Aspergillus* spp. was found at autopsy as part of disseminated aspergillosis in 13 (62%) of 21 patients, most of whom lacked clinical manifestations and laboratory evidence of thyroid dysfunction. After *Aspergillus* spp., *Candida* spp. were the second most common cause; other fungal etiologies reported include *Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum*, and *Pseudallescheria boydii*.

Pneumocystis jirovecii (then called *Pneumocystis carinii*), now classified as a fungus, was not included in the review by Goldani et al.; however, *P. jirovecii* has been found to be a cause of thyroid infections, almost exclusively in patients with AIDS. Yu et al. identified *P. jirovecii* as the causative agent in 16 of 19 cases of fungal thyroiditis in their literature review.

Mycobacterium tuberculosis as well as atypical mycobacteria have been described as causes of thyroid infection. Thyroidal tuberculosis occurs in the setting of miliary or disseminated disease. Disseminated *Mycobacterium avium-intracellulare* infection in patients with AIDS has resulted in thyroidal infection. In their literature review, Yu et al. found that mycobacterial organisms were isolated in 12 of 130 (9%) cases of culture-positive AST. Unlike patients with pyogenic bacterial AST, those with mycobacterial thyroiditis are typically symptomatic for months and are much less likely to experience pain, tenderness, and fever.

Involvement of the thyroid gland by parasites is extremely rare and typically occurs in the setting of disseminated disease. In the United States, only nine cases of echinococcal (tapeworm) thyroiditis have been reported. These patients had chronic symptoms (1.5–35 years in duration), were generally diagnosed as having goiters, and were discovered to have thyroidal echinococcosis at the time of surgery. *Strongyloides stercoralis*, which is endemic in the southeastern United States and tropical climates, has been reported as a cause of thyroid infection only in the setting of disseminated disease in immunocompromised patients.

Although several viruses (including influenza, Epstein–Barr, adenovirus) have been associated with subacute thyroiditis, viral infection causing AST has never been definitively proved. In postmortem studies of patients with AIDS, cytomegalovirus (CMV) inclusions have been found in thyroid tissue in association with disseminated CMV infection. However, symptomatic thyroiditis due to CMV has not been reported in these patients.

Clinical manifestations

The symptoms and signs of AST may be indistinguishable from those of a variety of both infectious and noninfectious inflammatory conditions of the anterior neck. Most patients with AST present with fever, pain, and a tender, firm swelling in the anterior aspect of the neck that moves on swallowing and develops over days to a few weeks. In this clinical scenario, the differential diagnosis includes such entities as subacute thyroiditis, Graves' disease (toxic diffuse goiter), thyroid cancer, hemorrhage into the thyroid, cervical lymphadenitis, and cellulitis (Box 5.2).

Other typical signs and symptoms of AST include dysphagia, dysphonia (both of which have been attributed to compression of local structures, including the recurrent laryngeal nerve), and concurrent pharyngitis. On examination the thyroid is tender, with warmth and erythema of the overlying skin and, in the case of abscess formation, fluctuance. Suppurative areas may include one lobe, both lobes, or only the isthmus of the gland. Because a firm nodule may progress to become fluctuant over the course of 1 to 3 days, repeated physical examinations are advisable.

Children with AST present similarly; however, there are a few noteworthy differences. The left lobe of the thyroid gland

is more frequently involved in pediatric cases because pyriform fossa fistulas are predominantly observed on the left. Neonates and infants are more likely than adults to present with stridor and respiratory distress from tracheal compression by an enlarged thyroid gland.

Suppurative thyroiditis that occurs as part of a disseminated infectious process differs from locally spread bacterial thyroiditis in several important ways. First, suppurative thyroiditis due to a systemic infection often occurs in the absence of any clinical manifestations of thyroiditis. Second, the etiologic organisms are typically opportunistic pathogens such as fungi, *P. jirovecii*, and mycobacteria, which tend to present with a chronic, insidious course. Finally, in contrast to bacterial thyroiditis, preexisting thyroid disease is not a significant risk factor for suppurative thyroiditis that occurs as part of a disseminated infection; rather, patients who are immunocompromised are at particular risk for the latter type of infectious thyroiditis.

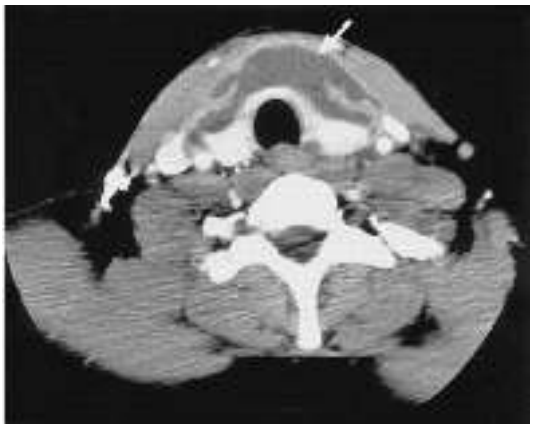

FIGURE 5.3 CT scan of neck with contrast showing an abscess of the left lobe of the thyroid gland (*arrow*).

From Jacobs A, David-Alexandre CG, Gradon JD. Thyroid abscess due to *Acinetobacter calcoaceticus*: Case report and review of the causes of and current management strategies for thyroid abscesses. *South Med J*. 2003;96:300–307.

Diagnosis

Leukocytosis and an elevated erythrocyte sedimentation rate and C-reactive protein level are nonspecific but are commonly seen in AST. Although thyroid function test results are within normal limits in the majority of patients with AST, destruction of glandular tissue with release of preformed thyroid hormone into the circulation can lead to transient thyrotoxicosis. Hypothyroidism has also been reported. Although most patients with bacterial AST are euthyroid, Yu et al. found that those with fungal infections were often hypothyroid (63%) and that half of patients with mycobacterial infections were hyperthyroid.

Imaging studies help to differentiate AST from other causes of anterior neck pain and fever (Box 5.2). Plain neck radiography may reveal tracheal deviation or soft-tissue gas formation indicative of infection with anaerobic gas-forming organisms, such as *Clostridium* spp. CT, ultrasonography (US), and MRI often reveal unilobular thyroidal swelling and are extremely useful in the identification of parathyroidal abscesses and spread of infection to contiguous structures (Figure 5.3). For acutely ill patients with suspected AST, the preferred initial imaging modality is CT, which provides a comprehensive view of the neck and upper mediastinum and can thus be used to identify potential extrathyroidal involvement.

In a review of imaging studies performed on 60 patients with AST, Masuoka and colleagues found that, during the acute stage of AST, both CT and US may show nonspecific inflammation in and around the affected thyroid lobe, which may lead to an erroneous diagnosis of subacute thyroiditis. US may be very helpful in leading to the correct diagnosis, as specific US findings differ between AST and subacute thyroiditis; for example, in cases of AST, hypoechoic lesions are typically unifocal, and the hypoechoic lesions seen in subacute thyroiditis are usually multiple and often bilateral.

The most useful test in AST is FNA, which will frequently be diagnostic. FNA is especially helpful when there is no associated bacteremia or fungemia and when the patient's tenderness is limited to a localized area. Specimens for cytology, Gram stain, and aerobic and anaerobic cultures should be obtained. In the appropriate clinical setting, mycobacterial and fungal cultures as well as special stains for *P. jirovecii* and acid-fast bacilli should also be performed.

BOX 5.2

Causes of painful anterior neck mass

Thyroid-related

- Hashimoto's thyroiditis (chronic lymphocytic thyroiditis)
- Graves' disease (toxic diffuse goiter)
- Thyroid cancer, with or without hemorrhage
- Hemorrhage into the thyroid secondary to trauma
- Radiation damage to thyroid
- Acute suppurative thyroiditis

Nonthyroid-related

- Cervical lymphadenitis due to infection or malignancy
- Cellulitis
- Infections of thyroglossal duct remnant, branchial cleft cyst, or cystic hygroma

Modified from Shah and Baum, 2000.

Management

Antimicrobial treatment must be targeted at the underlying etiology of AST. In cases of bacterial AST high-dose parenteral antibiotics should be started promptly because early treatment may prevent complications such as bacteremia and abscess formation. Given the

great variety of bacterial species that can cause AST, broad-spectrum antibiotics should be administered while cultures are pending.

In adults, empiric antibiotics should be selected to include coverage for MRSA and *Streptococcus pyogenes* as well as penicillin-resistant gram aerobic gram-negative bacilli and anaerobes. Several options exist for appropriate initial antibiotic regimens: cefepime or ceftazidime along with clindamycin; a β-lactam/β-lactamase inhibitor with vancomycin; or a carbapenem with vancomycin. In the cases of patients for whom it may be preferable to avoid Vancomycin, alternative agents such as linezolid or daptomycin may be used for MRSA coverage.

In pediatric or recurrent cases of AST, it is particularly important to cover oral anaerobes, which are commonly involved in these infections. Empiric antibiotic therapy for children with AST should also provide adequate coverage for *S. aureus* and *S. pyogenes*.

If clinical examination or radiographic findings are consistent with an abscess or gas formation, surgical drainage is indicated. If an infection persists despite antibiotic treatment (e.g., continued leukocytosis and fever, progressive local inflammation) or involves extensive necrosis, lobectomy may be required.

Patients with AST should be evaluated for the presence of predisposing conditions. Any preexisting thyroid pathology that is discovered, such as a goiter or adenoma, should be treated. Because a pyriform sinus fistula is the most common route of infection in bacterial AST, most patients with their first episode and all patients with recurrent episodes should undergo a barium swallow, CT scan, or MRI of the neck to exclude the presence of a communicating fistula. Because the tract may be obscured by inflammatory material during an acute phase of infection, imaging studies may not reveal a fistula until after the completion of antibiotic therapy. Surgical excision or cauterization treatment of such fistulas is necessary to prevent recurrent infections.

With appropriate treatment the prognosis of AST is excellent, and the vast majority of patients recover completely. Rarely, however, episodes of AST are followed by hypothyroidism, which is almost always transient; vocal cord paralysis; and recurrent infection. As a result of severe, diffuse inflammation and necrosis of the gland, some patients may develop transient or prolonged hypothyroidism requiring L-thyroxine replacement therapy. Management of AST also includes diagnosing and treating any preexisting thyroid pathology, such as a goiter or adenoma, which may have served as a predisposing condition.

Suppurative thyroiditis due to pathogens other than bacteria generally occurs in the setting of a disseminated infection, most commonly in immunocompromised hosts. In such cases, systemic therapy for the underlying disease (e.g., fungal infection, mycobacterial infection) usually results in treatment of the thyroiditis.

Conclusion

AST is a rare disease, but one that carries considerable morbidity unless promptly treated. Imaging techniques are very useful in demonstrating a focus of infection in the thyroid. This infection can occur as a result of systemic infection, in which case hematogenous or lymphatic spread settles in the thyroid. It can also be a result of direct spread from a surface wound or through local invasion from infected congenital anomalies of the neck. In view of the multiplicity and variability of the potential pathogens and their antimicrobial sensitivities, every attempt should be made to identify the offending pathogen. In the case of systemic infections (e.g., bacteremias, fungemias, and disseminated tuberculosis), cultures of blood and other infected sites may be sufficient to establish the etiology. When AST is the single site of infection, prompt FNA should be performed to identify the organism and dictate appropriate therapy.

Suggested reading

Ahn E, Lee GJ, Sohn JH. Ultrasonographic characteristics of pyriform sinus fistulas involving the thyroid gland. *J Ultrasound Med*. 2018;37:2631–2636.

Brook I. Role of methicillin-resistant *Staphylococcus aureus* in head and neck infections. *J Laryngol Otol*. 2009;123:1301–1307.

Farwell AP. Subacute thyroiditis and acute infectious thyroiditis. In Braverman LE, Utiger RD, eds. *Werner & Ingbar's the Thyroid: A Fundamental and Clinical Text*, 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2005: 536–547.

Goldani LZ, Zavascki AP, Maia AL. Fungal thyroiditis: An overview. *Mycopathologia*. 2006;161:129–139.

Jacobs A, David-Alexandre CG, Gradon JD. Thyroid abscess due to *Acinetobacter calcoaceticus*: Case report and review of the causes of and current management strategies for thyroid abscesses. *South Med J*. 2003;96:300–307.

Masuoka H, Miyauchi A, Tomoda C, et al. Imaging studies in sixty patients with acute suppurative thyroiditis. *Thyroid*. 2011;10:1075–1080.

Nishihara E, Miyauchi A, Matsuzuka F, et al. Acute suppurative thyroiditis after fine-needle aspiration causing thyrotoxicosis. *Thyroid*. 2005;15:1183–1187.

Paes JE, Burman KD, Cohen J, et al. Acute bacterial suppurative thyroiditis: A clinical review and expert opinion. *Thyroid*. 2010;20:247–255.

Shah SS, Baum SG. Diagnosis and management of infectious thyroiditis. *Curr Infect Dis Rep*. 2000;2:147–153.

Tan J, Shen J, Fang Y, et al. A suppurative thyroiditis and perineal subcutaneous abscess related with *aspergillus fumigatus*: A case report and literature review. *BMC Infect Dis*. 2018;18:702.

6

Otitis

Stephen I. Pelton

Introduction

The clinical burden from acute (AOM) and chronic suppurative otitis media (CSOM) and their associated morbidities is substantial, especially in children. In industrialized countries, AOM remains the most frequent reason for pediatric office visits and recurrent otitis media (ROM); persistent middle ear fluid and associated hearing loss reduces quality of life. In developing nations, infectious complications of AOM include suppurative intracranial infection and CSOM with severe hearing loss.

The prescription of antimicrobials increases bacterial resistance, so the role of antimicrobials in AOM has been re-evaluated, using an evidence-based approach.

ROM and CSOM usually begin in the first year of life, due to *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae* (NTHi), or *Morexalla catarrhalis*. Studies of children undergoing tympanostomy report biofilms on middle ear mucosa and positive PCR assays for otopathogens despite negative cultures. Although pneumococcal conjugate vaccine (PCV7) reduced office visits for AOM by ~15%, a multidrug-resistant nonvaccine serotype, 19A, emerged as a prevalent cause of AOM and mastoiditis. Asecond-generation conjugate vaccine (PCV13) that included pneumococcal polysaccharide 19A (as well as 1, 3, 5, 6A, and 7F) was introduced in 2010, and observational studies report a decline in AOM due to serotype 19A in young children. In children at risk for CSOM, the impact of PCV 7 has been more modest. Although disease due to the seven serotypes in PCV declined, disease due to nonvaccine serotypes increased.

Diagnosis

Current American Academy of Pediatrics (AAP) guidelines recommend diagnosing AOM in children who present with moderate to severe bulging of the tympanic membrane or new onset of otorrhea not due to otitis externa (Figure 6.1). Children with mild bulging of the tympanic membrane and recent (less than 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the tympanic membrane should also be diagnosed with AOM. Older children with AOM usually describe rapid onset of ear pain. However, in young children, otalgia is suggested by tugging/rubbing/ holding of the ear, excessive crying, fever, or changes in the child's sleep or behavior pattern. The combination of a "cloudy," bulging tympanic membrane with impaired mobility was the best predictor of AOM. A tympanic membrane that was hemorrhagic, strongly red, or moderately red also correlated with the presence of AOM, but a tympanic membrane that was only "slightly red" was not helpful diagnostically.

Clinical symptoms and signs do not differentiate specific otopathogens. The one clinical finding that is consistently associated with a specific pathogen is conjunctivitis with NTHi.

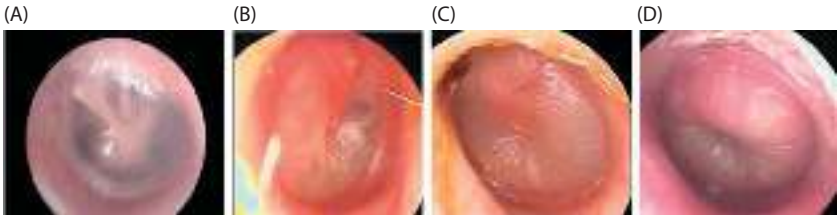

FIGURE 6.1 (A) Normal tympanic membrane. (B) Tympanic membrane with mild bulging. (C) Tympanic membrane with moderate bulging. (D) Tympanic membrane with severe bulging.

Courtesy of Alejandro Hoberman.

Microbiology of aom in the era of universal immunization with pneumococcal conjugate vaccine

The pathogenesis of AOM reflects that nasopharyngeal otopathogens ascend the Eustachian tube into the middle ear. Therefore, although the etiology of individual episodes can only be established by sampling the middle ear (tympanocentesis), the spectrum of otopathogens colonizing the nasopharynx will define the microbiology of AOM.

The introduction of PCV7 reduced invasive pneumococcal disease due to the seven vaccine serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), decreased episodes of vaccine serotypes pneumococcal otitis media as well as overall clinical episodes and tympanostomy tube insertion, and impacted substantially on pneumococcal serotype distribution in the nasopharynx. In clinical trials of PCV7 (FinOM) a 34% overall reduction in pneumococcal otitis was reported; the reduction in vaccine serotype AOM was greater but an increase in episodes due to nonvaccine serotypes of *S. pneumoniae* was observed, providing initial evidence that "replacement" disease (that due to nonvaccine serotypes or alternative otopathogens) was significant. Initially replacement of disease due to vaccine serotype with nonvaccine serotype reduced episodes of AOM due to penicillin-nonsusceptible pneumococci. This was a result of the clustering of resistance among a limited number of pneumococcal serotypes, primarily the vaccine serotypes.

Subsequently nonvaccine serotypes, dominated by serotypes 19A and 6A, emerged. Specifically, serotype 19A became the most commonly recovered pneumococcal serotype in studies of nasopharyngeal colonization and in invasive pneumococcal disease and was a frequent cause of treatment failure in children with acute AOM. In 2010 a 13-valent pneumococcal conjugate vaccine was introduced (serotypes 1, 3, 5, 6A, 7F, and 19A), in part due to the burden of pneumococcal disease due to multidrug-resistant 19A. A decline in both nasopharyngeal colonization and invasive pneumococcal disease with serotype 19A has been observed; however, specific data on AOM is limited. Dagan has reported a decline in AOM due to the PCV13 unique serotypes in observational studies of children undergoing tympanocentesis as part of clinical management in Israel.

Knowledge of the current distribution of pathogens in children with AOM and the prevalence of penicillin-nonsusceptible *S. pneumoniae* or β-lactamase production among NTHi is limited. Studies of nasopharyngeal isolates in the postPCV13 ear demonstrate high prevalence of penicillin-nonsusceptible isolates of *S. pneumoniae* and β-lactamase production among isolates of NTHi; however, strains highly resistant to penicillin and/or ceftriaxone appear to be decreasing. Reports of isolates of NTHi with altered penicillin-binding proteins and increased minimal inhibitory concentrations for amoxicillin–clavulanate have appeared; however, such strains remain uncommon in the United States.

Treatment

Pain is a common symptom in AOM. Antibiotic therapy, even when effective, does not appear to provide symptomatic relief over the first 24 hours. Analgesics are effective for pain relief and should be prescribed regardless of whether initial management included antibiotics. Ibuprofen or acetaminophen is effective, and topical agents such as Auralgan may offer symptomatic relief. *For children with severe pain, myringotomy is an effective method to attain relief.* The treatment of otalgia is reviewed in Table 6.1.

The role of antibiotics in the treatment of AOM continues to undergo re-evalution. Multiple questions must be addressed to formulate a strategy for treatment of AOM.

Do children treated with antimicrobial therapy improve more quickly than those assigned to analgesia alone?

Antimicrobial therapy for AOM has reduced suppurative complications dramatically, specifically mastoiditis, over the past five decades. Similarly, in special populations such as Native Americans and Eskimo children, the prevalence of CSOM has declined in association with both the introduction of antimicrobial therapy and the improvement in public health and socioeconomic conditions. Today, AOM resolves in the majority of children without complications with or without antimicrobial therapy.

The observation that 20% to 30% of episodes are culture negative and that a proportion of children with acute bacterial otitis spontaneously clear the pathogen (approximately 15% of those with pneumococcal disease, 40% of those due to NTHi, and up to 75% of those with AOM due to *M. catarrhalis*) led some experts to suggest that symptomatic therapy should be the initial approach. Historically, Engelhard and associates reported greater than 70% failure in children with AOM who received myringotomy alone and Kaleida and colleagues observed a 2-fold higher failure rate among children with temperature greater than 103°F treated with myringotomy plus

TABLE 6.1 **TREATMENT OF OTALGIA**

Modality	Comments
Acetaminophen, ibuprofen	• Effective analgesia for mild to moderate pain • Readily available • Mainstay of pain management for AOM
Home remedies: (no controlled studies that directly address effectiveness) Distraction External application of heat or cold Oil	• May have limited effectiveness
Topical agents: Benzocaline (Auralgan®, Americaine Otic®) Naturopathic agents (Otikon Otic Solution®)	• Additional, but brief, benefit over acetaminophen in patients >5 years of age • Comparable to amethocaine/ phenazone drops (Anaesthetic®) in patients >6 years of age
Homeopathic agents	• No controlled studies that directly address pain
Narcotic analgesia with codeine or analogs	• Effective for moderate or severe pain • Requires prescription • Risk of respiratory depression • Altered mental status • Gastrointestinal upset and constipation
Tympanostomy/myringotomy (EBOM 227–240)	• Requires skill and entails potential risk

placebo compared with antibiotics (23.5% vs. 11.5%). They also observed an approximately 2-fold greater failure rate in children with nonsevere episodes who were treated with placebo compared with those who received amoxicillin (7.7% vs. 3.9%). However, studies by Little and coworkers challenged the impact of antimicrobial therapy on AOM symptoms. Their studies compared the outcome of AOM in children initially treated with amoxicillin with those given a prescription to be filled only if symptoms persisted for 72 hours. The authors concluded that immediate antibiotic prescription provided symptomatic benefit mainly after the first 24 hours, when symptoms were already resolving. For children who are not very unwell systemically, a wait and see approach was feasible and acceptable to parents and should substantially reduce the use of antibiotics for acute otitis media. However, both the enrollment criteria and the accuracy of diagnosis in their study were criticized. McCormick and colleagues evaluated "watchful waiting" as a strategy for children with nonsevere AOM. Increased treatment failures and persistent symptoms were observed, especially in those younger than 2 years old assigned to delayed antibiotic treatment. Although delayed resolution was observed in the cohort assigned to watchful waiting, parent satisfaction was not different among the early treatment and the initial observation groups. Increased rates of mild adverse events as well as increases in the prevalence of nonsusceptible *S. pneumoniae* in the nasopharynx were observed in the early treatment group.

Two recent randomized trials of initial antimicrobial therapy vs. placebo for infants and toddlers concluded that treatment reduced the time to resolution of symptoms and the overall symptom burden. Treatment failure with "rescue" antibiotic treatment and signs of persistent acute infection on otoscopic examination were more prevalent in the placebo group (Table 6.2). Table 6.3 summarizes the potential benefits and harms of initial antimicrobial therapy for AOM and provides the current recommendation from the American Academy of Pediatrics.

Does persistence of bacterial infection within the middle ear correlate with persistence of clinical signs or symptoms?

The outcome measure selected is critical for determining the impact of antimicrobial treatment on the course of AOM. If

TABLE 6.2 **COMPARISON OF OUTCOMES BETWEEN INITIAL TREATMENT WITH AMOXICILLIN–CLAVULANATE AND PLACEBO IN CHILDREN WITH ACUTE OTITIS MEDIA**

Outcome	Amoxicillin–clavulanate	Placebo (n = 158)	Difference (95% CI)
Treatment failure	30 (18.6%)	71 (44.9%)	−26.3 (−36.5 to −16.1)
No improvement by day 3	12 (7.5%)	22 (13.9%)	−6.5 (−13.2 to 0.3)
Worsening of condition	15 (9.3%)	32 (20.3%)	−10.9 (−18.7 to −3.2)
Tympanic membrane perforation	1 (0.6%)	5 (3.2%)	−2.5 (5.5 to 0.4)
"Rescue" treatment	11 (6.8%)	53 (33.5%)	−26.7 (−35.5 to −17.9)
Use of antipyretics/analgesic	133 (84.2%)	134 (85.9%)	−1.7 (−9.6 to 6.2)%

Modified from Tähtinen *et al.* A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med*. 2011;364:116–126.

TABLE 6.3 **AAP RECOMMENDATIONS FOR ANTIMICROBIAL TREATMENT OF AOM ADAPTED FROM LIEBERTHAL AS. THE DIAGNOSIS AND MANAGEMENT OF ACUTE OTITIS MEDIA. *PEDIATRICS* 2013;131;E964**

Condition	Potential for benefit	Potential for harm	Denouement
Severe symptoms	Increased likelihood of more rapid resolution of symptoms. Increased likelihood of resolution of AOM	Adverse events attributable to antibiotics, such as diarrhea, diaper dermatitis, and allergic reactions. Overuse of antibiotics leads to increased bacterial resistance. Cost of antibiotics	Preponderance of benefit over harm
Nonsevere bilateral AOM in young children	Increased likelihood of more rapid resolution of symptoms. Increased likelihood of resolution of AOM	Adverse events attributable to antibiotics, such as diarrhea, diaper dermatitis, and allergic reactions. Overuse of antibiotics leads to increased bacterial resistance. Cost of antibiotics	Preponderance of benefit over harm
Nonsevere unilateral AOM in young children	Moderately increased likelihood of more rapid resolution of symptoms with initial antibiotics. Moderately increased likelihood of resolution of AOM with initial antibiotics	Adverse events attributable to antibiotics, such as diarrhea, diaper dermatitis, and allergic reactions. Overuse of antibiotics leads to increased bacterial resistance. Cost of antibiotics	Observation becomes an alternative as the benefits and harms approach balance
Nonsevere AOM in older children	Slightly increased likelihood of more rapid resolution of symptoms; slightly increased likelihood of resolution of AOM	Adverse events attributable to antibiotics, such as diarrhea, rashes, and allergic reactions. Overuse of antibiotics leads to increased bacterial resistance.	Observation is an option as the benefits and harms approach balance

outcome parameters such as resolution of signs and symptoms by day 7 to 10 or persistence of middle ear fluid at day 14 or 28 are selected, no differences between antimicrobial treatment and watchful waiting strategies can be consistently established. Effective antimicrobial therapy sterilizes the middle ear, resulting in a more rapid resolution of clinical signs (bulging and erythema) and symptoms (fever, earache, irritability). Therefore, evaluating outcomes within the first 3 to 5 days is necessary to demonstrate improved outcomes in antibiotic-treated cohorts as well as between antibiotic regimens.

Both Dagan and Carlin observed greater improvement in signs and symptoms in children with bacterial AOM when the middle ear fluid was sterilized by days 4–6 compared to children who had persistent middle ear infection. Figure 6.2 details the changes in clinical symptom score in children with effective antimicrobial therapy and sterilization of the middle ear compared to those with ineffective antimicrobial therapy and persistence of middle ear infection. The results also demonstrate that many children with persistent middle ear bacterial infection have decreased symptoms at days 4–6 compared to initial presentation.

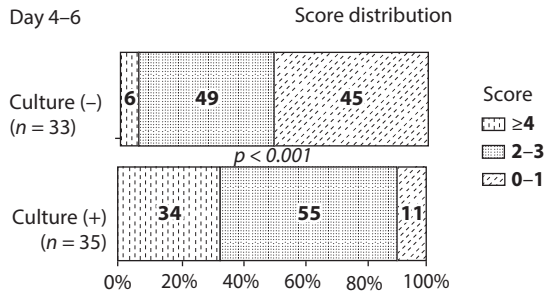

FIGURE 6.2 Symptoms score in children with acute otitis media (AOM).

Is the risk of recurrence greater in children who are not initially treated with antimicrobial therapy?

Patients with clinical improvement or cure on days 4–6 but culture-positive middle ear fluid were shown to have an increased rate of recurrent AOM compared to those with culture-negative middle ear fluid and clinical improvement or cure (Figure 6.3). Molecular analysis of the otopathogens isolated at recurrence and those identified on days 4–6 found concordance in 66% of patients. These observations emphasize the benefit of bacteriologic eradication in AOM.

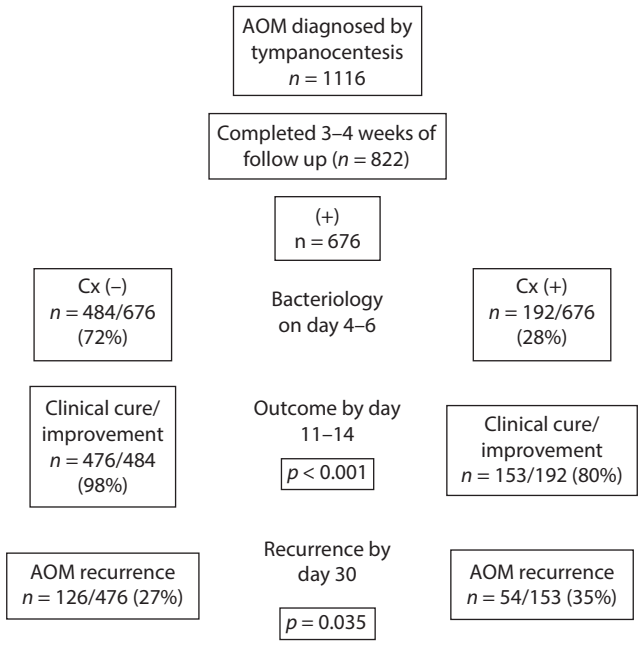

FIGURE 6.3 Association between eradication of middle ear pathogens during treatment and improvement in clinical symptoms. Cx, culture.

Does amoxicillin remain the initial drug of choice when the decision to use antimicrobial therapy has been made?

The selection of antimicrobial therapy should be based on knowledge of the microbiology of AOM, pharmacodynamic principles, and clinical trials using both clinical and microbiologic outcomes. Eighteen antibiotics are currently approved by the US Food and Drug Administration (FDA) for treatment of AOM; however, the emergence of otopathogens with reduced susceptibility to β-lactam antibiotics (SP and NTHi) has limited the efficacy of some antimicrobials. In the majority of cases of AOM, the specific pathogen is unknown, and presumptive therapy is based on the potential pathogens and their in vitro susceptibility. The proportion of isolates of NTHi-producing β-lactamase has slowly risen to nearly 50% over a 25-year period. A very limited number of β-lactamase-producing, amoxicillin-clavulanate-resistant isolates have also been reported in the United States. The recent emergence of nonvaccine serotypes of pneumococci with reduced susceptibility to β-lactam agents as well as macrolides and trimethoprim–sulfamethoxazole must also be considered in selection of antimicrobial therapy. Because there are no clinical differences between cases with resistant and susceptible pathogens, epidemiologic risk features must be assessed and tympanocentesis employed when a specific microbiologic etiology is needed.

Children with infrequent episodes of OM, without recent antimicrobial therapy, without conjunctivitis, older than 2 years, or not in day care are at low risk for drug-resistant *Streptococcus pneumoniae* (DRSP) or β-lactamase-producing NTHi. For these children the AAP guidelines recommend amoxicillin (Table 6.4).

Children with recent antimicrobial therapy or conjunctivitis are at higher risk for disease due to nonsusceptible *S. pneumoniae* or β-lactamase-producing NTHi. In these children only oral high-dose amoxicillin and intramuscular ceftriaxone achieve middle ear concentrations high enough to exceed the minimal inhibitory concentration (MIC) of all *S. pneumoniae* that are intermediately sensitive to penicillin and of many, but not all, highly resistant strains as well as strains of NTHi that do not produce β-lactamases. Cefuroxime axetil, cefprozil, and cefpodoxime represent alternatives to high-dose amoxicillin; however, each achieves sufficient middle ear concentration to be effective against only approximately 50% of *S. pneumoniae* isolates that are intermediately susceptible to penicillin. Also, cefprozil has limited activity against NTHi. Macrolides are very effective when fully susceptible isolates of *S. pneumoniae* are present. Because amoxicillin clavulanate resists destruction by β-lactamase, it effectively eradicates middle ear infection caused by NTHi. Although the AAP guidelines recommend the consideration of amoxicillin clavulanate as initial therapy only for children with severe disease, the increasing prevalence of AOM due to NTHi warrants consideration for broader use of amoxicillin clavulanate as first-line therapy in selected children.

Initial therapy for children with type I allergy to penicillin (urticaria, laryngeal spasm, wheezing, or anaphylaxis) is limited. Alternatives to β-lactams are limited because of substantial resistance among otopathogens. Macrolides, including azithromycin and clarithromycin, are active against most pneumococcal isolates; however, up to 40% of *S. pneumoniae* have MIC that are beyond the breakpoints for these agents. Resistance to trimethoprim sulfamethoxazole among *S. pneumoniae* and NTHi also is frequent. In the current era, β-lactamase-producing NTHi has emerged as the most common pathogen in children failing initial therapy with amoxicillin (Figure 6.4). The current distribution of pneumococcal serotypes found in the nasopharynx and reported from middle ear cultures includes isolates with reduced susceptibility to β-lactam antibiotics and macrolides (Table 6.5); however, the prevalence of MDR and specifically penicillin-resistant (MIC > 2.0 μg/mL) isolates has declined. For these children, a three-dose regimen of ceftriaxone (50 mg/ kg/day) has demonstrated efficacy (Table 6.6). Anecdotal data support the efficacy for clindamycin and linezolid against nonsusceptible SP; however, neither is active against *Haemophilus influenza*. High-dose amoxicillin in combination with cefixime or ceftibuten and standard-dose amoxicillin in combination with amoxicillin-clavulanate are also appropriate. Clinical studies of quinolones (specifically gatifloxacin and levofloxacin) demonstrate rapid sterilization and clinical resolution of middle ear infection due to both *S. pneumoniae* and NTHi. Currently, quinolones are not licensed for use in children for the treatment of AOM.

Prevention of recurrent acute otitis media

Middle ear disease has been identified as the most common reason for ambulatory healthcare visits, and persistent middle ear fluid with conductive hearing loss is frequent.

TABLE 6.4 **AAP/AAFP RECOMMENDED ANTIBACTERIAL AGENTS**

Temperature ≥ 39°C and/or severe earache	At diagnosis for patients being initially treated with antibacterial agents or clinically defined treatment failure at 48–72 hours after initial management with observation	
	Recommended	**Alternative for penicillin allergy**
No	Amoxicillin 80–90 mg/Kg/day	Non-type I: Cefdinir Cefuroxime Cefpodoxime Type I: Azithromycin Clarithromycin
Yes	Amoxicillin-clavulanate 90/6.4 mg/Kg/day	Ceftriaxone 1 or 3 days

AAP/AAFP Clinical Practice Guideline: Diagnosis and Management of Acute Otitis Media 2004.

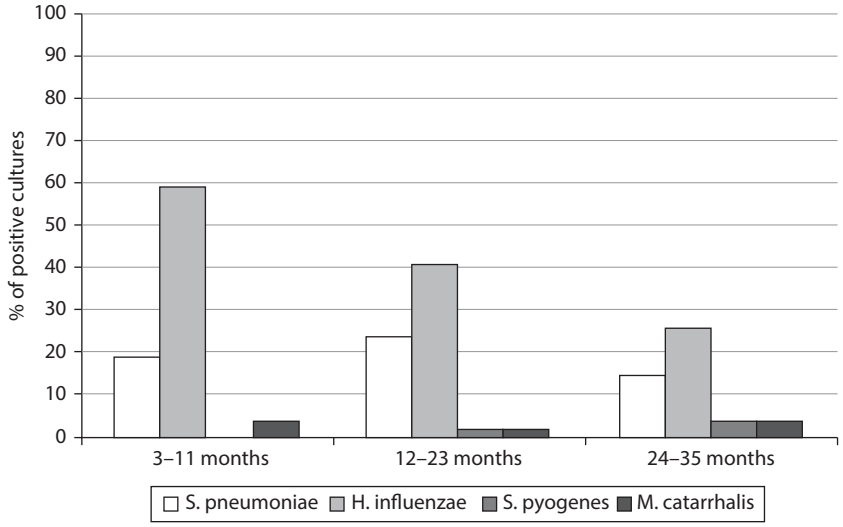

FIGURE 6.4 Microbiology of bacteria causing recurrent acute otitis media (AOM) and AOM treatment failure in young children in Spain: Shifting pathogens in the post-pneumococcal conjugate vaccination era.

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TABLE 6.5 ANTIBIOTIC SUSCEPTIBILTY PATTERNS AMONG ISOLATES RECOVERED BY TYMPANOCENTESIS FROM CHILDREN WITH RECURRENT EPISODES OF ACUTE OTITIS MEDIA

		S. pneumoniae			
		19A (*N* = *9*)	**Other (*N* = *16*)**	**NTHi (*N* = 54)**	***M. catarrhalis* (*N* = 3)**
Antibiotic/test	Resistant (MIC)	*n*(%)	*n*(%)	*n*(%)	*n*(%)
Cefotaxime	≥4	3(33)	0(0)	0	0
Erythromycin	≥1	8(89)	6(38)	–	–
Penicillin G	≥8	0	2(13)	–	–
Amoxicillin	≥8	7(78)	3(19)	–	–
Ampicillin	≥4	–	–	8(15)	–
Cefpodoxime	≥2	2(78)	2(13)	0	0
Amoxicillin/clavulanic acid	≥8/4	–	–	7(13)[a,b]	0
Multidrug resistance	–	7(78)	3(19)	0	2(67)

N = number of isolates; *n*(%) =number(percentage of resistant isolates); – = not tested.
[a] Two were β-lactamase producing.
[b] All were also ampicillin resistant.
MIC, mean inhibitory concentration.

TABLE 6.6 AAP/AAFP RECOMMENDED ANTIBACTERIAL AGENTS

	Clinically defined treatment failure at 48–72 hours after initial management with antibacterial agents	
Temperature ≥ 39°C and/or severe earache	**Recommended**	**Alternative for penicillin allergy**
No	Amoxicillin- clavulanate 90/6.4 mg/Kg/day	Non-type I: Ceftriaxone 3 days Type I: Clindamycin
Yes	Ceftriaxone 3 days	Tympanocentesis Clindamycin

AAP/AAFP Clinical Practice Guideline: Diagnosis and Management of Acute Otitis Media 2013.

Prevention of recurrent AOM can be achieved by preventing nasopharyngeal colonization with otopathogens, preventing viral respiratory infection, or providing specific antibacterial immunity. Insertion of tympanostomy tubes does not reduce the frequency of acute episodes substantially; however, the presence of such tubes shortens the duration of middle ear effusion and restores the conductive hearing loss frequently associated with such effusions. Antimicrobial prophylaxis lowers the frequency of colonization with respiratory otopathogens and decreases the number of acute episodes. Mandel and colleagues found a decrease in acute episodes from 1.04 per child per year in the placebo group to 0.28 in a group receiving prophylactic amoxicillin. The reduction in acute episodes was accompanied by a reduction in persistent MEF. The greatest benefit occurs in otitis-prone children who have multiple episodes per year and in whom recurrences continue despite increasing age; however, chemoprophylaxis offers short-term benefits only. Most otitisprone children continue to have recurrent episodes once prophylaxis is discontinued, until their immune systems and Eustachian tube function have matured.

The pathogenesis of AOM involves coinfection with respiratory viruses in more than 85% of episodes. Immunization with influenza vaccine reduces febrile AOM episodes as well as insertions of tympanostomy tubes during a winter season. Annual immunization is recommended for children with risk factors for ROM, such as attendance at out-of-home child care, family history of recurrent AOM, or early onset of disease. Seven-valent pneumococcal conjugate vaccines (PCVCRM and PCVOMP), administered at 2, 4, and 6 months with a booster at 12 to 15 months of either 7-valent PCV or 23-valent pneumococcal polysaccharide vaccine have been demonstrated to reduce AOM due to vaccine serotypes of *S. pneumoniae* by approximately 60%, and all episodes of pneumococcal otitis media by one-third. However, the overall reduction in clinical episodes of AOM was more modest (6% to 10%). A critical concern in the studies was the small increase in episodes of AOM due to nonvaccine serotypes and NTHi. Postlicensure studies have confirmed an increase in the proportion of AOM due to nonvaccine serotypes of SP. Follow-up of the original clinical trials of PCV7 in both the Northern California Kaiser Permanente cohort and the FinOM cohort identified significant reductions in tympanostomy tube insertions in the children immunized in infancy with PCV7. Studies of PCV7 in children with frequent recurrences of otitis media or those at risk for CSOM have failed to demonstrate a significant reduction in recurrent episodes. Veenhoven observed that disease due to vaccine serotypes of *S. pneumoniae* was only a small proportion of overall episodes in children with a history of ROM. Leach and colleagues found a nonsignificant reduction in episodes of chronic suppuration in the first year of life in Aboriginal children immunized with PCV7.

In 2010, PCV13 was introduced as a second-generation pneumococcal conjugate vaccine to broaden coverage against serotypes more commonly causing disease outside of North America (serotypes 1, 3, and 5) as well as replacement serotypes, specifically 19A, 7F, and 6A. Early observational data have demonstrated a further decline in overall pneumococcal AOM episodes including those due to serotype 19A.

Complications of acute otitis media

Perforation of the tympanic membrane is the most common complication of AOM and occurs most frequently in younger children. Certain ethnic groups, such as Alaskan Eskimos and Native Americans, have a higher rate of spontaneous perforation. Differentiation between AOM with perforation and acute otitis externa can be difficult. In general, the history of increasing pain with relief when otorrhea occurs is found with AOM, whereas increasing pain without relief in the face of otorrhea is seen with otitis externa. The microbiology of AOM in children with acute perforation reports a greater proportion of episodes due to group A streptococcus (GAS) and *Staphylococcus aureus*. However, *S. pneumoniae*, NTHi, and *M. catarrhalis* remain predominant. The natural history of AOM with perforation is usually complete resolution with healing of the tympanic membrane. A small proportion of patients can have persistent dry perforation or experience CSOM (otorrhea persisting for more than 6 to 12 weeks). *Streptococcus pneumoniae* and NTHi are the most common pathogens in infants and toddlers whereas *S. aureus* and *Pseudomonas aeruginosa* are frequent pathogens in older children and during the summer months. An increasing proportion of the *S. aureus* isolates, even those acquired in the community, are resistant to methicillin. Topical otic suspensions, either ofloxacin or ciprofloxacin, is the preferred therapy for uncomplicated episodes of acute otorrhea through a tympanostomy tube. Both of the quinolones are active against pseudomonas as well as the respiratory otopathogens. Amoxicillin is generally effective for acute otorrhea through a tympanostomy tube when disease is due to respiratoy pathogens, and results in rapid clearing of bacterial pathogens and a resolution of otorrhea. When methicillin-resistant *S. aureus* (MRSA) is the pathogen, fluoroquinolone and sulfacetamide ototopical medications were found to be effective. Adjunctive therapy with oral antibiotics, bactrim and clindamycin respectively, did not improve resolution rates. Topical vancomycin (25 mg/mL) drops or the use of trimethoprim–sulfamethoxazole orally in combination with gentamicin otic has also been reported as successful. Caution with both of these regimens is necessary as safety has not been established.

Facial palsy as a complication of AOM has become less prominent with the routine use of antibiotic therapy. Facial weakness and earache are the predominant symptoms. Management with antimicrobial agents and myringotomy (with or without tube insertion) is usually sufficient to achieve complete resolution.

An unusual complication, inflammatory cast of the tympanic membrane causing hearing loss, may occur after AOM with perforation. Patients present with unilateral persistent hearing loss. The diagnosis is suspected by comparison of the affected and unaffected tympanic membranes. On the affected side, a thin, hard cast is observed. Removal results in improvement in hearing.

The incidence of mastoiditis has decreased dramatically with the routine use of antimicrobial therapy. However, it remains the most common suppurative complication of AOM. Although the potential for re-emergence of mastoiditis when antimicrobial agents are withheld for AOM has been a concern, there are few convincing data to suggest an increase in incidence. The management of acute mastoiditis depends on disease classification. *Acute mastoiditis with periostitis* results from an obstruction of the connection between the middle ear and mastoid space (aditus ad antrum). Postauricular erythema, tenderness, and edema are the clinical manifestations. AOM is often but not universally present. *S. pneumoniae*, GAS, and NTHi are most common but *Pseudomonas aeruginosa* was found in 29% and *Staphylococcus epidermidis* in 31% of cases in one large series. *Pseudomonas* and *Staphylococcus* should be suspected when a history of otorrhea precedes development of acute mastoiditis.

Labyrinthitis develops when AOM spreads (through the round window) into the cochlear space. The process may be suppurative or serous (due to toxins). The onset of labyrinthitis is often sudden, with vertigo and hearing loss being characteristic. Acute surgical intervention (myringotomy with tube insertion) with antimicrobial therapy is the treatment of choice. Additional rare complications of AOM are brain abscess, lateral sinus thrombosis, and otic hydrocephaly.

Gradenigo's syndrome is a rarely seen complication of AOM where infection spreads to the apex of the petrous temporal bone. A triad of symptoms consisting of unilateral periorbital pain due to trigeminal nerve involvement, diplopia due to sixth nerve palsy, and persistent otorrhea is present. This classical triad has become very uncommon in the antibiotic era.

Otitis externa

Acute otitis externa (AOE) is primarily a pediatric disease occurring most frequently in children 6 to 12 years of age. The disease results from a disruption of integrity of the ear canal and the normal self-cleaning process of epithelial migration toward the external os. Swimming, local trauma, accumulation of debris from dermatologic conditions, or the wearing of hearing aids are predisposing factors. The early manifestations are itching, pain, and erythema of the canal but the disease can progress with severe swelling and obstruction of the external canal or extension to the bony external canal or even the base of the skull in the elderly or in patients with comorbidity (see discussion ofmalignant external otitis in Chapter 148, *Pseudomonas*, *Stenotrophomonas*, and *Burkholderia*).

Early in the course, minimal, odorless secretions and erythema of the external canal in association with mild pain and pruritus are present. As the disease progresses, erythema increases and edema of the canal becomes manifest. Seropurulent secretions may be present and acute pain is elicited by movement of the auricle or direct pressure on the tragus. Severe disease is noted by edema of the canal wall obstructing the lumen, intense pain, and extension to cervical adenitis or auricular cellulitis.

The diagnosis of AOE requires rapid onset of symptoms over several days with evidence of inflammation of the external ear canal manifest by otalgia, itching, tenderness of the tragus or pinna, and/ or diffuse erythema. Systemic manifestations such as cervical adenitis or cellulitis of the pinna may be present. Distinguishing AOE from AOM is critical as the therapy is markedly different. Identification of complications that may be manifest by facial paralysis, vertigo, or meningeal signs or cranial nerve palsy or the presence of granulation tissue at the junction of the boney and cartilaginous portions of the canal is critical. A furuncle may be observed in the external canal. Often referred to as localized otitis externa, this represents an infected hair follicle in the outer third of the external canal. History is helpful in discriminating AOE from AOM. Often the pain in AOE is progressive whereas in AOM the pain will usually abruptly improve when perforation occurs. The tympanic membrane in both AOM and AOE is frequently erythematous but in AOE pneumatic otoscopy reveals normal motility. Otomycosis may manifest as thick otorrhea, white debris with hyphae in the canal (*Candida*), or a white plug with dark debris (*Aspergillus niger*).

Topical therapy is the initial choice for diffuse, uncomplicated AOE as there is no need for systemic antimicrobials unless there are comorbid conditions that are associated with disease complications, there is progression to cellulitis of the pinna or adenitis, or topical therapy is contraindicated. AOE is primarily a bacterial disease with *Pseudomonas aeruginosa* the dominant pathogen followed by *S. aureus*. Fungal infection is uncommon except in those who have failed initial topical therapy. Mild disease can be treated with 2% acetic acid with or without a steroid. Compliance may be poor as acetic acid is irritating and frequently causes stinging when administered topically. Topical antimicrobial preparations containing an aminoglycoside, polymyxin B, or a quinolone with or without a steroid are effective but should only be used when the tympanic membrane is intact. These topicals achieve local tissue concentrations 1000-fold that of systemic administration. No significant difference in clinical outcome has been established for antiseptic vs. antimicrobial preparations, for quinolone vs. nonquinolone formulations, or for steroid-antimicrobial preparations compared with antimicrobials alone. However, when a perforation of the tympanic membrane is suspected, a tympanostomy tube is in place, or the tympanic membrane has not visualized, only quinolone formulations are approved for use. Critical for topical therapy to be successful is the delivery. Self-administration is difficult and often unsuccessful. Ototopical formulations should be administered with the patient lying on his/ her side. The canal should be filled and, if necessary, the pinna pulled forward and back to assist filling. Some clinicians use aural lavage for removal of debris either initially or, if necessary, repeatedly. Pain may limit the ability to perform aural lavage or suction. If edema is present, a wick of either compressed cellulose or ribbon gauze will enable complete delivery of the ototopical agent. Once the edema resolves, the wick may be removed and therapy continued to complete 7 to 10 days. Adverse events with topical therapy are not common; however, sensitization especially to those formulations that contain neomycin can occur. If infection has spread beyond the ear canal, or in patients at risk of rapid progression, or if signs and symptoms fail to improve, systemic antimicrobial therapy should be added based on the results of susceptibility testing of external ear canal culture.

Fungal disease, most commonly *Candida* or *Aspergillus*, is most often found in patients failing initial topical therapy. Two approaches have been used successfully: ketoconozole cream can be applied to the external canal directly once with follow-up examination in 5 to 7 days and repeat application if needed or Cresylate otic is applied three times a day. Both treatments achieve greater than 80% cure rates. Most recently, community-acquired methicillin-resistant *S. aureus* (CaMRSA) has emerged as an increasing cause of AOE. Treatments used successfully in the treatment of MRSA otitis externa were aural toilet and fusidic acid-betamethasone 0.5%. Most CaMRSA are susceptible to quinolones and it would be expected that ofloxacin or ciprofloxacin formulations should be effective.

Pain management is an integral part of treatment of AEO. Nonsteroidal anti-inflammatory agents and benzocaine otic have been used successfully to manage the discomfort of AOE.

In children with recurrent otitis externa, strategies such as the use of acidifying ear drops before or after swimming, the use of a hair dryer to dry the ear canal after swimming or bathing, or the use of ear plugs while swimming have all been used successfully. If recurrences persist, allergies or underlying inflammatory dermatologic conditions should be sought and the underlying causes addressed.

Necrotizing otitis externa is a complication of otitis externa in which infection extends from the external auditory canal to the base of the skull. It is seen commonly in elderly patients with diabetes and immunocompromised hosts, often in those with advanced HIV. The most common pathogen is *Pseudomonas aeruginosa*; however, a spectrum of pathogens including *Aspergillus* species, *S. aureus, Proteus mirabilis, Klebsiella oxytoca, Burkholderia cepacia*, and *Candida parapsilosis* has been reported. The presentation is characterized by severe pain; cranial nerve involvement is reported in a significant proportion. On physical exam granulation tissue is often visible at the bone–cartilage junction of the external auditory canal. Systemic fluoroquinolones, third-generation cephalosporins, and surgical debridement are the mainstay of treatment.

Suggested reading

Carlin SA, Marchant CD, Shurin PA, *et al*. Host factors and early therapeutic response in acute otitis media. *J Pediatr*. 1991;118(2): 178–183.

Cheng J, Javia L. Methicillin-resistant *Staphylococcus aureus* (MRSA) pediatric tympanostomy tube otorrhea. *Int J Pediatr Otorhinolaryngol*. 2012;76(12):1795–1798.

Dagan R, Leibovitz E, Greenberg D, *et al*. Early eradication of pathogens from middle ear fluid during antibiotic treatment of acute otitis media is associated with improved clinical outcome. *Pediatr Infect Dis J*. 1998;17:776–782.

Del Mar C, Glasziou P, Hayem M. Are antibiotics indicated as initial treatment for children with acute otitis media? A meta-analysis. *Br Med J*. 1997;314:1526–1529.

Eskola J, Kilpi T, Palmu A, *et al*. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med*. 2001; 344(6):403–409.

Leibovitz E. The challenge of recalcitrant acute otitis media: Pathogens, resistance, and treatment strategy. *Pediatr Infect Dis J*. 2007; 26(10 Suppl):S8–S11.

Lieberthal AS, Carroll AE, Chonmaitree T, *et al*. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131; e964–e999.

Pumarola F, Marès J, Losada I, *et al*. Microbiology of bacteria causing recurrent acute otitis media (AOM) and AOM treatment failure in young children in Spain: shifting pathogens in the post-pneumococcal conjugate vaccination era. *Int J Pediatr Otorhinolaryngol*. 2013;77(8): 1231–1236.

Rosenfeld RM, Brown L, Cannon CR, *et al*. Clinical practice guideline: acute otitis externa. *Otolaryngol Head Neck Surg*. 2006;134: S4–S23.

Rosenfeld RM, Kay D. Natural history of untreated otitis media. In: Rosenfeld RM, Bluestone CD, eds. *Evidence-Based Otitis Media*, 2nd edn. Hamilton, ON, Canada: BC Decker Inc; 2003:180–198.

Rosenfeld RM, Pynnonen M, Tunkel DE, Schwartz SR. AAO-HNS Clinical Practice Guideline on Tympanostomy Tubes. *Otolaryngol Head Neck Surg*. 2013; 149(2 Suppl):P26.

Tahtinen P, Laine MK, Huovinen P, *et al*. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med*. 2011;364:116–126.

7

Sinusitis

Rachel Kominsky and Todd D. Otteson

Sinusitis is commonly diagnosed yet criteria for its diagnosis vary and a standard treatment protocol is nonexistent. The majority of patients with acute sinusitis improved without any therapy or with over-the-counter remedies. The temptation to treat an upper respiratory infection with antimicrobials should be avoided, especially in light of increasing bacterial resistance profiles. An understanding of the anatomy, pathophysiology with predisposing factors, and common microbiology helps drive therapeutic decision making.

Sinus anatomy

The paranasal sinuses consist of paired maxillary, ethmoid, sphenoid, and frontal sinuses. The maxillary and ethmoid sinuses are present at birth and fully pneumatize during childhood. The paired sphenoid and frontal sinuses appear in childhood and continue to pneumatize into early adulthood in some cases. The maxillary, anterior ethmoid, and frontal sinuses drain into the ostiomeatal complex (OMC). The OMC is a functional physiologic unit comprising the ethmoid infundibulum, middle meatus, and surrounding structures. The OMC and its patency are the keys to normal sinus drainage and the maintenance of physiologic mucociliary clearance.

Pathophysiology

Any anatomic anomaly, environmental exposure, or disease process, acute or chronic, that prevents the normal mucociliary clearance either by functional obstruction or by thickening of nasal secretions may result in pathogen overgrowth and sinusitis. Typically these processes or exposures affect not only the paranasal sinus mucosa but also the intranasal mucosa, prompting use of the term "rhinosinusitis." Table 7.1 outlines causes of obstruction, thickened secretions, and dysfunction of mucosal cilia. Rarely, direct inoculation of bacteria from odontogenic infection or during swimming or diving may cause acute sinusitis as well.

The bacteriology of sinusitis has been well documented. The results have been consistent for decades, with the most common organisms isolated in acute sinusitis being *Streptococcus pneumoniae*, *Haemophilus influenza*, and *Moraxella catarrhalis*. Since the vaccination of children with pneumococcal vaccine became commonplace after its introduction in 2000, there has been a decline in the recovery rate of *S. pneumoniae* and a corresponding increase in *H. influenza*. Individual resistance to antibiotics has increased. The spectrum of organisms widens in chronic sinusitis to include anaerobic bacteria, *Staphylococcus aureus*, and gram-negative organisms, particularly *Pseudomonas aeruginosa*. Much research has been dedicated to the role of biofilm formation in the pathophysiology of chronic rhinosinusitis. A biofilm is a complex polysaccharide matrix synthesized by bacteria that is protective of bacterial colonies and renders them somewhat resistant to antibiotic therapy. *Pseudomonas aeruginosa* is a known biofilm former in patients with chronic

TABLE 7.1 **CONDITIONS PRECIPITATING SINUSITIS**

Ostiomeatal complex (OMC) obstruction	**Secretion thickness**
Concha bullosa	Allergic rhinitis
Mucosal edema secondary to rhinitis	Cystic fibrosis
Nasal foreign body	Viral upper respiratory infection
Nasal septal deviation	
Nasogastric/nasotracheal tubes	**Ciliary dysfunction**
Polyps	Primary ciliary dyskinesia

rhinosinusitis. Anaerobic isolates are more common when the etiology of the infection is thought to be odontogenic.

Diagnosis

Diagnosis of sinusitis is based on history and physical examination with radiographic support in certain cases. The physical examination consists of anterior rhinoscopy before and after topical decongestion. Any purulent drainage or edema in the area of the middle meatus should be documented as well as the general appearance of the nasal mucosa. Nasal endoscopy allows a more detailed examination of the nasal cavity. Palpation of the paranasal sinuses may elicit focal tenderness. Transillumination of the sinuses may be helpful in adults if the exam is normal or completely absent but is not reliable in children.

Distinguishing between bacterial sinusitis and viral upper respiratory infection may be difficult but is important in planning a treatment strategy. A set of standardized definitions for rhinosinusitis based on symptom profile and duration is well accepted. Symptoms are described as major or minor and include facial pain, nasal obstruction, nasal discharge/postnasal drip, hyposmia/anosmia, purulence on examination (major), headache, halitosis, dental pain, fatigue, cough, and ear pain/pressure (minor). Rhinosinusitis is acute when symptoms last 4 weeks or less, subacute when symptoms are present for 4 to 12 weeks, and chronic for symptoms present longer than 12 weeks. Recurrent acute rhinosinusitis occurs in patients with four or more episodes per year with disease-free intervals in between. An acute exacerbation of chronic sinusitis is defined as a sudden worsening of symptoms with return to baseline after treatment. If the onset of an acute sinusitis is severe, with fever of at least 39°C (102°F) and purulent nasal discharge for at least 3 to 4 consecutive days at the beginning of the illness, the consideration to starting treatment earlier than the usual 7 to 10 days of symptoms should be entertained.

Plain films add little to the diagnosis, especially if sinuses other than the maxillary sinuses are involved. If the clinical situation warrants it, the suspicion of sinusitis is confirmed by CT, which can demonstrate characteristic changes in the paranasal sinuses and especially the OMC. The best time to obtain a CT scan is at the end of a treatment course when the patient is not acutely ill. The CT scan is crucial if any surgical intervention is required. If there is concern for invasive fungal sinusitis in an immunocompromised patient, a CT and an MRI should both be obtained. Figure 7.1A shows the paired maxillary sinuses (M) with dependent fluid in the right maxillary sinus. Note also the right nasal septal deviation. Figure 7.1B shows the ethmoid sinuses (E) with some right anterior ethmoid opacification. Note also the proximity of the ethmoid sinuses to the orbit (O); the lamina papyracea is a layer of thin bone separating the structures. The sphenoid sinuses posteriorly are also present in this image. Figure 7.1C shows the frontal sinus (F).

Treatment

The treatment of acute sinusitis involves appropriate antibiotic therapy and should improve the patency of the sinus ostia. Topical decongestants such as oxymetazoline may alleviate nasal obstruction and decreased nasal mucosal edema but they can only be used for a short time. Systemic decongestants and mucolytics may assist with clearance of secretions. While treatment with these adjunctive therapies may provide some temporary symptomatic relief in some patients, there is no evidence supporting the use of antihistamines, decongestants, nasal steroids, mucolytics, or nasal irrigations for an acute sinusitis.

Ideal antimicrobial therapy eliminates the common bacteria that cause acute sinusitis with as narrow a spectrum as possible. Current antibiotic treatment recommendations for acute bacterial rhinosinusitis take into account emerging antimicrobial resistance patterns. In children, the first-line antibiotic therapy for acute sinusitis is amoxicillin-clavulanate dosed 90 mg/kg/d twice a day and is recommended for children from locations with high rates of penicillin-nonsusceptible *S. pneumoniae*, who were recently hospitalized, or who were treated with another antibiotic course in the past month. For penicillin-allergic patients, levofloxacin is an alternative to amoxicillin–clavulanate. Treatment failure after 72 hours may require directed cultures and treatment with a broader spectrum second-line agent.

Treatment of chronic sinusitis is aimed at alleviation of symptoms and diminishing sinus inflammation. Irrigation of the nasal cavity with normal saline as well as treatment with topical steroids, systemic antihistamines, or systemic decongestants may be attempted but data supporting them are inconclusive. Longer term antimicrobial therapy lasting 4 weeks with a second-line antibiotic may improve symptoms when shorter courses have failed.

If patients with either chronic sinusitis or recurrent acute sinusitis fail to respond to these medical measures, consultation with an otolaryngologist should be considered. Investigation into the etiology of the inflammation causing rhinosinusitis, including any anatomic or physiologic source, should be undertaken and surgical management, consisting of endoscopic sinus surgery, considered. The goal of surgical intervention is to restore sinus drainage while preserving as much paranasal sinus and nasal mucosa as possible. More recent innovations such as steroid-eluting stents decrease mucosal edema and secondary scarring. Another option for patients who fail maximal medical therapy is balloon sinus dilation or sinus ostial dilation, a procedure in which sinus outflow tracts are widened endoscopically without tissue removal. This is only

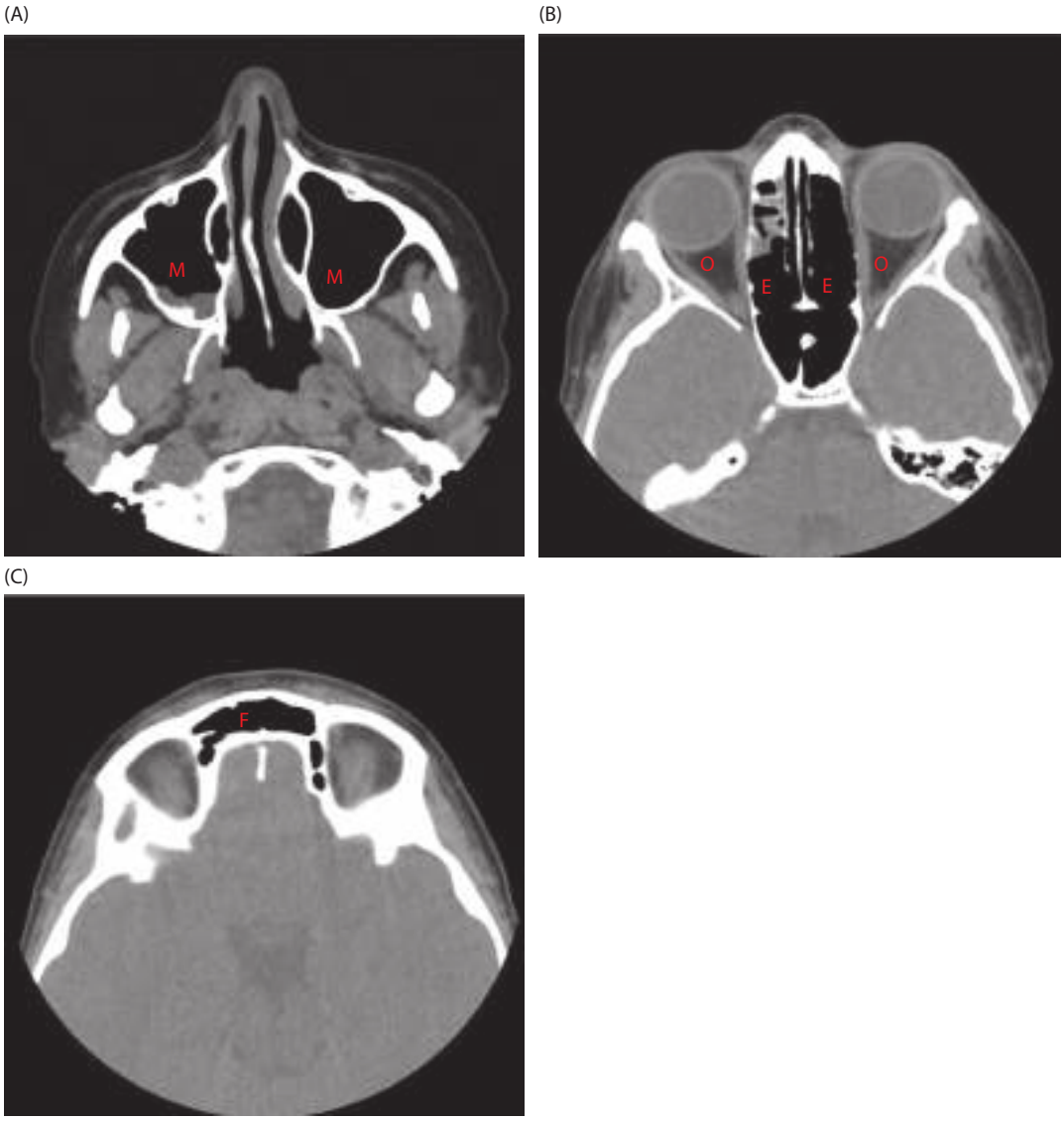


FIGURE 7.1 (A) Paired maxillary sinuses (M) with dependent fluid in the right maxillary sinus. (B) Ethmoid sinuses (E) with some right anterior ethmoid opacification and orbit (O). (C) Frontal sinus (F).

appropriate for certain patients with favorable anatomy as it generally is done as an in-office procedure with local anesthesia. Balloon dilation can be specifically useful in creating frontal sinus patency, both for patients who have not had prior surgery and patients who have had prior frontal sinusotomy with subsequent restenosis. Balloon sinus dilation has been shown to improve quality of life of patients with chronic rhinosinusitis when compared to medical therapy alone.

Complications

Complications of sinusitis are almost exclusively a phenomenon of acute sinusitis and involve spread of infection to adjacent structures. Acute ethmoid sinusitis may cause orbital infection that ranges from preseptal cellulitis to orbital cellulitis to subperiosteal orbital abscess to orbital abscess with possible secondary cavernous sinus thrombosis (Figure 7.2). Frontal sinus may precipitate meningitis or intracranial abscess. Therapy involves intravenous (IV) antibiotic therapy and possibly surgical drainage of the affected sinuses or sinuses.

Fungal sinusitis

Fungal sinusitis typically occurs in patients with immunodeficiency for any reason, including uncontrolled diabetes mellitus and patients taking immunosuppressive medications after transplant or hematologic malignancy. Treatment in these cases involves IV antifungal medications and aggressive surgical debridement. Reversal of the immunosuppression is advised if possible. Less aggressive form of

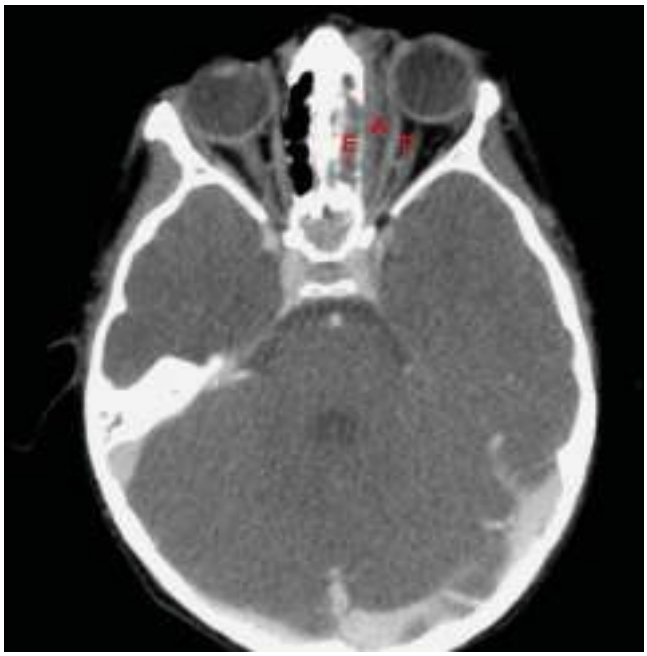


FIGURE 7.2 Axial CT demonstrating a left subperiosteal abscess (A). This image shows the opacification of the left ethmoid sinuses (E) and the abscess formation between the lamina papyracea and the periorbital contents (P).

chronic invasive fungal sinusitis has been described in immunocompetent patients.

Allergic fungal sinusitis is characterized by an allergic inflammation of the sinonasal mucosa from colonizing fungi. Tissue samples showed no mucosal invasion. The allergic response of the mucosa is immunoglobulin E (IgE)-mediated inflammation. The production of thick, tenuous, allergic mucin is pathognomonic. Histologic examination of the mucosa reveals chronic inflammation with eosinophils. The mucin demonstrates fungal hyphae characteristic of the species involved and Charcot–Leyden crystals. Treatment consists of conservative surgical debridement, either topical or systemic antifungal therapy, and topical or systemic steroids depending on the clinical situation. A fungal ball, or *mycetoma*, typically involves a single sinus, is not considered invasive, and may masquerade as chronic sinusitis. Treatment is surgical, addressing only the sinus(es) in question with no subsequent medical therapy required.

Suggested reading

Brook, I. Acute sinusitis in children. *Pediatr Clin North Am*. 2013;60:409–424.

Cryer J, Schipor I, Perloff J, et al. Evidence of bacterial biofilms in human chronic rhinosinusitis. *ORL J Otorhinolaryngol Relat Spec*. 2004;66(3):155–158.

Hoyt AEW, Borish L, Gurrola J, Payne S. Allergic fungal rhinosinusitis. *J Allergy Clin Immunol Pract*. 2016 Jul-Aug;4(4):599–604.

Lemiengre MB, van Driel ML, Merenstein D, et al. Antibiotics for acute sinusitis in adults. *Cochrane Database Syst Rev*. 2018 Sep. 10;9(9) CD006089. doi:10.1002/14651858.CD006089.pub5.

Piccirillo JF, Payne SC, Rosenfeld RM, Baroody FM, Batra PS, et al. Clinical consensus statement: Balloon dilation of the sinuses. *Otolaryngol Head Neck Surg*. 2018;158(2), 203–214.

Setzen G, Ferguson BJ, Han JK, et al. Clinical consensus statement: Appropriate use of computed tomography for paranasal sinus disease. *Otolaryngol Head Neck Surg*. 2012;147:808–816.

Shaikh Nader, Wald ER. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. *Cochrane Database Syst Rev*. 2014 Oct 27;2014(10):CD007909. doi:10.1002/14651858.CD007909.pub4.

Smith MJ. Evidence for the diagnosis and treatment of acute uncomplicated sinusitis in children: A systematic review. *Pediatrics*. 2013;132:e284–e296.

Sng WJ, Wang DY. Efficacy and side effects of antibiotics in the treatment of acute rhinosinusitis: A systematic review. *Rhinology*. 2015 Mar;53(1):309.

Wald ER, Applegate KE, Bordley C, et al. Clinical Practice Guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics*. 2013 Jul;132(1):e262–280.

8

Dental infections

Jessica Moskovitz, Bridget Hathaway, Jennifer Rubin Grandis, and Jonas T. Johnson

Introduction

Odontogenic infections and their complications may be encountered by any clinician who treats diseases of the mouth and throat. Understanding the anatomy and pathophysiology related to odontogenic infection provides the basis for knowledge of how a patient will present and how the patient needs to be treated. The average hospital cost for patients treated with odontogenic infection is $9,417. Slightly more than 4 million people with dental-related complaints presented to the emergency departments in the United States between 2008 and 2010. Although treatment of early dental infections can be less expensive and performed on an outpatient basis, delayed treatment is considerably more expensive due to the serious complications that can occur. Knowledge of signs and symptoms that indicate need for inpatient treatment of is therefore important for clinicians. Additionally, prompt diagnosis and treatment at early stages may reduce the healthcare burden related to odontogenic disease. Increasing access to regular preventative dental care may reduce the morbidity and cost associated with these infections.

Anatomy

The treatment of odontogenic infections requires an understanding of maxillomandibular dentition and the fascial spaces of the face and neck (Figure 8.1).

Dentition

Although both maxillary and mandibular teeth can become infected, infections of mandibular dentition are more common. If untreated, odontogenic infections tend to erode through the thinnest, closest cortical plate. The thinner bone in the maxilla is on the labial-buccal side, the palatal cortex being thicker. In the mandible, the thinnest region is on the lingual aspect around the molars and the buccal aspect anteriorly.

Fascial spaces of the face and neck

Fascial spaces surrounding maxillary dentition

Anatomic spaces involved by maxillary infections include the canine and buccal spaces, with the orbit and cavernous sinus less commonly affected. The canine space is that region between the anterior surface of the maxilla and the levator labii superioris (Figure 8.2). Infection of this fascial space usually results from

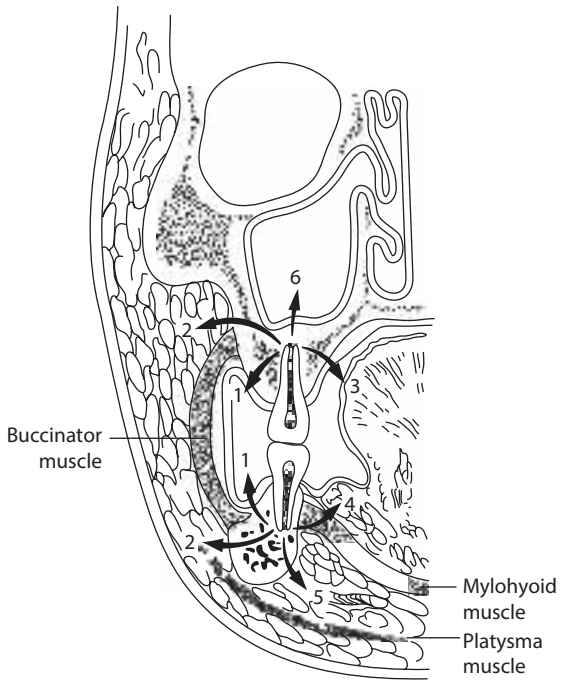


FIGURE 8.1 An odontogenic infection can express itself after erosion through jaw bone depending on the thickness of the overlying bone and the nature of the surrounding soft tissues. This illustration displays six possible locations: (1) vestibular abscess, (2) buccal space, (3) palatal abscess, (4) sublingual space, (5) submandibular space, and (6) maxillary sinus.

From Cummings CW, et al. *Otolaryngology: Head & neck surgery*, 4th ed. St. Louis: Mosby; 2005.

maxillary canine tooth infection. The buccal space is located between the buccinator muscle and the skin and superficial fascia. Infections of this space usually result from maxillary molar processes, with the premolars as the rare culprits.

Fascial spaces surrounding mandibular dentition

The primary mandibular spaces include the submental, sublingual, and submandibular fascial spaces. The submental space is that area between the anterior belly of the digastric muscle, the mylohyoid muscle, and the skin. Infection here usually results from the mandibular incisors (Figure 8.3). Medially, the sublingual and submandibular spaces are typically affected by the mandibular molars. Multiple fascial spaces can be infected simultaneously. For example, the sublingual space lies between the oral mucosa and the mylohyoid and communicates along the posterior boundary of the mylohyoid muscle with the submandibular space.

The secondary mandibular spaces include the pterygomandibular, masseteric, and temporal spaces. These fascial spaces become infected as the result of secondary spread from more anterior spaces, including the buccal, sublingual, and submandibular spaces. The pterygomandibular space lies between the medial aspect of the mandible and the medial pterygoid muscle. The masseteric space is the area between the lateral mandible and the masseter muscle, and the temporal space is superior and posterior to the pterygomandibular and masseteric spaces. Infection of these areas almost uniformly produces trismus as a result of masticatory muscle inflammation.

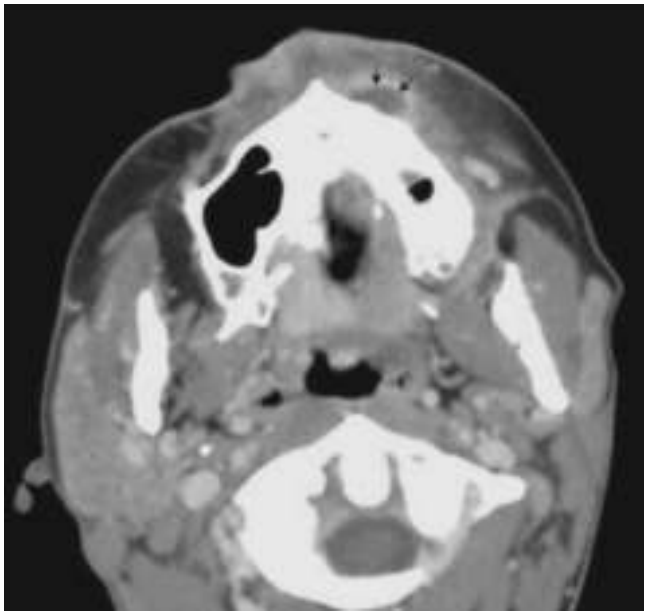


FIGURE 8.2 CT image demonstrating an abscess of the canine space (*black arrows*).

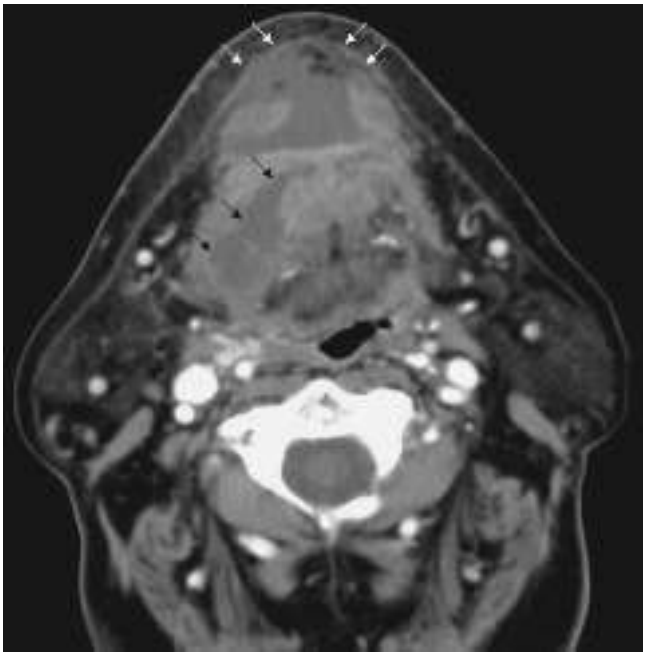


FIGURE 8.3 CT image demonstrating an abscess of the floor of mouth (*black arrows*) and submental space (*white arrows*).

Cervical fascial spaces

Odontogenic infection can extend beyond the mandibular spaces to the neck to involve the cervical fascial spaces. Infection in these spaces may progress to the deep neck spaces, which include the lateral pharyngeal (parapharyngeal) space, the retropharyngeal space, and the prevertebral space (see Chapter 10 for further detail of deep neck infections). Thirty percent of deep neck infections may result from odontogenic processes. Deep neck infections may spread distally into the mediastinum.

Pathophysiology

Most odontogenic infections are minor and self-limited, confined to the offending tooth and its apex. Under certain circumstances, however, the infectious process may break through the bony, muscular, fascial, and mucosal barriers and spread to contiguous spaces, resulting in soft-tissue infections.

Infections originate within the dental pulp, periodontal tissue, or pericoronal tissue from a carious tooth. This results in bacterial invasion and a local inflammatory response, which includes vasodilatation and edema leading to increased pressure, which exacerbates the pain and decreases the blood supply. This sequence of events exacerbates the periapical necrosis, with subsequent bacterial invasion into bone and erosion of the bony cortex into surrounding soft tissues. This nonvital pulp lacks blood supply and therefore proliferating bacteria in necrotic root canals makes it difficult for antibiotic penetration. Additionally, carious teeth result from bacterial biofilms which exhibit resistance to host defense. The spreading infection can result in a chronic sinus tract or, under the appropriate circumstances (e.g., perforation of the cortical bone above the muscular attachment), a fascial space collection.

Whether the infection is in the sublingual or submandibular space is determined by the relationship between the area of perforation and the mylohyoid attachment. Specifically, if the apex of the offending tooth is superior to that of the mylohyoid (e.g., premolars, first molar, and occasionally second molar), the sublingual space is affected; if the infection is inferior (e.g., third molar and occasionally second molar), the submandibular space is involved. Alternatively, infections involving the maxillary dentition may spread to involve the maxillary sinus and present as unilateral maxillary sinusitis. Orbital cellulitis or cavernous sinus thrombosis are unusual but serious manifestations of maxillary infection. Under such circumstances, the infection most likely spreads both by direct extension as well as hematogenously.

The microbiology of odontogenic infection reflects the normal endogenous oral flora. A large number of bacteria are contained in the mouth, particularly around the dental crevices. It has been estimated that 40% to 70% of all oral bacterial species have yet to be cultivated and phenotypically characterized. Infections that result from the spread of these organisms into surrounding soft tissue spaces are often polymicrobial and predominantly due to anaerobic bacteria.

The phyla *Firmicutes* (e.g., genera *Streptococcus*, *Dialister*, *Filifactor*, and *Pseudoramibacter*) and *Bacteroidetes* (e.g., genera *Porphyromonas*, *Prevotella*, and *Tannerella*) comprise more than 70% of the species found in dental abscesses. Other frequently identified species belong to the phyla *Fusobacteria* (e.g., genera *Fusobacterium* and *Leptotrichia*), *Actinobacteria* (e.g., genera *Actinomyces* and *Propionibacterium*), *Spirochaetes* (e.g., genus *Treponema*), *Synergistetes* (e.g., genus *Pyramidobacter*), and *Proteobacteria* (e.g., genera *Campylobacter* and *Eikenella*).

Patient evaluation and diagnostic considerations

History and physical exam

Patients with odontogenic infections commonly present with pain and swelling around the infected tooth. A sinus tract may develop with infection progression, and this is usually detected by the patient with drainage and decreased discomfort. Infectious spread into the surrounding soft tissues and fascial spaces often leads to systemic signs and symptoms such as fever, leukocytosis, and dehydration. As the infection spreads, local signs and symptoms may diminish thus obscuring the odontogenic origin of the fascial space infection. Initial evaluation should seek to determine the site and nature of the infectious process.

Signs and symptoms of fascial space involvement include swelling of the face and lateral neck, trismus, dysphagia, and airway compromise. To assess the airway for impending compromise, one should note tongue mobility, floor-of-mouth edema, uvular deviation, and lateral pharyngeal swelling.

Adjunctive testing

Imaging

Information regarding the causative dentition as well as the extent of infection may be gained through radiographic evaluation. A panoramic radiograph (Panorex) of the maxilla and mandible is useful to examine the bone morphology and presence of impacted teeth or caries. When there is clinical suspicion of infection extending to the soft tissues of the head and neck, CT or MRI is warranted.

CT with contrast is generally considered to be the first-line imaging modality given its lower cost, greater availability, and patient tolerance relative to MRI. However, in a prospective study of 47 patients, Muñoz et al. concluded that MRI was superior to CT in the initial evaluation of odontogenic infections in terms of anatomic discrimination, lesion conspicuity, and extension of the processes. MRI was also more precise in identifying the number of spaces involved. However, CT is more sensitive in detecting intralesional gas. It is yet unclear whether these advantages of MRI translate into improved patient outcomes to warrant its routine use in this setting.

Microbiology

It is often not difficult to obtain material for Gram stain and culture. One approach is needle aspiration. However, precautions should be taken to obtain the material in a sterile fashion, process it under anaerobic conditions, and make an effort to evaluate the Gram stain before starting antibiotics. Techniques for isolating and identifying anaerobic bacteria tend to be labor- and time-intensive. Molecular biology techniques including polymerase chain reaction (PCR) and pyrosequencing have enhanced our understanding of the microbiology of oral flora and odontogenic infections.

Therapeutic management

Medical

The general condition of the host (e.g., dehydration, predisposing conditions such as diabetes mellitus [DM] and immunocompromise) must be taken into consideration when devising a treatment plan. Appropriate control of blood sugar is essential. The administration of antibiotics is necessary under most circumstances and should be administered before surgical drainage or for associated cellulitis.

The choice of antimicrobial agent(s) sometimes must be made empirically and depends on the ability of the clinician to correctly predict the offending organism(s). Monotherapy is generally preferable because of reduced cost, fewer potential side effects, and greater ease of administration. Endogenous oral cavity flora most frequently leads to polymicrobial infections, and therefore antibiotics should cover both oral anaerobes and streptococci.

Penicillin G, once a first choice for odontogenic infection, is now rarely used because of the rising incidence of penicillin-resistant streptococci as well as the frequency of β-lactamase-producing *Bacteroides* species (estimated to be >30%). If one chooses a cephalosporin, it should be noted that the higher "generations" tend to sacrifice gram-positive aerobic activity for gram-negative efficacy. First-generation agents, such as cefazolin and cefoxitin, are likely more effective than other, broader spectrum drugs. Studies have shown good antibiotic susceptibility for treatment of odontogenic infections with amoxicillin, amoxicillin-clavulanate, linezolid, and clindamycin. A relatively high proportion of bacteria cultured were resistant to metronidazole, erythromycin, and azithromycin. Additionally, metronidazole is effective against oral anaerobes but not aerobic organisms and would require an additional antimicrobial. Amoxicillin or amoxicillin-clavulanate is an acceptable first-line agent for the treatment of early or mild odontogenic infections. Clindamycin is an effective alternative for penicillin-allergic patients.

Antibiotics should be administered parenterally for severe infections and in the perioperative period (e.g., 24–48 hours). Ampicillin-sulbactam is an appropriate first-line choice for parenteral therapy. Once the drainage catheters are removed and the patient is ready for discharge, the oral route of administration is adequate. Decisions regarding the duration of antimicrobial administration are made empirically, but a 2-week course usually is adequate. Macrolides should be used with caution in patients who are on other drugs that prolong the Q-T interval as this can result in a potentially lethal cardiac arrhythmia (torsades de pointes).

Surgical

Airway management

In all cases, special attention should be paid to the status of the airway. Ideally, a team of clinicians with expertise in difficult airway management is involved. In Ludwig's angina, urgent tracheotomy is usually required. Other, less rapidly progressing, maxillomandibular space infections can usually be managed with careful endotracheal intubation. Flexible fiberoptic intubation (transnasal or transoral) should be considered. If the airway compromise continues in the postoperative period, the patient should remain intubated or an elective tracheotomy should be performed.

Dental extraction

Removal of the infectious source without delay is imperative for treatment of odontogenic infections. The combination of a biofilm microenvironment in carious teeth and the lack of blood supply to necrotic pulp results in a requirement for mechanical eradication of the infectious source. This includes removal of the tooth, curettage of the socket, root canal treatment, or root scaling. Root canal treatment or root scaling may be used for restorable teeth. Dental extraction is recommended for nonrestorable teeth or restorable teeth in the setting of life-threatening infections.

The timing of dental extraction has historically been debated. The controversy has been settled for several decades as studies advocating for delayed extraction are either from the preantibiotic era or from lower level evidence studies (i.e., Level IV). Although post-antibiotic era studies were also lower level of evidence (Level III; retrospective case series), these studies noted that early extraction did not lead to central nervous system involvement or serious infection. The debate was settled with a randomized, controlled trial (Level 1b) that found severe infection was associated with delayed dental extraction. Watchful waiting with antibiotics alone is no longer considered acceptable. In patients with maxillofacial infections, extraction of the causative tooth correlates with shorter mean hospital stay compared to patients without removal of the offending tooth. Additionally, dental extraction resulted in faster resolution of biologic parameters such as axillary temperature, white blood cell count, and C reactive protein levels (Igomenakis 2015).

Incision and drainage

Evacuation of the purulent collection is the standard of care for odontogenic infections. Cellulitis may resolve with antibiotic therapy, however, the patient must be followed closely and surgery undertaken if abscess develops. Surgery may entail a minor procedure, such as drainage of a periapical abscess, or extensive debridements of adjacent fascial compartments in the case of necrotizing fasciitis.

The route of drainage should be evaluated on an individual basis. General principles to be followed include stabilization of the airway, protection of vital structures, adequate visualization at the time of drainage, copious irrigation of the abscess cavity with saline solution, and postoperative drainage of the wound. Canine and isolated sublingual space infections can usually be drained transorally. Buccal space infections can be drained transorally or extraorally with care taken to identify Stensen's duct and the buccal branch of the facial nerve. The submental space is best approached extraorally via an incision that parallels the inferior border of the mandibular symphysis. Buccal, submandibular, masseteric, pterygomandibular, and sublingual spaces can all be drained extraorally via a horizontal incision parallel to the inferior angle of the mandible.

Drainage catheters are generally used when a transcutaneous route is used and should be left in place until wound drainage has essentially ceased (≤10 mL in 24 hours). In our experience, the catheters do not serve as a route for infection (i.e., to draw bacteria inward).

Surgical emergencies

Necrotizing fasciitis

Necrotizing fasciitis is a life-threatening soft tissue infection that requires a high degree of suspicion given the lack of specific symptoms at early onset with rapid clinical deterioration. The reported hallmark for diagnosis is pain disproportionate to or in the absence of clinical exam findings. The majority of cases of necrotizing fasciitis are odontogenic in origin with a minority caused by pharyngeal etiologies or unknown/idiopathic causes. There is a propensity for development in those with immunocompromise including patients with DM, HIV, and chronic renal failure. Steroid therapy, alcoholism, intravenous (IV) drug abuse, and obesity are also risk factors. Initial physical exam signs may mimic cellulitis with tense, erythematous skin changes. Without treatment, overlying skin blisters and necrosis as well as skin anesthesia may develop. The presence of palpable subcutaneous air or air on radiographs is an indication of infection by gas-forming organisms and is pathognomic for necrotizing fasciitis. A 2018 meta analysis of 375 cases of noted that only about half (56.8%) of CT scans revealed subcutaneous air, and therefore its absence does not reliably exclude the diagnosis. Foul-smelling "dishwater pus" noted at time of surgical debridement is the most commonly cited definitive diagnostic criteria. Although the most common pathogen identified is strep, necrotizing fasciitis can also be due to polymicrobial infections.

Aggressive resuscitation and antimicrobial therapy are key to successful management; however, early surgical debridement is the single most important modality for determining patient outcome. Surgical debridement involves widely opening the neck and debriding necrotic tissue down to bleeding tissue. The wound should be packed open for observation and potential further debridement. Choice and frequency of dressing changes varies in the literature; however, several studies have shown that repeat debridement (ranging from 2.5 to 7 debridements) is usually required. Negative bacterial cultures have been reported, and surgical tissue cultures that yield the most positive results included tissue at the edge of abnormal appearing tissue. Histopathology in the early stages of disease may show dermal edema and superficial epithelial hyaline necrosis without inflammatory cells. As the disease progresses, vascular thrombosis and necrosis becomes apparent.

Early tracheostomy should be considered; however, in those with extensive involvement of the anterior and inferior part of the neck, caution should be exercised due to risk of infection tracking into the thorax. Descending cervical necrotizing mediastinitis has been reported to occur in almost one-third of patients, and the presence of mediastinal involvement should prompt consultation with a cardiothoracic surgeon. Adjunctive medical therapies that have demonstrated mortality reduction include hyperbaric oxygen therapy and IV immunoglobulin (in patients with group A strep infections).

BOX 8.1

Emergency considerations

Presence of subcutaneous air
Consider necrotizing fasciitis
Ludwig's angina—progressive severe soft-tissue edema
Consider tracheotomy

Ludwig's angina

When infection involves the primary mandibular spaces bilaterally it is known as Ludwig's angina. Patients may develop this widespread fascial space infection as a result of second or third molar infection or widespread periodontal disease. Cellulitis of the floor of mouth rapidly becomes a spreading, gangrenous process producing elevation and displacement of the tongue and brawny induration of the entire submandibular region. Airway compromise can occur precipitously (Box 8.1), hence appropriate precautions should be undertaken. Airway compromise is one of the leading causes of mortality associated with Ludwig's angina. Spontaneous sublingual hematoma, a pseudo-Ludwig's phenomenon, can occur as a complication of oral anticoagulation. Patients may have notable ecchymosis in the floor of mouth and/or anterior neck which can distinguish this scenario from infectious etiology on clinical exam. Patients should be managed with reversal of anticoagulation and securing the airway.

Conclusion

The successful treatment of odontogenic infections depends on a combination of accurate diagnosis and institution of appropriate therapy in a timely fashion. Adjunctive laboratory and radiographic tests may confirm the diagnosis and help plan the drainage procedure, but a thorough history and physical examination often

provides the clinician with sufficient information. Early recognition of potential surgical emergencies such as Ludwig's angina and necrotizing fasciitis can be life-saving.

Suggested reading

Brescó-Salinas M, Costa-Riu N, Berini-Aytés L, Gay-Escoda C. Antibiotic susceptibility of the bacteria causing odontogenic infections. *Med Oral Patol Oral Cir Bucal*. 2006;11(1):E70–E75.

Bridgeman A, Wiesenfeld D, Newland S. Anatomical considerations in the diagnosis and management of acute maxillofacial bacterial infections. *Aust Dent J*. 1996;41:238–245.

Eisler L, Wearda K, Romatoski K, et al. Morbidity and cost of odontogenic infections. *Otolaryngol Head Neck Surg*. 2013;49(1):84–88.

Flynn TR, Shanti RM, Hayes C. Severe odontogenic infections, Part 2: Prospective outcomes study. *J Oral Maxillofac Surg*. 2006;64: 1104–1113.

Flynn TR, Shanti RM, Levi MH, et al. Severe odontogenic infections, Part 1: Prospective report. *J Oral Maxillofac Surg*. 2006;64:1093–1103.

Gunaratne DA, Tseros EA, Hasan Z, et al. Cervical necrotizing fasciitis: Systematic review and analysis of 1235 reported cases from the literature. *Head Neck*. 2018; 40:2094–2102.

Igoumenakis D, Giannakopoulos N, Parara E, et al. Effect of causative tooth extraction on clinical and biological parameters of odontogenic infection: A prospective clinical trial. *J Oral Maxillofac Surgery*. 2015;73:1254–1258.

Langford FP, Moon RE, Stolp BW, et al. Treatment of cervical necrotizing fasciitis with hyperbaric oxygen therapy. *Otolaryngol Head Neck Surg*. 1995;112:274–278.

Munōz A, Castillo M, Melchor MA, et al. Acute neck infections: prospective comparison between CT and MRI in 47 patients. *J Comput Assist Tomogr*. 2001;25(5):733–741.

Siqueira JF, Rocas IN. Microbiology and treatment of acute apical abscesses. *Clin Microbiol Rev*. 2013:26(2):255–273.

Stefanopoulos PK, Kolokotronis AE. The clinical significance of anaerobic bacteria in acute orofacial odontogenic infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2004;98:398–408.

9

Salivary and lacrimal gland infections

Alexandre E. Malek, Johny Fares, and Issam I. Raad

Introduction

Salivary gland infection or inflammation, also known as sialadenitis, occurs in different age groups ranging from neonates to elderly people. It constitutes the majority of non-neoplastic diseases that involve principally the major salivary glands, which comprise the paired parotid, submandibular, and, to a lesser extent, the sublingual glands. Infections can be related to a variety of organisms including mainly bacterial, viral, or mycobacterial. Acute bacterial parotitis and submandibular sialadenitis are the most frequently reported conditions. In acute bacterial suppurative parotitis, *Staphylococcus aureus* and oral aerobes and/or anaerobes are among the most encountered pathogens. Noninfectious causes can lead to salivary glands inflammation as well, including systemic inflammatory process and, recently, sialadenitis secondary to Nivolumab has been reported. Etiologic classification of sialadenitis is outlined in Box 9.1.

The salivary glands are exocrine organs responsible for saliva secretion, which provides several biologic properties and acts as a natural barrier for infection. Saliva contains many proteins like amylase, mucins, peroxidases, and lysozymes that comprehensively play a crucial role as antimicrobials. In addition, the saliva's flow inside the salivary ducts promotes debris removal and clearance of bacteria to avoid an ascending infection.

Risk factors for salivary glands infection

The cause of sialadenitis may be secondary to a variety of local or systemic factors affecting salivary output either by decreasing production or outflow. Decreased production can be related to dehydration conditions such as decreased oral intake, bowel rest, or water restriction. Medical conditions such as malnutrition, dementia, or renal failure may predispose patients to dehydration as well. Moreover, multiple medications can be associated with decreased saliva production and can contribute to oral dryness.

Additionally, local radiation or radioactive iodine therapy and autoimmune diseases such as sarcoidosis, Sjögren syndrome, primary biliary cirrhosis, and immunoglobulin (IgG4)-related disease are accompanied with decreased saliva production. Many conditions can lead to thicker saliva, such as cystic fibrosis. The disruption of outflow may be linked to either occupational or iatrogenic injuries of the salivary gland ducts or of the ductal orifice, such as trauma or dental procedures. Decreased outflow occurs secondary to ductal obstruction due to stricture, tumors, or sialolithiasis. Many other risk factors have been identified including poor oral hygiene/dental infection, systemic infection (HIV and mumps), immunosuppression, and mucositis. These risk factors are summarized in detail in Table 9.1.

BOX 9.1

Etiologic classification of sialadenitis

Acute bacterial sialadenitis

- Acute purulent parotitis
- Acute postoperative parotitis
- Acute bacterial submandibular sialadenitis

Chronic bacterial sialadenitis

- Chronic recurrent parotitis
- Chronic recurrent submandibular sialadenitis
- Chronic sclerosing sialadenitis of submandibular gland

Miscellaneous infectious causes of sialadenitis

- Actinomycosis
- Cat-scratch disease
- Tuberculosis
- Nontuberculous mycobacterium
- Parasitic

Viral sialadenitis

- Mumps
- Human immunodeficiency virus
- Cytomegalovirus infection
- Other viruses (coxsackievirus, Epstein–Barr virus, measles, echovirus, influenza A, parainfluenza, lymphocytic choriomeningitis, adenovirus, enterovirus, human herpesvirus 6, parvovirus B19, and hepatitis C)

Granulomatous sialadenitis

- Infectious causes (tuberculosis, syphilis, tularemia, toxoplasmosis, cat-scratch disease, blastomycosis, and coccidiomycosis)
- Noninfectious etiologies (sarcoidosis, Wegener's granulomatosis, Churg-Strauss granulomatosis, or Crohn's disease)

Acute bacterial sialadenitis

Suppurative or acute bacterial sialadenitis can occur when salivary stasis permits retrograde ascending transmission or seeding of the collecting ducts of the salivary glands by the oral flora bacteria. Abscess formation can in turn arise by extension of contiguous infection or hematogenous seeding to the lymph nodes either inside or around the glands, such as the parotid. While all glands can be involved, the parotid and submandibular glands are predominantly affected. A recent study by Watanabe et al. showed the incidence of acute suppurative sialadenitis is 2.9% among end-stage cancer patients, and the submandibular gland is the most common salivary gland affected.

Acute bacterial parotitis

Suppurative parotitis or pyogenic parotitis often occurs in the setting of debilitation, dehydration, or poor oral hygiene, especially among elderly postoperative patients. Historically, this entity was called "surgical mumps" because it has been attributed to postsurgical hypovolemia and fluid imbalance, particularly in abdominal surgery or intra-abdominal trauma, despite its arising in outpatients. Other risk factors are described in Table 9.1. Neonatal suppurative sialadenitis is uncommon and is usually related to prematurity, decreased saliva production secondary to prolonged orogastric or nasogastric feeds, dehydration, sialolith, and abnormalities of salivary duct. Transient bacteremia during birth is thought to contribute to the development of neonatal acute bacterial parotitis (ABP). Unlike in adults, neonatal ABP is more frequently bilateral.

The pathogenesis is largely related to ascending contamination of the Stensen's duct by the oral flora or through bacteremia seeding to intraparotid or periparotid lymph nodes.

The clinical manifestation is characterized by sudden onset of a firm, painful erythematous swelling over the parotid gland and in the preauricular area extending occasionally to the angle of the mandible. High fevers and chills are common, while further systemic

TABLE 9.1 **RISK FACTORS FOR SALIVARY GLANDS INFECTION**

Decrease saliva production

- Dehydration (neonates, elderly, recent surgery and anesthesia, bowel rest)
- Medications (anticholinergics, antidepressants, antipsychotics, antihistamines, diuretics, antihypertensives, chemotherapeutics agents, antispasmodics, antisialagogues)
- Malnutrition
- Dementia
- Renal or hepatic failure
- Local radiation
- Radioactive iodine therapy
- Autoimmune diseases (sarcoidosis, Sjögren's syndrome, primary biliary cirrhosis, and IgG4-related disease)

Decrease saliva outflow

- Cystic fibrosis
- Occupational injury (trauma)
- Iatrogenic injury (dental procedures)
- Ductal obstruction (strictures, tumors, or sialolithiasis

Other risk factors

- Poor oral hygiene
- Dental infection
- Systemic infection (human immunodeficiency, mumps, etc)
- Immunosuppression
- Mucositis

findings such as leukocytosis with left shift, elevated sedimentation rate, and increased serum amylase are frequent. Trismus and dysphagia are reported as well. Tenderness is noted in physical exams, and, in one-half of cases, purulence expressible at Stensen's duct may be observed.

The most common pathogens responsible for ABP are quite variable and usually polymicrobial. *Staphylococcus aureus* followed by anaerobes are by far the most commonly reported pathogens, with *S. aureus* being the most frequently isolated bacteria in the setting of nosocomial (hospitalized) and community-acquired infections. Group A Streptococcus, *Streptococcus viridans*, and strict anaerobes, such as *Fusobacterium* spp., *Prevotella*, *Porphyromonas* spp., and *Peptostreptococcus* spp., may also play a major role.

Brook et al. reported that 43% of patients were diagnosed with an anaerobic infection while 57% had a mixed aerobes-anaerobes etiology. Gram-negative organisms encompassing *Klebsiella* spp., *Pseudomonas, E. coli, Proteus* spp., *Eikenella*, and *Haemophilus influenza* are common in immunocompromised and critically ill patients. Rare causes of ABP include *Salmonella* spp., *Streptococcus pneumonia, Moraxella catarrhalis, Arachnia, Treponema pallidum*, cat scratch bacillus, *Actinomyces* spp., and *Mycobacterium tuberculosis.*

The diagnosis of suppurative parotitis is made mainly by a comprehensive medical history followed by a subsequent characteristic physical examination of the findings. Laboratory studies, such an elevated serum amylase in the absence of pancreatitis, support the diagnosis made. Furthermore, imaging data (when available) are very helpful in assessing for inflammation or duct obstruction by salivary stones and in ascertaining the presence of acute suppurative parotitis, abscess, or even a solid tumor. If purulent secretions are found, bacteriological studies (Gram stain and culture) are of paramount importance in narrowing the differential diagnosis and guiding the appropriate antimicrobial therapy. If abscess is present, ultrasound-guided needle aspiration is recommended, and specimens should be sent for aerobes, anaerobes, and fungi, as well as mycobacteria.

Ultrasound, CT, and magnetic resonance sialography are all options for imaging evaluation; however, ultrasound is a preferred first choice since it can localize the inflammation of the salivary gland and pinpoint the location of stones in the duct or gland parenchyma, along with its capacity to depict and differentiate between obstructive versus nonobstructive sialoadenitis. CT scan is a very sensitive tool for distinguishing parotitis from frank abscess. Magnetic resonance sialography is superior to conventional sialography as it can be used during acute infection without requiring an injection of contrast material.

The differential diagnosis of bacterial parotitis includes viral parotitis, collagen vascular and autoimmune diseases, alcoholism, and neoplasms. Causes of parotid gland enlargement are outlined in Box 9.2.

The management of suppurative parotitis is a multidisciplinary approach which entails improving hydration, reducing modifiable risk factors, and administering appropriate intravenous (IV) antibiotics. This approach should be carried out empirically based on expected microbiology including *S. aureus, H. influenza,* and anaerobes or guided by culture and susceptibility testing when available. Surgical intervention should be considered if abscess is present or no clinical response is seen after 48 hours of empirical therapy. Importantly, to ensure adequate antibacterial coverage and appropriate selection of the initial therapy, risk factor stratification should be implemented to assess whether the patient is a normal or an immunocompromised host while taking into consideration the circumstances of community-acquired or hospital-acquired infections.

BOX 9.2

Causes of salivary gland swelling

- Acute bacterial sialadenitis
- Viral sialadenitis
- Salivary gland stones
- Salivary gland tumors (benign or malignant)
- Chronic bacterial sialadenitis
- Radioactive iodine sialadenitis
- Sarcoidosis
- IgG4-related diseases
- Sjögren's syndrome
- Sialadenosis (malnutrition, anorexia nervosa, bulimia, beriberi, pellagra, diabetes, alcoholism)
- Reaction to intravenous contrast

In community-acquired sialoadenitis among immunocompetent hosts, the preferred initial antibiotic regimen suggested is ampicillin-sulbactam or cefuroxime plus metronidazole. An alternative antistaphylococcal regimen includes nafcillin or vancomycin or linezolid is recommended based on risk factors for methicillin-resistant *S. aureus* (MRSA), along with a regimen of either ceftriaxone or levofloxacin plus metronidazole or clindamycin. Knowing the risk factors for MRSA is an important step in choosing gram-positive antibiotic coverage. These factors consist of history of IV drug use, renal failure, hemodialysis, diabetes mellitus, prior stroke, decubitus ulcers, residence in a nursing home, and history of hospitalization within the last 12 months.

For immunocompromised patients or hospital-acquired infections the spectrum of initial antibiotic regimen should have additional activity against MRSA, *Enterobacteriaceae*, and *Pseudomonas*. This could take the form of a combination of vancomycin or linezolid and one of the following antibiotics: cefepime plus metronidazole or imipenem versus meropenem or piperacillin-tazobactam. The duration of therapy is tailored to the patient's risk factors and immune status, as well as the extension of the infection; generally, patients with uncomplicated infections should receive 10 to 14 days of therapy.

Adjuvant treatment incorporates optimal oral hygiene, nutritional support, warm compresses and massage, discontinuation of anticholinergic drugs that reduce salivary flow or increase the viscosity of the saliva, and usage of sialagogic agents such as lemon juice. Irradiation of the glands is no longer recommended.

Suppurative parotitis can potentially progress and spread to deep neck and head tissue leading to local or systemic complications such as osteomyelitis, respiratory obstruction, parapharyngeal space infection, and possible septic jugular thrombophlebitis, known as Lemierre's syndrome. Other described yet relatively rare complications are facial nerve palsy or fistula.

Acute bacterial submandibular sialadenitis

Acute bacterial submandibular sialadenitis (ABSS), unlike ABP, is most commonly associated with physical obstruction of Wharton's duct either by stones or strictures. Sialolithiasis occurs in 80% of cases secondary to the several reasons that predispose to stone formation. The anatomy of submandibular salivary glands, including the ductal system, is described as lying superior to the glands, having the length and thin wall of Wharton's duct and a passage of the duct within two acute bends through the muscles, as well as a narrow orifice opening (sphincteric mechanism); the glands retain alkaline and high-calcium salt contents in submandibular gland saliva. All these factors may contribute to calculus formation, obstruction, and subsequently infection.

Clinical manifestation is usually pain and swelling in the submandibular region which occur at mealtime, with frequent history of prior episodes. Cervical lymph nodes may be present. Of interest, ABSS is mainly a community-acquired infection and is less commonly associated with hospital-associated infection or dehydration in comparison to ABP. The majority of causative organisms are a mixture of oral flora comprising *S. aureus* and *Peptostreptococcus* spp. Treatment consists of antibiotic coverage similar to ABP, optimal hydration, and salivary ductal system decompression by sialolith removal via sialoendoscopy, sialolithotomy, or sialodochoplasty.

Chronic bacterial sialadenitis

Chronic bacterial sialadenitis or recurrent bacterial sialadenitis can affect the parotid or submandibular salivary glands, and it is defined as repeated episodes of ABS that are separated by periods of remission. Of interest, recent study described the presence of bacterial biofilm in the submandibular gland sections in patients with chronic sialadenitis and suggests its role in maintaining the chronicity of sialadenitis.

Chronic recurrent bacterial parotitis

This clinical entity often follows an episode of ABS, but it may be idiopathic or is sometimes associated with Sjögren syndrome, autoimmune disease, strictures, congenital ductal abnormalities, or following viral infection. It could also be manifested secondary to trauma or foreign bodies.

Two categories of chronic recurrent bacterial parotitis (CRBP) have been described; adult and juvenile forms. Chronic juvenile recurrent parotitis is a combination of a congenital ductal malformation and ascending seeding of bacteria from the oral mouth flora. It is characterized by male predilection with unilateral parotid enlargement. This form is closely related to *Streptococcus viridans* infection, while *S. aureus* is the major bacteria in adult form. Nevertheless, other species such as *Streptococcus pneumoniae*, mixed aerobic-anaerobic oral flora, and, to a lesser extent, opportunistic organisms have been described.

Clinical manifestation is characterized by unilateral or bilateral edema of the parotid gland that can vary in duration from few days to months separated by period of remission. During exacerbation episodes, constitutional symptoms might be present with increased white blood cell count and inflammatory markers such as elevated erythrocyte sedimentation rate (ESR). Sialography is the main diagnostic tool for making the diagnosis of chronic parotitis. In addition to plain radiographs, CT sialography may provide supplementary data. Histologically, parenchymal structures are replaced by fibrosis and fat. The initial treatment should be conservative; patients with chronic parotitis should be instructed to carefully massage the involved gland in a dorsoventral direction four to six times a day and to eat sour foods to stimulate parotic secretion. Systemic antibiotics and proper oral hygiene are helpful, and sialoendoscopy seems to be an ideal treatment especially by dilation of the ductal system. In spite of medical treatment, some recalcitrant cases advocate for surgical management via parotidectomy.

Chronic recurrent submandibular sialadenitis

Chronic recurrent submandibular sialadenitis (CRSS) is reported more commonly than CRBP, generally follows an acute episode of ABSS, and is usually associated with sialolithiasis. Sialography is an important test for confirming the diagnosis by demonstrating sialadenitis and showing poor gland emptying rates, which is considered a reliable sign of poor gland function.

Treatment consists of empiric antibiotics therapy, hydration, sialogogues, and sialolithotomy if indicated. Sialoadenectomy is recommended in recurrent episodes or in nonfunctional submandibular glands.

Chronic sclerosing sialadenitis

Chronic sclerosing sialadenitis of the submandibular gland (Kuttner's tumor [KT]) is a chronic inflammatory process that produces a firm (sometimes painful) swelling in the submandibular area that mimics malignancy and is difficult to distinguish from tumor. Chronic sclerosing sialadenitis is often diagnosed only after excision of the gland. Submandibular glands are most often involved, but implication of other major and minor salivary glands has been reported.

In 29% to 83% of cases, it is associated with sialolithiasis and is most commonly seen in the elderly. It is a benign disease and no additional treatment is warranted.

Acute viral sialadenitis

Viral diseases of the salivary glands are a frequent condition mainly affecting the parotid glands. Mumps, being the most common infection, is usually accompanied by a nonspecific systemic prodrome such as fever, malaise, headache, myalgias, and anorexia. However, many other non-mumps viruses have been described and may mimic mumps clinical presentation, including influenza and parainfluenza viruses (type 1 and 3), echovirus, Coxsackie viruses (A and B), Epstein–Barr virus, and lymphocytic choriomeningitis virus. HIV, cytomegalovirus (CMV), and adenoviruses have also been identified.

Mumps

Mumps virus belongs to the genus of paramyxovirus and is by far the most common viral infection of the salivary gland leading to viral parotitis. This disease is very contagious and is transmitted by aerosol droplets coming from the saliva and nasopharyngeal secretions of an infected individual. The incubation period lasts from 2 to 3 weeks, followed by 1 to 2 days of fever, chills, and headache, which in turn is succeeded by rapid and painful swelling of the parotid gland that could be unilateral or bilateral in nature. The submandibular glands may also become involved.

In 30% to 40% of the infected patients, no clinical symptoms are noticed. Mumps is predominantly a childhood disease, and in 85% of cases, it affects children under the age of 15 years. It is more frequent in boys than in girls. Young adults may also be affected and have a more aggressive clinical course. Mumps is often preceded by a viral infection in the oral cavity or the nose, leading to viremia and hematogenous infections of the salivary glands.

Infection can be complicated by orchitis, pancreatitis, meningoencephalitis, and neurosensorial hearing loss. Laboratory studies could reveal leukopenia with relative lymphocytosis, and an elevation of serum amylase is observed as well. Serologic diagnosis can be made using a complement-binding reaction or a fourfold increase in antibody titer, usually at the end of the second week. Apart from vaccination, no effective treatment for mumps is available.

Human immunodeficiency virus

HIV can affect head and neck systems in 5% to 10% of infected patients. The clinical manifestations include xerostomia that can mimic Sjögren syndrome, parotid gland enlargement, and lymphadenopathy. Parotid HIV is a very well described clinical entity which may present as a painless gland enlargement with or without lymphoepithelial cysts. Given that the parotid gland possesses intraglandular lymph nodes, these are prone for HIV involvement, leading to reactive lymphadenopathy and sometimes to CD8 lymphocytic infiltration of the gland parenchyma, which results in cyst formation. Another condition that can occur in HIV-positive patients is benign lymphoepithelial lesion (BLLs) of the parotid glands; however, BLLs can progress to lymphoma or carcinoma. These cysts can be evaluated by ultrasound-guided fine-needle aspiration that can confirm diagnosis if cystic fluid is positive for amylase. The management of these cystic lesions consists of observation, serial drainage, or sclerotherapy. Clinicians should maintain solid tumors in the differential diagnosis as well.

Cytomegalovirus

CMV sialadenitis is rare and usually presents as pain and swelling of the salivary gland. The diagnosis is usually based on an elevated complement fixation titer of antibodies to CMV, a positive CMV titer, and detection of CMV in the salivary gland. Other viruses that produce sialadenitis are coxsackievirus, infectious mononucleosis, measles, echovirus, influenza A, parainfluenza, HIV, lymphocytic choriomeningitis virus, adenovirus, human herpesvirus 6, parvovirus B19, and Epstein–Barr virus. Most of these viral infections have a self-limiting condition which produces lifelong immunity. Chronic hepatitis C virus (HCV) infection has been associated with mild lymphocytic sialadenitis.

Miscellaneous infectious causes of sialadenitis

Actinomycosis

Actinomyces are branching, gram-positive, microaerophilic, non–acid-fast bacteria that can affect the salivary glands in 10% of cervicofacial actinomycosis cases, with the parotid gland being most frequently involved. Human actinomycosis is primarily caused by *Actinomyces israelii*, and many other species have been described such as *A. odontolyticus*, *A. naeslundii*, *A. meyeri*, *A. viscosus*, *A. propionicus*, *A. pyogenes*, and *A. eriksonii*.

The hallmark of actinomycosis is the tendency to invade the salivary glands following a tissue injury or mucosal breach, and they can usually spread without respecting anatomical barriers, which can lead to multiple fistulous tracts. As a result, odontogenic infections or salivary gland trauma are common preexisting events. The infection can take three forms of clinical presentation, the first being acute suppurative infection. The second is chronic in nature, has indolent induration, and may be misdiagnosed as a neoplasm. The third form is subacute and is manifested by a slightly tender mass attached to the mandible. Diagnosis is usually made by culturing the organism from an appropriate specimen, ideally from biopsy culture to avoid contamination. Findings of sulfur granules in histologic examination are also pathognomonic of this condition. Treatment is the same as that utilized for cervicofacial actinomycosis, including prolonged courses of antibiotics (preferred high-dose penicillin for 4 to 6 months) which are adjusted according to susceptibility testing combined with surgical intervention if indicated.

Cat-scratch disease

Cat-scratch disease (CSD) is frequently reported as a major cause of regional lymphadenopathy among children and adolescents, and it can by contiguity evolve to the salivary glands and lead to sialadenitis, mostly of the parotids. It occurs about 2 weeks following

skin inoculation by the bacteria *Bartonella henselae*, which is a gram-negative bacterium considered to be the etiologic agent in most cases. A probable diagnosis is made based on typical clinical presentation, such as proximal lymphadenopathy to inoculation site arising after recent contact with cats and fleas. Laboratory testing, including serology and polymerase chain reaction (PCR), confirm the clinical impression. Previously, antibiotics therapy in localized CSD was controversial because it is considered a self-limited disease. However, the current trend and practice is to treat all patients with CSD, even those who are immunocompetent, in an effort to prevent systemic complications since the pathogen can disseminate to vital organs and to shorten the course of the disease. For localized infection, single-drug therapy is suggested (e.g., azithromycin). For disseminated disease, a combination therapy is preferred, including two of the following medications: rifampicin, azithromycin, doxycycline, Bactrim, or gentamicin.

Tuberculous sialadenitis

Tuberculous involvement of the salivary glands is exceedingly rare and primary tuberculous infection is very unusual. Salivary glands can be involved by the hematogenous route of *Mycobacterium tuberculosis* from a distant source, such as primary pulmonary tuberculosis, or through contiguous infection by ascending lymphatic spread from cervical lymph nodes to the intraglandular lymph nodes. Two types of tuberculous sialadenitis have been described: the circumscribed or nodular form, which is more common, and the diffuse or infiltrative involvement of gland parenchyma. The pathogenesis of the former is related to lymphatic spreading to intraglandular lymph nodes and usually leads to unilateral parotid swelling, whereas the latter is related to the hematogenous route of infection.

Tuberculous sialadenitis can manifest as an acute or a chronic form producing a tumor-like lesion. Disseminated tuberculosis secondary to pulmonary tuberculosis can affect mainly the submandibular and cervical lymph nodes chain, resulting in tuberculous cervical lymphadenitis, also known as *scrofula*. Diagnosis is ideally made by the QuantiFERON-TB TB Gold test, followed by fine-needle aspiration for acid-fast bacilli cultures. Management is similar to pulmonary tuberculosis treatment, and entails combination therapy including isoniazid, rifampicin, ethambutol, and pyrazinamide. The duration of therapy depends on clinical response but usually varies between 6 and 9 months.

Nontuberculous mycobacterium sialadenitis

Atypical mycobacteria can involve the salivary glands, mainly the parotid and submandibular. The infection occurs commonly in children, but adults can also be infected, especially those in the immunocompromised state. *Mycobacterium avium intracellulare* and *M. scrofulaceum* are the main reported causative organisms. The diagnosis relies principally on culture taken from excisional biopsy of the salivary glands or lymph node. Treatment is mainly medical management, keeping surgical intervention, excision, and drainage as an adjunctive tools for medical therapy.

Parasitic salivary gland infection

Parasitic sialadenitis is extremely rare. *Paragonimus* trematodes and *Filariasis* worms have been reported to involve the salivary glands, mainly in highly endemic countries (paragonimiasis in China; filariasis in Africa and Central America). The diagnosis is made by salivary gland biopsy and other supportive laboratory findings such as peripheral eosinophilia. *Filariasis* therapy consists of antiparasitic medications, including ivermectin, diethylcarbamazine, or albendazole, combined with surgical excision of the affected area; praziquantel is administered for paragonimiasis.

Granulomatous sialadenitis

Granulomatous sialadenitis is a rare condition that may be related to infectious or noninfectious causes, localized or systemic etiologies. This condition can arise secondary to reactive regional lymph nodes and can lead to salivary parenchymal involvement. It is reported that obstructive sialadenopathy secondary to calculi or other causes (e.g., tumor with rupture of ducts and leakage of ductal contents, particularly mucin) plays a crucial role in developing a granulomatous inflammation with multinuclear foreign-body giant cells. The parotid gland is commonly involved; condition presents as painless firm nodules with noncaseous granulomas on histologic examination. Different types of granulomatous diseases affect the salivary glands, such as tuberculosis, syphilis, tularemia, toxoplasmosis, cat-scratch disease, blastomycosis, and coccidiomycosis. Xanthogranulomatous sialadenitis of the parotid gland presenting as B-cell lymphoma has also been reported. Other noninfectious etiologies include sarcoidosis, Wegener's granulomatosis, Churg-Strauss granulomatosis, or Crohn's disease. Treatment is directed against the etiology responsible for this clinical entity.

Lacrimal system infection

The lacrimal apparatus incorporates the lacrimal gland and the nasolacrimal drainage system. The lacrimal gland is responsible for producing tears, and each gland is characterized by approximately 12 to 14 lacrimal ductules. Tears on the ocular surface are drained through superior and inferior canaliculi to form a common canaliculus before entering the lacrimal sac followed by the nasolacrimal duct. The canaliculi and the lacrimal sac are prone to infections and can lead to three different types of infections: canaliculitis, dacryocystitis, and dacryoadenitis.

Canaliculitis

Canaliculitis is a clinical entity characterized by inflammation of the upper and lower canaliculus and is frequently associated with lacrimal outflow obstruction. Infection affects mainly the lower eyelid rather than the upper eyelid, and women are more susceptible than

men, which can be possibly related to the female's higher rate of dry eyes with punctal plug or cosmetics usage. For the most part, primary canaliculitis is a unilateral disease and is idiopathic in nature. However, a few predisposing factors, such as diverticulum or outflow obstruction, are described. Canaliculus blockage enhances bacterial overgrowth.

This disorder can manifest clinically as epiphora or unilateral conjunctivitis with itchiness, burning sensation, redness, and mucopurulent discharge from the punctum, and it is also associated with excessive tears. The causes of canaliculitis range from bacteria to viruses and fungi. According to a Kaliki et al. study, *Staphylococcus* spp. is the most common organism, followed by *Streptococcus* spp. and *Actinomyces* spp., whereas in other reports *Actinomyces israelii* is the most common cause reported for canaliculitis. Other organisms less frequently reported include *Fusobacterium*, *Enterobacter cloacae*, *Lactococcus lactis*, *Eikenella corrodens*, *Nocardia*, *Candida albicans*, *Pityrosporum pachydermatis*, *Aspergillus*, and *Mycobacterium chelonae*. Viruses like herpes simplex, adenovirus, and varicella zoster can also be involved.

The diagnosis is usually made clinically, but dacryocystography and biomicroscopy might support the diagnosis of canaliculitis. Gram stain and culture on appropriate media of exudative secretions help in identifying the causative organism. Treatment approach consists of systemic and topical antibiotics and punctal dilatation with canalicular expression combined with canalicular antibiotic irrigation. Although conservative treatment provides improvement, it is associated with high recurrent rates of infection among 33% of patients. Therefore, punctoplasty with canalicular curettage is highly efficient, and canaliculotomy may be indicated specifically as a method to prevent recurrence. Antibiotic treatment is outlined in Table 9.2. Delay in diagnosis may lead to chronic conjunctivitis, corneal infection, or canalicular stenosis.

Dacryocystitis

Dacryocystitis is an infection of the lacrimal sac and nasolacrimal duct, which can present either as an acute process or as a chronic infection. It constitutes the most common infection of the lacrimal apparatus and usually arises from functional or anatomic nasolacrimal duct obstructions. In the neonate period, it is often attributed to dacryocystocele and presents in the form of a duct cyst. In older infants and children, nasolacrimal duct obstruction may occur as a consequence of ethmoidal sinusitis or facial fracture. It also is common in adults older than 40, with obstruction occurring at the opening of the nasolacrimal duct into the inferior meatus secondary to nasal polyps or thickening mucosa. Dacryocystitis can be subdivided into acute and chronic forms.

Acute dacryocystitis

Acute dacryocystitis is considered a medical urgency which manifests as a rapid onset of pain, swelling, and erythema, along with tenderness and induration of the lacrimal sac below the medial canthal tendon. The microbiologic spectrum encompasses *Staphylococcus aureus, Streptococcus pneumonia, Streptococcus pyogenes, Haemophilus influenza, Escherichia coli, Proteus species*, and *Pseudomonas aeruginosa*. Anaerobes, including *Peptostreptococcus* and *Propionibacterium*, have been detected. In addition, fungal infections such as *Candida* or *Aspergillus* are reported and are associated with dacryoliths. Dacryocystitis can worsen and progress to preseptal or orbital cellulitis, meningitis, or sepsis, hence it should be treated with systemic antibiotics, warm compresses, and anti-inflammatory medications.

Chronic dacryocystitis

Chronic dacryocystitis may be asymptomatic. The patient can present with epiphora or mucopurulent drainage from the lacrimal punctum, and, in patients with tear deficiency, epiphora could be subclinical. The cause of infection is mainly secondary to mixed bacterial organisms, with *Streptococcus pneumonia* and *Staphylococcus* spp. being most common. The treatment consists of systemic antibiotics and removal of the obstruction if present; thus, dacryocystorhinostomy is indicated if chronic dacryocystitis is associated with nasolacrimal duct obstruction. The surgery may be performed either transcutaneously or through the nasal mucosa.

Dacryoadenitis

Dacryoadenitis is a condition characterized by an inflammation of the lacrimal gland that could be related to a variety of infectious and noninfectious etiologies. The route of infections can be secondary to hematogenous seeding or ascending contamination through the ductules. The microorganisms responsible

TABLE 9.2 **TREATMENT OF LACRIMAL SYSTEM INFECTION**

	Antibiotic treatment	Surgical treatment
Canaliculitis	Topical antibiotic drops plus antibiotic irrigation of canaliculi (Pen G) plus intravenous/oral Pen V or macrolides	Punctoplasty with canalicular curettage or Canaliculotomy
Acute dacryocystitis	Systemic antibiotics such as amoxicillin-clavulanate or guided by culture results	Decompression of the nasolacrimal duct and transcutaneous pus aspiration
Chronic dacryocystitis	IV antibiotics	Intranasal or transcutaneous dacryocystorhinostomy
Acute dacryoadenitis Chronic dacryoadenitis	Systemic antibiotic Directed toward specific cause	Incision and drainage if no improvement Rarely required

for infection include bacteria, viruses, fungi, and parasites. The most commonly encountered bacteria are *Staphylococcus* spp., *Streptococcus* spp., *Haemophilus influenza, Neisseria gonorrhoeae, Chlamydia trachomatis, Mycobacteria tuberculosis, M. leprae, Treponema pallidum, Lymphogranuloma venereum,* and *Bartonella henselae*. Among viral species, mumps, measles, influenza, Epstein–Barr virus, herpes zoster, herpes simplex are most often implicated. *Phycomycetes, Schistosoma haematobium*, and *Onchocerca volvulus* are reported as fungal and parasitic microorganisms. This clinical entity has also been associated with *Acanthamoeba* keratitis, Wegener's granulomatosis, sarcoidosis, and Sweet's syndrome. Another entity, known as lacrimal gland ductulitis secondary to *Actinomyces* infection, has been described in a group of patients complaining of chronic mucopurulent conjunctivitis.

Dacryoadenitis typically exhibits symptoms of localized tenderness and swelling of the lacrimal gland and is usually unilateral in nature with signs of eyelid swelling and ptosis. Clinically, patients with acute dacryoadenitis complain of severe pain in the lacrimal gland region, edema, redness, and swelling, whereas in chronic dacryoadenitis only minimal eyelid edema and mild tenderness can be observed. Management of dacryoadenitis includes symptomatic treatment with local hot compresses or systemic antibiotics in cases of bacterial illness. In viral dacryoadenitis, the treatment is supportive unless the patient has herpes simplex or herpes zoster infections; the treatment then is valacyclovir for 1 week. The standard treatment for acute idiopathic inflammatory dacryoadenitis is oral corticosteroids. Some patients might benefit from intralesional steroid injection. If symptoms persist, irradiation or cyclosporine may be an option. Surgical drainage is necessary for abscess formation.

Suggested reading

Al-Dajani N, Wootton SH. Cervical lymphadenitis, suppurative parotitis, thyroiditis, and infected cysts. *Infect Dis Clin North Am*. 2007;21(2):523–541, viii.

Bradley PJ. Microbiology and management of sialadenitis. *Curr Infect Dis Rep*. 2002;4:217–224.

Brook I. Anaerobic bacteria in upper respiratory tract and head and neck infections: Microbiology and treatment. *Anaerobe*. 2012;18(2):214–220.

Brook I. The bacteriology of salivary gland infections. *Oral Maxillofac Surg Clin North Am*. 2009;21(3):269–274.

Capaccio P, Sigismund PE, Luca N, Marchisio P, Pignataro L. Modern management of juvenile recurrent parotitis. *J Laryngol Otol*. 2012;126 (12):1254–1260.

Capaccio P, Torretta S, Osio M, et al. Botulinum toxin therapy: A tempting tool in the management of salivary secretory disorders. *Am J Otolaryngol*. 2008;29(5):333–338.

Freedman JR, Markert MS, Cohen AJ. Primary and secondary lacrimal canaliculitis: A review of literature. *Surv Ophthalmol*. 2011;56(4):336–347.

Hackett AM, Baranano CF, Reed M, et al. Sialoendoscopy for the treatment of pediatric salivary gland disorders. *Arch Otolaryngol Head Neck Surg*. 2012;138(10):912–915.

Hay-Smith G, Rose GE. Lacrimal gland ductulitis caused by probable Actinomyces infection. *Ophthalmology*. 2012;119(1):193–196.

Kaliki S, et al. Primary canaliculitis: Clinical features, microbiological profile, and management outcome. *Ophthal Plast Reconstr Surg*. 2012;28(5):355–360.

McQuone S. Acute viral and bacterial infections of the salivary glands. *Otolaryngol Clin North Am*. 1999;32(5):793–811.

Onkar PM, Ratnaparkhi CN, Mitra K. High-frequency ultrasound in parotid gland disease. *Ultrasound Q*. 2013;29(4):313–321.

Raad II, Sabbagh MF, Caranasos GJ. Acute bacterial sialadenitis: A study of 29 cases and review. *Rev Infect Dis*. 1990;12:591–601.

Schrøder SA, et al. Morphological evidence of biofilm in chronic obstructive sialadenitis. *J Laryngol Otol*. 2018;132(7):611–614.

Stafford JA, Moore CA, Mark JR. Acute sialadenitis associated with 2017–2018 influenza A infection: A case series. *Laryngoscope*. 2018;128(11):2500–2502.

Takahashi S, et al. Nivolumab-induced sialadenitis. *Respirol Case Rep*. 2018;6(5):e00322.

Tan VE, Goh BS. Parotid abscess: A five-year review–clinical presentation, diagnosis and management. *J Laryngol Otol*. 2007;121(9) 872–879.

Watanabe H, Odagiri T, Asai Y. Incidence of acute suppurative sialadenitis in end-stage cancer patients: A retrospective observational study. *J Pain Sympt Mgmt*. 2018;55(6):1546–1549.

Zhang G, et al. Acute submandibular swelling complicating arteriography with iodide contrast: A case report and literature review. *Medicine*. 2015;94.33:e1380.

10

Deep neck infections

Jeremy D. Gradon

Introduction

Infections of the deep spaces of the neck are becoming more common. Hospital admissions for such infections in the United Kingdom more than doubled between 1996 and 2005. These infections are often life-threatening, and even stable-appearing patients are at grave risk for sudden clinical decompensation. Clinical severity is related to both the anatomic nature of the space involved, due to the numerous adjacent critical structures, and the nature of the hosts themselves (Figure 10.1). The elderly and diabetics are more likely to have complicated infections than their counterparts. Mortality rates range from 7% to as high as 40% for deep neck structure infections.

Patients with deep neck infections are frequently either diabetic, HIV-infected (irrespective of antiretroviral therapy status), or immunocompromised in some other way. In addition, a history of injection drug use (IDU), neutropenia, or exogenous steroid therapy is common. A dental source is frequently present. On rare occasions, deep neck space infection may complicate congenital abnormalities or cancers of the head and neck. Cases complicating traumatic airway intubation have also been reported. An example of a deep neck infection with associated necrotizing fasciitis is shown in Figure 10.2.

Deep neck infections are usually polymicrobial, reflecting the oral cavity source of most of these infections. When associated with IDU, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is the most likely organism encountered. The microbiology of these infections is shown in Box 10.1. The increasing prevalence of multidrug-resistant gram-negative rods, especially in the nosocomial setting, complicates therapy. Wound botulism as a complication of deep neck infection may occur in IDUs.

Attempts to devise an algorithm-based approach to help with clinical management decision-making have been made. Factors considered important include the presence/absence of airway obstruction, depth of neck involvement, ability to open mouth, ability to swallow, and any recent antibiotic usage. A scoring system reflecting these factors has been proposed (see Gallo et al. in the "Suggested reading" list).

Relevant anatomy of the deep neck spaces

The deep neck spaces are bound by a variety of anatomic landmarks and are anatomically distinct. However, all have the potential for communicating with each other, and thus infection may spread from one region to another during the course of the illness. Thus, involvement of multiple anatomically distinct deep neck spaces may occur concurrently.

It is important to delineate the various spaces clinically and radiologically so that appropriate management can be provided. The main spaces are as follows:

- The submandibular space (composed of two spaces separated by the mylohyoid muscle: the sublingual space, which is superior, and the submaxillary space, which is inferior).

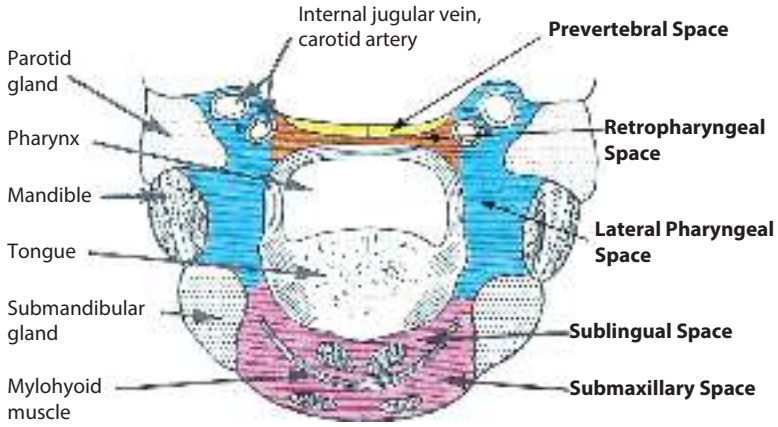


FIGURE 10.1 Oblique section of top of neck. Note contiguity of spaces and resultant potential for spread.
Adapted with permission from Hollingshead WH. *Anatomy for surgeons. Vol. 1: The head and neck*, 2nd ed. New York: Harper & Row; 1968.

- The lateral pharyngeal spaces (anterior and posterior)
- The retropharyngeal spaces (including the retropharynx, the prevertebral space, and the "danger space").

FIGURE 10.2 Recurring deep neck abscess of lateral pharyngeal space caused by *Nocardia asteroides* in an HIV-infected patient with a CD4 count of 86/mm^3.

Radiologic testing in deep neck infections

CT and MRI are excellent diagnostic tools for deep neck infections. However, it must be appreciated that these patients are critically ill with a risk for acute airway obstruction at any time in their clinical course. Thus, appropriately trained personnel must accompany these patients when they go for such scans. Equipment must be brought along to allow immediate airway protection should acute airway obstruction develop in (or on the way to) the radiology department.

In the postoperative setting, rim enhancement (>50%) of fluid collections in the neck seen on CT scanning correlates with abscess formation.

Submandibular space infections (Ludwig's angina)

This bilateral infection of the submandibular space most commonly arises from infection of the posterior two molar teeth. There is the

BOX 10.1

Pathogens encountered in deep neck space infections

Common

Viridans and other streptococci
Staphylococcus aureus (including MRSA)
Prevotella, Fusobacterium, Bacteroides, Porphyromonas

Rare

Moraxella
Haemophilus spp.
Pseudomonas spp.
Actinomyces spp.

BOX 10.2

Management of deep neck space infections

NEVER LEAVE THE PATIENT UNATTENDED out of a monitored unit.
Protect the airway—experienced otolaryngology evaluation is essential.
CT or MRI of mouth, neck, mediastinum to evaluate for drainable collections, airway compression, vascular complications, or mediastinal involvement
Dentist/oral surgery evaluation for a (removable) dental source of infection
Correct underlying medical issues: maximize glycemic control, correct neutropenia, taper steroids (if feasible), etc.

rapid onset of fever, mouth pain, and drooling of oral secretions. Soft-tissue spread of infection causes woody induration of the submandibular space and a stiff neck. Because the tongue may be displaced upward and backward, acute airway obstruction may develop. Tracheal compression due to surrounding edema is another cause of airway failure in this infection. Fatalities continue to be reported in this condition. Management is outlined in Boxes 10.2 and 10.3 and complications in Box 10.4.

BOX 10.3

Antibiotic therapy[a]

Nonimmune compromised host[b]

Penicillin G 3 million units IV q4h plus IV metronidazole 500 mg q6h
or
Ampicillin-sulbactam 3 g IV q6h
or
Clindamycin 600 mg IV q8h plus moxifloxacin 400 mg IV q24h

Immune-compromised host[b]

Meropenem 500 mg–2 g IV q8h plus vancomycin 1 g IV q12h
or
Piperacillin–tazobactam 4.5 g IV q6h plus vancomycin 1 g IV q12h

[a] These antibiotic recommendations are only examples of appropriate regimens. Multiple other combinations of antibiotics providing polymicrobial coverage for both aerobes and anaerobes are appropriate as well.

[b] In the setting of injection drug use, HIV infection, or the recent use of antibiotics (within ≤3 months), add anti-MRSA coverage with either vancomycin, ceftaroline, daptomycin, or linezolid.

BOX 10.4

Complications of deep neck space infections

Submandibular space infection

Acute airway obstruction
Aspiration pneumonia
Tongue necrosis
Carotid artery erosion
Jugular vein thrombosis
Spread to the lateral pharyngeal space

Anterior lateral pharyngeal space

Spread of infection to the parotid gland

Posterior lateral pharyngeal space

Carotid artery erosion
Suppurative jugular vein thrombosis
Cranial nerve palsies (IX–XII)

Retropharyngeal space

Respiratory distress
Spread to cervical vertebrae

Danger space

Spread of infection to mediastinum
Spread of infection to the pleural space

Prevertebral space

Spread of infection along the length of the vertebral column

Lemierre's syndrome

Jugular venous thrombosis
Septic pulmonary emboli
Empyema
Septic arthritis

Lateral pharyngeal space infections (anterior and posterior)

These are the most common forms of deep neck space infection. Infections of the lateral pharyngeal spaces can result from preexisting submandibular space infections or may develop secondary to dental, salivary gland, lymph node, or retropharyngeal space infections. IDU, with the patient attempting to access deep neck (jugular) veins with nonsterile needles, is the most common cause of lateral pharyngeal space infections in the urban setting.

Patients present with fever, neck pain, and rigors. If the anterior portion of the lateral pharyngeal space is involved, then trismus may develop. This may mimic the cephalic form of tetanus.

However, posterior lateral pharyngeal space infection is not associated with either trismus or visible neck swelling. Management is outlined in Boxes 10.2 and 10.3 and complications in Box 10.4.

Retropharyngeal space infections

The retropharyngeal space

Patients present with fever, sore throat, dysphagia, systemic toxicity, and neck stiffness. Inspection of the retropharynx will frequently demonstrate bulging or swelling of the retropharyngeal soft tissues. On occasion, the lesion may penetrate the posterior pharynx and pus may be visible on the anterior wall of the retropharynx. Infection may occur as a complication of local pharyngeal infection or be due to hematogenous seeding from a distal site. The infection may be due to dental infection, follow direct spread from acute cervical vertebral osteomyelitis, or follow penetrating trauma to the area. Diagnosis can be difficult, resulting in management delay and development of deep structure complications. The differential diagnosis is shown in Box 10.5.

The "danger space"

The "danger space" is an anatomical potential space that connects the deep neck spaces with the mediastinum. Access to the mediastinum is via the pretracheal fascia to the parietal pericardium and posterior mediastinum via the "danger space" from the retropharynx. As a result of this connection, acute bacterial mediastinitis may develop as a consequence of deep neck space infection. Other predisposing factors for mediastinal extension of a deep neck infection include older age, involvement of two or more deep neck spaces, and diabetes.

In addition, postoperative mediastinal infections may track up to the retropharynx and present as an apparent primary neck infection.

The prevertebral space

This fascial plane runs from the base of the skull to the coccyx along the anterior borders of the vertebrae. Thus, infection may spread from the retropharyngeal space to the whole length of the vertebral column. Management is outlined in Boxes 10.2 and 10.3 and complications in Box 10.4.

BOX 10.5

Differential diagnosis of retropharyngeal space infections

- Bacterial meningitis
- Cervical vertebral osteomyelitis
- Pott's disease
- Calcific tendonitis of the neck muscles
- Inflammatory tumor/neoplasm
- Mediastinal infection with spread via the "danger space"

BOX 10.6

Management of Lemierre's syndrome

- IV antibiotics (as shown in Box 10.3)
- Drainage of metastatic abscesses (other than septic pulmonary emboli) *Rarely*: ligation and resection of involved jugular vein (for unrelenting sepsis)
- No clear role for anticoagulation

Lemierre's syndrome

Lemierre's syndrome is an eponym describing internal jugular vein septic thrombophlebitis. It is the most common vascular complication of parapharyngeal space infection. The most commonly encountered cause is the anaerobe *Fusobacterium necrophorum*. Other causative bacteria include *Bacteroides*, MRSA, anaerobic streptococci, and other assorted mouth flora.

This infection classically affects young adults and is preceded by a sore throat followed by fever, systemic toxicity, and tenderness to palpation along the angle of the jaw and sternocleidomastoid muscle. Trismus is not present. As a consequence of this endovascular infection, bacteremia develops, with associated septic pulmonary emboli, empyema formation, and septic arthritis.

Routine screening of throat swabs for *Fusobacterium* in 15- to 24-year-olds presenting with pharyngitis has been suggested but is not a standard of care at present.

Lemierre's syndrome can also develop as a complication of attempts to access the jugular vein either for intravenous line placement or for purposes of IDU. The management of Lemierre's syndrome is outlined in Box 10.6.

Carotid artery erosion

This may occur as a complication of almost any deep neck space infection. Initially, this entity may be difficult to recognize due to the tight fascia binding the carotid artery. Once a false aneurysm has developed the patient may develop "herald bleeding" from the nose, mouth, or ears. Once major bleeding occurs death is common. Treatment involves urgent vascular surgical repair, and the risk of stroke is high. Successful cases of treatment with endovascular stenting for infection-induced carotid pseudoaneurysm have been reported.

Suggested reading

Alansari K, Sheikh R, Sheehan PZ, Joseph V, Hoffman RJ. Confluent lateral pharyngeal and peritonsillar MRSA infection in an infant. *Pediatr Emerg Care*. 2018;34:e161–e164.

Gallo O, Mannelli G, Lazio MS, Santoro R. How to avoid life-threatening complications following head and neck space infections: An algorithm-based approach to apply during times of emergency. When and why to hospitalize a neck infection patient. *J Laryngol Otol*. 2018;132:53–59.

Gouveia C, Mookherjee S, Russell MS. Wound botulism presenting as a deep neck infection. *Laryngoscope*. 2012;122:2688–2689.

Huang TT, Tseng FY, Liu TC, et al. Deep neck infection in diabetic patients: Comparison of clinical picture and outcomes with nondiabetic patients. *Head Neck Surg*. 2005;32:943–947.

Huang TT, Tseng FY, Yeh TH, et al. Factors affecting the bacteriology of deep neck infection: A retrospective study of 128 patients. *Acta Otolaryngol*. 2006;126: 396–401.

Kang SK, Lee S, Oh, HK, et al. Clinical features of deep neck infections and predisposing factors for mediastinal extension. *Korean J Thorac Cardiovasc Surg*. 2012;45:171–176.

Liu C-F, Weng S-F, Lin Y-S, et al. Increased risk of deep neck infection among HIV-infected patients in the era of highly active antiretroviral therapy: A population based follow up study. *BMC Infect Dis*. 2013;13:183. doi:10.1186/1471–2334–13–183.

Mark R, Song S, Mark P. Taking heed of the "danger space." Acute descending necrotising mediastinitis secondary to primary odontogenic infection. *Br Med J Case Rep*. 2018: doi:10.1136/bcr-2018-225019.

Miller CR, VonCrowns K, Willoughby V. Fatal Ludwig's angina: Cases of lethal spread of odontogenic infection. *Acad Forensic Pathol*. 2018;8:150–169.

Ridder GJ, Technau-Ihling K, Sander A, et al. Spectrum and management of deep neck space infections: An eight year experience of 234 cases. *Otolaryngol Head Neck Surg*. 2005;133:709–714.

Wang CP, Ko JY, Lou PJ. Deep neck infection as the main initial presentation of primary head and neck cancer. *J Laryngol Otol*. 2006;120:305–309.

Section 3

Clinical Syndromes: Eye

11

Conjunctivitis

Elmer Y. Tu

Conjunctivitis is a nonspecific term used to describe inflammation of the ocular surface and conjunctiva from either infectious or noninfectious causes. Infectious conjunctivitis is most commonly due to exogenous inoculation of the mucous membranes lining the surface of the eye and eyelid, resulting in an activation of a local inflammatory response. The vast majority of cases are acute but it may also present as chronic or recurrent. Although most cases of acute infectious conjunctivitis are self-limited and result in few long-term sequelae, appropriate evaluation and therapy are indicated with specific presentations.

Clinical features

The hallmark of conjunctivitis is injection or hyperemia of the conjunctival vessels, resulting in a red eye as well as tearing and/or mucopurulent discharge. Conjunctivitis may also result in complaints of irritation, foreign-body sensation, mattering or crusting of the eyelids, and mild visual blurring primarily due to alterations of the tear layer. The local inflammatory response may manifest as conjunctival lymphoid follicles or vascular papillae, eyelid edema, and/ or preauricular adenopathy. Complaints of severe eye pain, photophobia, significant visual loss, or referred pain should alert the examiner to the possibility of other, more ominous, etiologies. Similarly, loss of normal corneal clarity, either diffuse or focal, proptosis, pupillary abnormalities, conjunctival scarring, or restriction of eye movement are criteria for a detailed ophthalmic evaluation (Table 11.1).

Etiology

Numerous studies have demonstrated that, regardless of the etiology, acute conjunctivitis follows a benign course and results in few sequelae even without specific antibiotic therapy. Because characteristic signs and symptoms can distinguish bacterial and viral syndromes, the diagnosis of conjunctivitis is based largely on clinical history and examination. Cultures are normally reserved for neonatal or hyperacute conjunctivitis or in patients with a course greater than 2 to 3 weeks, classified as chronic conjunctivitis. A history of contact with other patients with conjunctivitis, bilateral involvement, or exposure to groups of children is associated with the more contagious viral agents. Signs of preauricular lymph node swelling (with the exception of hyperacute or chlamydial conjunctivitis), a follicular palpebral conjunctival reaction, and clear discharge or copious tearing are also more consistent with acute viral conjunctivitis. A papillary conjunctival reaction, mucopurulent discharge, and the lack of local lymph node swelling is more suggestive of bacterial conjunctivitis. When indicated, diagnostic workup consists of conjunctival swabs for Gram and other histologic stains as well as culture.

TABLE 11.1 **RED EYE: DIFFERENTIAL FEATURES**

	Conjunctivitis			Keratitis			
	Bacterial	**Viral**	**Allergic**	**Bacterial**	**Viral**	**Iritis**	**Glaucoma (acute)**
Blurred vision	0	0	0	+++	0 to ++	+ to ++	++ to +++
Pain	0	0	0	++	0 to +	++	++ to +++
Photophobia	0	0	0	++	++	+	+ to ++
Discharge	Purulent + to +++	Watery + to ++	White, ropy +	Purulent +++	Watery +	0	0
Injection	+++	++	+	+++	+	0 to + (limbal)	+ to ++ (limbal)
Corneal haze	0	0	0	+++	+ to ++	0	+ to +++
Ciliary flush	0	0	0	+++	+	+++ to +++	+ to ++
Pupil	Normal	Normal	Normal	Normal or miotic (iritis)	Normal	Miotic	Mid-dilated Nonreactive
Pressure	Normal	Normal	Normal	Normal	Normal	Normal, low or high	High
Preauricular nodes	Rare	Usual	0	0	0	0	0
Smear	Bacteria PMNs	Lymphs	Eosinophil	Bacteria PMNs	0	0	0
Therapy	Antibiotics	Nonspecific	Nonspecific	Antibiotics	Antivirals (if herpes)	Cycloplegia Topical steroids	Medical or surgical

+, Mild; ++, moderate; +++, severe; PMNs, polymorphonucleocytes.

Viral conjunctivitis

Acute conjunctivitis, defined as less than 2 to 3 weeks duration, is most commonly viral, especially in adults. Adenovirus is a commonly identified pathogen in outbreaks of acute viral conjunctivitis. Although usually associated with types 8 and 19, epidemic keratoconjunctivitis (EKC) has been associated with several other serotypes and is highly contagious, spread by direct contact from hand to eye. In addition to the classic signs of viral conjunctivitis, patients with EKC may develop an immune keratitis consisting of corneal subepithelial infiltrates approximately 2 or 3 weeks after the onset of the conjunctivitis. The corneal inflammation results in complaints of foreign-body sensation, photophobia, and, possibly, decreased vision sometimes lasting days to months. Pharyngoconjunctivitis has a similar ocular presentation but is associated with serotypes 3 and 7 and includes fever and pharyngitis. Viral cultures are reserved for tracking large outbreaks because results usually are available after symptoms have subsided. The recent introduction of an in-office, rapid, reproducible adenovirus antigen screening test should prove to be of more clinical utility. The virus may remain viable on surfaces for many days to weeks, making control of outbreaks problematic. True EKC may remain highly transmissible from patient to patient for 2 weeks or more, and, therefore, requires strict hygiene instruction as well as isolation precautions, especially during the phase of copious discharge. Acute hemorrhagic conjunctivitis associated with enterovirus 70 and Coxsackievirus A24 is a highly transmissible follicular conjunctivitis with preauricular adenopathy with the added feature of subconjunctival hemorrhages (Figure 11.1). Currently available topical antivirals are not efficacious in any of these entities, making primary treatment supportive with topical lubricants, cool compresses, and topical nonsteroidal anti-inflammatory drugs (NSAIDs). Topical corticosteroids have been used cautiously in patients with debilitating symptoms of EKC-related keratitis, but their use is controversial.

Either herpes simplex type 1 or 2 may result in a primary follicular conjunctivitis seen in children and young adults. Primary conjunctivitis is normally unilateral with a palpable preauricular lymph node associated with a classic vesicular eyelid or periorbital eruption (Figure 11.2). Systemic antivirals are indicated for primary infection. Because vision-threatening sequelae are associated with corneal involvement, topical trifluridine 1% five to nine times per day or topical ganciclovir five times per day may also be added to either treat or reduce the risk of herpes simplex virus (HSV) keratitis by

FIGURE 11.1 Self-limited acute hemorrhagic conjunctivitis.

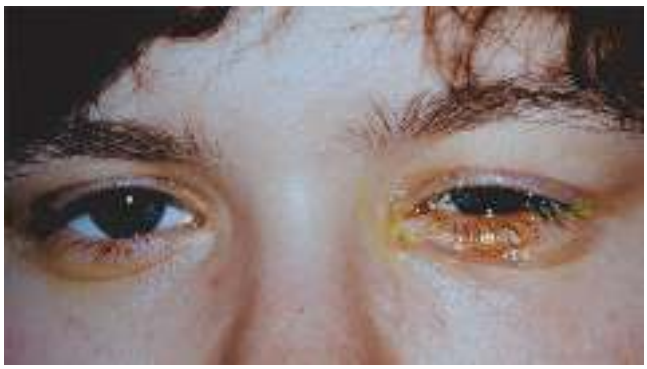


FIGURE 11.2 Primary herpes simplex blepharitis and conjunctivitis.

shortening the duration of the HSV conjunctivitis. Recurrence is common.

Chronic viral conjunctivitis may be associated with molluscum contagiosum, usually seen in children. The chronic follicular conjunctivitis is caused by viral shedding into the eye from an eyelid or periorbital molluscum, characteristically a pearly white nodule with an umbilicated center (Figure 11.3). These lesions are typically small and multiple and spread by direct contact. Immunocompromised individuals may present with much larger lesions. Treatment of the molluscum lesion by incision and curettage of its center or excision is curative of the associated conjunctivitis.

Bacterial conjunctivitis

Most bacterial conjunctivitides are self-limited, have low morbidity, and respond well to most available topical broad-spectrum antibiotics, obviating the need for microbiologic identification. Definitive evaluation and specific treatment is, however, required in hyperacute conjunctivitis, a rapidly progressive, purulent, destructive infection, and neonatal conjunctivitis to avoid local and systemic complications more common to these two entities.

FIGURE 11.3 Molluscum contagiosum chronic follicular conjunctivitis.

Hyperacute conjunctivitis

Hyperacute conjunctivitis is usually associated with *Neisseria* species, most commonly *Neisseria gonorrhoeae* in newborns and young sexually active adults. A copious, rapidly accumulating mucopurulent discharge, intense redness, and periorbital swelling are characteristic of hyperacute conjunctivitis. It is one of the few acute bacterial conjunctivitides that develops a preauricular lymphadenopathy. Rapid corneal and conjunctival penetration can result in severe corneal ulceration and ocular destruction if left untreated. It is considered a true ocular emergency. This potential for ocular complications and systemic infection with *N. gonorrhoeae* necessitates microbiologic identification as well as systemic antibiotic therapy (see Table 11.2). Local sterile saline lavage can be symptomatically helpful. Because of a significant incidence of coinfection, systemic therapy directed against *Chlamydia* infection is recommended in these cases (see below). Less commonly, *Neisseria meningitidis* may result in hyperacute conjunctivitis in a similar, but muted, presentation. The infection may be a primary conjunctivitis but is more likely secondary to systemic meningococcemia, requiring aggressive systemic therapy to prevent systemic complications.

Neonatal conjunctivitis

Conjunctivitis occurring within the first month of life is termed neonatal conjunctivitis and is either nosocomial or contracted during passage through the birth canal. The pathogens most commonly identified include *Chlamydia trachomatis* (30–50%), *Staphylococcus aureus*, and *N. gonorrhoeae*, with *Streptococcus pneumoniae*, *Haemophilus* spp., and *Pseudomonas* also identified. Prophylaxis with a single topical application of antibiotic within the hour of delivery has drastically reduced the incidence of neonatal conjunctivitis. The original solution of 1% silver nitrate (*Crede prophylaxis*) has been largely supplanted by topical erythromycin 0.5% or tetracycline 1% ointment both for better

TABLE 11.2 **SYSTEMIC TREATMENT OF GONOCOCCAL CONJUNCTIVITIS**

Adults	**Dosage**
Ceftriaxone (drug of choice)	1 g IM, single dose
Ciprofloxacin	500 mg PO, single dose
Ofloxacin	400 mg PO, single dose
Spectinomycin	2 g IM, single dose
Children (≤ 45 kg)	**Dosage**
Ceftriaxone	125 mg IM, single dose
Spectinomycin	40 mg/kg IM (max = adult dosage), single dose
Neonates	**Dosage**
Ceftriaxone	25–50 mg/kg IV or IM (max = 125 mg), single dose

coverage for *Chlamydia* and for a lower incidence of toxicity. Signs and symptoms are not helpful in discerning between these infections, necessitating microbiologic identification to direct appropriate therapy.

Infection with *N. gonorrhoeae* causes hyperacute conjunctivitis 1 to 13 days after birth and constitutes an ocular emergency. Clinical signs, symptoms, and treatment are similar to those seen in adults as described above. The proper use of neonatal prophylaxis reduces the incidence of gonococcal conjunctivitis to less than 2% in infected children born to infected mothers.

Neonatal inclusion conjunctivitis is caused by *C. trachomatis* and presents 5 to 14 days after birth. Signs may include lid swelling, redness, water, or mucopurulent discharge. In some cases a pseudomembrane may occur. Diagnostic workup is detailed below. Ocular infection can be associated with pneumonia and/or otitis media in up to 50% of patients, necessitating both topical and systemic therapy consisting of oral erythromycin or erythromycin ethylsuccinate 50 mg/ kg/day in four divided doses.

Most other bacterial infections will respond to a topical broad-spectrum antibiotic such as erythromycin, sulfacetamide, aminoglycoside, or fluoroquinolone.

HSV may also result in ophthalmia neonatorum either as an isolated conjunctivitis/ keratitis or as part of a serious systemic neonatal infection. Prophylaxis of the mother with acyclovir or valacyclovir has been shown to reduce viral shedding during delivery. This combined with cesarean section, in the presence of active genital herpes, has reduced the incidence of HSV neonatal infection. Transmission may, however, still occur in asymptomatic individuals and should be considered in the differential of neonatal conjunctivitis. Classic vesicular lesions are usually noted on the eyelid with a concomitant follicular conjunctivitis. Dendritic lesions of the cornea indicate HSV keratitis with the potential for loss of vision secondary to corneal scarring. Intraocular involvement may lead to more serious ocular damage. Although HSV type 2 is more common, HSV type 1 has also been isolated. Superficial scraping for smear and culture is helpful but not integral to diagnosis. Treatment includes systemic antivirals as well as topical trifluridine 1% nine times per day or topical ganciclovir five times per day. Other forms of neonatal viral conjunctivitis are otherwise uncommon.

Acute bacterial conjunctivitis

Overall, the majority of acute conjunctivitis is viral, except in the pediatric population, where more bacterial pathogens are seen. Clinical features include a mild to moderate mucopurulent discharge, a papillary conjunctival inflammatory response, injection (hyperemia), and initial unilaterality. With few exceptions (see hyperacute conjunctivitis, chlamydia in this chapter), routine bacterial conjunctivitis does not result in preauricular adenopathy. Cultures and smears are not normally performed in its management, but, in prospective series, gram-positive bacteria, *S. pneumoniae*, *Streptococcus viridans, S. aureus*, and *Haemophilus* predominate. Gram-negative bacteria are seen less frequently. *S. pneumoniae* may cause a bilateral conjunctivitis with characteristic small petechial hemorrhages of the conjunctiva. Seen more commonly in children, *Haemophilus* may cause discoloration of the involved eyelid described as "violaceous" and create significant upper eyelid edema resulting in a characteristic S-shaped upper eyelid.

Treatment of acute bacterial conjunctivitis with any of a number of broad-spectrum topical antibiotics will achieve local concentrations that can easily overcome even mild to moderate resistance. The average duration of untreated acute bacterial conjunctivitis is 2 to 7 days. Topical antibiotics have been shown to shorten the overall course when administered early in the course of infection and to improve clinical and microbiologic signs of disease. Addition of antibiotics later in the course after day 4 is of limited benefit. Broad-spectrum antibiotics are administered four to six times daily for 5 to 7 days (see Table 11.3). In adults

TABLE 11.3 **COMMON TOPICAL OPHTHALMIC ANTIBIOTICS AND STEROID FORMS**

Antibiotic	Common brand names	Form	Steroid-containing combination product brand name
Sulfacetamide	Bleph-10	Drop/ointment	Blephamide, Vasocidin
Erythromycin	Generic	Ointment	None
Bacitracin	Generic	Ointment	None
Bacitracin–polymyxin B	Polysporin	Ointment	
Polymyxin B–trimethoprim	Polytrim	Drop	None
Neomycin–polymyxin B		Drop/ointment	Maxitrol, Cortisporin
Tetracycline–polymyxin B	Terramycin	Ointment	None
Gentamicin	Garamycin	Drop/ointment	Pred-G
Tobramycin	Tobrex	Drop/ointment	Tobradex, Zylet
Ciprofloxacin	Ciloxan	Drop/ointment	None
Ofloxacin	Ocuflox	Drop	None
Levofloxacin	Quixin	Drop	None
Gatifloxacin	Zymar	Drop	None
Moxifloxacin	Vigamox	Drop	None

presenting with conjunctivitis, it has been suggested that a delay in treatment for 3 to 4 days, instituted only with a lack of resolution, would significantly reduce the unnecessary use of topical antibiotics in viral or self-limited bacterial cases with no significant impact on overall outcome. Although unnecessary, the use of antibiotic–steroid combinations (Table 11.3) may speed symptomatic relief but may potentiate serious masquerading conditions and should, therefore, be used with caution if the diagnosis is in question. Because of a relationship between Haemophilus conjunctivitis and acute otitis media or other involvement, the addition of appropriate systemic antibiotics is strongly considered, especially if systemic signs are present.

Chronic bacterial conjunctivitis

Conjunctivitis persisting for greater than 2 weeks is considered chronic and requires more detailed ophthalmic examination as well as Gram and Giemsa staining and culture. Chronic or recrudescent bacterial conjunctivitis may persist because of characteristics of the causative organism or a persistent local or external reservoir of the organism not exposed to normal ocular surface defense mechanisms. Although contaminated prosthetic devices such as contact lenses may be a source for pathogen reintroduction, the most common reservoir is the eyelids in the form of blepharitis, dacryocystitis, or, rarely, dacryoadenitis.

Blepharitis, or eyelid margin inflammation, is most commonly associated with chronic colonization by *S. aureus* or epidermidis and is characterized by eyelash debris, eyelid margin thickening, and telangiectasias (Figure 11.4). Angular blepharitis refers to infection of the lateral canthus causing inflammation and irritation of the eyelid skin and is associated with *Moraxella lacunata*. Seen more commonly in alcoholics and immunocompromised individuals, it may also result in conjunctivitis and keratitis. Swabs for Gram stain demonstrate the classic "double boxcar" gram-negative organisms. A concomitant conjunctivitis may accompany any form of blepharitis. Signs and symptoms are similar to other forms of bacterial conjunctivitis and respond to lid hygiene and topical antibiotic ointment such as erythromycin, bacitracin, or sulfacetamide at bedtime.

FIGURE 11.4 *Staphylococcus aureus*-related chronic blepharoconjunctivitis.

Chlamydial conjunctivitis

Serotypes A to C are associated with trachoma, a follicular bacterial conjunctivitis that because of its chronicity results in scarring of the superior tarsus. These cicatricial changes may lead to entropion and trichiasis, inward turning eyelashes, resulting in chronic corneal trauma and scarring. Seen primarily in endemic areas of the developing world, it is one of the most common causes of blindness. Diagnostic workup consists of conjunctival swabs/scrapings for culture or direct immunofluorescence. Courses of systemic erythromycin, doxycycline 100 mg twice daily for 7 days, or a single 1-g oral dose of azithromycin are effective and curative, but because of its endemic nature, whole community programs are required to prevent recurrent reinfection. Alternatives include erythromycin, ofloxacin, and levofloxacin.

Adult inclusion conjunctivitis is also caused by *C. trachomatis* (serotypes D through K). The conjunctivitis is concurrent with, but may occur independent of, active genital infection. Transmission to the eye is by direct contact with contaminated secretions. Nonspecific symptoms of tearing, foreign-body sensation, photophobia, and eyelid edema are presenting complaints. *Chlamydia* causes a follicular conjunctivitis with preauricular lymphadenopathy, but unlike trachoma, the lower eyelid is normally more involved. As in trachoma, systemic azithromycin or doxycycline is effective but also requires appropriate evaluation and treatment of sexual contacts.

Miscellaneous causes

In addition to *Neisseria* spp. and *Chlamydia* spp., several other forms of conjunctivitis may be related to systemic infection. Parinaud's oculoglandular syndrome is the association of a follicular conjunctivitis, conjunctival granuloma, and an ipsilateral lymphadenopathy. Cat scratch disease caused by *Bartonella henselae* is the most common cause of Parinaud's and is transmitted by contact with an infected cat. The conjunctival granuloma may be single or multiple and is surrounded by intense inflammation accompanied by ipsilateral head, neck, or axillary lymphadenopathy. Other causes of Parinaud's include tularemia, sporotrichosis, tuberculosis, syphilis, and coccidioidomycosis (Table 11.4). Evaluation should include a detailed history of exposures and appropriate serologic tests and systemic cultures. Treatment is directed toward the underlying process.

Chronic use of any topical ophthalmic medication may result in ocular medicamentosa. Signs and symptoms include tearing, redness, photophobia, and irritation, masquerading as an infectious conjunctivitis. Although it is most commonly associated with over-the-counter vasoconstrictors, it is also seen with topical antibiotics and may cause a self-perpetuating conjunctivitis until medication use is discontinued. Other etiologies should be considered in chronic conjunctivitis, including neoplasm, allergy, toxicity, autoimmune disease, and unusual pathogens.

TABLE 11.4 **CAUSES OF PARINAUD'S OCULOGLANDULAR SYNDROME**

Disease	Agents
Cat scratch disease	*Bartonella henselae*
Tularemia	*Francisella tularensis*
Sporotrichosis	*Sporotrichum schenckii*
Tuberculosis	*Mycobacterium tuberculosis*
Syphilis	*Treponema pallidum*
Coccidioidomycosis	*Coccidioides immitis*
Paracoccidioidomycosis	*Paracoccidioides brasiliensis*
Actinomycosis	*Actinomyces israelii, A. propionicus*
Blastomycosis	*Blastomyces dermatitidis*
Infectious mononucleosis	Epstein–Barr virus
Mumps	Paramyxovirus
Pasteurellosis	*Pasteurella multocida (septica)*
Yersinia infection	*Yersinia pseudotuberculosis Yersinia enterocolitica*
Glanders	*Burkholderia mallei*
Chancroid	*Haemophilus ducreyi*
Lymphogranuloma venereum (LGV)	Chlamydial LGV agent L, L_2, L_3
Rickettsiosis (Mediterranean spotted fever)	*Rickettsia conorii*
Listerellosis	*Listeria monocytogenes*
Ophthalmia nodosa (noninfectious)	Lepidoptera (caterpillars) Tarantula hairs

Suggested reading

American Academy of Ophthalmology. *Conjunctivitis, Preferred Practice Pattern*. San Francisco, CA: American Academy of Ophthalmology; 2003.

Buznach N, Dagan R, Greenberg D. Clinical and bacterial characteristics of acute bacterial conjunctivitis in children in the antibiotic resistance era. *Pediatr Infect Dis J*. 2005;24:823–828.

Cortina MS, Tu EY. *AAO Focal Points: Antibiotic Use in Corneal and External Eye Infections*. San Francisco, CA: American Academy of Ophthalmology; 2011.

Mah FS. New antibiotics for bacterial infections. *Ophthalmol Clin North Am*. 2003;16:11–27.

Rubenstein JB. Disorders of the conjunctiva and limbus. In: Yanoff M, ed. *Ophthalmology*. Philadelphia, PA: Mosby; 1999: 5.1.2–5.1.11.

Sambursky R, Tauber S, Schirra F, *et al*. The RPS adeno detector for diagnosing adenoviral conjunctivitis. *Ophthalmology*. 2006;113:1758–1764.

Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database Syst Rev*. 2006;(2): CD001211.

Stern GA. *AAO Focal Points: Chronic Conjunctivitis*, Part 1. San Francisco, CA: American Academy of Ophthalmology, 2012.

Stern GA. *AAO Focal Points: Chronic Conjunctivitis*, Part 2. San Francisco, CA: American Academy of Ophthalmology, 2012.

Tarabishy AB, Hall GS, Procop GW, Jeng BH. Bacterial culture isolates from hospitalized pediatric patients with conjunctivitis. *Am J Ophthalmol*. 2006;142:678–680.

12

Keratitis

Elmer Y. Tu, Francis S. Mah, and Jules Baum

Keratitis is an ocular emergency that can lead to severe visual disability and requires prompt diagnosis and treatment. Sequelae can vary in severity from little or no visual loss to corneal scarring, perforation, endophthalmitis, and loss of the eye. Although the corneal surface is awash with microorganisms of the normal flora, an intact corneal epithelium and ocular defense mechanism serve to prevent infection in the normal eye. Although some organisms such as *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Corynebacterium diptheriae*, *Listeria*, and *Shigella* can penetrate an intact epithelium, all others require damage to the epithelial layer to invade the cornea. Several risk factors predispose the cornea to infection. Dry eyes from Sjogren syndrome, Stevens–Johnson syndrome, or vitamin A deficiency can result in bacterial keratitis. Prolonged corneal exposure from ectropion, lagophthalmos, or proptosis can lead to secondary infection. Entropion and trichiasis resulting in epithelial defects put the cornea at risk. Neurotropic keratopathy from cranial neuropathy, prior herpes simplex, or zoster infections predispose to secondary infections. Some systemic conditions such as chronic alcoholism, severe malnutrition, immunosuppressive drug use, immunodeficiency syndromes, and malignancy can impair immune defenses and allow infection by unusual organisms. Prior ocular surgery such as penetrating keratoplasty or refractive procedures is also a risk factor. Trauma is a common predisposing factor of bacterial keratitis, especially for patients at the extremes of age and in developing countries. Injury to the corneal surface and stroma allows invasion of normal flora as well as organisms harbored by foreign bodies.

Contact lens wear is the most common established risk factor for bacterial keratitis in developed countries. All types of contact lenses have been linked to infection, with extended-wear soft lenses conferring greater risk than daily wear hard or soft lenses. Corneal changes from contact lens use include an induced hypoxic and hypercapnic state promoting epithelial cell derangement and allowing bacterial invasion. Contact lenses also induce dry eye and corneal hypesthesia. Overnight rigid gas-permeable lens use for orthokeratology has also been associated with bacterial keratitis, but with a disproportionately high incidence of *Acanthamoeba* keratitis.

Although there are geographic variations in the order of incidence, the most common pathogenic organisms associated with bacterial keratitis include *Staphylococcus* species, *Streptococcus* species, *Pseudomonas aeruginosa*, and enteric gram-negative rods. A 5-year review of bacterial keratitis isolates from Pittsburgh showed a change in distribution with a decrease in gram-positive organisms, whereas gram-negative isolates remained stable (Figure 12.1). In South Florida, an increase in gram-positive isolates with a decrease in gram-negative isolates over a 30-year period has been reported. *Pseudomonas aeruginosa* is commonly associated with contact lens-related bacterial keratitis, causing up to two-thirds of cases, although a decline in the frequency of *P. aeruginosa* isolates in these patients has been noted. Nontuberculous mycobacteria are being reported with increasing frequency as a cause of infectious keratitis after laser *in situ* keratomileusis (LASIK). Although the reported incidence of infection after LASIK is low, this condition is a management challenge requiring proper diagnosis and treatment. Bacterial colonization of the eyelid and conjunctiva is normal and helps reduce opportunities for pathogenic strains from gaining a foothold. Host defense mechanisms can be overcome, however, and this leads to serious ocular morbidity if the pathogen is not treated properly. Although the clinical manifestations of corneal infections may be characteristic of certain pathogens, further laboratory evaluation with cultures and antibiotic susceptibility testing provides a definitive diagnosis and more focused treatment after empirical therapy has been initiated.

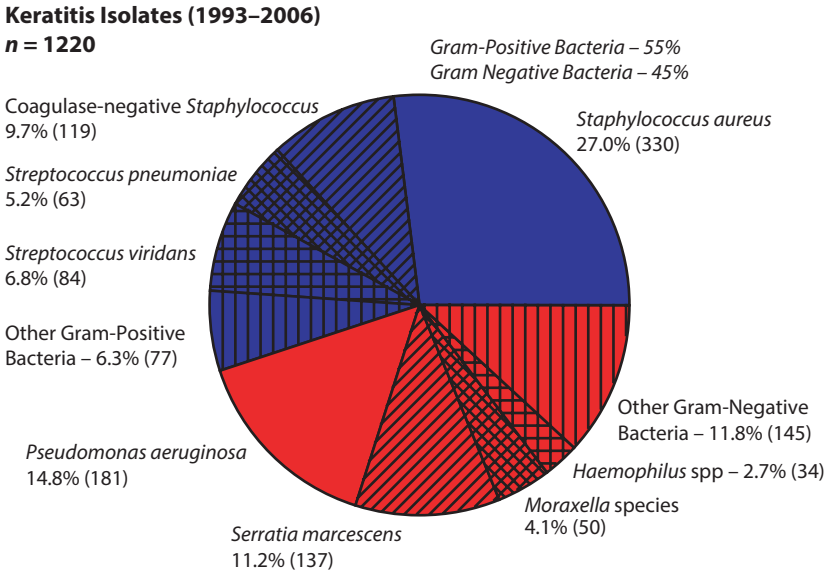


FIGURE 12.1 Keratitis isolates (1993–2006).

Clinical features

The presenting symptoms, clinical history, and exam findings may suggest an infectious keratitis but are seldom pathognomonic for a particular organism. The presenting signs of bacterial keratitis vary depending on the virulence of the organism, duration of infection, structural status of the cornea, and host inflammatory response.

Common presenting symptoms include pain, decreased vision, tearing, and photophobia. Eyelid edema, conjunctival hyperemia with a papillary reaction, and chemosis are typical findings. A corneal epithelial defect with adherent mucopurulent exudate and underlying stromal infiltrate is a hallmark sign for infectious keratitis (Figure 12.2). Multiple focal infiltrates can be seen with contact lens use or with polymicrobial infections. Migration of inflammatory cells causes a diffuse cellular infiltration adjacent to and within the ulcerated stroma. Ananterior chamber reaction can range from mild cells and flare to a marked hypopyon (Figure 12.3). A cornea damaged from prior disease can present with less distinct signs and symptoms. Pre-existing corneal scars, epitheliopathy, or inflammation confuse the picture as does prior use of antibiotics and corticosteroids. On examination, all ocular abnormalities should be documented in detail to help track the clinical course on subsequent visits. Repeat measurements of the size of the epithelial defect, the depth of the stromal infiltrate, and the severity of inflammation can be used to assess the effectiveness of treatment.

Nontuberculous mycobacterial keratitis has been reported with increasing frequency after LASIK, including several clusters of cases. In two recent reviews of post-LASIK corneal infections, *Mycobacterium* represented the most common etiologic organism. The isolated subtypes include the fast-growing *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium fortuitum*, and *Mycobacterium mucogenicum*, as well as the slow-growing *Mycobacterium szulgai*. Non-tuberculous keratitis after LASIK is characterized by a delayed onset with an indolent course. Time of onset from fast-growing organisms averaged 3.4 weeks after the procedure, whereas the slow-growing *M. szulgai* can present 6 to 24 weeks after surgery. Symptoms can range from a mild foreign-body

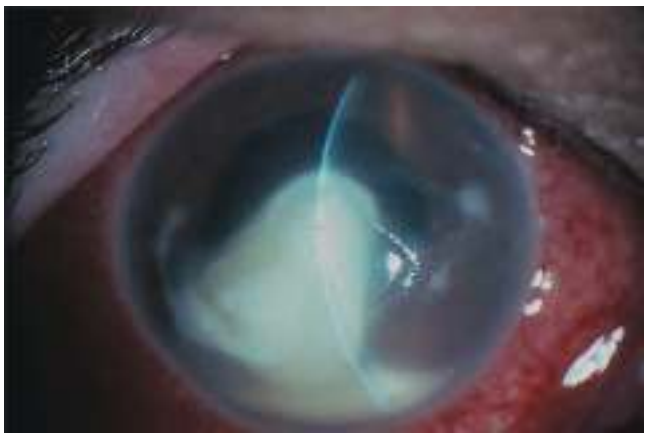
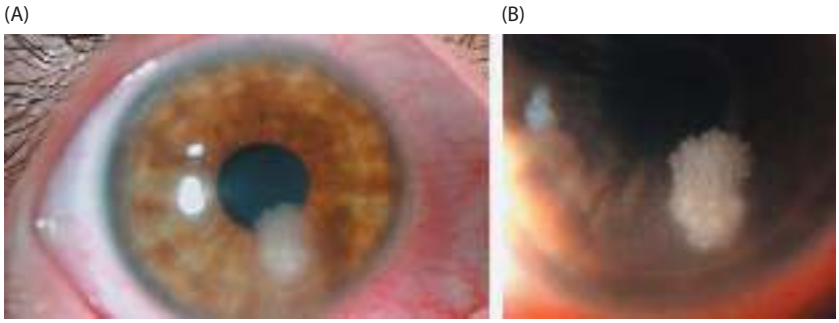


FIGURE 12.2 Infectious keratitis.

FIGURE 12.3 Hypopyon.



FIGURES 12.4 (A and B) Infectious crystalline keratopathy.

sensation to pain, redness, photophobia, and decreased vision. The infiltrate, which can be multiple, begins in the interface and spreads to adjacent stroma of the flap and stromal bed. Anterior perforation through the flap can occur with progression of infection. The location can be central, paracentral, or peripheral. In addition to a focal infiltrate, a cracked windshield appearance of infectious crystalline keratopathy has been reported (Figures 12.4A and B).

Diagnostic techniques

Currently, routine culture of corneal infections is not the usual practice in the community. A small peripheral ulcer may be treated empirically, but a large, purulent, central ulcer that extends to the middle to deep stroma should be cultured. In addition, ulcers that are atypical or clinically suspicious for fungal, mycobacterial, or amebic infections or are unresponsive to initial broad-spectrum antibiotics warrant cultures. Topical anesthesia with proparacaine hydrochloride is preferred because it has fewer antibacterial properties than other topical anesthetics that might interfere with culture yields. A sterile platinum spatula is used to scrape the leading edge as well as the base of the ulcer while carefully avoiding contamination from the lids and lashes. Organisms such as *Streptococcus pneumoniae* are more readily recovered from the ulcer edge, whereas other organisms such as *Moraxella* are characteristically recovered from the base. The scrapings are inoculated onto solid media (blood, chocolate, and Sabouraud's agar) by streaking a row of Cs. New material is recovered for each row. Scrapings are also placed on microscope slides and stained with Gram and Giemsa stains. Special stains include Ziehl–Neelsen acid-fast stain for *Mycobacterium*, *Actinomyces*, and *Nocardia*. Acridine orange is a fluorescent dye that may be helpful in identifying bacteria when yields are low, but this stain does not yield classification information that Gram stain provides.

In vivo confocal microscopy may be helpful in atypical, nonbacterial corneal infections where the organisms are larger and not as amenable to culture or identification. In cases of deep stromal suppuration that is not readily accessible or a progressive microbial keratitis unresponsive to therapy, a corneal biopsy may be warranted. A round 2-mm to 3-mm sterile disposable skin trephine is used to incise the anterior corneal stroma, and lamellar dissection is performed with a surgical blade. The specimen is then ground in a mortar with trypticase soy broth and plated on media.

Treatment

Routes of administration

The topical application of drugs with eyedrops is the preferred method of treatment of bacterial keratitis. Increased drug penetration can be achieved by higher concentrations, more frequent applications, and by the typical presence of an epithelial defect. Fortified antibiotics are made by mixing the powdered drug or diluting the parenteral form with artificial tears or balanced salt solution. These freshly prepared solutions remain stable for up to a week without significant loss of activity. Although ointments prolong corneal contact time and lubricate the ocular surface, peak corneal concentrations may be limited when compared with solutions. They also retard the absorption of antibiotics delivered in eyedrop form. Ointments can be used as adjunctive therapy at bedtime in less severe cases.

The need for other routes of antibiotic administration in bacterial keratitis is rare. Subconjunctival injections may not have a therapeutic advantage over topical solutions. However, they may be indicated in certain clinical situations such as imminent perforation or spread of infection to adjacent sclera, especially when patient compliance is an issue. Soft contact lenses and collagen shields can act as drug depot/ delivery devices and aid in sustaining high corneal drug levels. These "bandage" contact lenses may also provide protection to promote reepithelialization. Systemic therapy is indicated for gonococcal infections as well as for young children with severe *H. influenzae* or *P. aeruginosa* keratitis. Systemic antibiotics are also indicated for perforations and scleral involvement.

Empiric therapy

Because bacterial keratitis can rapidly progress and threaten vision, treatment should begin when an infectious process is suspected to limit further damage in an effort to preserve vision. Topical broad-spectrum antibiotics are initially used and later modified according to culture results, antibiotic susceptibilities, and clinical response. For severe cases, combination therapy with fortified β-lactam (cefazolin 50 mg/mL) and aminoglycoside (tobramycin or gentamicin 14 mg/mL) (Figure 12.5) provides adequate coverage of both gram-positive and -negative organisms that cause bacterial keratitis. Vancomycin (50 mg/mL) can be substituted for cefazolin in cases of penicillin allergy or resistance in *Staphylococcus* species. Because of

FIGURE 12.5 Topical aminoglycosides are combined with β-lactam therapy.

a high prevalence of methicillin resistance in some centers, vancomycin instead of cefazolin is utilized as a first-line agent. A loading dose is achieved with a drop every 5 minutes for five applications. Antibiotic is then continued every 30 minutes to 1 hour around the clock for several days and then rapidly tapered once control of the infection has been achieved.

Single-agent therapy with fluoroquinolones has previously been shown to be as effective as combination therapy in treating bacterial keratitis. The widespread systemic use of the second (ciprofloxacin and ofloxacin) and third (levofloxacin) generation fluoroquinolones has, however, led to the emergence of resistance in several bacterial species, including *Pseudomonas aeruginosa*. The fourth-generation fluoroquinolones, gatifloxacin and moxifloxacin, have been developed to improve coverage of gram-positive and atypical mycobacterial pathogens. They require two mutations to establish resistance and, therefore, are more effective against gram-positive organisms that already have a single mutation and are resistant to older generation fluoroquinolones. Unfortunately, large surveys have noted that the vast majority of methicillin-resistant *Staphylococcus aureus* is also resistant to all currently available topical ophthalmic fluoroquinolones.

Regardless of the susceptibility profile, a favorable response to empiric therapy merits continuing the treatment. Positive signs of clinical improvement include decreased pain and discharge, consolidation of the stromal infiltrate, decreased anterior chamber reaction, and corneal reepithelialization. Culture and antibiotic susceptibility results can be used to focus therapy against the offending organism or to discontinue unnecessary drugs. Clinical improvement may not be seen during the first 2 days due to increased inflammation and suppuration from bacterial exotoxins. Toxicity from topical medications can also mask changes. A lack of improvement or clinical worsening after 48 hours may warrant repeat cultures, although concomitant antibiotic therapy will decrease yields. Topical therapy can be tapered as the clinical picture improves.

Management of nontuberculous mycobacterial keratitis after LASIK can be challenging and requires aggressive treatment. The flap should be lifted for smears and culture as well as for soaking of the stromal bed and flap with antibiotics. Fortified amikacin, clarithromycin, and azithromycin are the drugs of choice. Fourth-generation fluoroquinolones have also been shown to be effective against mycobacterial keratitis. Combination therapy is recommended due to emergence of resistance on monotherapy. Lack of clinical improvement warrants repeat culture and tailoring of antibiotics accordingly. Flap amputation may also be necessary to allow increased antibiotic penetration.

Adjunctive therapy

Bacterial keratitis is often associated with severe pain. Pain control with analgesics may provide not only comfort but also better compliance with the difficult regimen of around-the-clock topical drop instillation. Cycloplegic agents should also be used to decrease discomfort from ciliary spasm and to prevent synechiae formation. Cyanoacrylate glue can be used to reinforce an area of corneal thinning, a descemetocele, or a small perforation. A "bandage" contact lens is placed after the glue hardens. This procedure allows for further treatment of the infection and inflammation while postponing surgery. A corneal patch graft is an alternative for small perforations, whereas larger necrotic perforations require a therapeutic penetrating keratoplasty. Surgical interventions are most successful after patients have received therapeutic dosing of antibacterial drugs prior to surgery.

Corticosteroids may play a role in treating bacterial keratitis with their potential for reducing the host inflammatory response and resultant corneal scarring but this must be balanced by their potential to inhibit corneal wound healing. Other adverse effects may include potentiation of microbial replication, recrudescence of infection, steroid-induced glaucoma, and cataract formation. The use of corticosteroids prior to the initiation of effective antimicrobial therapy is associated with a significantly poorer outcome in bacterial keratitis and their use in eyes with pre-existing corneal disease increases the risk of the development of ulcerative keratitis. The only prospective, randomized trial of corticosteroid administration in treated bacterial keratitis failed to show any increase in adverse events with corticosteroid use, but also did not demonstrate a visual benefit at 3 months. General guidelines for the use of corticosteroids include: (1) consider use only in those patients with vision-threatening infections in or around the central cornea, (2) corticosteroids should be used only after establishing effective antibiotic therapy with an appropriate response of the infection, (3) continue use of concomitant antibiotics, and (4) do not use steroids if the infection is not responding appropriately to topical antibiotics or if there is suspicion for an atypical or nonbacterial pathogen.

Herpetic keratitis is the most common cause of corneal blindness in developed nations. Herpes simplex virus (HSV) can manifest as a blepharitis, conjunctivitis, epithelial keratitis, stromal keratitis, limbitis, endotheliitis, uveitis, or retinitis. As elsewhere, in

immunocompetent individuals, the infection is usually self-limited, but once established in any facial dermatome will become latent in the trigeminal ganglia. Recurrences may occur for a patient's lifetime in any dermatome including the eye and periocular region and visual loss is strongly associated with the number of recurrences and location within the cornea. Pediatric patients have a high rate of corneal scarring, increasing in severity with the age of first onset. Both HSV-1 and HSV-2 have been detected with HSV-1 marginally more common in eye infections. There is often a history of labial or genital herpes as well as a history of a recurrent, nonspecific red eye or frank vesicular lesions in the periorbital region.

HSV keratitis may be bilateral in a minority of cases (<10%) but is usually unilateral. The initial corneal infection may be minimally symptomatic and is characterized by a dendritic epithelial lesion with terminal bulbs which stain with Rose Bengal but may also be geographic. This usually will leave a ghost imprint on the anterior stroma. Subsequent recurrences may be either epithelial, stromal, endothelial or some combination thereof. Stromal HSV keratitis appears inflammatory with either a diffuse stromal edema and interstitial keratitis or a disciform keratitis reminiscent of *Acanthamoeba* keratitis. Isolated corneal edema may be characteristic of associated endotheliitis and elevated intraocular pressure seen with HSV trabeculitis. Most patients will have some loss of corneal sensation which may lead to an unstable epithelium and dry eye.

Treatment for the initial and recurrent episodes may be either topical or systemic. Currently available topical agents include trifluridine and ganciclovir as well as acyclovir, which is available outside of the United States. Significant toxicity can be seen with trifluridine and treatment with any topical agent should be limited to 7 to 10 days after which a reassessment should be done as to whether findings are either still due to active infection or due to the complications of neurotropic keratitis or medication toxicity. Systemic therapy consists of acyclovir, valacyclovir, or famivir in the same doses used for dermatologic therapy and is as effective as topical therapy without the local side effects. Treatment has been shown to reduce the duration of the infection by 1 to 2 days but has no preventive effect in reducing recurrences or progression to stromal keratitis. However, long-term maintenance oral antiviral therapy has been shown to reduce the number of recurrences of herpetic eye disease. Corticosteroids may be used in stromal keratitis to reduce pain and discomfort while the patient is on effective antiviral therapy.

Other viruses in the herpes family can also cause keratitis, including herpes zoster (HZV), Epstein–Barr, and cytomegalovirus. Of these, HZV is the most commonly recognized and like HSV may cause a retinitis, uveitis, epithelial keratitis, and stromal keratitis initially occurring within 3 months of an episode of Vth nerve zoster. Clinical findings are similar to HSV, but the pseudodendrites are lacking in terminal bulbs and keratitis may be treated with corticosteroids, which are a contraindication in HSV epithelial keratitis. The neurotropic keratitis seen with HZV is often more profound than with HSV. As in HSV, initial episodes should be treated with dermatologic treatment doses of oral antivirals for zoster. Subsequent "recurrences" are largely inflammatory, but some epithelial lesions may require topical antivirals for resolution. Vaccinations for HZV should be approached with caution in a zoster ophthalmicus patient for fear of reactivation, which has been reported. In other patients, however, vaccinations should prove to partially protect from episodes of shingles.

Acanthamoeba keratitis is a rare opportunistic infection that affects an estimated 18 to 20 patients per million contact lens wearers per year in the United Kingdom and more recently in the United States where there are approximately 36 million contact lens users. Acanthamoebae are ubiquitous protozoa found in both soil and water that exist in two forms: trophozoites (the active form) and cysts (the inactive form). In stressful environments, trophozoites transform into cysts within hours that are resistant to extremes of temperature, pH, and desiccation. Because the cysts are notoriously difficult to kill, the infestation of the corneal stroma is very difficult to eradicate. Indeed, only one class of commonly compounded ophthalmic medications, the biguanides (polyhexylmethylbiguanide [PHMB], chlorhexidine, pentamidine), has cystocidal activity.

The initial report of *Acanthamoeba* keratitis in 1973 occurred in a non contact lens wearer who sustained eye trauma. The infection remained rare until the mass market introduction of soft contact lenses was followed by an outbreak of infection in wearers in the late 1980s, largely attributed to nonsterile homemade saline contact lens care solutions. More than 85% of all acanthamoeba infections are in contact lens wearers with additional risk factors of ocular trauma, corneal transplantation, and exposure to contaminated lake water, sea water, or hot tubs. Starting in 2003, an alarming increase in the rate of *Acanthamoeba* keratitis has been observed, prompting the Centers for Disease Control and Prevention (CDC) and academic centers to attempt to identify a cause which persists despite the identification and recall of an at-risk contact lens solution, AMO Complete Moisture Plus, in 2007.

Acanthamoeba infection presents with similar nonspecific symptoms as bacterial keratitis. Pain that is out of proportion to clinical findings is classic but not universal. Early corneal infection manifests as epithelial involvement, including elevated epithelial lines that may appear as dendritic, punctuate epithelial erosions, microcysts, and epithelial haze (Figure 12.6). Stromal findings,

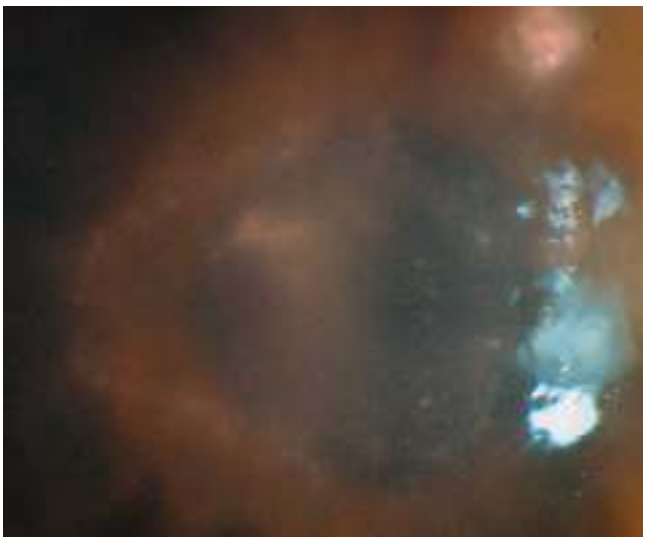


FIGURE 12.6 Epithelial haze.

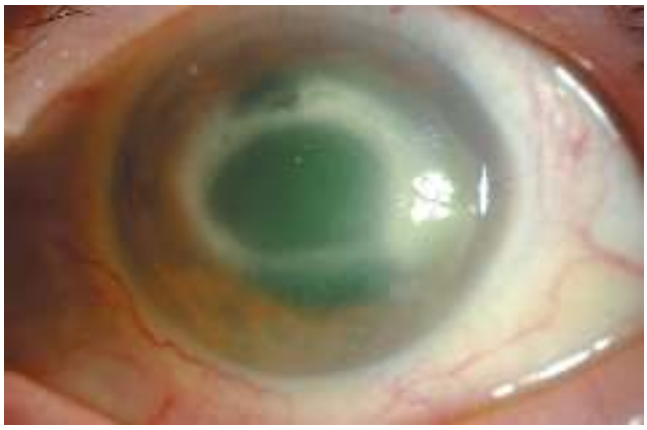


FIGURE 12.7 Ring infiltrates.

which occur later in the infection, include single or multiple stromal infiltrates and nummular keratitis. Ring infiltrates or satellite lesions usually suggest advanced disease (Figure 12.7). Tropism of the *Acanthamoeba* organism for corneal nerves causes radial keratoneuritis, the reason for the extreme pain (Figure 12.8).

Diagnosis is typically delayed because the clinical appearance mimics other etiologies. Early infections are commonly treated as bacterial keratitis, especially because many practitioners rely on empiric treatment with broad-spectrum topical fluoroquinolones. Early disease is commonly misdiagnosed as herpes simplex, whereas later disease can be confused with fungal keratitis characterized by severe pain and a minimally necrotic deep stromal infiltrate. A significantly poorer prognosis is associated with deeper corneal involvement, which is increasingly likely with this delay in diagnosis.

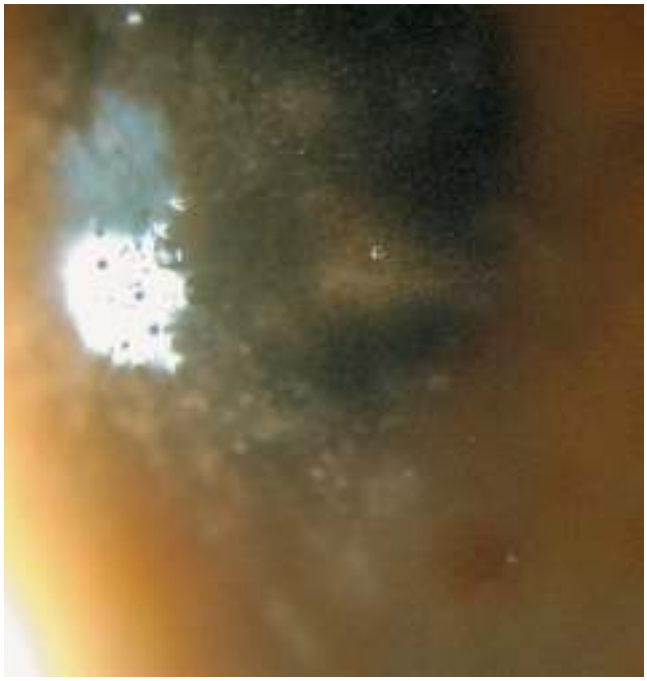


FIGURE 12.8 Radial keratoneuritis.

Treatment of *Acanthamoeba* keratitis may last weeks to years, involves toxic medications, and may be unsuccessful in curing the infection if the infection involves the deep cornea or involves a resistant pathogen. A combination of topical antiamebic agents, including biguanides (e.g., PHMB and chlorhexidine), and diamides (e.g., propamidine) are typically used. Second-line agents include azole and triazole antifungals, specifically voriconazole (oral and/or topical) or clotrimazole, and topical neomycin. Monotherapy with a biguanide alone can be curative. Most of these medications are not available commercially in the United States and they must be either compounded (biguanides, topical azole and triazole antifungals) or imported (diamidines) by a specialty pharmacy before use. Medications are often used for months, starting with hourly dosages and tapering off as the clinical situation improves. The use of steroids is controversial; it likely has no role in an appropriately resolving *Acanthamoeba* keratitis, but may be necessary in patients with extraocular inflammatory manifestations such as scleritis or dacryoadenitis.

Fungal infections of the cornea are more common in hot, humid environments, such as India or Florida, where fungal keratitis accounts for 40% and 16% of all cornea infections, respectively. Fungi are ubiquitous in the environment and can be broadly divided into yeast (*Candida* species) and molds (filamentous fungi, e.g., *Fusarium* and *Aspergillus*). Yeast infections are more common in temperate climates while filamentous fungi predominate in more tropical environments. However, trends in the United States show an increasing frequency of filamentous fungal keratitis over the last decade not only with *Fusarium* spp., which remains the single most common corneal pathogen, but also with drug-resistant, uncommon molds such as *Paecilomyces*, *Scedosporium*, and *Alternaria*. The epithelial barrier is the most important defense mechanism against all forms of infectious keratitis, including fungi. By far the most important risk factor for fungal keratitis is ocular trauma, especially when the trauma involves contact with soil or vegetable matter. Other risk factors include ocular surface disease such as neurotropic keratitis and chronic use of steroids. Patients with atopic disease, immunocompromised patients, or those hospitalized in intensive care units are also at increased risk for fungal keratitis. Although contact lens wear has not been considered a major risk factor for fungal keratitis, a cluster of *Fusarium* keratitis cases in otherwise healthy soft-contact lens wearers was noted throughout the world in 2006 (Figure 12.9). Multiple studies around the world found a strong association with the use of a contact lens cleaning solution Renu with MoistureLoc, which was withdrawn from the market in April 2006. This resulted in a substantial reduction of the number of reported cases of *Fusarium* keratitis in contact lens wearers to near the baseline incidence prior to the solution's market introduction.

Clinical signs of fungal infection include nonspecific signs of any corneal infection. Specific clinical features that should raise suspicion include infiltrates with indistinct or "feathery" edges, multifocal infiltrates, satellite lesions, immune rings, and endothelial plaques (Figure 12.10). The patient history is an important clue to the diagnosis as patients typically have a history of outdoor trauma and a waxing and waning course of symptoms and signs that have been unresponsive to empiric management. Severe pain and elevated intraocular pressure are common. Early diagnosis is critical for

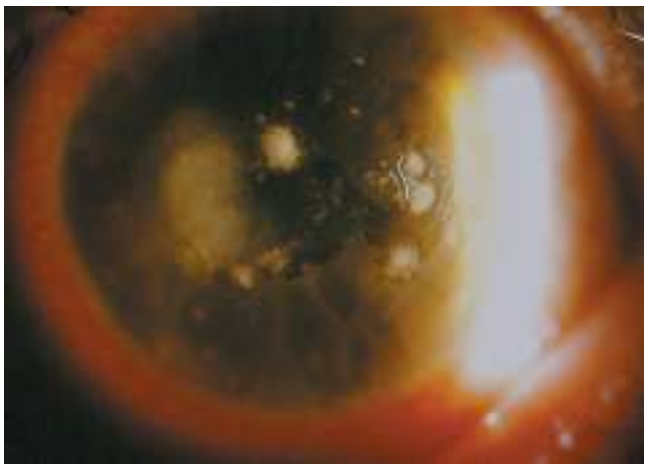


FIGURE 12.9 Fungal keratitis.

successful treatment because ophthalmic topical antifungals have variable penetration into the deep corneal stroma and corneal fungal pathogens have a propensity to proliferate vertically and to penetrate an intact Descemet's membrane, leading to endophthalmitis. The diagnosis of fungal keratitis is often delayed because it is uncommon, resulting in a low index of clinical suspicion, and because the organism can be difficult to recover if it has spread deep into the cornea. In vivo confocal microscopy can be a powerful tool in detecting filamentous fungal pathogens. Culture and vital staining is the gold standard of diagnosis, but is often negative.

Treatment of fungal keratitis is also challenging because currently available antifungal medications have a limited spectrum of activity and often have poor penetration into the cornea. The most widely used topical antifungal medications are the polyenes, amphotericin B, and natamycin (Pimaricin). Natamycin is the only commercially available antifungal topical medication in the United States. Earlier-generation azole compounds have been used topically (clotrimazole and miconazole) and systemically (ketoconazole, fluconazole, and itraconazole). Of the newer triazoles, voriconazole has been used extensively for both topical and systemic treatment of fungal keratitis. Unfortunately, multiple case series and a randomized trial have demonstrated its inferiority to natamycin as a primary empiric agent in this disease. Voriconazole, posaconazole, and the echinocandins (caspofungin and micafungin) remain useful as either adjunctive or secondary agents, however, in ulcers resistant to natamycin and/or amphotericin B, especially if in vitro sensitivities suggest susceptibility. Treatment of fungal keratitis is prolonged and often lasts for weeks to months. The use of a topical steroid is contraindicated because it can worsen disease and interferes with the efficacy of certain antifungal agents.

FIGURE 12.10 Fungal keratitis endothelial plaques.

Suggested reading

Alfonso EC, Forster RK, Garg P, Sharma S. Fungal infections. In: *Smolin and Thoft's The Cornea: Scientific Foundations & Clinical Practice*, 4th edn. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:405–425.

Dart JK, Radford CF, Minassian D, Verma S, Stapleton F. Risk factors for microbial keratitis with contemporary contact lenses: a case-control study. *Ophthalmology*. 2008;115:1647–1654, 1654.e1–1654.e3.

Dart JK, Saw VP, Kilvington S. Acanthamoeba keratitis: diagnosis and treatment update 2009. *Am J Ophthalmol*. 2009;148:487.e2–499.e2.

Fintelmann RE, Hoskins EN, Lietman TM, *et al*. Topical fluoroquinolone use as a risk factor for in vitro fluoroquinolone resistance in ocular cultures. *Arch Ophthalmol*. 2011;129:399–402.

Hau SC, Dart JK, Vesaluoma M, *et al*. Diagnostic accuracy of microbial keratitis with in vivo scanning laser confocal microscopy. *Br J Ophthalmol*. 2010;94:982–987.

Joslin CE, Tu EY, Shoff ME, *et al*. The association of contact lens solution use and *Acanthamoeba* keratitis. *Am J Ophthalmol*. 2007;144:169–180.

Lee GA, Gray TB, Dart JK, *et al*. *Acanthamoeba* sclerokeratitis: treatment with systemic immunosuppression. *Ophthalmology*. 2002;109:1178–1182.

Mascarenhas J, Srinivasan M, Chen M, *et al*. Differentiation of etiologic agents of bacterial keratitis from presentation characteristics. *Int Ophthalmol*. 2012;32:531–538.

Matsumoto Y, Murat D, Kojima T, Shimazaki J, Tsubota K. The comparison of solitary topical micafungin or fluconazole application in the treatment of *Candida* fungal keratitis. *Br J Ophthalmol*. 2011;95:1406–1409.

Oldenburg CE, Lalitha P, Srinivasan M, *et al*. Emerging moxifloxacin resistance in *Pseudomonas aeruginosa* keratitis isolates in South India. *Ophthalmic Epidemiol*. 2013;20:155–158.

Prajna NV, Krishnan T, Mascarenhas J, *et al*. The mycotic ulcer treatment trial: a randomized trial comparing natamycin vs voriconazole. *Arch Ophthalmol*. 2013;131: 422–429.

Tu EY, Joslin CE, Shoff ME. Successful treatment of chronic stromal acanthamoeba keratitis with oral voriconazole monotherapy. *Cornea*. 2010;29:1066–1068.

13

Iritis

Alice Lorch and Ann-Marie Lobo

Definition of uveitis

The uveal tract in the eye is the darkly pigmented, vascular, "middle layer" of the eye. It sits between the inner retinal layer and outer corneal–scleral layer, and is composed of the choroid, ciliary body, and iris. Uveitis is inflammation of the uveal tract. Uveitis can be classified according to anatomic structures involved: the iris or anterior ciliary body (anterior uveitis or iritis) the posterior ciliary body or anterior vitreous (intermediate uveitis), or choroid (posterior uveitis). Posterior uveitis can also include inflammation of the retina (retinitis), retinal blood vessels (vasculitis), and optic nerve (optic neuritis.) Many of the inflammatory and infectious etiologies of uveitis can cause both anterior and posterior uveitis, known as panuveitis. Therefore, anterior uveitis can be isolated or a harbinger of posterior uveitis and all patients with uveitis should have careful evaluation of both chambers. Only anterior uveitis, or iritis, will be discussed in this chapter, as intermediate and posterior uveitis are discussed elsewhere.

Anterior uveitis is most commonly idiopathic, but can be diagnosed as either inflammatory or infectious in etiology. Anterior uveitis can also be due to reactive inflammation from mild trauma or corneal disease. Neoplasias such as retinoblastoma or lymphoma can present as anterior uveitis, with tumor cells in the anterior chamber. Finally, iritis can be drug-related: cidofovir, diethylcarbamazepine, pamidronic acid, interleukin-3 and interleukin-6, oral contraceptives, quinidine, rifabutin, streptokinase, and sulfonamides are among medications that have been implicated in the past.

Infectious causes are generally either bacterial or viral, but can be related to protozoa or worms. Again, many of these diseases present with anterior segment findings but also have posterior involvement on further examination.

Clinical presentation

Anterior uveitis can present with sudden onset or chronic signs and symptoms. Classic symptoms of acute iritis are eye pain, redness, photophobia, and blurred vision. Examination is significant for conjunctival injection, described as ciliary flush when at the corneal limbus, without discharge. Slit-lamp examination reveals white blood cells floating in the anterior chamber; when white cells are layered forming a visible white line, this is referred to as a hypopyon (Figure 13.1). The presence of a hypopyon should always raise concern for an infectious endophthalmitis in patients with a history of recent surgery, trauma, or possible endogenous source (i.e., fungemia.) Anterior uveitis with hypopyon is otherwise most commonly seen in patients with HLA-B27-related disease or Behçet's disease. Keratic precipitates are another common finding in anterior uveitis; these are deposits of white blood cells on the posterior cornea. Keratic precipitates can be "fine," indicating a nongranulomatous disease such as Fuch's iridocyclitis, HLA-B27-related disease, or juvenile idiopathic arthritis. In granulomatous disease, such as sarcoidosis, syphilis, tuberculosis, or toxoplasmosis, keratic precipitates are large and yellowish, described as "mutton fat." White blood cells can also deposit

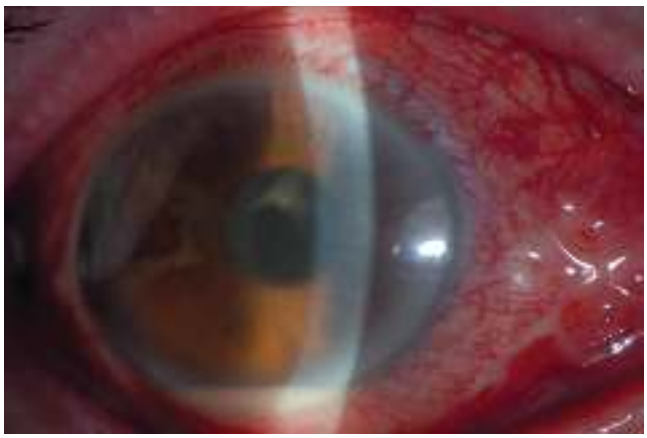


FIGURE 13.1 Slit-lamp photograph of a hypopyon in a patient with infectious endophthalmitis after cataract surgery.

on the iris, particularly in granulomatous uveitis; these are called Busacca nodules if in the iris stroma and Koeppe nodules if at the pupillary margin. Chronic iris inflammation can lead to adhesions between the iris and lens, known as posterior synechiae; these can lead to the appearance of a small or irregular pupil.

Diagnostic tests

Laboratory testing is pursued for patients with anterior uveitis that is recurrent, bilateral, or if there are concerns for a particular systemic disease. A large number of cases of anterior uveitis are classified as "idiopathic" when results of serologies are negative. These cases are thought to be due to an underlying unknown autoimmune or viral condition. Newer diagnostic modalities may help both in distinguishing between known etiologies of uveitis and in making a diagnosis in cases otherwise designated as "idiopathic."

Molecular diagnostic tests have enabled the use of small quantities of ocular fluid samples to be tested for certain infections. Anterior chamber paracentesis is a safe procedure that can be performed by an ophthalmologist at the slit lamp to obtain a small-volume sample of aqueous for testing. Aqueous samples can be tested for antibodies to determine the Goldmann–Witmer coefficient, a ratio of the total immunoglobulin in aqueous compared with that in the serum. A ratio greater than three indicates the true presence of antibodies in ocular fluid (and not just spillover from serum due to leaky inflamed blood vessels). Polymerase chain reaction (PCR), a technique used to amplify small amounts of DNA or RNA for microbial identification, can be used to identify specific viruses in intraocular fluid. Real-time PCR can quantify virus in a small volume of intraocular fluid. PCR does not have high sensitivity for all viruses and so must be used in conjunction with clinical suspicion and other diagnostic tests. Currently, PCR is used to detect herpesviruses (including herpes simplex virus [HSV] type 1 and 2, cytomegalovirus [CMV], Epstein–barr virus [EBV] and varicella-zoster virus [VZV]), toxoplasmosis, and bacterial 16S rRNA.

Infectious etiologies (Box 13.1)

Endophthalmitis

Patients with inflammation or hypopyon in the anterior chamber after intraocular surgery or trauma should be suspected of having endophthalmitis rather than anterior uveitis. Endophthalmitis can be acute, presenting with decreased vision and pain soon after surgery; these infections are generally due to staphylococcus or streptococcus infections. Delayed-onset endophthalmitis after cataract surgery can be due to *Proprionibacterium acnes*. Classically, patients with *P. acnes* endophthalmitis have white plaques on the posterior lens capsule. Endophthalmitis can also be endogenous; this is seen in patients with indwelling catheters, intravenous drug users, or others with risk of bacterial or fungal seeding of the blood. Candidemia can lead to a panuveitis with fluffy white lesions in the retina or vitreous. Endophthalmitis, whether exogenous or endogenous, must be treated immediately by an ophthalmologist with injection of antimicrobial agents into the vitreous or vitrectomy to prevent vision loss.

Herpesviruses

Herpesviruses, including HSV-1 and HSV-2, CMV, or VZV, are the most common type of infectious anterior uveitides. HSV anterior uveitis can be seen in patients with prior or concurrent HSV keratitis; however, simultaneous keratitis is not necessary for diagnosis. Herpes zoster ophthalmicus is caused by involvement of VZV in the ophthalmic branch of the trigeminal nerve. Diagnosis of herpetic uveitis can be made definitively by PCR of an aqueous sample, but treatment, with antiviral agents and topical steroids, is usually initiated based on clinical appearance. Characteristic findings of herpetic uveitis are unilateral disease and sectoral iris atrophy. Herpetic uveitis is one of the few uveitic processes that can be associated with increased intraocular pressure (others include

BOX 13.1

Infectious etiologies of iritis

- Endophthalmitis
- Herpesviruses
- Syphilis
- *Bartonella*
- Tuberculosis
- Lyme disease
- Brucellosis
- Whipple's disease
- Leprosy
- Chikungunya
- Leptospirosis
- Toxoplasmosis
- HIV

sarcoidosis and toxoplasmosis.) Like the HSV virus, CMV can also cause anterior uveitis associated with high intraocular pressure and iris atrophy.

The herpesviruses can cause devastating vision loss if there is posterior involvement. Acute retinal necrosis (ARN) is a rapidly progressive necrotizing retinitis that can lead to retinal ischemia and retinal breaks and requires immediate and aggressive therapy. ARN is most commonly seen in immunocompetent patients, although it also can be seen in the immunocompromised. The initial presentation of ARN can be anterior uveitis and so it is essential that all patients with anterior uveitis receive a dilated fundus examination. Progressive outer retinal necrosis (PORN) is a retinitis similar to ARN that develops primarily in immunocompromised patients and is most commonly associated with VZV. As described above, PCR of ocular fluids can be used to identify herpetic viruses. Treatment of both ARN and PORN is with intravenous antiviral medications (acyclovir, ganciclovir) and potentially intravitreal antiviral medications (ganciclovir, foscarnet).

Syphilis

Syphilis usually produces a granulomatous uveitis (although nongranulomatous presentations have been reported) that can involve all parts of the eye. Congenital syphilis presents with interstitial keratitis accompanied by anterior uveitis that presents in teenage years with "salt-and-pepper" fundus changes. In acquired syphilis, the onset of ocular involvement is in secondary or tertiary disease, and is most commonly iritis. Other common presentations of ocular syphilis include posterior placoid chorioretinitis, retinal vasculitis, vitritis, and papillitis and so a dilated fundus exam is essential for complete diagnosis.

Patients with suspected ocular syphilis should have indirect (rapid plasmin reagent [RPR] or Venereal Disease Research Laboratory [VDRL]) and direct serum testing (fluorescent treponemal antibody [FTA-ABS]). Patients with positive serum tests should undergo lumbar puncture for diagnosis of neurosyphilis. Screening for HIV also should be performed. Ocular syphilis is treated the same as neurosyphilis, with intravenous penicillin G. Topical steroids and mydriatics can be used as an adjunct to systemic treatment. Systemic steroids can be used to prevent a Jarisch–Herxheimer reaction at the time of treatment.

Bartonella species (cat scratch disease)

Bartonella (including *Bartonella henselae* and *Bartonella quintana*) is spread via contact with a contaminated cat. Patients can present with Parinaud's oculoglandular syndrome, which is a constellation of granulomatous conjunctivitis and regional lymphadenopathy. *Bartonella* can also cause a neuroretinitis that clinically presents with optic nerve edema and a "star'-like pattern of exudates in the macula (referred to as a macular star). Anterior uveitis alone is rare, but patients can present with a panuveitis with neuroretinitis. Diagnosis is confirmed by serologies as other infections can also present with neuroretinitis. Treatment with antimicrobial agents, including doxycycline and rifampin, is based on the severity of disease.

Tuberculosis

The diagnosis of ocular tuberculosis (TB) can be very difficult since many patients may have no history of systemic TB. Recent exposure to TB or a positive tuberculin skin test in a patient with chronic granulomatous uveitis should raise suspicion. The recently introduced interferon-gamma release assay (Quantiferon-Gold) can distinguish between exposure to *Mycobacterium tuberculosis* and to atypical mycobacteria or the bacille Calmette–Guérin vaccine; however, this test cannot distinguish between latent and active TB. Aqueous and vitreous cultures are often falsely negative and PCR testing is unreliable. The most characteristic eye findings are granulomatous anterior uveitis with multifocal choroiditis and occasionally choroidal tubercles. Treatment is with an antituberculous multidrug regimen (isoniazid, rifampin, pyrazinamide, ethambutol) and systemic steroids.

Lyme disease

Lyme disease results from tick-borne transmission of *Borrelia burgdorferi* and ophthalmic symptoms can vary and include unilateral or bilateral anterior uveitis, intermediate uveitis, oculomotor palsies, and scleritis. Patients generally present in Stage 2 disease, and may have systemic symptoms of headaches, arthritis, meningitis, or peripheral neuropathies. Presenting ocular complaints can include blurred vision, photophobia, eye pain, or diplopia. Patients should be screened in high-prevalence areas of the Northeastern and Midwestern United States, in the habitat of the bacteria's vector, the *Ixodes* tick. Serologic testing is performed using screening ELISA followed by a confirmatory Western blot. Treatment for ocular involvement is equivalent to that for neurologic involvement in Lyme disease, most commonly with intravenous ceftriaxone. Topical steroids and mydriatics can be used as an adjunct to systemic treatment.

Rare diseases

Brucella is a rare cause of uveitis; this bacterium is harbored in the genitourinary tract of sheep and cows and transmitted via direct contact or airborne spread from contaminated animals, meat, or dairy products. *Brucella* produces a granulomatous uveitis and is treated with topical steroids and mydriatics. Traditional systemic therapy includes doxycycline with either rifampin or streptomycin.

Whipple's disease, primarily a disease of malabsorption of the gastrointestinal tract, is caused by *Tropheryma whipplei*. Patients generally present with a chronic nongranulomatous anterior uveitis but can also have vitritis and sheathing of the retinal vessels. Definitive diagnosis is made by jejunal biopsy. Treatment includes an initial course of either IV ceftriaxone or IV streptomycin with penicillin G followed by a prolonged course of trimethoprim–sulfamethoxazole for systemic disease; periocular or systemic steroids can often make the uveitis worse.

The majority of patients with ocular leprosy present with bilateral, chronic and relapsing iridocyclitis. Examination can reveal prominent corneal nerves with a "beaded" appearance. Iris "pearls," or aggregations of bacilli, are pathognomonic for the disease; these are white spots along the pupil margin that can coalesce and become pedunculated, falling into the anterior chamber and leaving an atrophic appearance to the iris. Involvement of the posterior segment is rare but there have been reports of white lesions in the peripheral fundus, also resembling "pearls." Treatment is for systemic disease, with dapsone and rifampin for paucibacillary disease and the addition of clofazimine for multibacillary disease.

Chikungunya is a viral disease spread by *Aedes* mosquitoes, initially discovered in Africa but with outbreaks in Asia and India. The disease is characterized by persistent fever, arthritis, and skin rash. The most common ocular manifestations are iridocyclitis and retinitis. Treatment is with systemic and topical anti-inflammatory medications.

Leptospirosis is transmitted via bacteria in the urine of infected animals; it is active as long as it is moist and so outbreaks commonly occur in tropical environments. Patients can present with a nongranulomatous hypopyon anterior uveitis or panuveitis with vitritis and retinal vasculitis. Leptospirosis is treated with systemic antibiotics, although evidence for their efficacy has not been conclusive. IV penicillin G is generally used in severe cases, although doxycycline and third-generation cephalosporins have also been tried.

Of note, toxoplasmosis is the most common infectious uveitis in the world and can present with anterior chamber inflammation, but findings are predominantly posterior uveitis and as such it is not discussed in detail in this chapter.

Human immunodeficiency virus

HIV can cause a nongranulomatous uveitis as part of seroconversion or in association with a high viral load. Patients with HIV anterior uveitis often have fine keratic precipitates and no retinal findings. The inflammation does not respond to topical steroids but does respond well to highly active antiretroviral therapy. The association between HIV and anterior uveitis is more frequently due to the increased susceptibility of HIV patients to infections such as syphilis or CMV.

Summary

Anterior uveitis can be caused by a variety of infectious or inflammatory diseases. Diagnosis of a particular infection is made based on clinical history as well as ocular and systemic exam findings. All patients with anterior uveitis should also have a thorough examination of the posterior segment for signs of intermediate or posterior uveitis. Ocular inflammation after surgery or in the setting of disseminated infection should always raise the concern for infectious endophthalmitis, which must be treated emergently by an ophthalmologist. Emerging diagnostic techniques might enable more rapid diagnosis of known infectious causes or the discovery of novel infectious etiologies of uveitis in the future.

Suggested reading

Doris JP, Saha K, Jones NP, et al. Ocular syphilis: the new epidemic. *Eye (Lond)*. 2006;20(6): 703–705.

Hunter R, Lobo A. Current diagnostic approaches to infectious anterior uveitis. *Int Ophthalmol Clin*. 2011;51(4):145–156.

Kunavisarut P, Sirirungsi, W, Pathanapitoon K, et al. Clinical manifestations of human immunodeficiency virus-induced uveitis. *Ophthalmology*. 2012;19:1455–1459.

Mahendradas P, Ranganna S, Shetty R, et al. Ocular manifestations associated with chikungunya. *Ophthalmology*. 2008;115:287–291.

Rathinam SR. Ocular manifestations of leptospirosis. *J Postgrad Med*. 2005;51: 189–194.

Silverio CD Jr, Imai YD, Cunningham ET Jr. Diagnosis and management of herpetic anterior uveitis. *Int Ophthalmol Clin*. 2002; 42(4):43–48.

Tabbara KF, Al-Kassimi H. Ocular brucellosis. *Br J Ophthalmol*. 1990; 74:249–250.

Touitou V, Fenollar F, Cassoux N, et al. Ocular Whipple's disease: therapeutic strategy and long-term follow-up. *Ophthalmology*. 2012; 119(7): 1465–1469.

Van Gelder R. Diagnostic Testing in Uveitis. Focal Points: Clinical Modules for Ophthalmologists. American Academy of Ophthalmology. Module 4. 2013.

Yeh S, Sen HN, Colver M. Update on ocular tuberculosis. *Curr Opin Ophthalmol*. 2012; 23(6):551–556.

14

Retinitis

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This chapter discusses the most clinically important forms of infectious retinitis: cytomegalovirus retinitis (CMVR), acute retinal necrosis (ARN), progressive outer retinal necrosis (PORN), ocular toxoplasmosis, and syphilitic retinitis. Additional infectious etiologies of retinitis (including Zika virus and tuberculosis) are well described in the literature but beyond the scope of this chapter. For information on endophthalmitis, including bacterial and fungal etiologies, please see the dedicated chapter in this text.

CMV retinitis

CMVR is the most common and clinically significant opportunistic ocular infection seen in immunocompromised patients, including those with AIDS as well as patients with compromised immunity following organ transplantation or chemotherapy for systemic malignancy. With the extensive use of highly active antiretroviral therapy (HAART) in HIV-positive patients, there has been a marked decrease in the incidence of CMVR in these patients (23 per 10,000 HIV/AIDS cases in the pre-HAART era to 8 per 10,000 HIV/AIDS cases in the post-HAART era). Rarely, CMVR may occur in apparently immunocompetent individuals due to relative immune dysfunction related to advanced age, diabetes, and use of steroids or other immunosuppressive agents.

CMVR usually begins as a unilateral condition but progresses to involve the contralateral eye in approximately 20% of cases. The onset may be insidious, with 50% of patients being asymptomatic. In patients known to have HIV or to be immunosuppressed, CMV retinitis has traditionally been diagnosed via the recognition of pathognomonic clinical exam findings, with the diagnosis confirmed by positive blood cultures for CMV. In recent years, aqueous and/or vitreous fluid analysis for viral DNA by polymerase chain reaction (PCR) has become an indispensable tool in the initial diagnosis of suspected infectious retinitis. Real-time quantitative PCR can also be used to monitor patients while on therapy or to ensure that viral DNA concentration is not increasing in the setting of refractory disease, which may occur in patients with viral strains that develop antiviral drug resistance.

During the initial stage of active CMVR, three patterns of retinal lesions have been described: (1) fulminant/edematous pattern consisting of large areas of retinal hemorrhage in a background of confluent retinal necrosis (Figure 14.1), (2) indolent/granular pattern consisting of granular satellite lesions with little or no hemorrhage, and (3) exudative pattern, also known as frosted branch angiitis, with extensive vascular sheathing. In each of these clinical patterns, vitreous inflammation is minimal or absent. Following the active retinitis, the second stage of CMVR is characterized by widespread necrosis and retinal tears. Visual loss may be severe if the macula or optic nerve is involved. Without treatment, CMV retinitis will become bilateral in 80% of cases and eventually will result in blindness from retinal atrophy, retinal detachment, or optic nerve involvement.

Successful treatment of CMVR depends on the restoration of immune function. In HIV/AIDS patients, the use of HAART lowers the progression of CMV retinitis and incidence of vision loss. To halt progression of the retinitis and improve visual outcomes, treatment with a virostatic agent that competitively inhibits CMV DNA polymerase is also required. The current, recommended systemic treatment options for CMVR

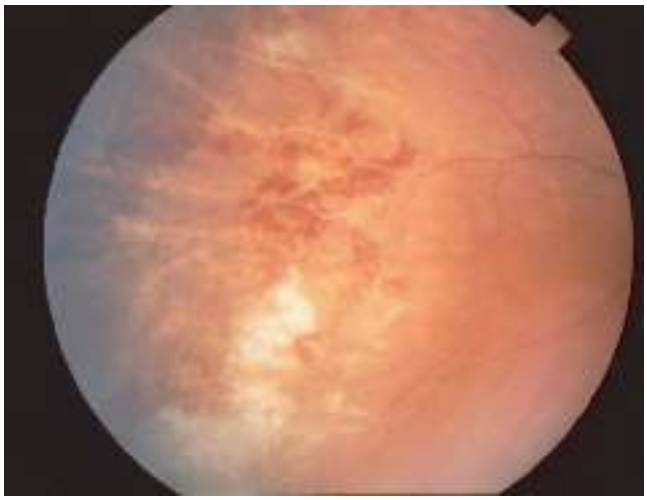

FIGURE 14.1 Photo of the peripheral fundus showing an area of retinal necrosis associated with retinal hemorrhages, representing an active chorioretinal lesion due to cytomegalovirus retinitis.

include ganciclovir, valganciclovir, and foscarnet (see Table 14.1). The choice of the antiviral agent and its route of delivery should be based on the potential medication side effects and the effectiveness of prior treatments.

Ganciclovir may be administered intravenously, orally, or intravitreally. Intravenous (IV) ganciclovir can be used as induction therapy for 14 days, followed by maintenance therapy by either an IV or oral route. In patients with impaired renal function, the full dosage of ganciclovir cannot be tolerated and requires reduction. The most common side effect of ganciclovir is neutropenia, which arises in 20% to 40% of patients and is reversible on discontinuation of the drug. A sustained-release ganciclovir implant placed directly into the vitreous cavity of the eye was previously available but was removed from the market in 2014.

The introduction of valganciclovir, a prodrug of ganciclovir with good penetration into the vitreous, has considerably advanced the treatment of CMVR by providing an oral treatment option. It has become the mainstay CMVR treatment for induction and maintenance therapy. It is usually dosed orally for 3 to 6 weeks, followed by prophylactic dosing. A treatment response equivalent to IV ganciclovir has been demonstrated, and the adverse effects of the two drugs are similar.

Foscarnet is an alternate treatment option for CMVR. It is typically administered intravenously for 3 weeks as induction therapy, followed by maintenance therapy indefinitely. The most common side effect of foscarnet is nephrotoxicity, which occurs in 25% of patients and is reversible with early cessation of the drug. Because foscarnet undergoes renal elimination and is nephrotoxic, careful monitoring of renal function is necessary. However, it is often effective in the treatment of ganciclovir-resistant retinitis and remains an important treatment option.

Intravitreal therapy should be considered in addition to systemic therapy if the retinal disease threatens the fovea. Either intravitreal foscarnet or intravitreal ganciclovir is generally used in such cases. Given the high concentration of drug delivered via intravitreal injection, this mode of therapy may also be beneficial in patients with recurrent disease or in whom there are concerns for relative drug resistance.

There may be differences between the treatment of CMVR seen in HIV patients versus non–HIV-related CMVR, which has recently been termed *chronic retinal necrosis*. In the non-HIV patient

TABLE 14.1 **THERAPY FOR VIRAL RETINITIS**

Drug	Regimen	Side effects	Viral coverage	Condition
Ganciclovir	**IV:** 500 mg q12h × 14 days **IVt:** 2–5 mg/0.1 mL, 3×/wk	Granulocytopenia, thrombocytopenia, anemia	HSV1, CMV>>VZV, HSV2	CMVR, ARN, PORN
Valganciclovir	**Oral:** 900 mg BID × 3–6 wks **Prophylactic dose:** 450 mg PO BID	Granulocytopenia, anemia, headache, GI symptoms, renal dysfunction	HSV1, CMV>>VZV, HSV2	CMVR, ARN, PORN (not initial tx; maintenance only)
Foscarnet	**IV:** 40–60 mg/kg q8h ×3 wks **IVt:** 2.4 mg/0.1 mL q3–4d	Nephrotoxicity, seizures/ headache, GI symptoms	HSV1, HSV2, VZV > CMV	ARN, PORN, CMVR
Acyclovir	**IV:** 1,500 mg/m^2/d divided q8h ×14 days followed by **Oral:** 800 mg 5×/d × 4–6 wks **Prophylactic dose:** 400 mg PO BID–TID	GI symptoms, hypersensitivity reactions, renal and/or CNS dysfunction	HSV1, HSV2, VZV, EBV >> CMV	ARN, PORN
Valacyclovir	**Oral:** 1–2 g q8h × 6 wks **Prophylactic dose:** 1 g PO BID	GI symptoms, hypersensitivity reactions, renal and/or CNS dysfunction	HSV1, HSV2, VZV >> CMV	ARN, PORN (not initial tx; maintenance only)
Famciclovir	**Oral:** 500 mg q8h	Headache, GI symptoms, rash	HSV1>HSV2>VZV	ARN, PORN (not initial tx; maintenance only)

Abbreviations: IV = intravenous; IVt = intravitreal; CMVR = cytomegalovirus retinitis; ARN = acute retinal necrosis; PORN = progressive outer retinal necrosis; HSV = herpes simplex virus; ZVZ = varicella zoster virus; BID = twice daily; TID = three times daily; GI = gastrointestinal; CNS = central nervous system; tx = treatment; wks = weeks; mos = months

with this more indolent, granular retinitis, intravitreal therapy alone may potentially be used to induce regression of retinitis while reducing systemic medication side effects.

The initial response to any antiviral therapies usually occurs 1 to 2 weeks after the initiation of the induction regimen and is evidenced by termination of the extension of the retinal lesions and gradual atrophy of the involved retina. Ophthalmologists should examine patients' fundi every 2 to 3 weeks to monitor the effectiveness of the antiviral therapy. Recurrence of CMV retinitis occurs in 30% to 50% of patients receiving maintenance doses of systemic antiviral therapy. The treatment of recurring CMVR is reinduction for 2 weeks followed by indefinite maintenance therapy. In the era of HAART therapy, HIV-positive patients with CMV retinitis having a sustained CD4+ T-cell count >100 cells/mm^3 for 3 to 6 months can terminate maintenance therapy. However, maintenance therapy needs to be restarted if the immune status is compromised (CD4+ T-cell count 50–100 cells/ mm^3). Furthermore, these patients should undergo ophthalmic screening at 3- to 6-month intervals, depending on the patient's underlying immune status.

Complications of CMVR can include retinal detachment, which in one study occurred at a median interval of 1.5 months from the time of initial diagnosis. Retinal detachment is generally repaired using vitrectomy surgery with silicone oil instillation.

Acute retinal necrosis

ARN is a necrotizing retinitis most often associated with infection by the varicella-zoster virus (VZV) or, less commonly, the herpes simplex virus (HSV) types 1 and 2. In addition, rare reports of CMV and Epstein–Barr virus (EBV) causing ARN have appeared in the literature. Although initially described only in immunocompetent patients, recent cases have been reported in immunosuppressed individuals, including those with AIDS.

Clinically, ARN presents as patchy or confluent areas of white retinal necrosis in the far periphery (Figure 14.2), which may spread to the posterior pole rapidly within days. The onset of ARN typically is unilateral, although bilateral involvement may occur in up to 30% of patients, usually within several weeks of onset. In addition, moderate to severe vitritis and occlusive retinal vasculitis (arteritis and phlebitis) are seen. Anterior uveitis, ischemic vasculopathy involving the optic nerve, and macular edema may be associated findings. The active phase of inflammation generally lasts several weeks and is followed by a convalescent phase. As many as 52% of patients with ARN develop retinal breaks and subsequent rhegmatogenous retinal detachments. Retinal detachments may occur from 9 days to 5 months after the onset of retinitis.

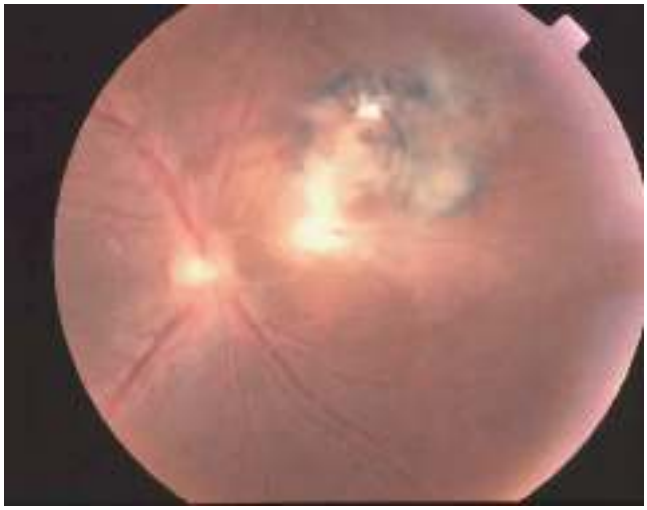

FIGURE 14.2 Photo of the peripheral fundus showing confluent white areas of retinal necrosis with occlusive retinal vasculitis and retinal hemorrhages suggestive of acute retinal necrosis.

Early initiation of appropriate antiviral medication is paramount in the treatment of ARN. This serves to eliminate active viral infection in the involved eye and reduces the risk of involvement of the fellow eye. Historically, patients were hospitalized in order to receive IV acyclovir for 14 days followed by oral acyclovir for 4 to 6 weeks. In recent years, however, there has been a shift toward outpatient management using oral and intravitreal antivirals. Oral valacyclovir and famciclovir are both prodrugs that are active against VZV and HSV and can be used as alternate induction agents because they have greater bioavailability and achieve systemic concentrations similar to that of IV acyclovir. Valganciclovir is another oral treatment option. These antiviral medications are generally slowly tapered after complete resolution of retinitis is observed.

Intravitreal injection of antiviral agents can also be given in cases of severe or refractory viral retinitis. Early administration of intravitreal antivirals also provides an opportunity for vitreous sampling (akin to a "tap and inject" procedure for endophthalmitis), allowing for PCR-based analysis to help identify the causative agent. Intravitreal foscarnet has been used to treat ARN caused by HSV and VZV. Intravitreal ganciclovir may assist in treatment of necrotizing herpetic retinitis in immunocompetent patients.

Systemic or ocular corticosteroids are often used to treat intraocular inflammation and associated intraocular sequelae but should only be added after initiation of antiviral therapy. The use of prophylactic retinal laser to decrease the rate of retinal detachment in patients with viral retinitis has been an issue of great debate. Several studies have reported this to be of benefit when applied posterior to areas of active retinitis, while others have found no decrease in the risk of retinal detachment. Without prospective randomized controlled studies, this question may not be definitively answered.

Progressive outer retinal necrosis

PORN is a necrotizing retinitis that occurs in immunocompromised individuals (e.g., AIDS patients with low CD4 counts or posttransplant patients). It is rapidly progressive, highly destructive, and almost exclusively caused by infection with VZV. Extensive multifocal retinal lesions tend to begin at the posterior pole and spread toward the peripheral area, with rapid coalescence of satellite lesions (Figure 14.3). There is minimal vitritis, relative sparing of the retinal vasculature, and often little to no pain or photophobia, distinguishing this clinical presentation from that of ARN. The condition often starts in one eye, with the other eye frequently becoming involved in weeks to months. PORN tends to have a worse visual prognosis than ARN. There is a high risk of profound vision

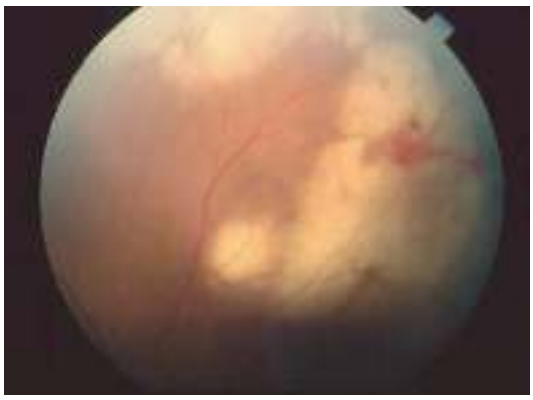

FIGURE 14.3 Fundus photo of the posterior pole showing white and confluent areas of retinal necrosis and hemorrhage in an AIDS patient suggestive of progressive outer retinal necrosis.

Photo courtesy of James Eadie, MD, at the University of Wisconsin, and Lisa Faia, MD, at Associated Retinal Consultants in Royal Oak, Michigan.

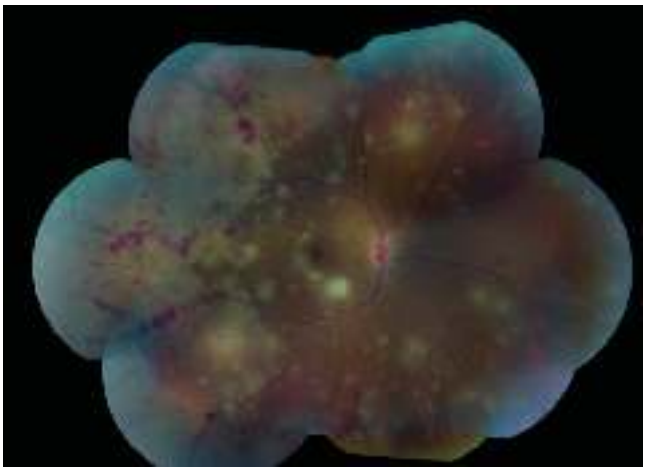

FIGURE 14.4 Fundus photo of the posterior pole showing an excavated atrophic chorioretinal scar and overlying epiretinal membrane consistent with resolved focal necrotizing chorioretinitis secondary to toxoplasmosis.

loss secondary to retinal necrosis and retinal detachment, with two-thirds of patients progressing to no light perception (NLP) vision.

Early initiation of aggressive systemic and intravitreal antiviral therapy is essential in the treatment of PORN. Systemic antiviral therapy includes IV foscarnet, IV ganciclovir, or IV acyclovir, although PORN may have a poor response to acyclovir alone. Better visual outcomes have been associated with combination therapy using IV ganciclovir and foscarnet, intravitreal ganciclovir combined with IV acyclovir or foscarnet, or intravitreal ganciclovir with foscarnet. After response to treatment, patients may be given maintenance dosing of oral valacyclovir, valganciclovir, or famciclovir.

Ocular toxoplasmosis

Ocular toxoplasmosis accounts for 30% to 50% of all cases of posterior uveitis and is caused by the obligate intracellular parasite *Toxoplasma gondii*. Infection may be congenital through transplacental transmission or acquired through contact with cat excreta or by ingestion of oocysts from undercooked meat. Most cases of ocular toxoplasmosis occur as a result of reactivation of congenital ocular lesions.

Symptoms of active infection include blurred vision and vitreous floaters. Most commonly, ocular toxoplasmosis presents as a white-yellow area of focal necrotizing retinitis adjacent to an old atrophic chorioretinal scar (Figure 14.4). Inflammation of the vitreous is typically present over the area of active retinitis, and granulomatous iridocyclitis or optic nerve swelling may also be present. Occasionally, toxoplasmosis can cause massive vitreous inflammation resulting in a "headlight in the fog" appearance. In HIV-positive individuals, the appearance of toxoplasmosis can be different from that seen in immunocompetent patients, often being much more diffuse, hemorrhagic, and potentially unassociated with scars from earlier infections. The various complications associated with larger lesions include rhegmatogenous or exudative retinal detachment, macular edema, retinal vessel occlusions, subretinal neovascularization, and epiretinal membranes.

Not all active retinal lesions require treatment when present in immunocompetent individuals. Small peripheral lesions, which often are self-limited and not visually threatening, can be observed. Without treatment, active lesions generally heal in 2–4 months. Medical therapy is indicated when the toxoplasma lesions involve or threaten the macula or optic nerve or when visually disabling vitreous inflammation is present.

The goal of treatment for ocular toxoplasmosis is to halt the infectious process and reduce scarring of the retina and vitreous (Table 14.2). The combination of pyrimethamine, sulfadiazine, and corticosteroids is considered the "classic" therapy for ocular toxoplasmosis. Pyrimethamine requires weekly complete blood counts and may be administered with folinic acid, 5 mg orally twice weekly, to reduce the incidence of bone marrow suppression. Prednisone at a dosage of 60 to 80 mg/d is often added to the treatment regimen after 3 days of antibiotic treatment and rapidly tapered based on clinical response and patient tolerance. Steroids should never be used in the treatment of ocular toxoplasmosis without the concurrent use of antibiotic agents.

A variety of other antibiotics have also been found to be effective in treating toxoplasmosis, greatly expanding the traditional treatment options. Clindamycin has been suggested in combination with sulfadiazine and pyrimethamine for severe ocular toxoplasmosis infections. Alternatively, intravitreal clindamycin has been used as local therapy in combination with dexamethasone. Trimethoprim-sulfamethoxazole is also usually effective and well-tolerated as an alternative treatment. Oral atovaquone has also been demonstrated to be effective as a single agent and has been shown in animal models to be active against the bradyzoite form of *T. gondii*. Maintenance therapy with pyrimethamine–sulfadiazine is useful in severely immunocompromised patients.

Syphilitic retinitis

Syphilis, caused by the spirochete *Treponema pallidum,* is known as the "great mimic" or "imitator" given its varied manifestations in the

TABLE 14.2 **TREATMENT OF OCULAR TOXOPLASMOSIS**

Drug	Dose	Side effects
Pyrimethamine[a]	75–100 mg PO loading dose, then 25–50 mg/d PO × 4–6 wks	Bone marrow suppression, hypersensitivity reaction, photosensitivity
Sulfadiazine[a]	2–4 g PO loading dose, then 1 g PO QID × 4–6 wks	Bone marrow suppression, hypersensitivity reaction crystalluria
Trimethoprim-sulfamethoxazole	160 mg/800 mg PO BID × 6 wks	Bone marrow suppression, hypersensitivity reaction
Atovaquone	750 mg PO QID × 3 mos	Hypersensitivity reaction
Clindamycin[b]	**Oral:** 300 mg QID × 4–6 wks **IVt:** 1.5 mg/0.1 mL weekly × 4 wks	**Oral:** Diarrhea, pseudomembranous colitis **IVt:** Risks of IVt injection
Dexamethasone	**Ivt:** 400 µg/0.1 mL given with IVt Clindamycin.	**IVt:** Risks of IVt injection, elevated IOP, cataract

[a]These antibiotics are used in combination as "classic therapy," along with oral prednisone and folinic acid.
[b]Oral clindamycin is used in combination with classic therapy for severe ocular toxoplasmosis infections.
Abbreviations: IVt = intravitreal; BID = twice daily; QID = four times daily; PO = by mouth; IOP = intraocular infection; wks = weeks; mos = months

eye. While the most common presentation is uveitis, other findings can include vitritis, retinal vasculitis, retinitis, papillitis, and scleritis. The prevalence of syphilis worldwide has increased over the past 10 to 15 years, especially in men who have sex with men and patients co-infected with HIV.

Retinitis caused by syphilis usually presents in one of two ways: (1) a punctate inner retinitis with dew-drop like collections along the surface of the retina (Figure 14.5) or (2) a more diffuse yellowish or grayish outer retinitis which can form consolidated lesions (with the latter termed *acute syphilitic posterior placoid chorioretinitis*). The retinitis is often associated with vasculitis, vitreous inflammation, and anterior segment inflammation.

Misdiagnosis can lead to a delay in appropriate treatment and subsequent vision loss, particularly if the ocular condition is erroneously treated as a noninfectious uveitis upon presentation. For this reason, maintaining a high index of suspicion and ordering appropriate diagnostic testing is paramount. Testing should include both treponemal tests (FTA-ABS or MHA-TP) and nontreponemal tests (VDRL or RPR). Newer testing, including PCR assays and rapid specific treponemal tests, may be available in some clinical settings. All patients with syphilitic eye disease should undergo a lumbar puncture to aid in the diagnosis of possible neurosyphilis and guide therapy. While ocular syphilis is always a sign of tertiary syphilis, the presence of optic neuritis and retinitis specifically are considered diagnostic of neurosyphilis. Thus, treatment of syphilitic retinitis requires a 14-day course of IV aqueous penicillin G at 3 to 4 million units every 4 hours. Therapeutic success may be gauged by improvement in clinical findings and seroconversion or low titers on subsequent nontreponemal (VDRL or RPR) testing. Once the infection has been treated, treatment with corticosteroids may be used for any residual ocular inflammation. If left untreated, syphilitic retinitis can lead to worsening inflammation, secondary glaucoma, retinal necrosis, and optic atrophy. With early diagnosis and appropriate therapy, however, patients with syphilitic retinitis can have good visual outcomes.

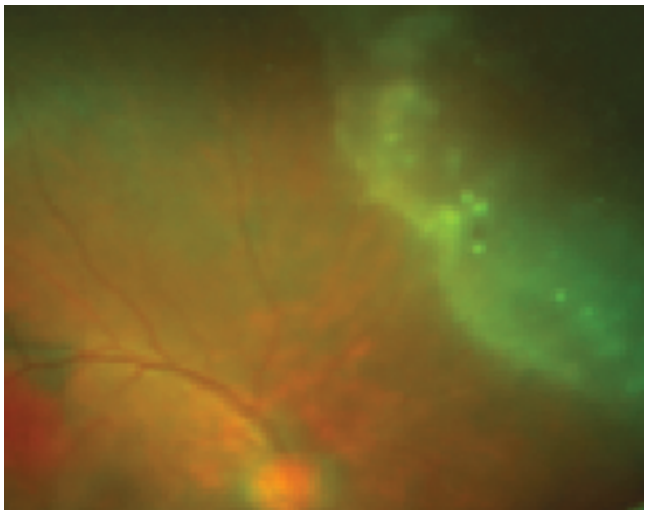

FIGURE 14.5 Fundus photo showing an area of retinal whitening with a discrete, scalloped border and numerous yellowish white precipitates characteristic of syphilitic punctate inner retinitis with dewdrop-like collections along the surface of the retina.

Acknowledgments

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Suggested reading

Deschenes J, Murray P, Rao N, Nussenblatt R. International Uveitis Study Group: Clinical classification of uveitis. *Ocular Immunol Inflam*. 2008;16(1):1–2.

Furtado JM, Arantes TE, Nascimento H, et al. Clinical manifestations and ophthalmic outcomes of ocular syphilis at a time of re-emergence of the systemic infection. *Sci Rep*. 2018;8(1).

Koo L, Young LH. Management of ocular toxoplasmosis. *Int Ophthalmol Clin*. 2006;46:183–193.

Kozak I, McCutchan JA, Freeman WR. HIV-associated infections. In Ryan SJ, ed. *Retina*, vol. 2. London: Elsevier; 2013:1441–1472.

Lau CH, Missotten T, Salzmann J, Lightman SL. Acute retinal necrosis features, management, and outcomes. *Ophthalmology*. 2007;114(4):756–762.

Lee JH, Agarwal A, Mahendradas P, et al. Viral posterior uveitis. *Survey Ophthalmol*. 2017;62:404–445.

Lin P. Infectious uveitis. *Curr Ophthalmol Rep*. 2015;3(3):170–183.

Pearce WA, Yeh S, Fine HF. Management of cytomegalovirus retinitis in HIV and non-HIV patients. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47(2):103–107.

Tsai JH, Rao NA. Spirochetal infections. In Ryan SJ, ed. *Retina*, vol. 2. London: Elsevier; 2013: 1486–1489.

Wiegand TW, Young LH. Cytomegalovirus retinitis. *Int Ophthalmol Clin*. 2006;46(2):91–110.

15

Endophthalmitis

Roy D. Brod, Harry W. Flynn, Jr., and Lili G. Kaplan

Introduction

Endophthalmitis is a vision-threatening inflammation of the inner eye fluids and tissues. Infectious endophthalmitis results from either exogenous or endogenous entry of microbes into the eye. In reported clinical series, exogenous endophthalmitis is much more common than endogenous (or metastatic) endophthalmitis. By far the most common cause of exogenous infection is intraocular procedures. Until recently, cataract surgery was the most frequently performed type of intraocular procedure, accounting for the greatest number of exogenous endophthalmitis cases. Intravitreal injection has now surpassed cataract surgery as the most frequently performed intraocular procedure and consequently is a significant contributor to the total number of exogenous endophthalmitis cases reported. Exogenous endophthalmitis can also occur after other types of intraocular surgery, including secondary lens implantation, glaucoma filtering surgery, vitrectomy surgery, and corneal transplantation. Organisms may also enter the eye during penetrating trauma, intraocular injection of medication, and from contiguous spread into the eye from an infected corneal ulcer. Gram-positive bacteria are the most common cause of exogenous endophthalmitis.

Incidence

Postoperative endophthalmitis cases from the University of Miami (Bascom Palmer Eye Institute) over an 8-year period (2002–2009) demonstrated the incidence of nosocomial endophthalmitis after cataract surgery to be 0.025%. In another retrospective series of endophthalmitis cases occurring after intravitreal medication injection from Bascom Palmer Eye Institute (2005–2017) the rate of endophthalmitis was 0.013%. Endophthalmitis occurs after open-globe injuries in 3% to 30% of patients depending on the nature of the injury and following glaucoma filtering surgery in 0.45% to 1.3% of cases. The rate of development of *Candida* endogenous endophthalmitis in patients with documented candidemia has been reported to range from 2.8% to 45%. Endogenous bacterial endophthalmitis is less common than fungal infection with an incidence of 2% to 11% in patients with septicemia.

Clinical features

Most cases of acute-onset endophthalmitis post-cataract surgery present within 2 weeks of intraocular surgery (Figure 15.1). Symptoms may start as early as 12 hours after the surgery. The classic symptoms include marked visual loss and ocular pain in 75% of cases. The loss of vision is typically profound, and vision is reduced out of proportion to the usual postoperative course. The presenting signs often include lid edema, conjunctival injection and swelling, conjunctival discharge, corneal edema, anterior chamber inflammation,

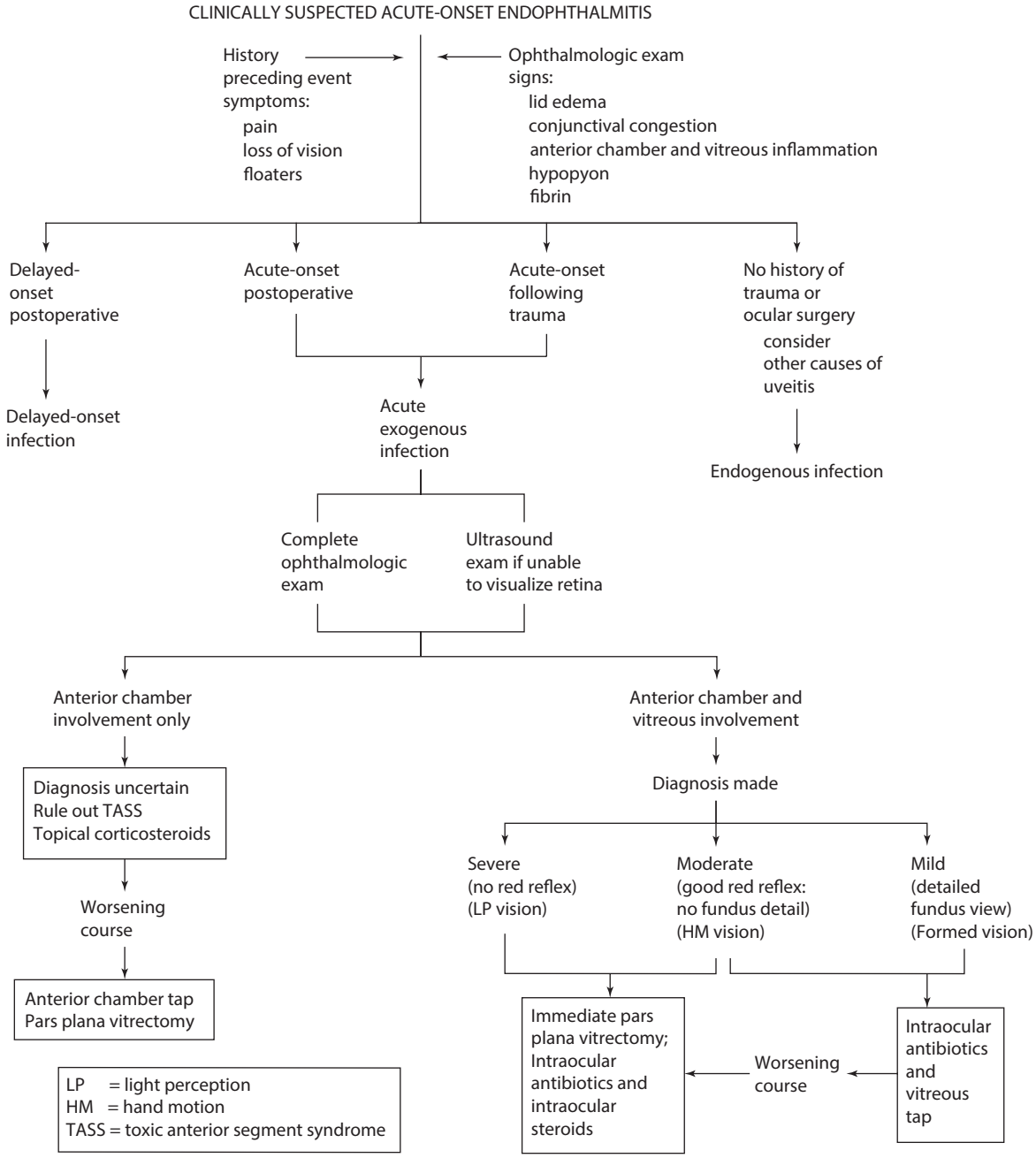

FIGURE 15.1 Algorithm for management of acute-onset endophthalmitis.

fibrin formation, and vitreous inflammatory response. In most cases, a layer of inflammatory cells (hypopyon) can be visualized in the inferior portion of the anterior chamber (Figure 15.2). Redness and purulent discharge from the conjunctiva and lid margins are also commonly seen. A severe intraocular inflammatory response will often obscure a view of the posterior pole and may cause loss of the red reflex. In these cases echographic exam of the eye may be useful in ruling out posterior segment complications such as retinal detachment and retained lens fragments.

In the Endophthalmitis Vitrectomy Study (EVS), the coagulase-negative staphylococci were the most commonly cultured organisms (68%) among patients with confirmed growth. Other gram-positive organisms were cultured in 22% of patients and included *Streptococcus* and *Staphylococcus aureus*. Gram-negative organisms were isolated in 6% of the cases in the EVS, and more than one species was confirmed in 4% of the cases. Fortunately, the coagulase-negative staphylococci are one of the least virulent causes of acute-onset postoperative endophthalmitis. *S. aureus*, *Streptococcus* spp., and the gram-negative organisms usually produce a more rapidly progressive and fulminant inflammation often leading to severe visual loss.

Another subgroup of post-cataract surgery endophthalmitis is the delayed-onset category (Figure 15.3). These patients present 6 weeks or more after cataract surgery with a slowly progressive,

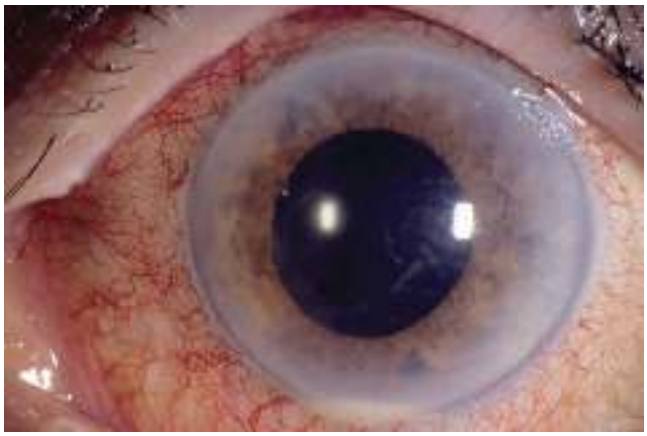

FIGURE 15.2 Hypopyon (layering of white blood cells in the anterior chamber) in an eye with acute-onset post–cataract surgery endophthalmitis.

often milder, inflammatory response. The inflammation can be isolated to the anterior segment or involve both the anterior segment and vitreous. The intraocular inflammation may respond initially to topical steroid therapy but usually recurs as the topical steroids are tapered. A common cause of delayed-onset postoperative endophthalmitis is *Propionibacterium acnes*. This is a ubiquitous, gram-positive, non–spore-forming pleomorphic bacillus. Clinical features of intraocular infections caused by this organism include granulomatous inflammation with large keratitic precipitates (clumps of inflammatory cells) on the corneal endothelium. A characteristic diagnostic feature is the presence of white intracapsular plaque, which has been shown to be composed of organisms mixed with residual lens cortex (Figure 15.4). Because *P. acnes* is a slow-growing anaerobic organism, it is important for the microbiology laboratory to be instructed to keep these anaerobic cultures for at least 2 weeks. Other organisms responsible for delayed-onset

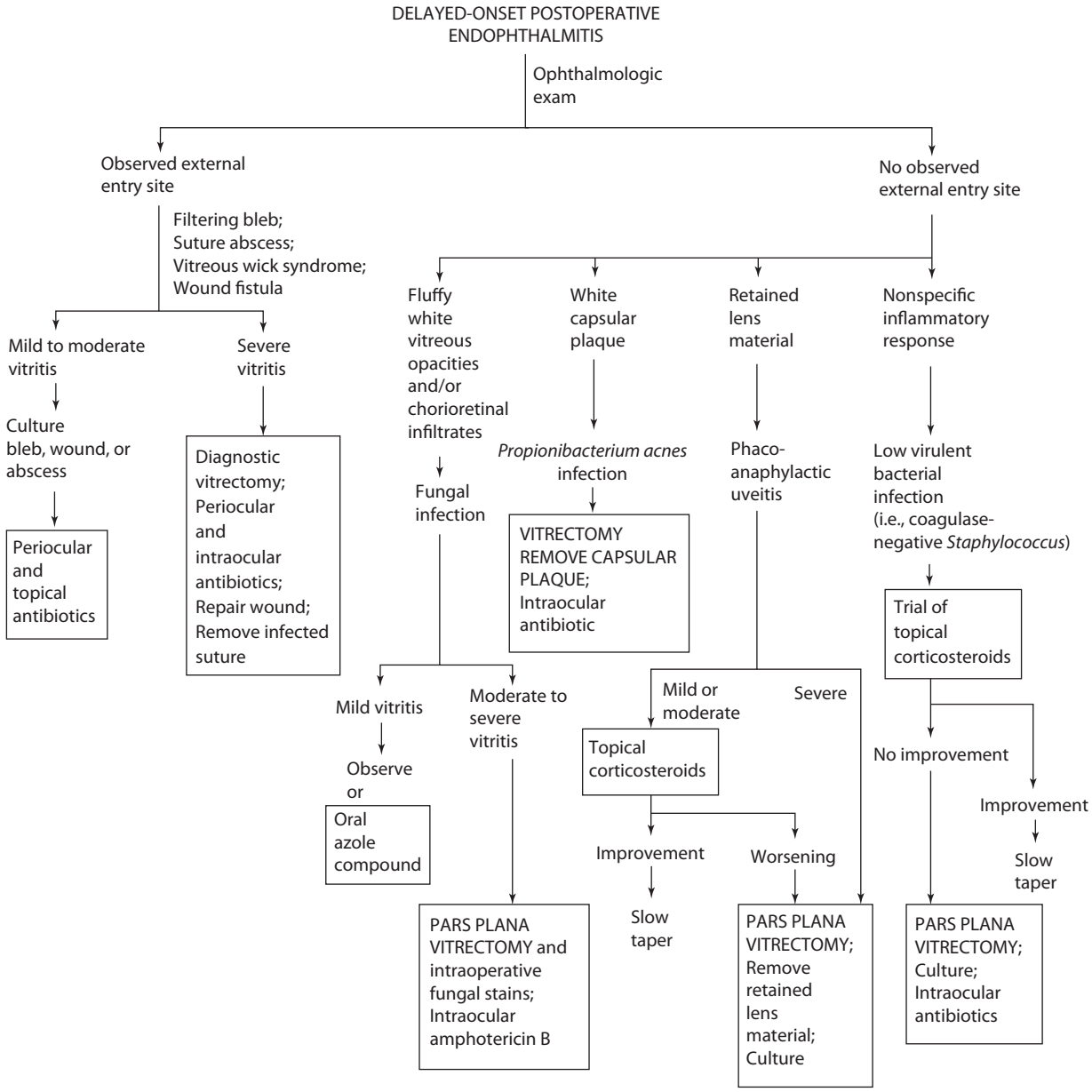

FIGURE 15.3 Algorithm for management of delayed-onset endophthalmitis.

FIGURE 15.4 White capsular plaque in a patient with *Propionibacterium acnes* endophthalmitis.

TABLE 15.1 **EXOGENOUS ENDOPHTHALMITIS CATEGORIES AND MOST FREQUENTLY ASSOCIATED ISOLATES**

Exogenous endophthalmitis categories	Most frequent isolates
Acute-onset postoperative	Coagulase negative staphylococcus
Delayed-onset postoperative	*Propionibacterium acnes*
Conjunctival filtering bleb associated	*Streptococcus*
Open globe-associated	*Bacillus* spp.
Associated with microbial keratitis	Fungi
Associated with intravitreal injections	*Staphylococcus* and *Streptococcus*

postoperative endophthalmitis include *Candida*, *Staphylococcus epidermidis*, and *Corynebacterium* species.

Delayed-onset endophthalmitis associated with conjunctival filtering blebs may present months or even years after glaucoma filtering surgery. The organisms enter the eye directly through the thin wall of the conjunctival bleb, which may develop purulent material initially (Figure 15.5). The presenting symptoms and signs are similar to acute-onset postoperative endophthalmitis. Streptococcal species are the most common organisms isolated. *Haemophilus influenzae* is also a common cause of this category of endophthalmitis. Because these organisms are more virulent than those causing acute-onset postoperative endophthalmitis, the visual outcomes are generally worse. Optic nerve damage from the preexisting glaucoma may also be a factor in poor visual outcomes. Fewer than half of the eyes achieve 20/400 or better vision. The treatment is similar to that for acute-onset postoperative endophthalmitis.

Endophthalmitis after open-globe trauma should be suspected whenever a greater than expected inflammatory response is observed. Because the organisms (e.g., *Bacillus* spp. and *Streptococcus* spp.) causing open globe-related endophthalmitis are, in general, more virulent than organisms causing postoperative endophthalmitis, the final visual outcome is often poor. The associated trauma to the eye and the frequent delay in diagnosis also contribute to a poor visual prognosis. A high index of suspicion and early diagnosis are important because even traumatized eyes infected with virulent organisms can sometimes be salvaged when treatment is promptly initiated. Prophylactic antibiotic treatment from high-risk injuries (rural setting, injuries involving vegetable matter or soil, contaminated eating utensils, retained foreign bodies) should be administered. The management of open globe-related endophthalmitis is similar to other endophthalmitis categories and often includes vitrectomy and intravitreal, subconjunctival, and topical antibiotics and steroids.

Endogenous endophthalmitis results from hematogenous spread of organisms to the eye (Table 15.1). Fungi are a more common cause than bacteria, and *Candida albicans* is the most common fungus isolated. The classic ocular finding is white vitreous opacities attached to each other by inflammatory vitreous bands in a configuration termed "string of pearls" (Figure 15.6). The second most frequently encountered fungus is *Aspergillus* spp. *Streptococcus* spp., *S. aureus*, and *Bacillus* spp. are the most common cause of endogenous bacterial endophthalmitis. These patients are frequently debilitated or immunocompromised with indwelling catheters, although endogenous endophthalmitis can occur in drug abusers and rarely in otherwise healthy patients after dental procedures or childbirth. The infection may be caused by a transient bacteremia or fungemia, in which case blood cultures may be negative. Sepsis with deep organ involvement may also be

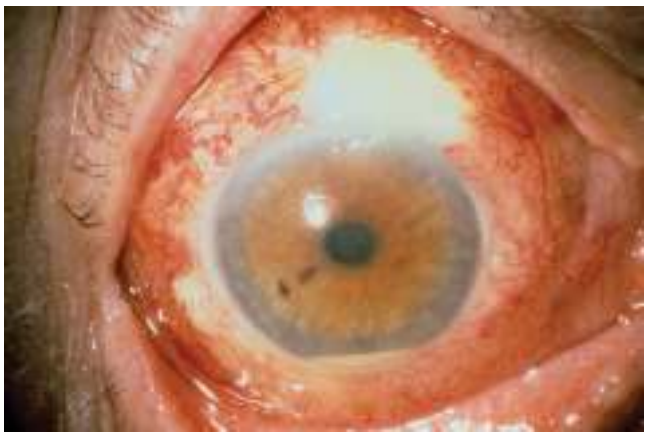

FIGURE 15.5 Purulent material in a filtering bleb in an eye with endophthalmitis 6 months following glaucoma filtering surgery.

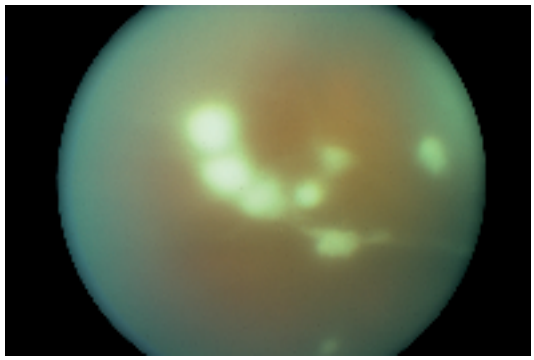

FIGURE 15.6 White inflammatory vitreous opacities in a "string of pearls" configuration in a patient with endogenous *Candida* endophthalmitis.

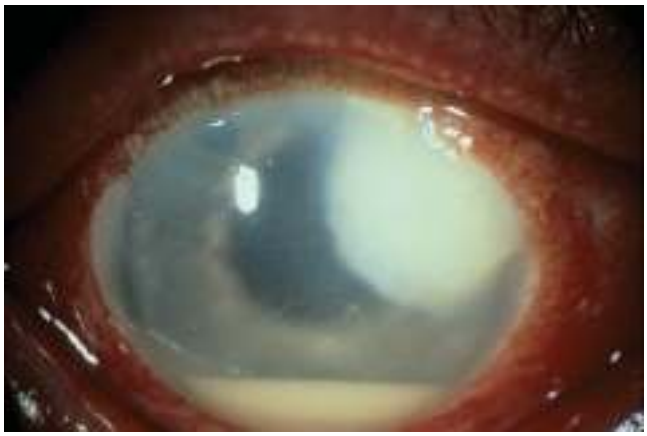

FIGURE 15.7 Infectious corneal ulcer associated with endophthalmitis.

present. When the source of infection is not apparent, a systemic workup is indicated.

Endophthalmitis can occur from direct spread of organisms into the eye from an infected corneal ulcer (Figure 15.7). Factors predisposing to the development of endophthalmitis associated with microbial keratitis include corticosteroid use and systemic immune dysfunction, as well as local ocular factors such as prolonged wear of contact lenses or contaminated lens solutions. Visual outcomes are poor due to the unusual and virulent nature of the infecting organisms.

Endophthalmitis may also occur following intravitreal injection of medications. The greater utilization of this route of therapy to treat various retinal diseases has increased the prevalence of this subgroup of endophthalmitis. Despite the growing number of intravitreal injections administered, endophthalmitis remains an uncommon complication. It has been reported after intravitreal injection of most medications, including vascular endothelial growth factor (VEGF) inhibitors and triamcinolone acetonide (IVTA). The incidence of endophthalmitis resulting from intravitreal injections ranges from 0.01% to 0.1% of injections. Since many patients receive multiple injections to treat a chronic retinal disease, an individual patient's risk approaches 1%. The clinical findings in intravitreal injection-related endophthalmitis may be similar to other forms of infectious endophthalmitis and include iritis, vitreitis, hypopyon, pain, red eye, and decreased vision. The median time to presentation is earlier in post-intravitreal injection cases (3 days) compared with postoperative cases, in which it is approximately 11 days. This may in part be related to the preponderance of more virulent organisms (streptococcal species) in the post-injection cases compared with postoperative cases. Hypopyon occurs less frequently in post-intravitreal injection cases (20%) compared with postoperative cases (64%). A sterile inflammatory uveitis may also occur after intravitreal drug injections and must be distinguished from true infection. The noninfectious cases usually present earlier following the injection (median 1.5 days but highly variable), and the external inflammatory signs such as redness, eyelid edema, and purulent discharge are usually less apparent. In addition, pain is much less common in noninfectious cases. Characteristics that may increase the risk of infection include blepharoconjunctivitis, poor patient cooperation, immunosuppression, decreased ocular barrier function (presence of filtering bleb), contamination during compounding the drug or drawing up the medication, and poor sterile injection techniques.

Diagnosis

Two important factors in the diagnosis of exogenous endophthalmitis include clinical recognition and microbiologic confirmation. Endophthalmitis should be suspected in any eye that has a marked inflammatory response out of proportion to that usually seen in the typical clinical course. Because of the potential for significant visual loss, diagnostic tests are usually performed concurrently with treatment.

The clinical diagnosis is confirmed by obtaining aqueous fluid and vitreous specimens. Although vitreous specimens are more likely to yield a positive culture than simultaneously acquired aqueous specimens, both are important because either one can be positive without the other. Aqueous cultures are obtained by needle aspiration. Vitreous cultures can be obtained using needle aspiration or using an automated vitrectomy instrument, which simultaneously cuts and aspirates the vitreous. Vitreous obtained by needle aspiration can be directly inoculated onto appropriate culture media including chocolate agar, 5% blood sheep agar, thioglycollate broth, or Sabouraud agar. A specimen obtained during vitrectomy can be concentrated by filtration though a 0.45-μm filter and is then placed on culture media. An alternative method for processing the vitrectomy specimen involves inoculating approximately 10 mL of the diluted vitrectomy specimen into standard blood culture bottles. The culture technique has been shown to yield a similar rate of culture positivity when compared with the traditional membrane filter technique. Gram stains are usually performed on aqueous and vitreous samples. In suspected fungal cases, cultures should be held at least 2 weeks, and additional information may be obtained using the Giemsa, Gomori's methenamine silver, and periodic acid–Schiff stains.

Treatment

Endophthalmitis can lead to rapid intraocular tissue destruction and irreparable damage. The mainstay of treatment for bacterial endophthalmitis is intraocular antibiotic therapy. The unique properties of the eye, including the fact that it is an enclosed cavity as well as the presence of a blood–ocular barrier, make intraocular injection of antibiotic an ideal way of achieving rapid and high antibiotic concentrations within the eye (Table 15.2).

Systemic antibiotics were traditionally used to supplement intravitreal antibiotic injections in the management of endophthalmitis but are less frequently used today. The EVS randomized patients received ceftazidime and amikacin versus no systemic antibiotic therapy, but all patients received intravitreal antibiotics. The results

TABLE 15.2 **TREATMENT FOR ACUTE-ONSET PRESUMED BACTERIAL POSTOPERATIVE ENDOPHTHALMITIS**

Route	Drug	Dose
Intravitreal	1. Vancomycin	1.0 mg/0.1 mL
	2. Ceftazidime	2.25 mg/0.1 mL
	or amikacin	0.4 mg/0.1 mL
	3. Dexamethasone	0.4 mg/0.1 mL
Subconjunctival (optional)	1. Vancomycin	25 mg/0.5 mL
	2. Ceftazidime	100 mg/0.5 mL
	3. Dexamethasone	10–24 mg/1.0 mL
Topical (optional)	1. Vancomycin	50 mg/mL
	2. Ceftazidime	100 mg/mL
	3. Steroids and cycloplegics	
Systemic (optional)	1. Vancomycin	1.0 g IV q12h
	2. Ceftazidime	1.0 g IV q12h
	(or fourth-generation fluoroquinolone for appropriate organism)	

of that study demonstrated there was no beneficial effect on final visual outcome or media clarity when these systemic antibiotics were used.

In addition to intravitreal antibiotics as the recommended treatment for suspected endophthalmitis, intravitreal dexamethasone (0.4 mg/0.1 mL) may also be used in acute-onset endophthalmitis. Although both animal studies and small retrospective clinical trials have shown improved endophthalmitis treatment results when intravitreal steroids were combined with intravitreal antibiotic injection, definitive proof of the value of intravitreal steroids is not available. The EVS protocol did not utilize intravitreal steroids, but EVS patients were placed on oral prednisone (60 mg/d) for 5 to 10 days. In addition to intravitreal dexamethasone, we also consider a 10 to 24 mg subconjunctival injection of dexamethasone at the time of initial treatment.

Vitrectomy surgery (Figures 15.1, 15.3, and 15.8) has often been recommended for more severe cases of endophthalmitis (e.g., initial visual acuity of light perception only and rapid onset within 2 days of surgery, more severe intraocular inflammation). Theoretical advantages of vitrectomy include the rapid removal of infecting organisms, intraocular toxins, vitreous opacities, and membranes that may lead to traction retinal detachment, and a more rapid clearing of the vitreous cavity. Vitrectomy also allows for collection of a greater volume of material for culture and the potential for enhanced distribution of intravitreal antibiotics.

The management of endogenous fungal endophthalmitis depends on the specific fungus isolated and the severity of infection (Figure 15.8). When a diagnosis of endogenous fungal endophthalmitis is suspected, a workup to look for other organ involvement is recommended. This should usually be done in conjunction with an internist or infectious disease subspecialist. The use and type of systemic antifungal therapy depends on the presence or absence of systemic fungal infection. When the infection is limited to the choroid and retina, systemic therapy alone may be adequate. Fluconazole or voriconazole may be used instead of amphotericin B as the systemic drug of choice for treating *Candida* endophthalmitis not associated with significant systemic involvement. Both fluconazole and voriconazole are systemically less toxic than amphotericin B and have better intraocular penetration. When moderate to severe vitreous involvement is present, a pars plana vitrectomy and intravitreal injection of amphotericin B (5–10 μg) or voriconazole (100 μg) is usually recommended. Eyes with minimal vitreous involvement may be treated with an intravitreal antifungal agent without vitrectomy.

Endogenous *Aspergillus* endophthalmitis more often occurs in immunocompromised patients, patients with *Aspergillus* endocarditis or pulmonary disease, or patients with a history of intravenous drug abuse. This organism has a propensity to involve the macular area, resulting in macular abscess and a layering of white blood cells under the retina or internal limiting membrane (Figure 15.9). A combination of local ocular therapy and systemic antifungal therapy (amphotericin B or voriconazole) is often recommended for treatment of this virulent organism.

Prevention

Because the ocular surface and adnexa are the primary sources of bacteria in exogenous endophthalmitis cases, the rate of postoperative endophthalmitis could theoretically be reduced by minimizing the eyelid and ocular surface flora, and this has been demonstrated in published clinical series. The administration of topical 5% povidone-iodine solution to the ocular adnexa and conjunctival surface significantly reduces the conjunctival bacterial colony count. Reduction of conjunctival organisms may also be enhanced with the addition of 1 to 3 days of topically applied, broad-spectrum antibiotics. Additional preventive measures include covering the eyelashes completely with a sterile plastic drape (Figure 15.10); meticulous surgical technique, including ensuring a water-tight wound closure; and aseptic technique. Minimizing excessive pooling of fluid around the wound may also be helpful.

The role of prophylactic intracameral antibiotics either as a single injection or added to the irrigating solution during the surgery is controversial. A multicenter European study demonstrated a significant reduction in the risk of developing endophthalmitis after cataract surgery when intracameral cefuroxime was administered at the time of surgery. In the EVS, 10 enrolled patients with endophthalmitis had a history of receiving intraocular antibiotics in the irrigating fluid during the cataract surgery. In addition, the potential for intraocular toxicity and development of resistant organisms limit the potential value of this method of prophylaxis. The use of intracameral vancomycin for prevention of endophthalmitis has dropped significantly due to reported cases of severe retinal toxicity known as *hemorrhagic occlusive retinal vasculitis* (HORV) developing 1 to 14 days after the vancomycin administration. Postoperative topical antibiotics are

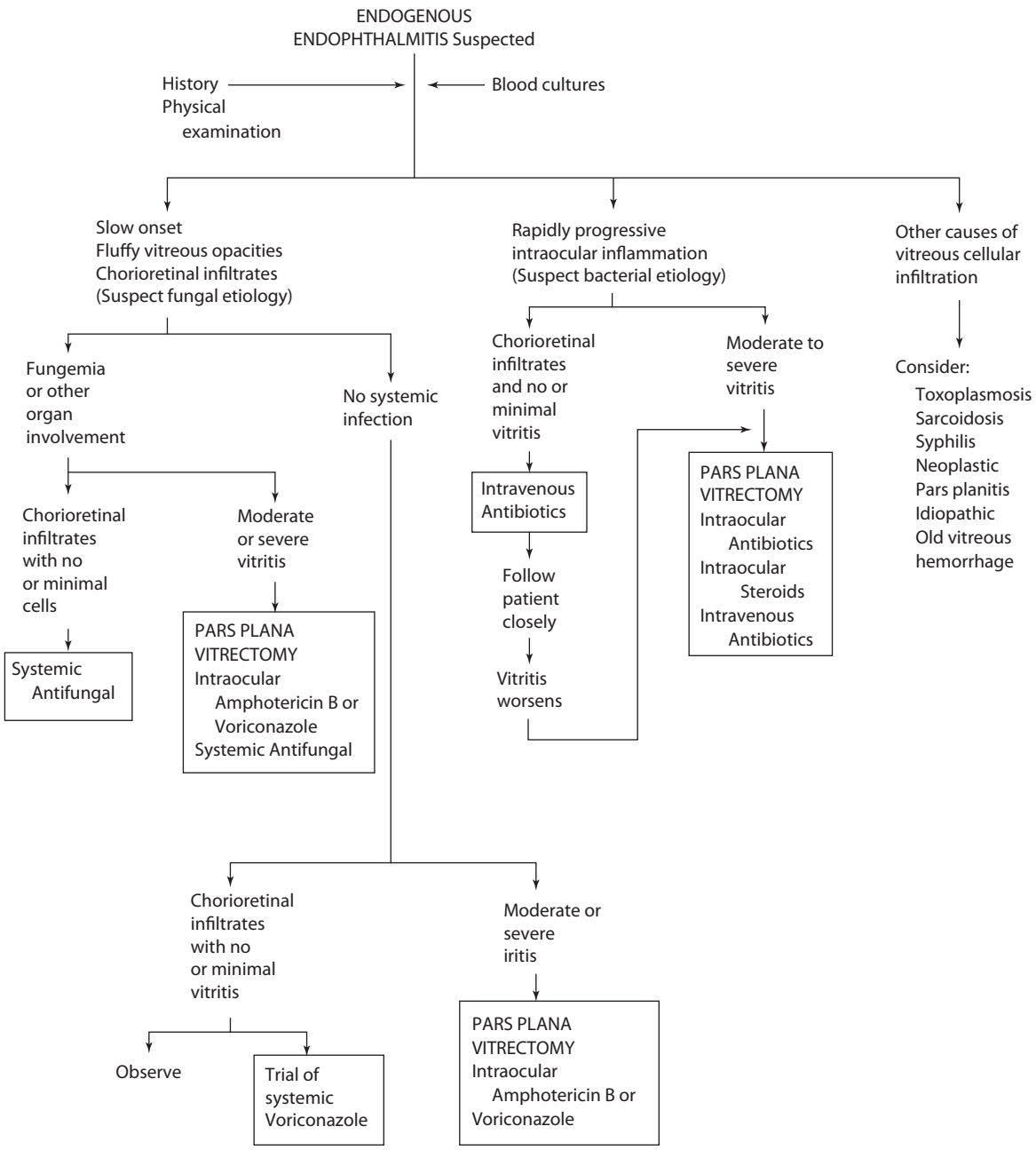

FIGURE 15.8 Algorithm for management of endogenous endophthalmitis.

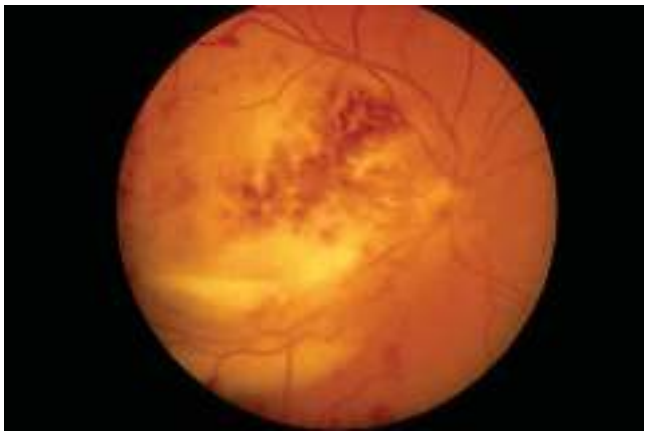

FIGURE 15.9 Macular abscess with a pseudohypopyon caused by endogenous *Aspergillus* infection.

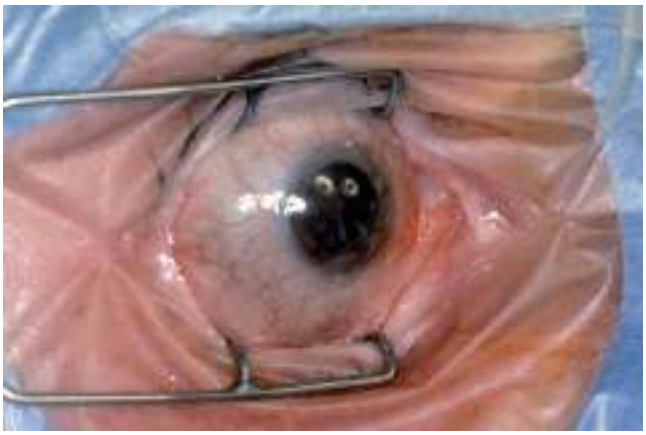

FIGURE 15.10 Eye undergoing surgery, demonstrating plastic drape covering eyelid margin.

commonly used, but again are unproved in reducing the incidence of postoperative endophthalmitis.

Suggested reading

Ahmed Y, Schimel AM, Pathengay A, et al. Endophthalmitis following open-globe injuries. *Eye*. 2012;26:212–217.

Brod RD, Flynn HW Jr, Miller D. Endogenous fungal endophthalmitis. In Tasman W, Jaaeger EA, eds. *Duane's Ophthalmology*. Philadelphia: Lipincott Williams & Wilkins; 2012.

Brod RD, Flynn HW Jr, Miller D. Endophthalmitis: Diagnosis, clinical findings, and management. In Spaeth GL, Danesh-Meyer H, Goldberg I, Kampik A, eds. *Ophthalmic Surgery Principles and Practice*. Philadelphia: Lippincott Williams & Wilkins; 2011.

Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy Study: A randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. *Arch Ophthalmol*. 1995;113:1479–1496.

Henry CR, Flynn HW Jr, Miller D, et al. Infectious keratitis progressing to endophthalmitis. A 15-year study of microbiology, associated factors and clinical outcomes. *Ophthalmology*. 2012; 119:2443–2449.

Schimel AM, Miller D, Flynn HW Jr. Evolving fluoroquinolone resistance among coagulase-negative *Staphylococcus* isolates causing endophthalmitis. *Arch Ophthalmol*. 2012;130:1617–1618.

Schwartz SE, Flynn HW Jr, Emerson GG, et al. Distinguishing between infectious endophthalmitis and noninfectious inflammation following intravitreal anti-VEGF injection. *J Vitreoretinal Surg*. 2018;3:42–44.

Seal BP, Gettinby G, Lees F, et al. ESCRS Endophthalmitis Study Group. ESCRS study of prophylaxis of postoperative endophthalmitis after cataract surgery: Preliminary report of principal results from a European multicenter study. *J Cataract Refract Surg*. 2006;32:407–410.

Wykoff CC, Flynn HW Jr, Rosenfeld PJ. Prophylaxis for endophthalmitis following intravitreal injection: Antisepsis and antibiotics. *Am J Ophthalmol*. 2011;152:717–719.

Wykoff CC, Parrott MB, Flynn HW Jr, et al. Nosocomial acute-onset endophthalmitis at a university teaching hospital (2002–2009). *Am J Ophthalmol*. 2010;150:392–398.

Yannuzzi NA, Gregori NZ, Rosenfeld PJ, et al. Endophthalmitis associated with intravitreal injections of Anti-VEGF agents at a tertiary referral center: In house and referred cases. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49:313–319.

16

Periocular and retro-orbital infections

Miriam B. Barshak and Marlene L. Durand

Periocular infections are infections of the soft tissues surrounding the globe of the eye. These include infections of the eyelids, lacrimal system, and orbit.

Eyelid infections

Each eyelid contains a fibrous tarsal plate that gives structure to the lid. Within each tarsal plate are 20 to 25 vertical meibomian glands that secrete sebum at the lid margins. Glands of Zeis, smaller sebaceous glands adjacent to the lid-margin hair follicles, also secrete sebum. Sebum prevents ocular surface drying by slowing the rate of tear film evaporation.

Hordeolum

An internal hordeolum is an acute infection of a meibomian gland and presents as a tender, swollen nodule within the lid, pointing either to the skin or conjunctival surface. An external hordeolum (stye) is an acute infection of a gland of Zeis and points to the lid margin. Both are usually caused by *Staphylococcus aureus* and respond to frequent warm compresses and topical bacitracin or erythromycin ointment.

Chalazion

A chalazion is a nontender nodule within the lid that points to the conjunctival surface and is due to a sterile granulomatous reaction to inspissated sebum within a meibomian gland. Most chalazia resolve spontaneously within 1 month, but intralesional triamcinolone or incision and curettage (I&C) may be used if conservative measures fail. A recent meta-analysis by Avcinena et al. reported that a single I&C was more effective than a single intralesional corticosteroid injection at resolving the chalazion (78% vs. 60%), but the benefit was less clear when comparing a single I&C (78% success) with two steroid injections (73%). Of note, I&C causes more pain and has a longer recovery time than do intralesional injections.

Recurrences of chalazia are common in patients with chronic blepharitis, and *Demodex* mite infestations of the lashes and lids have been implicated in both conditions. A study from China by Liang et al. reported that *Demodex* eyelid infestations, especially due to *D. brevis*, were more common in patients with than without chalazia (69% vs. 20%) and that patients with *Demodex* tended to have recurrent chalazia. Another study from China, by Yam et al., found benefit in using tea tree oil and shampoo to treat eyelids that were both *Demodex*-infested and had recurrent chalazia, although the study was small, had a short follow-up period, and had no control group. Persistent or recurrent chalazia should be biopsied to exclude squamous cell carcinoma.

Marginal blepharitis

Marginal blepharitis is a diffuse inflammation of the lid margins and is classified as anterior or posterior, with the former associated with seborrheic dermatosis or microbial colonization and the latter with meibomian gland dysfunction. Recurrent blepharitis may be treated with gentle lid scrubs and topical bacitracin; an oral tetracycline may be helpful if there is associated rosacea. Unusual causes of blepharitis have included *Pseudomonas*, *Capnocytophaga*, herpes simplex virus, crab lice, and *Demodex* mites. *Demodex* infestations, characterized by cylindrical dandruff around the lashes, have been associated with chronic blepharitis, and treatment with tea tree oil lid scrubs have been helpful in some studies (e.g., see Koo et al. in the "Suggested reading" list).

Infections of the lacrimal system

Tears are mainly produced by the lacrimal gland, which is located beneath the upper outer rim of the orbit. Tears flow medially across the eye; collect via the puncta, canaliculi, lacrimal sac, and lacrimal duct; and drain into the nose beneath the inferior nasal turbinate.

Dacryocystitis, or infection of the lacrimal sac, is the most common infection of the lacrimal system and results from obstruction of the lacrimal duct. Patients often give a history of chronic unilateral tearing (epiphora). Acute dacryocystitis presents as a painful, red swelling near the nasal corner of the eye (Figure 16.1). The most common bacteria involved are *S. aureus* and streptococci, although gram-negative bacilli such as *Escherichia coli* may be present in up to 25% of cases. Treatment requires systemic antibiotics and often incision and drainage of the lacrimal sac abscess. A dacryocystorhinostomy is often performed to treat the underlying chronic duct obstruction once the acute infection has subsided.

Dacryoadenitis, or infection of the lacrimal gland, is uncommon. Patients present with swelling in the lateral portion of the upper lid. Acute infection is most often due to *S. aureus* or streptococci, but Epstein–Barr virus may cause acute dacryoadenitis in mononucleosis. Chronic dacryoadenitis is usually seen as part of Sjögren's syndrome, sarcoidosis, or other inflammatory conditions, although *Mycobacterium tuberculosis* may rarely cause chronic dacryoadenitis. Tumors cause 25% of cases of chronic lacrimal gland enlargement.

Canaliculitis is usually a chronic infection of the canaliculi due to *Actinomyces israelii*, which forms concretions ("sulfur granules"). Staphylococci and streptococci are other etiologies. Treatment is usually office curettage of the concretions and/or topical antibiotic eyedrops. (See also Chapter 9, "Salivary and lacrimal gland infections.")

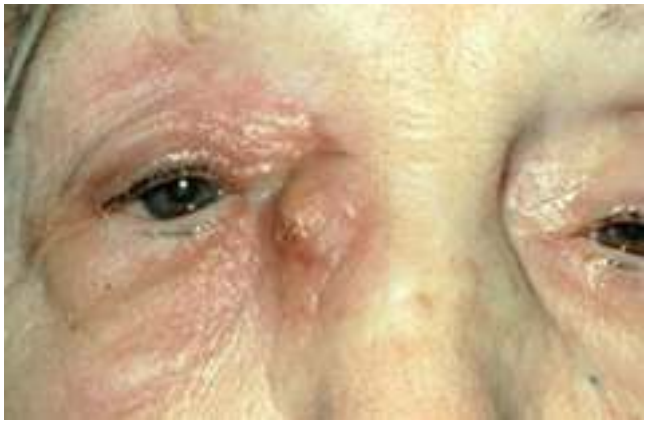

FIGURE 16.1 Acute dacryocystitis. Note swelling below the nasal corner of the right eye.

Preseptal and orbital infections

Although both preseptal and orbital infections may present with a similar external appearance of swollen, red eyelids, the distinction is important because orbital infections are usually much more serious. The barrier between the preseptal and orbital soft tissues is the orbital septum, a fibrous membrane that arises from the periosteum of the orbital rim and extends to the tarsal plates of the lids. Preseptal infections (sometimes called "periorbital") almost never extend beyond the orbital septum and into the orbit. Patients with either preseptal or orbital cellulitis present with swollen, red lids (Figure 16.2). The lids may be swollen shut, but it is essential to open them and examine the eye in order to determine if there are any "orbital signs." There are three orbital signs: decreased vision, proptosis (which may only be measurable and not obvious), and limitation in extraocular movement. Patients with orbital infections have at least one of these three findings, while patients with preseptal cellulitis have none. Both preseptal and orbital cellulitis occur more often in children than in adults. Sinusitis, especially ethmoid sinusitis, is the etiology of most orbital infections in any age group. The ethmoid sinus is separated from the orbit by the lamina papyracea, a

FIGURE 16.2 Lid swelling and erythema, shown here are features of both preseptal and orbital cellulitis; opening the eyelids is necessary to distinguish these entities.

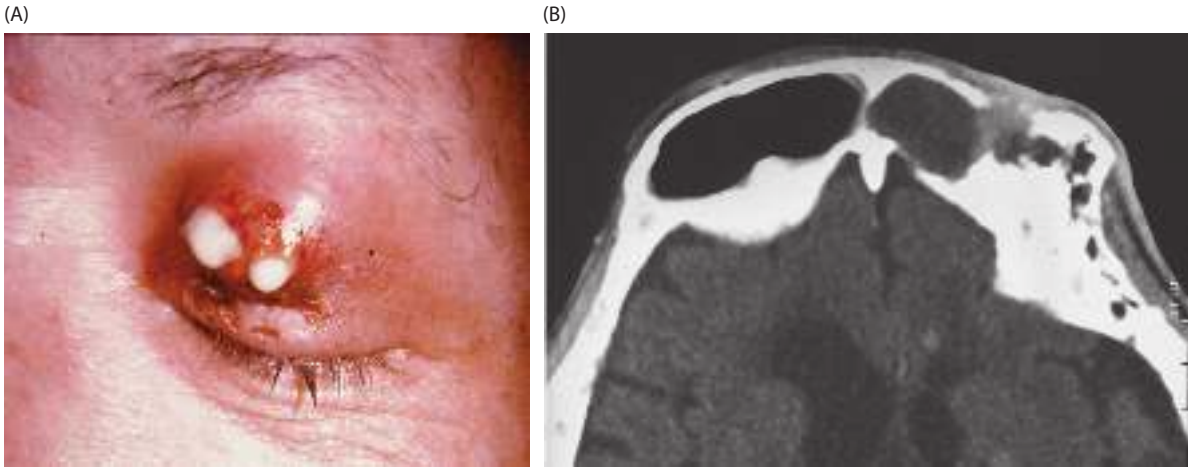

FIGURE 16.3 (A) Purulent drainage in upper lid from frontal sinusitis (superinfection of chronic frontal sinus mucocele). (B) CT of patient shown in A. Chronic frontal sinus infection led to erosion of the floor of the frontal sinus, which is also the roof of the orbit.

paper-thin bone. Frontal sinusitis may also lead to orbital infections, often from acute bacterial superinfection of a previously undiagnosed mucocele that has eroded the frontal sinus floor (orbital roof) through chronic pressure (Figure 16.3A, B).

Preseptal cellulitis is similar to facial cellulitis and is an infection of the superficial lid skin and preseptal soft tissues. It presents as unilateral redness and swelling of the eyelids but with normal vision and extraocular movements. There is no proptosis. The etiology is ethmoid sinusitis in many cases, and the bacterial etiology in sinogenic cases is presumed to be due to the usual sinus pathogens, *Streptococcus pneumoniae* and *Haemophilus influenzae*, in addition to *Staphylococcus aureus*. Some cases of preseptal cellulitis are due to superinfection of a break in the lid skin (e.g., insect bite, rash, and abrasion), and these cases are usually caused by *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]) or group A streptococci. A third etiology of preseptal cellulitis is bacteremic seeding. This is now very rare, although it was more common in the pre-Hib vaccine era when most cases were due to *H. influenzae* bacteremia. The entity is usually seen only in young children (e.g., under age 3) and is now caused by *S. pneumoniae*, group A streptococci, other streptococci, or occasionally nontypeable *H. influenzae*. These children should be hospitalized for treatment with intravenous (IV) antibiotics directed against the cause of the bacteremia. Preseptal or orbital cellulitis has been described as a rare manifestation of bacteremia due to *S. pneumoniae* in adults with lupus erythematosus or hematologic disorders. *Pseudomonas* bacteremia has also caused preseptal or orbital cellulitis in neutropenic cancer patients.

Orbital cellulitis is an infection of the soft tissues of the orbit. Orbital cellulitis was the most common diagnosis in admissions to US hospitals for primary ophthalmic conditions according to a recent study by Iftikhar et al., accounting for >14% of such admissions. Patients with orbital cellulitis present with unilateral eyelid swelling and erythema, eye pain, and some degree of ophthalmoplegia or proptosis or both. There is often pain with eye movement. The proptosis may not be obvious and should be measured with a Hertel's exophthalmometer. A difference of 2 mm or more between the eyes signifies proptosis. Vision may be decreased, and there also may be an afferent pupillary defect signifying optic nerve involvement. Fever and leukocytosis are usually present in pediatric cases but may be absent in adults. Nearly all cases of orbital cellulitis in children and most in adults are caused by sinusitis, and many patients give a history of recent sinusitis symptoms. Occasional cases in adults are caused by extension of infection from acute dacryoadenitis, dacryocystitis, endophthalmitis, peribulbar anesthesia, or penetrating orbital trauma. As noted earlier, pneumococcal and *Pseudomonas* bacteremia may rarely cause preseptal or orbital cellulitis in patients with certain risk factors. Diagnosis of orbital cellulitis is by physical examination and CT scan of the orbit. The CT scan shows inflammation in the orbital soft tissues (e.g., fat "stranding") but no abscess. Treatment is with IV broad-spectrum antibiotics directed against *S. aureus*, *S. pneumoniae* and other streptococci, anaerobes, and *H. influenzae*. Sinus drainage surgery is occasionally necessary as well. In neonates with community-acquired orbital cellulitis, MRSA is an important cause and is associated with bacteremia.

Several studies have evaluated the use of adjunctive corticosteroid treatment in children with orbital cellulitis. A study by Chen et al. found that children who received IV corticosteroids (dexamethasone 0.3 mg/kg/d q6h for 3 days) and antibiotics at the time of admission had significantly shorter hospital stays than those who received only antibiotics, whether or not surgical intervention was undertaken. A study by Davies et al. measured C-reactive protein (CRP) daily among patients with orbital cellulitis and added oral prednisone at 1 mg/kg/d for 7 days once the CRP was below 4 mg/dL. The corticosteroid treatment was associated with a shorter hospital stay, although there were only seven patients in the non-corticosteroid group. There were no cases of vision loss in either study.

Orbital subperiosteal abscess presents like orbital cellulitis, although symptoms are usually more severe. Because the ethmoid sinus is the source of infection in nearly all cases, the purulent collection is usually beneath the medial orbital periosteum. The periosteum bulges into the orbit, which may limit medial rectus

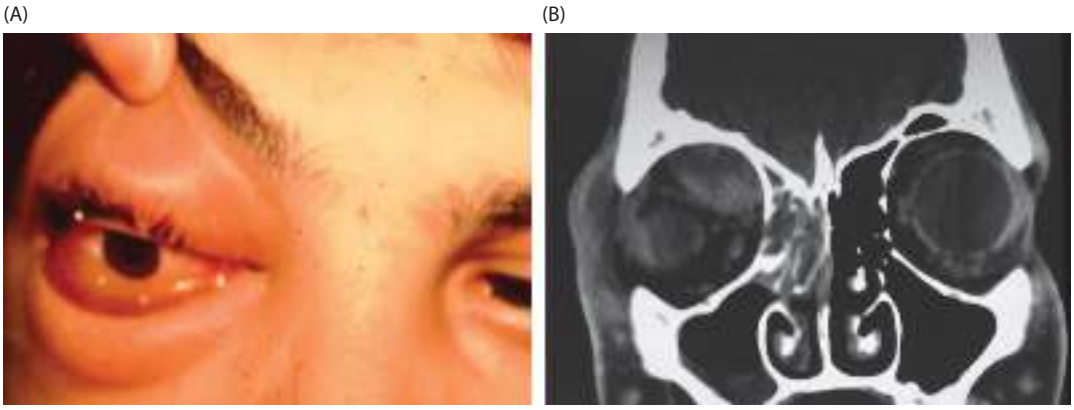

FIGURE 16.4 (A) Orbital abscess causing eye to look "down and out." (B) CT of patient in A. Note abscess in superomedial right orbit.

movement and cause the eye to look "down and out." Orbital CT scan demonstrates the collection. Most cases in older children and adults require prompt surgical drainage of the abscess in addition to IV antibiotics, while children <9 with normal vision and small, medial abscesses may respond to medical therapy alone. A study by Ryan et al. of 68 children with subperiosteal abscesses found that only one-third required surgery, and those requiring surgery were older (8 vs. 6 years) and had larger abscesses (>10 mm on CT). Broad-spectrum IV antibiotics (e.g., vancomycin, metronidazole, and ceftriaxone) should be given initially in all cases until culture results are available. Most cases of subperiosteal abscess are caused by a mixture of anaerobes and aerobes, with aerobes including one or more of the following: *S. aureus*, *Streptococcus anginosus* (*milleri*) group, group A streptococci, *H. influenzae*, or *Moraxella catarrhalis*.

Orbital abscess has clinical and microbiologic features identical to those of orbital subperiosteal abscess. The abscess is usually medial or superomedial in the orbit, which may cause the eye to look in the "down and out" directions (Figure 16.4A). An orbital CT scan reveals the collection (Figure 16.4B). Treatment is immediate surgical drainage and broad-spectrum IV antibiotics. Delay in drainage of the abscess may lead to permanent loss of vision.

Retro-orbital infections

Cavernous sinus thrombophlebitis (CST) is a very rare complication of orbital infections or of infections in the midface "danger triangle" (upper lip to root of the nose). The two cavernous sinuses are venous plexuses that are connected by intercavernous sinuses; involvement of one sinus can rapidly spread to the opposite side. Cranial nerves III, IV, V1, V2, and VI run through the cavernous sinus. Patients with CST typically present with headache, unilateral orbital cellulitis, and hypesthesia in the distribution of V1 and V2 (forehead and cheek). They sometimes then develop similar findings in the opposite eye. Diagnosis is by clinical findings supported by MRI and MR venography (MRV). The most common bacterial etiology is *S. aureus*, including MRSA, but streptococci (especially *S. anginosus* group), anaerobes, and gram-negative bacilli may be present depending on the origin of infection. Treatment is with broad-spectrum IV antibiotics. The value of anticoagulation is unknown (see also Chapter 77, "Intracranial suppuration").

Invasive fungal sinusitis usually presents with orbital cellulitis, orbital apex syndrome, and/or cavernous sinus involvement. At presentation, there may be hypesthesia of cranial nerve V divisions V1 and V2 due to orbital apex or cavernous sinus involvement. Mucormycosis should be suspected in any patient with risk factors who presents with symptoms and signs of orbital cellulitis. Risk factors include diabetes (often poorly controlled), hematologic malignancies, solid organ or hematopoietic cell transplantation, immunosuppression including chronic corticosteroid use, and deferoxamine therapy. Clinical findings include ophthalmoplegia, proptosis, and lid edema (Figure 16.5), and, in contrast with bacterial orbital cellulitis, lid erythema may be faint or absent rather than "hot" looking. While patients with bacterial orbital cellulitis complain of pain in their involved eye and orbit, patients with mucormycosis may complain that the most prominent pain is in the temple and forehead. Hypesthesia of the cheek and forehead is often present, and the periorbital skin, including the forehead, may be indurated. *Aspergillus* infections of the orbit and cavernous

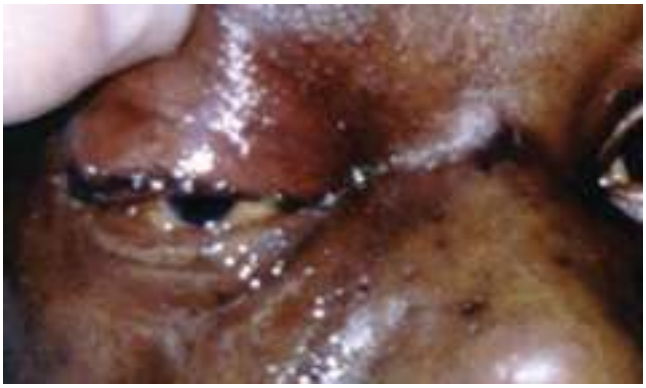

FIGURE 16.5 Rhinocerebral mucormycosis in a diabetic patient. The lids are swollen but less erythematous than they would be in typical acute bacterial orbital cellulitis.

sinus usually arise from invasive sphenoid sinus aspergillosis. Patients may present subacutely, with gradual onset of proptosis, ophthalmoplegia, and visual loss over days to weeks. There may be minimal lid swelling and erythema. The orbital apex may be involved first, leading to an orbital apex syndrome. The optic nerve and cranial nerves III, IV, VI, and V1 run through the orbital apex, so patients with this syndrome usually present with unilateral blindness, ptosis, proptosis, a fixed dilated pupil, and ophthalmoplegia. Invasive aspergillosis and mucormycosis are further discussed in Chapters 173 and 174.

Suggested reading

Aycinena AR, Achiron A, Paul M, et al. Incision and curettage versus steroid injection for the treatment of chalazia: A meta-analysis. *Ophthalmic Plast Reconstr Surg*. 2016;32:220–224.

Chen L, Silverman N, Wu A, et al. Intravenous steroids with antibiotics on admission for children with orbital cellulitis. *Ophthalmic Plast Reconstr Surg*. 2018;34:205–208.

Davies BW, Smith JM, Hink EM, et al. C-reactive protein as a marker for initiating steroid treatment in children with orbital cellulitis. *Ophthalmic Plast Reconstr Surg*. 2015;31:364–368.

Hossain P, Konstantopoulos A. Blepharitis remains a diagnostic enigma: A role for tea tree oil shampoo? *Eye (Lond)*. 2015;29:1520–1521.

Huang YY, Yu WK, Tsai CC, et al. Clinical features, microbiological profiles and treatment outcome of lacrimal plug-related canaliculitis compared with those of primary canaliculitis. *Br J Ophthalmol*. 2016 Sep;100(9):1285–1289.

Iftikhar M, Junaid N, Lemus M, et al. Epidemiology of primary ophthalmic inpatient admissions in the United States. *Am J Ophthalmol*. 2018;185:101–109.

Kobayashi D, Givner LB, Yeatts RP, et al. Infantile orbital cellulitis secondary to community-associated methicillin-resistant Staphylococcus aureus. *J AAPOS*. 2011;15(2):208.

Koo H, Kim TH, Kim KW, Wee SW, Chun YS, Kim JC. Ocular surface discomfort and Demodex: effect of tea tree oil eyelid scrub in Demodex blepharitis. *J Korean Med Sci*. 2012;27:1574–1579.

Liang L, Ding X, Tseng S. High prevalence of *Demodex brevis* infestation in patients with chalazia. *Am J Ophthalmol*. 2014;157:342–348.

Liao S, Durand ML, Cunningham MJ. Sinogenic orbital and subperiosteal abscesses: microbiology and methicillin-resistant *Staphylococcus aureus* incidence. *Otolaryngol Head Neck Surg*. 2010;143:392–396.

Peña MT, Preciado D, Orestes M, et al. Orbital complications of acute sinusitis: Changes in the post-pneumococcal vaccine era. *JAMA Otolaryngol Head Neck Surg*. 2013;139(3):223–227.

Rimon A, Hoffer V, Prais D, et al. Periorbital cellulitis in the era of *Haemophilus influenzae* type B vaccine: Predisposing factors and etiologic agents in hospitalized children. *J Pediatr Ophthalmol Strabismus*. 2008;45:300–304.

Ryan JT, Preciado DA, Bauman N, et al. Management of pediatric orbital cellulitis in patients with radiographic findings of subperiosteal abscess. *Otolaryngol Head Neck Surg*. 2009;140(6):907.

Seltz LB, Smith J, Durairaj VD, et al. Microbiology and antibiotic management of orbital cellulitis. *Pediatrics*. 2011;127(3):e566–e572.

Yam JC, Tang BS, Chan TM, et al. Ocular demidicidosis as a risk factor of adult recurrent chalazion. *Eur J Ophthalmol* 2014;24:159–163.

Younis RT, Anand VK, Davidson B. The role of computed tomography and magnetic resonance imaging in patients with sinusitis with complications. *Laryngoscope*. 2002;112:224–229.

Section 4

Clinical syndromes: Skin and lymph nodes

17

Fever and rash

John W. Sensakovic and Leon G. Smith

Fever and rash is one of the common symptom complexes presenting in medical practice. Because of the wide range of diseases that can present with this complex, the patient presenting with fever and rash is also one of the most challenging clinical syndromes.

Although both infectious and noninfectious disease processes can present with fever and rash, infectious causes are considered here. Nevertheless, noninfectious causes such as drug reactions, systemic vasculitis, serum sickness, erythema multiforme, toxic epidermal necrolysis, and Sweet's syndrome are often in the differential diagnosis.

The approach to the patient with infectious fever and rash should begin with the appreciation that causes include common infections that are often benign, serious emergent infections that can be rapidly fatal, and unusual infections that can pose a diagnostic challenge. Key features in the history and physical can be particularly important. These include childhood diseases and immunization history, seasonal diseases, travel history and geography, exposure, sexual history, and medication usage, as well as prodromal and accompanying symptoms. Physical examination, with particular attention to the characteristics of the rash, can be key, along with vital signs to assess severity of the illness, and particular attention to meningeal signs, lymph nodes, mucous membranes, conjunctiva, and joint examination. Features of the rash to consider include characteristics and distribution of the lesions, timing of onset of rash in relation to fever, and changes in morphology of the lesions.

When faced with the patient with fever and rash, the physician must be acutely aware of those several very serious infections that are commonly fulminant and that can be rapidly fatal. Thus, the physician must quickly address a series of important issues simultaneously (Box 17.1). These include the question of contagious potential to the medical staff, the need for rapid resuscitation in those patients who can present in shock, the rapid recognition of and therapeutic intervention for those infections that tend to be fulminant, and the need for a thorough evaluation and workup for the extensive list of diagnostic possibilities that can present with fever and rash.

Emergent conditions presenting with fever and rash

Rapid recognition and therapeutic intervention are essential in certain diseases presenting with fever and rash to minimize as much as possible the associated morbidity and mortality. The major conditions involved include meningococcemia, Rocky Mountain spotted fever, staphylococcal toxic shock syndrome, streptococcal toxic shock-like syndrome, bacteremia or endocarditis with septic emboli, and the rapidly spreading cellulitis (Table 17.1 and Box 17.2). All of these conditions can present with fever and rash in a fulminant, rapidly progressive form, requiring expedient therapeutic intervention, often on an empiric basis, before confirmation of the diagnosis, if the associated mortality rates are to be minimized.

BOX 17.1

Major issues in patients with fever and rash

Contagious potential
Resuscitation
Rapid therapy
Diagnostic evaluation
Clinical setting
Severity of illness
Nature of rash
Petechial
Cellulitic
Vesiculobullous Maculopapular

Generally, the most serious and rapidly progressive of these are associated with a petechial rash. These 1- to 2-mm purple lesions do not blanch with pressure, often coalesce to form larger ecchymotic areas, and usually are in the presence of leukocytosis and thrombocytopenia. Meningococcemia, Rocky Mountain spotted fever, and bacteremia/endocarditis with septic emboli are perhaps the most notable. However, other causes include gonococcemia, typhus, and rat-bite fever; viral infection, including dengue, hepatitis B, rubella, and Epstein–Barr virus (EBV); and noninfectious causes, including thrombotic thrombocytopenia purpura, Henoch–Schönlein purpura, vasculitis, and scurvy.

Rapidly progressive diseases with erythematous rash include staphylococcal toxic shock syndrome and streptococcal toxic shock-like syndrome, as well as the rapidly progressive cellulitis, which often have a vesicobullous component. In these conditions, as well as with necrotizing fasciitis, the patient often looks toxic out of proportion to the extent of the rash.

Meningococcemia

Of all the diseases presenting with fever and rash, meningococcemia is the one most likely to be rapidly fatal without early recognition and treatment. The ominous palpable purpura in an acutely ill, febrile patient characteristically suggests this disease. Other features that may be helpful in earlier diagnosis include sore throat, fever, muscle tenderness, and headache in the presence of significant leukocytosis and thrombocytopenia. The illness tends to occur in late winter and early spring and is well known to occur under crowded living conditions. The initial rash may be maculopapular, with the earliest petechial lesions occurring over pressure points such as the small of the back, and can easily be overlooked. The rash can progress rapidly over a few hours to the more classic, petechial form with peripheral acrocyanosis. Management requires immediate recognition, vigorous fluid replacement, and rapid therapy with aqueous penicillin or a third-generation cephalosporin, 12 to 24 million units daily intravenously (IV). Patients presenting with signs of adrenal insufficiency also require steroid replacement. The use of gamma globulin is controversial for patients with meningitis. Dexamethasone for 2 days started just before or with the first dose of antibiotics is indicated.

Rocky mountain spotted fever

Rocky Mountain spotted fever can also present with fever and petechial rash in an acutely ill patient, yet is different from meningococcemia in several respects. The illness begins with fever and severe headache, occurs between May and September in temperate-zone states, and there is a history of tick exposure in 75% of the cases. The rash appears several days into the illness, begins as a maculopapular rash on wrists and ankles, and progresses to a petechial form and spreads to palms,

TABLE 17.1 **APPROACH TO SERIOUSLY ILL PATIENTS WITH FEVER AND RASH**

Clues	Disease	Diagnosis
Multiple purpuric lesions Earliest lesions small of back Rapid progression over hours	Meningococcemia	Gram stain of pustules Blood cultures
Tick exposure, headache, fever, rash 2nd–6th days Wrists, ankles, progressing to palms, soles, trunk	Rocky Mountain spotted fever	DFA of skin biopsy Serology (CF)
Fever, rash, hypotension, menstruating female using tampons Surgical wound or skin infection	Toxic shock syndrome	Isolation of phage group I staphylococci
Fever, rash, hypotension, rapid onset of organ dysfunction	Group A streptococcal toxic shock-like syndrome	Evidence of group A streptococcal infection
Elderly or immunocompromised patient Several lesions, macular to necrotic pustules	Bacteremia with septic emboli	Gram stain of pustules Blood cultures Gram stain of buffy coat
Painful spreading lesions Local trauma	Rapidly spreading cellulitis	Clinical

Abbreviations: DFA = direct fluorescent antibody; CF = complement fixation.

BOX 17.2

Characteristics of serious rashes

Onset with or after fever
Petechial lesions
Rapid spread
Purpuric lesions
Palmar/plantar involvement

soles, and trunk. A leukocytosis with thrombocytopenia is commonly present. Therapy is doxycycline, 100 mg every 12 hours, and must be instituted early on a presumptive basis, before serologic confirmation, if mortality is to be significantly reduced. Alternative therapy is with chloramphenicol, 50 mg/ kg/day IV. In institutions where available, immunofluorescence staining of a skin biopsy specimen of the rash can yield a rapid diagnosis. A review from Duke University Medical Center cited 10 cases of illness without rash or with fleeting atypical skin eruptions, emphasizing the need for a high index of suspicion in acutely ill patients with endemic tick exposure.

Toxic shock syndrome

Toxic shock syndrome caused by the pyrogenic exotoxin of phage group 1 *Staphylococcus aureus* classically presented in a young menstruating female using a tampon. Causive strains produce staphyloccal exotoxin TSST-1. However, recently cases more commonly occur as a result of nonvaginal foci of staphylococcal infection, including surgical wound infections, infectious endocarditis nasal packing, and infected catheters. The rash tends to be diffuse and scarlatiniform in character, with associated conjunctival hyperemia and a "strawberry tongue." The rash is associated with fever, hypotension, and evidence of multisystem derangement. Therapy requires vigorous fluid replacement, removal of the infected tampon or other foreign body, or drainage of an identified infected focus, and nafcillin or oxacillin at 8 to 12 g/ day. Some experts also recommend vaginal lavage with a betadine solution as a local antibacterial agent as well as for removal of any nonabsorbed exotoxin.

Staphylococcal scalded skin syndrome can be seen in young children infected with a staphylococcal strain producing epidermolysin A or B. The result is a superficial sloughing of the skin with a painful erythema. Nikolsky's sign, "onion skin" peeling of the skin with gentle pressure, is seen.

A somewhat similar noninfectious entity, toxic epidermal necrolysis, is seen in adults. This typically is drug induced, and the sloughing of the skin occurs deeper, at the dermal–epidermal junction.

Group a streptococcal toxic shock-like syndrome

The changing epidemiology of group A streptococcal infections has been recognized as a resurgence in rheumatic fever and an increase in the frequency of invasive infections and bacteremia. In addition, the group A streptococcal toxic shock-like syndrome has been recently defined by its characteristic early onset of shock and multiorgan failure in the presence of group A streptococcal infection, often with a generalized erythematous rash that may desquamate. Most of the isolates produce pyrogenic exotoxin A, and some cases have been associated with necrotic soft-tissue infections. In group A streptococcal toxic shock-like syndrome, mortality up to 30% has been described compared to 3% with staphylococcal toxic shock syndrome.

Septic emboli

The diagnosis of septic emboli associated with bacterial bloodstream infection must be considered in any seriously ill patient with fever and rash. Such infections most commonly present in elderly or immunocompromised patients. Solitary or widely scattered purplish lesions, non-blanching and often with necrotic centers, suggest the diagnosis. The lesions often involve the digits. Ecthyma gangrenosum is one such lesion seen with *Pseudomonas aeruginosa* bacteremia. Such lesions are also seen most often in *S. aureus* bacteremia, *Candida albicans* fungemia, and infectious endocarditis. Gram stain of aspirates from the skin lesions and of the buffy coat of the blood can be rapidly diagnostic; blood cultures are confirmatory. Presumptive therapy should cover methicillin-resistant *S. aureus* as a problem; a regimen of vancomycin, 1 g IV every 12 hours, and gram-negative coverage is recommended pending culture identification.

Rapidly spreading cellulitis

The various types of rapidly spreading cellulitis associated with fever and rash are not difficult to recognize in most instances because of the painful spreading inflammatory lesion on the skin. The diagnostic difficulty involves differentiating the various types of rapidly spreading cellulitis based on probable causative organism or organisms and whether infection is confined to the surface or extends to deeper structures, including fascia and muscle. With deep extension, case adequate surgical debridement is essential, along with appropriate antibiotic therapy. "Flesh-eating" necrotizing fasciitis from group A streptococcus can be difficult to diagnose, and it is increasing in frequency.

Common infections presenting with fever and rash

The most common infections presenting with fever and rash also fortunately include conditions that are generally benign.

Many of these febrile exanthems are due to viral illnesses of children or inadequately immunized adults. Such illnesses as measles, varicella, rubella, erythema infectiosum due to parvovirus B19, and roseola infantum due to human herpesvirus type 6 (HHV-6) are typical. Kawasaki syndrome and streptococcal scarlet fever should also be considered in this age group.

In older children presenting with fever, rash, sore throat, and adenopathy, EBV infection is common. In young adults presenting in such fashion where EBV and group A *Streptococcus* have been ruled out, pharyngitis with fever and rash due to a recently described organism, *Arcanobacterium*, should be considered. This gram-positive bacillus is usually very sensitive to erythromycin.

Enteroviral infections due to Coxsackieviruses and echoviruses frequently present with febrile exanthem and should especially be considered during summer months and when accompanied with gastrointestinal symptoms.

TABLE 17.2 **RARE CAUSES OF FEVER AND RASH**

Infectious		
Viral		
Parvovirus	Hand-foot-mouth	West Nile
EBV	Herpes simplex	RSV
CMV	Herpes zoster	HHV-6
Coxsackie	HIV	Smallpox
Enterovirus (echo)	Hepatitis B and C	Vaccina
Dengue	Monkeypox	
Ebola	Rubella	
Bacteria		
Rat-bite fever	Leptospirosis	Neisseria
Mycoplasma pneumonia	Lyme	Gonorrhea
	Bartonella	Salmonella
BCG	Borrelia	
Mycobacteria		
Fungal		
Candida	Coccidiomycosis	Histoplasmosis
Sporotrichosis		
Noninfectious		
Erythema multiforme	Vasculitis's	Porphyria
Kawasaki	Sweet's syndrome	Drug reaction
Graft vs. host	Pyoderma gangrenosum	

Unusual infections that can pose a diagnostic challenge

A wide variety of less common infections that can present with fever and rash should also be considered, especially if associated with geographic or seasonal exposure (Table 17.2).

Lyme borreliosis can present with fever and a characteristic erythema migrans rash, resulting from geographic tick exposure. Diagnosis can be difficult early in the infection when serology can be negative and the rash can be atypical or missed. Follow-up serology may be diagnostic.

The recently recognized syndromes of West Nile virus infection, including West Nile fever, encephalitis, and facial paralysis, can present with fever and rash. The disease has a summer–fall prevalence and is associated most often with exposure to infected household mosquitoes. Other uncommon infections to be considered, also with geographic and seasonal occurrence, include ehrlichiosis, dengue fever, tularemia, plague, leptospirosis, and typhoid fever.

Although a wide variety of diagnostic tests and procedures can be helpful in the workup of the patient presenting with fever and rash, none of these is as important as a careful history and physical examination.

Suggested reading

Drage L. Life-threatening rashes: dermatologic signs of four infectious diseases. *Mayo Clin Proc*. 1999;74:68–72.

Kingston M, Mackey D. Skin clues in the diagnosis of life-threatening infections. *Rev Infect Dis*. 1986;8:1–11.

Mackenzie A, Fuite LA, Chan FT, et al. Incidence and pathogenicity of *Arcanobacterium hemolyticum* during a two year study in Ottawa. *Clin Infect Dis*. 1995;21: 177–181.

Oblinger M, Sands M. Fever and rash. In Stein JH, ed. *Integral Medicine*. Boston, MA: Little, Brown; 1983.

Sarkar R, Mishra K, Garg VK. Fever with rash in a child in India. *Indian J Dermatol Venereol Leprol*. 2012;78(3):251–262.

Schlossberg D. Fever and rash. *Infect Dis Clin North Am*. 1996;10:101–110.

Valdez L, Septinus E. Clinical approach to rash and fever. *Infect Dis Pract*. 1996; 20:1.

The Working Group on Severe Streptococcal Infections. Defining the group A streptococcal toxic shock syndrome. *JAMA*. 1993;269:390–391.

18

Toxic shock syndrome and Kawasaki disease

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Toxic shock syndrome

Staphylococcal and streptococcal toxic shock syndromes (TSS) are acute-onset multiorgan illnesses defined by criteria listed in Boxes 18.1 and 18.2. Staphylococcal TSS is caused by *Staphylococcus aureus* strains that produce pyrogenic toxin superantigens (SAgs). Human coagulase-negative staphylococci do not produce the causative toxins, though coagulase-negative strains from animals occasionally do produce SAgs. Streptococcal TSS is caused primarily by *Streptococcus pyogenes* (group A) strains but occasionally by groups B, C, and G strains. Several subsets of staphylococcal TSS exist, with two major categories being menstrual and nonmenstrual.

Menstrual TSS (Figure 18.1), which occurs within a day or two of or during menstruation, primarily has been associated with use of certain tampons, notably those of high absorbency, and is 100% associated with production of TSS toxin-1 (TSST-1) by the causative bacterium. When initially described, menstrual TSS occurred primarily in women aged 15 to 25. Presently, menstrual TSS occurs more often in younger females, particularly those aged 12 to 15; the reason for this shift in menstrual TSS to the younger age group is unclear. There are two major mechanisms that explain the association of tampons with menstrual TSS: (1) tampons introduce oxygen, which is absolutely required for production of TSST-1, into the otherwise anaerobic vagina; and (2) pluronic L-92, a surfactant present in the TSS-associated Rely tampon from the 1980s and no longer used in tampons, amplifies TSST-1 production.

Nonmenstrual TSS occurs in both males and females, adults and children, and is associated with *S. aureus* strains that produce TSST-1 or staphylococcal enterotoxins, notably enterotoxin serotypes B and C. These three SAgs are produced in amounts nearly 10^5 higher than most other SAgs. Nonmenstrual TSS occurs in association with nearly any kind of staphylococcal infection, but major forms have been identified: postsurgical, upper respiratory virus (influenza)-associated, RED syndrome (see later discussion), enterocolitis-associated, and occasionally with use of contraceptive diaphragms, sponges, and menstrual cups. Postsurgical TSS is often associated with *S. aureus* infections that do not result in pyogenic responses, and thus the infection source may be difficult to find. Influenza TSS may occur as a consequence of influenza or parainfluenza damage to the respiratory tract epithelium and superinfection with SAg-producing *S. aureus* (Figures 18.2 and 18.3); fatal cases of post-influenza TSS are almost always associated with TSST-1 *S. aureus* and not with strains producing enterotoxins B or C. This illness is highly fatal in children (as high as 90%). RED syndrome is a recalcitrant erythematous desquamating disorder in patients with AIDS that may last 70 or more days until the patients succumb. Recently, staphylococcal TSS has been associated with enterocolitis. Until enterocolitis became highly associated with *Clostridium difficile* infection, staphylococcal enterotoxins were associated with the illness. Although sometimes forgotten, staphylococcal SAgs should be considered as causes of enterocolitis with TSS symptoms when *C. difficile* cannot be isolated from patients. Finally, nonmenstrual TSS associated with use of diaphragms, sponges, and menstrual cups may be similar to menstrual, tampon-associated TSS.

BOX 18.1

Diagnostic criteria for confirmed staphylococcal toxic shock syndrome

Clinical criteria

- Temperature ≥38.9°C/101°F
- Systolic blood pressure ≤90 mm Hg for adults, <5th percentile for children, or >15 mm Hg orthostatic drop in diastolic blood pressure or orthostatic dizziness/syncope
- Diffuse macular rash
- Desquamation after 1–2 weeks
- Three of the following organ systems involved:

  Hepatic: Bilirubin, AST, ALT more than twice the ULN
  Hematologic: Platelets <100,000/mm^3
  Renal: BUN or creatinine more than twice the ULN or pyuria
  without urinary tract infection
  Mucus membranes: Hyperemia of the vagina, oropharynx, or conjunctivae
  Gastrointestinal: Diarrhea or vomiting
  Muscular: Myalgias or CPK more than twice the ULN
  Central nervous system: Disorientation or lowered level of consciousness in
  the absence of hypotension, fever, or focal neurologic deficits
  Laboratory criteria

- Negative serologies for measles, leptospirosis, and Rocky Mountain spotted fever; blood or CSF cultures negative for organisms other than *Staphylococcus aureus*

Probable case: Meets laboratory criteria and four of five clinical criteria.

Abbreviations; AST = aspartate transaminase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; CSF = cerebrospinal fluid; ULN = upper limit of normal

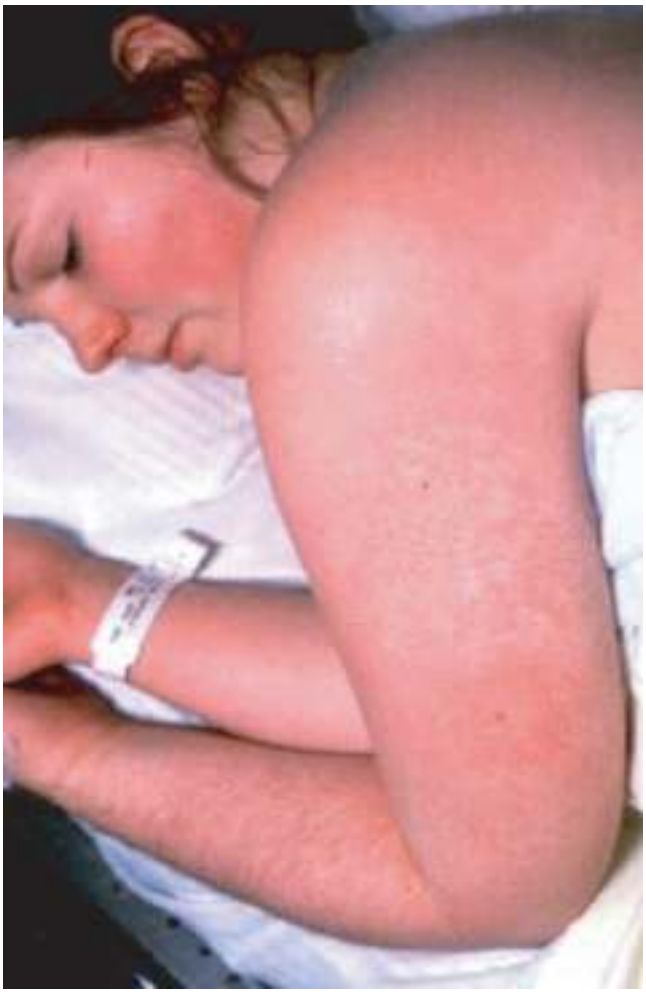

FIGURE 18.1 Menstrual toxic shock syndrome (vaginal colonization): diffuse blanching erythema.

Courtesy of David Schlossberg, MD.

BOX 18.2

Diagnostic criteria for streptococcal toxic shock syndrome

1. Isolation of group A streptococci:

   From a sterile site for a *definite* case
   From a nonsterile site for a *probable* case

2. Clinical criteria:

   Hypotension *and* two of the following:
   Renal dysfunction
   Coagulopathy
   Hepatic involvement
   Adult respiratory distress syndrome
   Erythematous macular rash
   Soft-tissue necrosis

FIGURE 18.2 Gangrenous fingers and skin peeling with nonmenstrual staphylococcal toxic shock syndrome (pulmonary infection).

Courtesy of Gary R Kravitz, MD, St. Paul Infectious Disease Associates, St. Paul, Minnesota.

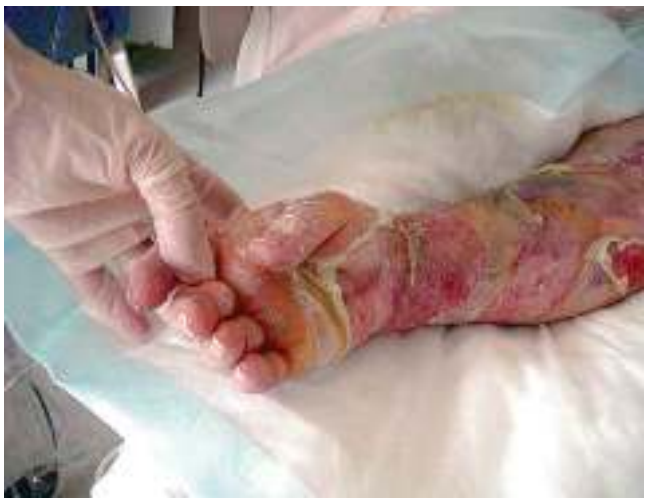

FIGURE 18.3 Same patient as in Figure 18.2 demonstrating extensive peeling and tissue damage.

Courtesy of Gary R Kravitz, MD, St. Paul Infectious Disease Associates, St. Paul, Minnesota.

Streptococcal TSS is primarily associated with group A streptococcal infections, particularly M serotypes 1, 3, and 18. The illness may or may not be associated with necrotizing fasciitis or myositis (Figures 18.4A–C). The case fatality rate is higher in cases with necrotizing myositis than when this condition is absent. Occasionally, streptococcal TSS is caused by other groups of streptococci, primarily groups B, C, and G.

Group A streptococcal strains that cause TSS produce streptococcal pyrogenic exotoxin SAgs. The major associations have been with serotypes A and C, but other family members contribute significantly. Non–group A streptococcal strains associated with TSS also produce streptococcal pyrogenic exotoxin SAgs that are related or identical to the group A streptococcal SAgs.

Major risk factors for development of streptococcal TSS include chickenpox in children, penetrating and nonpenetrating wounds, use of nonsteroidal anti-inflammatory agents, and pregnancy.

Kawasaki syndrome

Kawasaki syndrome (KS) is an acute multisystem vasculitis that occurs primarily in children <4 years of age (Box 18.3). KS shares many features with streptococcal scarlet fever and TSS except that hypotension is absent. KS is a leading cause of acquired heart disease in this age group. Coronary artery abnormalities, including aneurysms, develop in 15% to 25% of patients.

The causative agent of KS remains unclear, but studies suggest that staphylococcal and streptococcal SAgs may have important causal roles in many cases. It is noteworthy that some patients with staphylococcal TSS have also been described with coronary artery aneurysms.

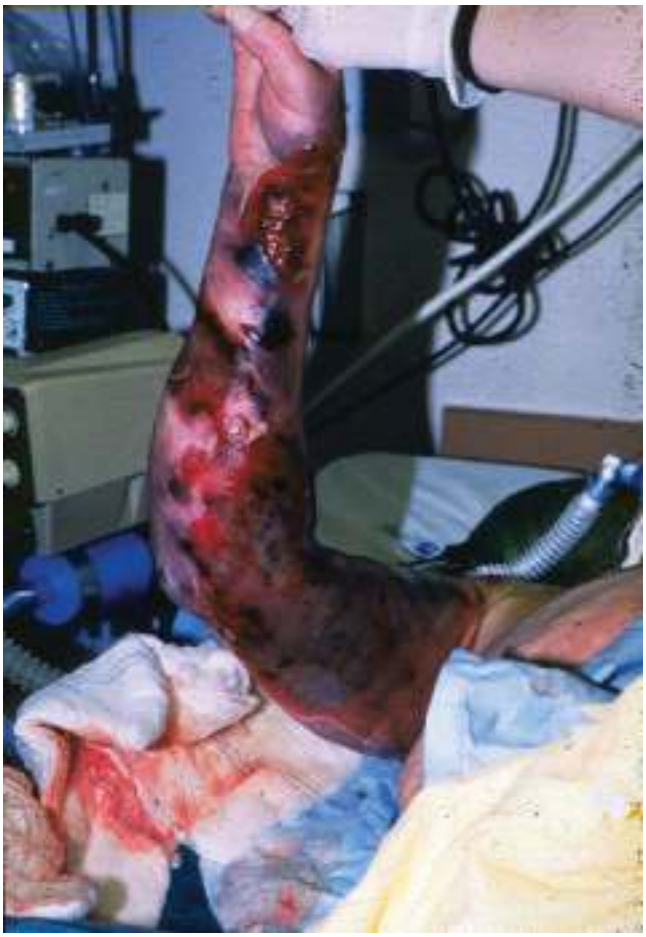

FIGURE 18.4 Necrotizing fasciitis. Note the extensive edema, erythema, bullae formation, and necrosis in this patient's thigh (A and B). At the time of presentation, this patient was hypotensive with multisystem organ failure and severe pain at the site of infection. (C) Leg after extensive debridement down to and below the level of the fascia.

With permission from the Regents of the University of California. From http://medicine.ucsd.edu/Clinicalimg/Necrosis4

BOX 18.3

Clinical criteria for Kawasaki syndrome

1. Fever, usually of at least 5 days' duration
2. Four of five of the following:
   - Extremity changes, induration, edema, erythema
   - Oropharyngeal and lip changes, strawberry tongue, cracked lips
   - Cervical lymphadenopathy: at least one node >1.5 cm
   - Injected conjunctivae
   - Rash, erythematous and polymorphous
3. Other diseases excluded

Probable cases may not meet the strict definition.

Evaluation and treatment of toxic shock syndromes

Differential diagnosis of toxic shock syndrome

- Viral disease, including measles, rubella, parvovirus B19
- Spotted fever group rickettsiae
- Leptospirosis
- Drug reactions, including Stevens–Johnson syndrome
- Collagen-vascular diseases, including systemic lupus erythematosus, and Still's disease
- Scarlet and rheumatic fevers
- Syphilis
- Typhoid fever

The physician should consider myositis or necrotizing fasciitis in any patient who presents with severe local pain, especially in an extremity, and other nonspecific influenza-like or gastrointestinal symptoms. Fever, erythema, and edema are usually absent. Early intervention is life-saving for patients with necrotizing soft tissue infections, so it is important to maintain a very high index of suspicion. An elevated creatinine, elevated creatine kinase (CK), or significant bandemia may suggest the diagnosis.

Initial evaluation

Possible sources of infection or foreign bodies must be identified. The physician should perform a vaginal examination, remove any tampon, and culture for *S. aureus*. Any wounds should be unpacked and inspected. A thorough examination of the skin and soft tissues should be undertaken, paying special attention to any painful areas even if typical signs of inflammation are absent. Cultures of blood and other sites, as appropriate, should be obtained. Early surgical intervention is extremely important. MRI may be used to identify deep soft-tissue necrosis and guide surgical intervention.

Supportive care

Supportive care is of primary importance. Patients often require large amounts of intravenous (IV) fluids, vasopressors, and management of associated comorbidities, such as acute renal failure, acute (adult) respiratory distress syndrome, disseminated intravascular coagulation, or myocardial suppression.

Antibiotics

Antistaphylococcal therapy decreases the risk of recurrence of staphylococcal TSS and will treat any active infection with *S. aureus* or β-hemolytic streptococci. Nafcillin (adults: 2 g IV q4h; children: 150 mg/kg/d IV divided q6h) or cefazolin (adults: 1–2 g IV q8h; children: 50–100 mg/kg/d IV divided q8h) can be used. However, for critically ill patients, sufficiently high prevalence of methicillin-resistant *S. aureus*, or patients with an anaphylactic penicillin or cephalosporin allergy, vancomycin (adults: 1 g IV q12h; children 40 mg/kg/d IV divided q6h), daptomycin (adults: 4–6 mg/kg IV q24h; children 4–10 mg IV 24 hours, varies with age), or linezolid (adults: 600 mg IV q12h; children 10 mg/kg q8h up to age 12) can be used. Clindamycin, a protein synthesis inhibitor (adults: 900 mg IV q8h; children: 40 mg/kg/d IV divided q6–8h), should be given in addition (unless linezolid is used) as experimental data suggest that it inhibits exotoxin and M protein production. Dosage adjustments for renal failure may be required.

Once a microbiologic diagnosis has been established, the spectrum of therapy can be narrowed, using penicillin (adults: 4 million units IV q4h; children: 250,000 U/kg/d IV divided q4h) ampicillin (adults: 2 g IV q6h; children 50 mg/kg/d divided q6h), ceftriaxone (adults: 2 g IV q24h; children: 50–75 mg/kg/d IV divided q12–24h) or clindamycin alone, as appropriate. Therapy should be given for approximately 10 to 14 days unless a diagnosis, such as osteomyelitis, is made that requires extended therapy.

Intravenous immunoglobulin

Lack of neutralizing antibodies seems to be a risk factor for staphylococcal and streptococcal TSS. Human and animal studies appear to support the use of IV immunoglobulin (IVIG) in these diseases. Preparations of IVIG may vary not only by manufacturer but also by batch in their ability to neutralize superantigenic toxins. Therefore, retreatment with a different preparation may be warranted in a patient who has not responded to initial therapy. Various IV doses have been used as follows: 1 g/kg on day 1 followed by 0.5 g/kg each day on days 2 and 3, 0.4 g/kg IV once daily for 5 days, or a single dose of 2 g/kg with a repeat dose at 48 hours if the patient remains unstable.

Steroids

The clinician should not miss the patient with absolute or relative adrenal insufficiency. However, steroids are not routinely given to patients with TSS.

Surgical intervention

Any obvious source of infection should be drained. There should be a low threshold to explore other sites as expected signs of inflammation may be absent, especially in streptococcal myositis. Radionuclide white blood cell (WBC) scanning has been used to identify undrained foci of necrotizing fasciitis in a nonresponding patient.

Prevention

Up to 30% recurrence has been suggested. Elimination of staphylococcal colonization can be attempted. Avoidance of further tampon use is prudent after menstrual TSS; patients with TSST-1 associated TSS do not develop protective antibodies. Additionally, it is now well-known that approximately 20% of individuals at 12 years of age or older do not develop protective antibodies to

TSST-1 and thus always retain susceptibility. Close household contacts of an index case of streptococcal TSS should be offered chemoprophylaxis.

Treatment of Kawasaki syndrome

Differential diagnosis of Kawasaki syndrome

- Acute adenoviral infection
- Other viral exanthemata, especially measles
- Scarlet fever
- Drug reactions, Stevens–Johnson syndrome, erythema multiforme
- Spotted fever group rickettsiosis
- TSS
- Staphylococcal scalded skin syndrome
- Juvenile rheumatoid arthritis
- Leptospirosis
- Mercury poisoning

Differential diagnosis

Irritability and gastrointestinal symptoms are common. Adenoviral infection may present the most common diagnostic dilemma. Incomplete KS, more common in children <12 months of age, may be diagnosed when the patient has 5 or more days of fever and two or more criteria for diagnosis. The risk of coronary artery aneurysms increases significantly in patients not treated within 10 days.

Supportive care

Cardiorespiratory monitoring, close clinical observation, and attention to fluid balance are required.

Aspirin

The physician should give high doses of aspirin (80–100 mg/kg/d in four divided doses, maximum of 4 g/day) until 48 hours after the fever is gone and then maintain low doses (3–5 mg/kg/d in single dose) for 6 to 8 weeks or until the platelet count and sedimentation rate are normal. Consider monitoring of serum salicylate levels in nonresponders. Some prefer high doses until day 14. Aspirin therapy should be continued indefinitely in any patient with coronary artery abnormalities. Influenza or varicella exposure may prompt discontinuation of aspirin therapy for up to 14 days because of the risk of Reye's syndrome. Dipyridamole (4–9 mg/kg/d divided BID or TID) may substitute during this time in high-risk patients. Give influenza vaccination yearly while on aspirin.

Intravenous immunoglobulin

The recommended dose is 2 g/kg IV given over 12 hours. Retreatment may be necessary in those whose fever persists or recurs. Measles, mumps, and rubella vaccines should be delayed for 11 months after IVIG unless there is high risk. If so, give the vaccination on schedule and repeat 11 months later.

Steroids

IV methylprednisolone will hasten the resolution of fever and improve laboratory markers of inflammation when given in 1 to 3 pulse doses of 30 mg/kg. This should be considered for patients who fail retreatment with IVIG.

Monitoring for cardiac complications

Inpatient and outpatient serial exams are important. Obtain electrocardiogram and cardiac echo early and repeat at 6 and 8 weeks. Pediatric cardiology consultation should be obtained. Stress testing and coronary angiography have value in specific clinical situations. The patient with coronary artery lesion requires more intensive monitoring.

Evaluation of therapy

If fever or signs of inflammation persist or recur, retreat with IVIG (1–2 g/kg over 10–12 hours) and with steroids if no response to IVIG retreatment. Patients who fail to respond to IVIG and steroids could be considered for treatment with tumor necrosis factor (TNF) inhibitors such as infliximab, other immunosuppressive agents, or plasmapheresis.

Long-term management

Restrict physical activity for 6 to 8 weeks. Determine frequency of follow-up on an individual basis. It is possible to identify a group of low-risk patients who may not require intensive follow-up. Complicated management issues, such as use of warfarin, calcium channel blockers, and angiography, are beyond the scope of this text. The reader is referred to the excellent reviews of KS found in the "Suggested reading" section.

Other issues

Antibiotics are not routinely used. Pentoxifylline has been tried experimentally but is of no proven benefit.

19

Viral exanthems

Romina Bromberg, Michael Thompson, Lisa M. Chirch, and Jane M. Grant-Kels

During the early 1900s, six common childhood exanthematous infections were identified and defined by the use of numbers 1 through 6. The microbiologic agents of these infections were unknown. Over the next century, the etiologies of these exanthems were defined, and four of the six were demonstrated to be caused by viruses (Table 19.1). The first exanthem was caused by the measles virus, the third by the rubella virus, the second and fourth by bacterial toxins, the fifth by parvovirus, and the sixth by human herpesvirus 6 (HHV-6). This chapter will address the epidemiology, clinical manifestations, and diagnosis of the classic childhood viral exanthems: measles (rubeola), German measles (rubella), and exanthem subitum (roseola), and parvovirus B19 (pB19). Viral exanthems seen more often in adults (Epstein–Barr virus [EBV], HIV), as well as emerging viruses with viral exanthems are also discussed in this chapter.

Classic viral exanthems of childhood

Rubeola (measles)

Epidemiology and virology

The incidence of measles has declined substantially in the past few decades due to global increased vaccination efforts. There were 89,780 deaths in 2016, down from 550,100 deaths in 2000. Despite the fact that global measles deaths have decreased by 84% worldwide in a recent update by the World Health Organization (WHO), measles is still common in developing countries, especially in parts of Africa and Asia. Historically, measles has primarily been a disease of young children. While the incidence of measles has decreased across all age groups with increased vaccination efforts, the relative incidence of measles has increased in groups which may be less likely to have been vaccinated or have insufficient immunity, including older adults, children under the age of 1 year, and social groups that eschew vaccinations. Unfortunately, there has been a rise in cases from 2018 through 2019. In 2019 alone, there have been 10 US states affected by the measles outbreak thus far, with a total of 127 cases just in less than 2 months, from January 1 to February 14, 2019.

Rubeola is caused by an RNA virus with one serotype and is classified in the genus *Morbillivirus* in the Paramyxoviridae family. Most cases of measles occur in the late winter or spring. Humans are the only natural hosts, and transmission occurs by exposure to infectious droplets. Rubeola is one of the most highly contagious of the infectious organisms. Appropriate isolation of cases in hospital settings is critical to limit nosocomial transmission. A patient hospitalized with measles requires airborne precautions for 4 days after the onset of rash. However, if the patient with measles is immunosuppressed, airborne precautions are required until the illness completely resolves. The measles virus is labile and survives only a short time on fomites. The highest rates of transmission occur in the home, and in daycare centers, nursery schools, primary

TABLE 19.1 **CLASSIC EXANTHEMS OF CHILDHOOD**

Order	Exanthems	Agent
First	Rubeola or measles	Measles virus
Second	Scarlet fever	Streptococcal toxin
Third	Rubella or German measles	Rubella virus
Fourth	Filatov–Dukes' disease	Unknown, possibly strep. or staph. toxin
Fifth	Erythema infectiosum	Parvovirus
Sixth	Exanthem subitum or roseola	Human herpesvirus 6

and secondary schools, colleges, and universities. School outbreaks can occur despite >95% immunity among students.

Clinical and laboratory diagnosis

Clinical measles demonstrates a fairly characteristic presentation. However, given the dramatically lower incidence of illness in recent years, many contemporary providers have not seen a classic measles infection, so diagnosis may not be obvious. In addition, presentation may be atypical in immunocompromised patients.

The incubation period is 10 to 12 days. There is a prodrome of low-grade fever, malaise, and headache. This is followed or accompanied by cough, coryza, and conjunctivitis. During the prodrome, an enanthem appears on the buccal mucosa and may spread to the hard or soft palate. The typical enanthem of measles (Koplik spots) consists of punctate white or gray lesions described as grains of sand on an erythematous base. As the infection evolves, the number of Koplik spots increases and lesions coalesce. These resolve with the onset of the rash. After about 4 days of increasing prodromal symptoms, the patient develops high fever and rash. The rash (Figure 19.1) begins as erythematous macules and papules at the hairline, on the forehead, behind the ears, and on the upper neck. This characteristic morbilliform exanthem occurs in the large majority of infected individuals. The rash spreads centrifugally to the trunk and extremities over the next 3 days, blanches on pressure and may coalesce; when it resolves, it may leave brownish hyperpigmentation resulting from capillary hemorrhage (siderophages) and melanophages. The eruption may not occur at all, or it could be severe in patients who are immunosuppressed. When present, the high fever and rash persist for 2 to 4 days. As the rash fades, the coryza and conjunctivitis clear, but the cough may persist for another 5 days. Immunocompetent patients are contagious from the onset of the prodrome until approximately 4 days after the onset of the rash.

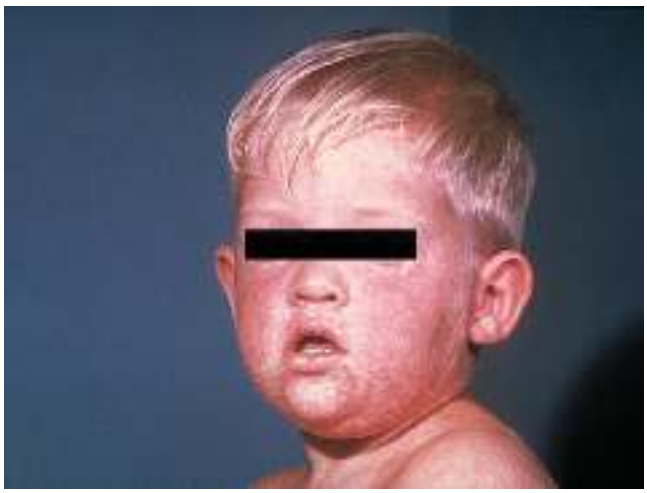

FIGURE 19.1 Measles in a boy presenting as morbilliform lesions on the face, trunk, and palms.

From https://phil.cdc.gov/Details.aspx?pid=1150

The most common complications of measles are secondary bacterial infections, including pneumonia and otitis media. Diarrhea may also occur as a complication. The risk of complications is highest for infants <1 year of age. Postinfectious encephalomyelitis occurs in approximately 1 per 1,000 measles cases within a few days of rash onset. Most patients recover, but many have persistent developmental sequelae. Acute disseminated encephalomyelitis (ADEM) is a demyelinating disease that occurs later, typically within 2 weeks of recovery. Also called postinfectious or postvaccine encephalomyelitis, ADEM may be related to an autoimmune response and carries a 10% to 20% mortality, with survivors commonly suffering neurologic sequelae. In contrast, subacute sclerosing panencephalitis (SSPE) occurs several years (classically 7–10) after natural infection and carries a very high mortality rate. This complication has become exceedingly rare with the dramatic decrease in measles cases over the past few decades due to immunization availability and utilization.

Measles can be confirmed by viral cultures of the nasopharynx, conjunctiva, blood, or urine. However, culture is technically difficult and not readily available. Sera may be obtained for measles antibody determinations both at the onset of the rash and 2 to 4 weeks later. A significant increase of measles immunoglobulin (IgG) antibody (acute and convalescent) is diagnostic. A measles-specific IgM antibody test is also available. This IgM antibody is detectable from about 3 to 30 days after the onset of the rash. Finally, isolation of measles virus RNA by polymerase chain reaction (PCR) from clinical specimens such as those just listed is diagnostic. Immunity after measles infection is lifelong, and a second attack is therefore very rare.

Treatment and prevention

Treatment of measles is usually supportive; acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) is used for pain and fever. Oral vitamin A supplementation may minimize morbidity and mortality in malnourished patients. For reasons that are not well defined, malnourished patients may suffer acute vitamin A deficiency when infected with measles. Vitamin A is necessary for the maintenance of epithelial integrity and for normal immune function. The WHO now recommends treatment with vitamin A supplementation once a day for 2 days for all children with acute measles; specific doses vary with age (200,000 IU for children 12 months and older; 100,000 IU for infants 6 to 11 months; 50,000 IU for infants under 6 months). Because measles may be complicated by secondary

bacterial infection, prophylactic antibiotics are sometimes prescribed although not generally recommended. The most common bacterial complication is pneumonia caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus*. Measles virus is susceptible in vitro to the antiviral agent ribavirin. However, ribavirin is not approved by the US Food and Drug Administration (FDA) for this indication and is associated with significant toxicity. There are anecdotal reports of successful use of intravenous and/or aerosolized ribavirin to treat severely ill, immunosuppressed patients with measles.

Measles vaccine is routinely recommended at ages 12 to 15 months. This vaccine is a live attenuated strain grown in chick embryo cells. In infants, the efficacy of this vaccine is hindered by passive maternal antibody, which is no longer present by 12 months. If the mother is immune via natural infection, not immunization, then maternal antibody can persist in the infant until 15 months. A second measles vaccine dose is recommended at 5 to 12 years of age. In areas of high measles prevalence, vaccine is given at <1 year of age to protect this particularly vulnerable population. However, due to possible interference from maternal antibody, vaccine doses administered at <1 year of age should not be counted toward vaccine requirements. Unimmunized children and adults should be given two measles doses at least 1 month apart. Following one measles vaccine dose, approximately 95% of patients will show a positive measles antibody response. This response rate increases to >99% following two doses.

Patients who are exposed to measles and have not been immunized may benefit from a measles vaccine if given within 72 hours of exposure. In addition, unimmunized patients susceptible to infection via close or household contact may receive immune globulin (IG; 0.25 mg/kg intramuscularly) within 6 days of exposure to prevent or minimize disease. Because measles inoculation is a live vaccine, it is not recommended for immunosuppressed patients (see Box 19.1 for contraindications). An exception to this rule is that vaccine should be administered to patients with well-controlled, stable HIV infection (with CD4 counts >200 cells/mm^3) because of the potentially devastating outcome of measles in this group. Severe immunocompromise or a low CD4% (<15%) would, however, be a contraindication to the live vaccine. Ensuring immunization of close contacts may confer additional protection for these patients by decreasing the chances of exposure.

International travelers should be evaluated for measles immune status and risk. Infants traveling to developing countries where measles is endemic may receive the measles vaccine as early as 6 months of age. Adults born after 1957 who have an inadequate or undocumented vaccine status may opt to have antibody testing to determine vaccination needs prior to travel.

BOX 19.1

Contraindications to measles vaccine

Pregnancy
Immunodeficiency except for well-controlled HIV infection
History of anaphylaxis to eggs
History of anaphylaxis to neomycin

Rubella (German measles)

Epidemiology and virology

Rubella virus is an enveloped togavirus with a single strand of RNA at its core. In 2004, Rubella was declared eliminated (absence of endemic transmission for 12 months or more) from the United States. Fewer than 10 cases (mostly imported) have been reported annually in the United States since elimination was declared. Since the vaccine was developed in 1969, rubella incidence in the United States decreased by >99%. Although Rubella is no longer endemic in the United States, approximately 10% of US-born persons remain susceptible to infection despite vaccination. Risk of infection is highest in those who are less likely to be vaccinated, such as people born outside of the United States and social groups who reject vaccination.

Before the widespread availability of the rubella vaccine, the primary danger posed by rubella virus was the specter of infection during pregnancy, which could lead to congenital rubella syndrome in the newborn. Women born outside the United States are less likely to have received immunization; therefore, the risk of congenital rubella in the United States is highest in infants born to those women. Since 2004, 60% of rubella infections have occurred in patients aged 20 to 49 years. The median age of infection is 32 years.

Clinical and laboratory diagnosis

Rubella infection in infants and children is usually mild; up to 50% of infections in children are asymptomatic. A prodrome characterized by tender posterior auricular, posterior cervical, and suboccipital adenopathy with malaise is common among adolescents and adults with rubella. The adenopathy may persist for weeks. The rubella exanthem begins on the face, neck, and scalp and spreads centrifugally to the trunk and extremities. The rash may be associated with fever, headache, myalgias, and arthralgias. The eruption consists of pink macules and papules that range in diameter from 1 to 4 mm. The exanthem fades as it spreads; thus, it may be absent on the face when it is prominent on the trunk. The enanthem, Forchheimer's sign, occurs in 20% of patients and is characterized by petechiae or red spots on the soft palate. It occurs during the prodrome or at the onset of the exanthem. Rubella is most commonly seen during late winter and early spring.

Rubella is spread by small droplets from the respiratory mucosa. Patients are most contagious from a few days before until up to 7 days after the onset of rash. Viral shedding can occur for up to 14 days after the onset of rash. Prolonged exposure usually is necessary for transmission. The incubation period is 14 to 23 days.

Complications of rubella are unusual. The most common complication is arthritis, which occurs almost exclusively in females and increases in incidence in older age groups. Rare complications include thrombocytopenia and encephalitis. The most devastating complication is congenital rubella syndrome. The frequency of

congenital rubella is 50% if rubella infection occurs during the first 12 weeks of pregnancy. This incidence diminishes to 25% for infections occurring from 13 to 24 weeks. Congenital rubella syndrome is rare if maternal infection occurs after 24 weeks' gestation. Congenital rubella syndrome is commonly characterized by deafness, congenital cataracts, and patent ductus arteriosus. Severe involvement is often fatal, and infection can involve many organs, including the skin (described as "blueberry muffin" lesions because of bluish areas due to extramedullary hematopoiesis).

Rubella can be diagnosed by the typical exanthem and associated posterior auricular adenopathy. The virus can be isolated from nasal secretions, but most laboratories do not have the proper reagents needed for isolation. Acute and convalescent (2–4 weeks after rash) serology should show a fourfold or greater rise in IgG antibodies. A rubella-specific IgM antibody test is also available and is indicative of recent infection. The IgM antibody persists for several months after acute infection. False-positive IgM titers are associated with rheumatoid arthritis, parvovirus infection, and heterophile antibodies. Molecular diagnosis and typing using reverse transcriptase PCR may be useful in epidemic settings.

Treatment and prevention

Typical rubella infection is mild and requires no therapy. The occasional patient with severe arthralgias or arthritis should respond to therapy with NSAIDs. Arthralgias and arthritis are much more common in females. The routine administration of IG after exposure is not recommended. However, the administration of intramuscular IG may be considered if a pregnant woman is exposed in early pregnancy.

Rubella vaccine should be given with measles and mumps vaccine (MMR) in the same two-dose schedule: the first dose at 12 to 15 months and the second at 5 to 12 years of age. Contraindications for rubella vaccine are listed in Box 19.2. Because rubella is a live vaccine and can potentially infect the fetus, it should not be given during pregnancy, although the risk of fetal infection is low. In a study of 226 susceptible women who were inadvertently immunized with rubella vaccine during the first trimester, there were no congenital abnormalities in the offspring, and two offspring showed asymptomatic infection. This benign outcome may reflect the fact that this is an attenuated viral vaccine. Although immunocompromising states are relative contraindications to receipt of MMR vaccine, immunization should be considered in susceptible patients with well-controlled HIV infection (see the section on Rubeola).

BOX 19.2

Contraindications to rubella vaccine

Pregnancy
Immunodeficiency except well-controlled HIV infection
Immunoglobulin in the last 3 months

Roseola (exanthem subitum)

Epidemiology and virology

Roseola is predominantly caused by HHV-6, a double-stranded DNA virus. There are two major groups of HHV-6, variants A and B. Ninety-seven to100% of primary infections with HHV-6 are caused by variant B. Though far less common, other causes of roseola include human herpesvirus 7 (HHV-7), enteroviruses (coxsackieviruses A and B, echoviruses), adenoviruses, and parainfluenza virus type 1.

At birth, newborns usually passively acquire HHV-6 antibody. This protects the infant until about 6 months of age. From 6 to 24 months of age, about 80% of infants become infected with HHV-6, and almost all children are seropositive by 4 years. Cases of roseola occur throughout the year. The mode of transmission is unknown. It is unusual to demonstrate roseola spreading from one infant to another. After acute infection, HHV-6 can often be isolated from saliva. Saliva transmission from an asymptomatic contact to a susceptible infant may be the most common route of transmission. HHV-6 can also be isolated from both peripheral blood lymphocytes and cerebrospinal fluid.

First isolated in 1986, HHV-6 is a herpesvirus distinct from herpes simplex 1 and 2, varicella-zoster virus, cytomegalovirus, and EBV. Soon after, the isolation of HHV-7 was reported in 1990. HHV-6 may be divided into two major groups, variants A and B. Primary infection is almost always caused by variant B strains. In addition to causing roseola, HHV-6 can cause a febrile illness without rash as well as a febrile illness with lymphadenopathy, gastroenteritis, upper respiratory infection, and otitis (see Chapter 186, "Human herpesvirus 6, 7, 8"). Reactivation of HHV-6 infection in immunocompromised patients, particularly those who have undergone bone marrow transplant, has myriad manifestations, including but not limited to rash, hepatitis, pneumonia, bone marrow involvement, and encephalitis.

Clinical and laboratory diagnosis

The incubation period of roseola is 9 to 10 days; the disease has no prodrome. Clinical illness begins with a high fever (38°C to 40°C/100°F to 104°F). Febrile seizures occur in a significant number of infected children. Roseola may account for at least 10% of visits to the emergency room for infants <2 years. In addition, roseola accounts for 33% of febrile and recurrent febrile seizures seen in emergency rooms. The fever typically lasts 3 days. When the fever resolves, the exanthem usually appears, but it may also begin before the fever resolves. The exanthem is characterized by discrete, pale pink macules, varying in size from 1 to 5 mm in diameter. Around each lesion is a pale areola. Distinct from the measles and rubella exanthems, the rash commonly begins on the trunk, on the neck, and behind the ears and spreads to the proximal extremities; it rarely involves the face or distal extremities. The rash may become confluent and usually lasts for 2 to 48 hours. Before the exanthem appears, an enanthem of erythematous macules may be present on the soft palate. Vertical transmission of HHV-6 occurs in 1% to

2% of births. The significance of vertical transmission of HHV-6 is unknown.

Acute HHV-6 infection may be diagnosed by seroconversion from HHV-6 antibody negative to HHV-6 positive. A specific IgM antibody peaks 7 to 14 days after the onset of illness and usually becomes undetectable in several weeks. However, HHV-6 IgM antibody may persist in some patients and thus may be present without acute infection. Specific IgG antibody develops 2 to 4 weeks after the onset of illness and remains detectable indefinitely. Also, the IgG antibody may intermittently rise and fall, especially in association with cytomegalovirus or EBV infections. HHV-6 can be cultured from saliva and from mononuclear cells, and viral DNA can be detected in blood and cerebrospinal fluid by PCR.

Treatment and prevention

At present, no treatment or prevention strategies are available for HHV-6 infection in normal children and adults. In immunocompromised individuals, possible therapies include ganciclovir, foscarnet, and cidofovir. Because the mechanism of spread is not definitively known, only standard precautions are recommended for hospitalized patients.

Viral exanthems of adolescence and adulthood

Infectious mononucleosis

Epidemiology and virology

Infectious mononucleosis is typically caused by EBV, also known as human herpesvirus-4, an enveloped DNA virus. Infection with EBV is prominent globally, with 90 to 95% of adults testing seropositive. When EBV is acquired in childhood, it is typically mild or asymptomatic. By contrast, approximately 75% of adolescents who are infected present with symptomatic infectious mononucleosis. In developing countries, infection with EBV occurs earlier in childhood, and clinical infectious mononucleosis is rare. Disease is more common in developed countries where infection tends to occur later in adolescence or early adulthood. The peak incidence of infectious mononucleosis transpires between 15 and 24 years of age. The disease is most commonly spread by saliva but can also be transmitted via semen and blood.

Clinical findings

Symptoms of infectious mononucleosis typically present 4 to 6 weeks after infection with EBV. The prodrome consists of usually severe persistent fatigue and myalgias and typically lasts 1 to 2 weeks. Following the prodrome, patients present with cervical lymphadenopathy, fever, severe sore throat due to pharyngeal inflammation, hepatomegaly, and splenomegaly. A generalized maculopapular, urticarial, or petechial rash may also be seen in some patients. The characteristic exanthem is a maculopapular rash involving the trunk and arms. It appears shortly after the onset of symptoms, lasts for 1 to 6 days, and is identified in 3% to 15% of patients. Complications from infectious mononucleosis are rare and may include splenic rupture, hepatitis, myocarditis, and central nervous system dysfunction secondary to meningitis or encephalitis. Ten percent of patients will develop persistent fatigue that lasts for >6 months.

Another potential severe complication of infectious mononucleosis is hemophagocytic lymphohistiocytosis (HLH), a life-threatening syndrome of excessive immune activation. HLH most commonly affects infants from birth up to 18 months of age but can also be seen in adults. HLH is precipitated by a cascade of events that disturb the immune system's homeostasis. HLH can be either primary (or familial HLH) or secondary (acquired HLH), and one of the most common viral infections associated with HLH is EBV. Common clinical manifestations of HLH are fever, hepatosplenomegaly, neurological findings (seizures, altered mental status, and ataxia), cytopenias, high ferritin, and liver function abnormalities. Physicians who have a high clinical suspicion for HLH should promptly work up their patients as delay in diagnosis and treatment has serious consequences and high mortality.

Diagnosis and treatment

Infectious mononucleosis is typically diagnosed clinically. Serology may be used to confirm infection with EBV, but results and interpretation can vary. In cases with inconclusive serological results, measurement of EBV viral load by real time PCR can be useful. Patients typically have lymphocytosis with >10% atypical lymphocytes.

Treatment for infectious mononucleosis is supportive. NSAIDs may be used to manage pain. Patients should be instructed to avoid vigorous physical activity in the first month as this may increase the risk for splenic rupture. Most patients with infectious mononucleosis who are treated with amoxicillin or ampicillin will develop a maculopapular rash. The mechanism for this antimicrobial rash in EBV patients is not entirely understood. EBV causes polyclonal B-cell activation, increased immunoglobulins, and increases atypical lymphocytes ($CD8^+$ T cells). Hypersensitivity is unlikely because there are no antibodies against ampicillin and rechallenging with the drug does not cause a reaction. One possible explanation is that polyclonal antibodies may form immune complexes with drugs and deposit in the dermis, causing tissue damage. Skin biopsies of affected patients have shown $CD8^+$ T-cell infiltration, suggesting that activated $CD8^+$ T cells react with drug antigens as another possible explanation.

Parvovirus B19

Epidemiology and virology

PB19 is a single-stranded, non-enveloped DNA virus, which is part of the Parvoviridae family in the *Erythrovirus* genus. There are three genotypes within the Erythroparvovirus genus. PB19 is

the predominant parvovirus pathogen in humans and the prototype genotype 1 strain. The only known host for pB19 is humans. Productive infection and replication occur only in human erythroid progenitor cells of the bone marrow. Parvovirus gains entry into cells by binding to P antigen, which are found in high concentration on red blood cells and other cell lines (i.e., endothelial cells, cardiomyocytes, megakaryocytes). Parvovirus causes cell lysis upon viral maturity.

PB19 is a common global infection, with seroprevalence increasing with age: 15% of preschool aged children, 50% of young adults, and 85% of older adults have measurable pB19-specific IgG antibodies. In the United States, pB19 infection is most common during the winter and early spring. Epidemics typically strike every 3 to 4 years, with most occurring in children. Adults who work closely with children, such as teachers and daycare workers, are also at risk of infection.

Clinical findings

Clinical manifestations of pB19 infection are variable, ranging from asymptomatic to life-threatening disease. The clinical appearance is influenced by age and hematologic and immunologic status. The five classic presentations associated with pB19 infection are erythema infectiosum, arthropathy, transient aplastic crisis, fetal infection, and pure red blood cell aplasia in immunocompromised individuals.

Erythema infectiosum is associated with the characteristic exanthem induced by pB19 at 1 to 4 days after the onset of fever. The exanthem starts as an erythematous facial rash, also known as a "slapped cheek" rash (see Figure 19.2). After 1 to 4 days, the rash becomes maculopapular and spreads to the trunk and extremities. Central clearing of the rash may give it a reticular, lace-like appearance. The rash on the trunk and extremities persists for 1 to 6 weeks. During this time, the intensity of the exanthem may vary with exposure to sunlight or heat. Rash most commonly occurs in children; when it occurs in adults, the eruption is often less characteristic.

Arthralgias following infection with pB19 occur in 8% of children but are more common in adolescents and adults. PB19 can precipitate aplastic crises in patients with chronic hemolytic anemias, such as those due to sickle cell disease or hereditary spherocytosis. These patients less commonly develop a rash but may present with clinical symptoms of anemia, such as pallor or malaise, following a mild febrile illness.

The most severe complication of pB19 infection is fetal loss from hydrops fetalis as a result of maternal infection that can occur in 5% to 10% of infected pregnant women.

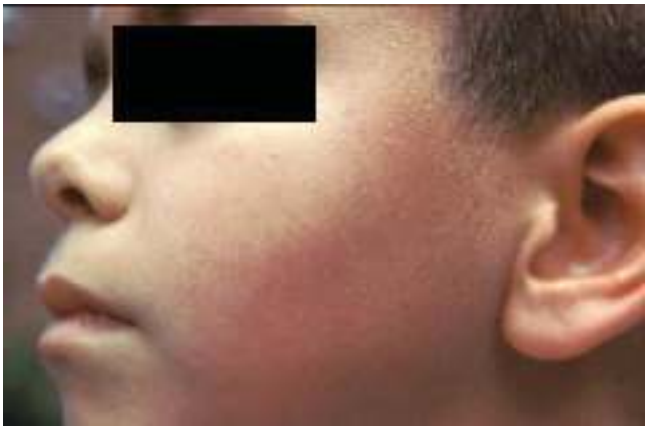

FIGURE 19.2 Right anterior-oblique view of a boy's face displaying the "slapped cheek" rash of erythema infectiosum, or Fifth disease, caused by the human parvovirus B19.

From https://phil.cdc.gov/details.aspx?pid=4508

Diagnosis and treatment

Diagnosis of pB19 can be made through serology or PCR. Detection of viral RNA or DNA through PCR is indicative of acute or persistent infection. PB19 IgM may be detected 10 days after infection and can persist for up to 4 months. PB19 IgG is present shortly after IgM and persists indefinitely.

Management of pB19 infection is primarily supportive and, in immunocompetent patients, is typically self-limited. In patients with aplastic crises from pB19, hospitalization and transfusion may be required. In fetuses with hydrops fetalis due to pB19, the administration of intrauterine erythrocyte transfusions can reduce fetal mortality. Beyond supportive red blood cell transfusion, more aggressive therapy with IVIG is generally limited to patients with chronic pB19 infection, chronic anemia, and in those who are immunosuppressed, as those with AIDS.

Hand, foot, and mouth disease

Epidemiology and virology

Hand, foot, and mouth disease (HFMD) is caused by multiple serotypes of enterovirus, a single-stranded RNA virus. Coxsackievirus A16 and enterovirus A71 cause the majority of cases of HFMD. Enterovirus A71 has been associated with major outbreaks of HFMD in Southeast Asia and the Pacific. Enterovirus A6 is emerging as a leading cause of outbreaks around the world. Viral transmission occurs via the fecal-oral route and person-to-person contact. Direct contact with vesicle fluid or oral and respiratory secretions can also lead to infection. The incubation period is typically 3 to 5 days.

Although HFMD can occur in patients of all ages, it typically impacts infants and children <5. Cases of HFMD occur worldwide, with an increased incidence in the summer and early fall.

Clinical findings

HFMD characteristically presents with low-grade fever and mouth or throat pain. Prodromal symptoms (e.g., nausea, abdominal pain, and diarrhea) tend not to occur but are sometimes seen.

Approximately 75% of patients with HFMD will present with both an oral enanthem and a cutaneous exanthem. The oral enanthem of HFMD typically occurs on the tongue and buccal mucosa and sometimes the buccal and palate mucosa. Oral lesions start out as erythematous macules that progress to vesicles before

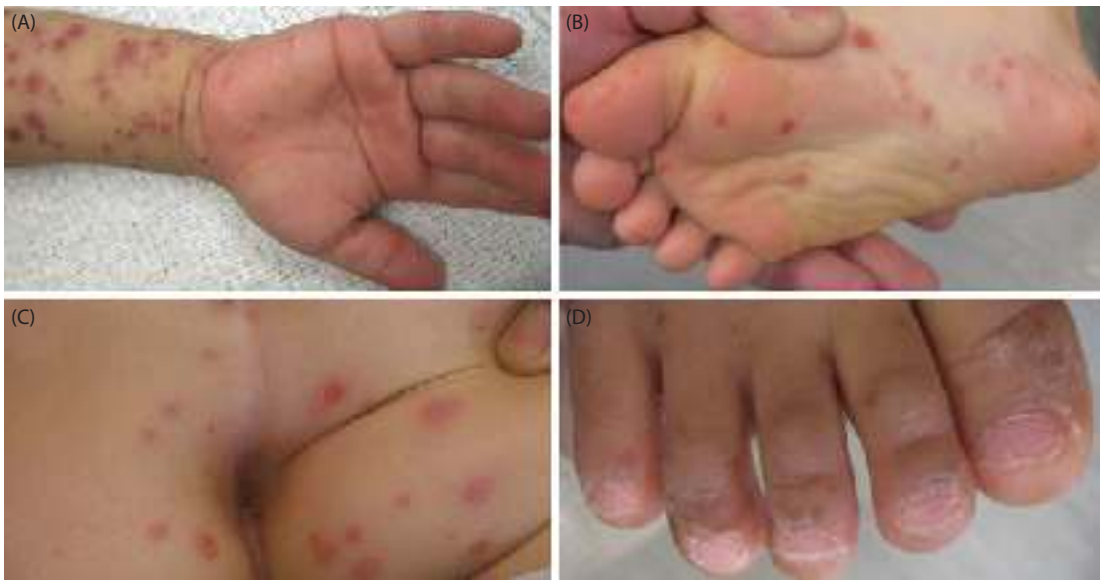

FIGURE 19.3 Diagnostic approach for adults with fever and maculopapular rash.
From https://wwwnc.cdc.gov/eid/article/18/2/11-1147-f1

forming superficial painful ulcers. The exanthem tends to occur on the hands, feet, buttocks, legs, and arms and may be maculopapular and/or vesicular. The rash lasts 3 to 4 days and is not classically pruritic or painful, unlike the atypical perioral exanthem that can be very painful. Outbreaks of HFMD with atypical skin manifestations have also been reported. The exanthem of atypical HFMD includes diffuse vesicles, bullae, and erosions. In addition to the classical locations of HFMD (hands, feet, buttocks, oral mucosa), atypical HFMD also occurs on the torso and perioral area (see Figure 19.3).

Diagnosis and treatment

Diagnosis is typically made clinically based on oral and skin manifestations. Confirmation of specific viral etiology can be obtained via PCR testing and viral culture from vesicular fluid, although this may be of limited clinical utility.

The clinical course of HFMD is generally mild and tends to resolve within 7 to 10 days. Management is generally supportive.

HIV: Primary infection

Epidemiology and virology

HIV is a member of the Retroviridae family. Its genome is made up of two pieces of single-stranded RNA. There are two types of HIV that can cause infection, HIV-1 and HIV-2. HIV-1 is found globally and is the subtype responsible for most HIV infections in the United States. HIV-2 is primarily found in Western Africa and has a lower infectivity than HIV-1.

HIV-1 most often enters the host through the anogenital mucosa then binds to and infects dendritic CD4 cells. Fusion of HIV-infected cells with $CD4^+$ T cells leads to spread of the virus. Once the virus has entered the blood, widespread dissemination occurs.

Since the height of the HIV epidemic in the 1980s, the incidence of HIV in the United States has decreased. An estimated 1.1 million persons aged 13 and older were living with HIV infection in the United States in 2015. Additionally, the estimated number of new HIV infections in the United States in 2015 was 38,500. Estimated annual HIV infections in the United States declined 8% from 2010 to 2015. Advances in HIV therapy have led to increased survival. All populations may be affected by HIV. Incidence is highest in men who have sex with men, followed by heterosexual African American women. HIV is transmitted through contact with infected bodily fluids including semen, preseminal fluids, blood, rectal fluids, vaginal fluids, and breast milk. In the United States, HIV is primarily transmitted through sexual intercourse and the sharing of infected needles.

Clinical findings

Primary HIV infection typically presents with fever, headache, malaise, weight loss, myalgia, lymphadenopathy, diarrhea, and rash occurring 2 to 6 weeks after exposure. About 30% to 50% of patients will develop a generalized rash during the acute phase of disease. The exanthem of primary HIV is maculopapular, with characteristically small (5–10 mm), well-circumscribed, oval lesions. Vesicular, pustular, and urticarial lesions have also been less commonly described. Rash occurs on the face, collar region, and upper thorax. Affected areas may also include the scalp, extremities, palms, and soles. Patients may have oral lesions with resultant dysphagia. Onset of rash typically occurs 48 to 72 hours after onset of fever and subsides after 5 to 8 days. Because this constellation of symptoms is transient and nonspecific it may be confused with a variety of other infectious etiologies; therefore, a high degree of clinical suspicion is required

to make the diagnosis. The importance of early diagnosis cannot be overestimated as earlier diagnosis translates into immune preservation in the infected individual and decreased transmission to others.

Diagnosis and treatment

Initial diagnosis of primary HIV is now usually with a fourth-generation combination HIV-1/2 immunoassay. This assay detects both HIV-1 and HIV-2 antibodies as well as HIV p24 antigen. Most people will test positive 7 to 28 days after infection. It is important to recognize that with any screening test for HIV, there is a "window" period just after infection during which no serologic test will return positive. As such, a high clinical suspicion of acute infection should drive the clinician to request HIV RNA testing by PCR, which is the earliest test to become positive after infection. Antiretroviral therapy, now extremely effective and well-tolerated, should be started in all patients who test positive for HIV as soon as possible.

Emerging viral exanthems

West Nile virus

Epidemiology and virology

West Nile virus (WNV) is a positive-sense RNA virus that is part of the *Flavivirus* genus. WNV is primarily transmitted by the *Culex* mosquito. It is most frequently found in North America, Africa, Europe, the Middle East, and West Asia.

WNV is the leading cause of arboviral encephalitis in the United States. As of October 2018, a total of 49 states and the District of Columbia have reported WNV infections in people, birds, or mosquitoes. Of the 2,204 reported cases of WNV disease, 1,342 (61%) were neuroinvasive and 862 (39%) were non-neuroinvasive (CDC). Incidence of infection is highest in older adults. Infections peak between August and October.

Clinical findings

About 80% of patients who are infected with WNV are asymptomatic. Those who do develop symptoms typically present 3 to 14 days after infection with fever, headache, myalgias, diarrhea, nausea, and vomiting. Patients may also develop a maculopapular rash which is concentrated on the trunk. Complications from WNV may include encephalitis, central nervous system damage, and death; these occur more frequently in the elderly and in patients with hypertension or diabetes. One in 150 patients will develop severe central nervous system infection, and, out of those, 1 in 10 will die. For those patients who are pregnant, it is possible for the virus to cross the placenta and infect the fetus. However, transplacental infection appears to be rare. Rare cases of congenital infection among neonates born to women who developed symptomatic WN virus infection have been reported.

Diagnosis and treatment

WNV infection may be diagnosed using serology. Anti-WNV IgM may be detected 3 to 8 days after infection. PCR or viral culture is also used for diagnosis. Treatment for WNV is primarily supportive, including adequate hydration. NSAIDs may be used to control pain and fever. Patients with severe disease may need to be hospitalized for supportive care.

Ebola virus

Epidemiology and virology

Ebola virus is an enveloped, single-stranded RNA virus which is part of the Filoviridae family. Three species of Ebola virus have been responsible for the majority of recent outbreaks in Africa: Zaire, Bundibugyo, and Sudan Ebola virus.

Ebola virus is found primarily in Western Africa. It was first discovered in 1976. Since then, it has periodically caused outbreaks. The largest outbreak to date occurred from 2014 to 2016 and was centered in Guinea, Sierra Leone, and Liberia. It spread to several other countries including Italy, Spain, the United Kingdom, and the United States. Since 2014, a total of 28,616 suspected infections occurred, with 11,310 deaths. There were four cases of Ebola in the United States during the outbreak. Most affected individuals were travelers to West Africa and healthcare workers who cared for patients with Ebola. Since the 2014–2016 outbreak, the incidence for Ebola has dropped substantially. In 2017, there were only eight known cases of Ebola, found in the Democratic Republic of Congo. In 2018, there has been one outbreak of Ebola in the Democratic Republic of Congo, resulting in 372 cases and 194 deaths as of November 2018. People at risk for Ebola virus include travelers to endemic regions in West Africa and healthcare workers who may be exposed to Ebola virus.

Clinical findings

Onset of symptoms typically occurs 6 to 12 days after exposure to Ebola virus. The initial syndrome is marked by abrupt onset of fever, chills, and malaise. Within a few days, patients generally develop gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Headache, weakness, myalgias, and high-grade fever may also occur.

Between days 5 and 7, patients may develop a diffuse erythematous maculopapular rash. Affected areas typically include the face, neck, trunk, and arms. The rash may desquamate. In the Sierra Leone outbreak, rash was described as rare; however, the eruption is generally easier to visualize in fair-skinned individuals.

Hemorrhage is frequently observed in patients with Ebola, most commonly manifested as blood in the stool, petechiae, ecchymoses, oozing from venipuncture sites, and/or mucosal bleeding. Clinically significant hemorrhage may be seen in the terminal phase of illness and in pregnancy.

Ebola infection can lead to multiorgan failure, septic shock, and ultimately may cause death. There is a high case fatality rate for Ebola, ranging from 18.5% in the United States and Europe to 74% in parts of Western Africa. In nonfatal cases of Ebola, patients

usually start to improve on day 6. They typically have a long recovery period, which can last up to 2 years.

Diagnosis and treatment

Clinicians should consider the diagnosis of Ebola virus for any person presenting with acute onset of a febrile illness who lives in or has recently been to West or Central Africa. An early diagnosis is essential to ensure implementation of proper infection control procedures and to reduce viral transmission. Laboratory diagnosis can be made using reverse transcriptase PCR. Treatment of Ebola virus infection is primarily supportive and mainly consists of volume resuscitation and pain control. There is currently no approved vaccine for prevention of Ebola virus. However, accelerated paths have been developed for introduction of vaccinations into field use during recent epidemics in West Africa.

Chikungunya

Epidemiology and virology

Chikungunya is an arthropod-borne alphavirus transmitted by mosquitos. The major mosquito vectors are *A. aegypti* and *A. albopictus*. Viral transmission can also rarely occur via maternal-fetal transmission and through blood products and organ transplantation.

While Chikungunya is endemic to parts of West Africa, outbreaks have occurred in Africa, Asia, Europe, islands in the Indian and Pacific Oceans, and, more recently, in the Americas. The first cases of Chikungunya were reported in Florida in 2014. Large outbreaks affecting 30% to 75% of populations have occurred.

Clinical manifestations

Abrupt onset of symptoms typically occurs 3 to 7 days after the mosquito bite. Typical symptoms include fever (often high-grade) and polyarthralgias (often >10 affected joints). Hands, wrists, and ankles are the most common affected joints involved. The word "*chikungunya*" is derived from an African word meaning "that which bends up" in reference to the stooped posture of infected patients due to severe arthritic symptoms.

Skin manifestations may occur in 40% to 75% of patients. A maculopapular rash typically presents 3 days after onset of illness. Affected areas include the trunk, limbs, and, less commonly, the face. Rash lasts approximately 3 to 7 days. Atypical skin manifestations such as bullous lesions and hyperpigmentation have been described.

Severe complications such as respiratory failure, renal failure, acute hepatitis, and meningoencephalitis can occur. A subset of patients will have persistent arthralgias and tenosynovitis in the months following illness.

Diagnosis and treatment

Chikungunya should be suspected in patients presenting with typical clinical manifestations and relevant epidemiological exposure. Diagnosis can be established via serologic testing and reverse-transcription PCR (RT-PCR). Immunoglobulin IgM anti-chikungunya virus antibodies are typically present 5 days after onset of symptoms.

Management of acute chikungunya virus is supportive. There is currently no antiviral therapy available.

Zika virus

Epidemiology and virology

Zika virus is a single-stranded RNA virus that is part of the *Flaviviridae* family. It is an arbovirus that is primarily transmitted by mosquitoes of the Culicidae family and the *Aedes* genus (Figure 19.4).

FIGURE 19.4 *Aedes aegypti* female.
Courtesy of CDC/Paul I. Howell, MPH; Prof. Frank Hadley Collins; https://wwwnc.cdc.gov/travel/page/world-map-areas-with-zika

TABLE 19.2 **EMERGING VIRUSES AND SKIN MANIFESTATIONS**

Virus	Onset	Characteristic
West Nile virus	3–14 days	Maculopapular rash on trunk
Ebola virus	5–7 days	Erythematous maculopapular rash. Affected areas typically include the face, neck, trunk and arms.
Chikungunya	3–7 days	Maculopapular rash. Affected areas include the trunk and limbs and sometimes the face.
Zika virus	2–14 days	Maculopapular rash. Typically originates on the trunk and then progresses to involve the lower extremities and sometimes the face and palms.

Prior to 2007, Zika infections were rare and occurred mainly in Asia and Africa. Since 2007, multiple Zika outbreaks have been reported in Southeast Asia and the Western Pacific. In 2015, Zika was first documented in the Western hemisphere with multiple large outbreaks reported in Brazil. Subsequent to 2015, Zika has spread throughout most of the Americas. In 2016, the incidence of Zika reached an all-time high in the United States with 5,168 symptomatic cases reported, of which 4,897 occurred in travelers from endemic areas and 224 resulted from presumed mosquito-borne transmission in Florida and Texas. In 2017, the incidence of symptomatic Zika in the United States fell to 433 cases. Travelers to Zika-affected regions are most at risk of contracting the infection. High-risk Zika regions include Africa, Southeast Asia, the Caribbean, the Pacific islands, and South and Central America.

Clinical findings

The majority of Zika infections are asymptomatic. When present, symptoms are typically mild. Common symptoms include fever, arthralgias, headache, and a maculopapular rash that typically originates on the trunk and then progresses to involve the lower extremities. The most serious consequence of Zika infection is the increased incidence of birth defects in infants born to Zika-infected pregnant women. These include a number of central nervous system defects including microcephaly, brain abnormalities, eye abnormalities, and neural tube defects. The incidence of birth defects in fetuses of women with laboratory evidence of Zika infection reported to the CDC's US Zika Pregnancy Registry was 5% between January 15 and December 26, 2016. For women with confirmed Zika infection in their first trimester of pregnancy, this number rose to 15%.

Diagnosis and treatment

Zika is definitively diagnosed by real-time RT PCR (rRT-PCR) for Zika virus RNA (in serum, urine, or whole blood) or Zika virus serology. The diagnostic approach depends on the timing of the clinical presentation after the onset of symptoms. There is no specific treatment for Zika virus, and management is essentially supportive care.

Conclusion

In this chapter, we have reviewed common viral infections plus emerging viral infections. Table 19.2 compares the skin lesions and rash distribution for each of the emerging viruses.

Suggested reading

Ablashi D, Agut H, Alvarez-Lafuente R, et al. Classification of HHV-6A and HHV-B as distinct viruses. *Arch Virol*. 2014;159:863–870.

Adams RD, Victor M, Ropper AH. Multiple sclerosis and allied demyelinative diseases. In Adams RD, Victor M, eds. *Principles of Neurology*, 6th ed. New York: McGraw-Hill; 1997: 902–927.

Aronson M, Auwaerter P. Infectious mononucleosis in adults and adolescents. In Post T, ed. UpToDate. 2018. www.uptodate.com.

Barnett ED, Christiansen E, Figueira M. Seroprevalence of measles, rubella, and varicella in refugees. *Clin Infect Dis*. 2002;35:403–408.

Bialecki C, Feder HM Jr, Grant-Kels JM. The six classic childhood exanthems: A review and update. *J Am Acad Dermatol*. 1989;21:891–903.

Broliden K, Tolfvenstam T, Norbeck O. Clinical aspects of parvovirus B19 infection. *J Intern Med*. 2006;260:285–304.

Burt FJ, Rolph MS, Rulli NE, et al. Chikungunya: A re-emerging virus. *Lancet*. 2012;379:662.

Calabrese LH, Proffitt MR, Levin KH, et al. Acute infection with the human immunodeficiency virus (HIV) associated with acute brachial neuritis and exanthematous rash. *Ann Intern Med*. 1987;107:849.

Centers for Disease Control and Prevention (CDC). Current trends risks associated with human parvovirus B19 infection. https://www.cdc.gov/mmwr/preview/mmwrhtml/00001348.htm. May 2, 2001.

Centers for Disease Control and Prevention (CDC). Interim guidance for specimen collection, transport, testing, and submission for patients with suspected infection with Ebola virus disease. http://www.cdc.gov/vhf/ebola/pdf/ebola-lab-guidance.pdf. February 22, 2018

Centers for Disease Control and Prevention (CDC). Ebola virus disease information for clinicians in US healthcare settings. http://www.cdc.gov/vhf/ebola/hcp/clinician-information-us-healthcare-settings.html. March 10, 2021.

Centers for Disease Control and Prevention (CDC). Subacute sclerosing panencephalitis surveillance—United States. *MMWR Morb Mortal Wkly Rep*. 1982;31:585–588.

Centers for Disease Control and Prevention (CDC). Elimination of rubella and congenital rubella syndrome—United States, 1969–2004. *MMWR Morb Mortal Wkly Rep*. 2005;54: 279–282.

Centers for Disease Control and Prevention (CDC). Measles outbreak associated with an arriving refugee—Los Angeles, California, August September 2011. *MMWR Morb Mortal Wkly Rep*. 2012;61:835–839.

Centers for Disease Control and Prevention (CDC). Global control and regional elimination of measles, 2000–2011. *MMWR Morb Mortal Wkly Rep*. 2013;62: 27–31.

Centers for Disease Control and Prevention (CDC). Measles cases and outbreaks. https://www.cdc.gov/measles/cases-outbreaks.html

Centers for Disease Control and Prevention (CDC). Today's HIV/AIDS epidemic. https://www.cdc.gov/

Centers for Disease Control and Prevention (CDC). Is it chikungunya or dengue? https://www.cdc.gov/chikungunya/pdfs/poster_chikv_denv_comparison_healthcare_providers.pdf

Centers for Disease Control and Prevention (CDC). Rubella. https://www.cdc.gov/rubella/hcp.html

Centers for Disease Control and Prevention (CDC). Zika virus. https://www.cdc.gov/zika.

Cherry JD, Harrison G, Kaplan SL, et al. Roseola infantum (exanthem subitum). In Feigin and Cherry's, ed. *Textbook of Pediatric Infectious Diseases*, 8th ed. New York: Elsevier; 2018:559.

Chevillon C, Briant L, Renaud F, Devaux C. The Chikungunya threat: An ecological and evolutionary perspective. *Trends Microbiol*. 2008;16:80.

Chirch L, Diekhaus K, Grant-Kels J. Classic viral exanthems. In Schlossberg D, ed. *Clinical Infectious Disease*. New York: Cambridge University Press; 2015:139–147.

Chorba T, Coccia P, Holman RC, et al. The role of parvovirus B19 in aplastic crisis and erythema infectiosum (fifth disease). *J Infect Dis*. 1986;154:383.

Chovel-Sella A, Tov A, Lahav E, et al. Incidence of rash after amoxicillin treatment in children with infectious mononucleosis. *Pediatrics*. 2013;131:1424–1427.

Cohen J. Epstein-Barr virus infections, including infectious Mononucleosis. In Kasper D, Fauci A, Hauser S, eds. *Harrison's Principles of Internal Medicine*. New York: McGraw Hill Education; 2015: 1186–1190.

Cohen JI. Epstein-Barr virus infection. In Freedberg IM, Eisen AZ, Wolff K, et al., eds. *Fitzpatrick's Dermatology in Internal Medicine*. 5th ed. New York: McGraw-Hill; 1999: 2458–2462.

Coughlin M, Beck A, Bankamp B, et al. Perspective on global measles epidemiology and control and the role of novel vaccination strategies. *Viruses*. 2017;9:11.

Davidkin I, Valle M, Peltola H, et al. Etiology of measles and rubella-like illnesses in measles, mumps and rubella-vaccinated children. *J Infect Dis*. 1998;178:1567–1570.

DeBolle L, Naesens L, De Clercq E. Update on human herpesvirus 6 biology, clinical features. *Clin Microbiol Rev*. 2005;18:217–245.

Decker BK, Sevransky JE, Barrett K, et al. Preparing for critical care services to patients with Ebola. *Ann Intern Med*. 2014;161:831.

DeCrom SC, Rossen JW, van Furth AM, Obihara CC. Enterovirus and parechovirus infection in children: A brief overview. *Eur J Pediatr*. 2016;175:1023.

Derrington S, Cellura A, McDermott L, et al. Mucocutaneous findings and course in an adult with zika virus infection. *JAMA Dermatol*. 2016;152–691–693.

Edington F, Varjão D, Melo P. Incidence of articular pain and arthritis after chikungunya fever in the Americas: A systematic review of the literature and meta-analysis. *Joint Bone Spine*. 2018;85:669.

Forgie S, Marrie TJ. Cutaneous eruptions associated with antimicrobials in patients with infectious mononucleosis. *Am J Med*. 2015;128:e1–2.

Froeschle JE, Nahmias AJ, Feorino PM, et al. Hand, foot, and mouth disease (Coxsackievirus A16) in Atlanta. *Am J Dis Child*. 1967;114:278.

Gatherer D, Kohl A. Zika virus: A previously slow pandemic spreads rapidly through the Americas. *J Gen Virol*. 2016;97:269–273.

German Advisory Committee Blood. Human immunodeficiency virus. *Transfus Med Hemother*. 2016;43:203–222.

Hall CB, Long CE, Schnabel KC, et al. Human herpesvirus-6 infection in children. *N Engl J Med*. 1994;331:432–438.

Infectious Disease Adviser. https://www.infectiousdiseaseadvisor.com/infectious-diseases/epstein-barr-virus-ebv/article/609527/

Ioos S, Mallet H, Goffart I, et al. Current Zika virus epidemiology and recent epidemics. *Med Mal Infect*. 2014;44:302–307.

Kahn AU, Walker JO. Acute human immunodeficiency virus type 1 infection. *N Engl J Med*. 1998;339(1):33.

Kaplan LJ, Daum RS, Smaron M, McCarthy CA. Severe measles in immunocompromised patients. *JAMA*. 1992;267:1237–1241.

Kassutto S, Rosenberg E. Primary HIV type 1 infection. *Clin Infect Dis*. 2004;38:1447–1453.

Kuhn J, Peters C. Arthropod-borne and rodent-borne virus infections. In Kasper D, Fauci A, Hauser S, eds. *Harrison's Principles of Internal Medicine*. New York: McGraw Hill Education; 2015: 1304–1323.

Lakshmi V, Neeraja M, Subbalaxmi MV, et al. Clinical features and molecular diagnosis of Chikungunya fever from South India. *Clin Infect Dis*. 2008;46:1436.

Lapins J, Gaines H, Lindbäck S, et al. Skin and mucosal characteristics of symptomatic primary HIV-1 infection. *AIDS Patient Care STDS*. 1997;11:67.

Lindsey NP, Staples JE, Fischer M. Chikungunya virus disease among travelers: United States, 2014–2016. *Am J Trop Med Hyg*. 2018;98:192.

Martinez M, Salim A, Hurtado J, et al. Ebola virus infection: Overview and update on prevention and treatment. *Infect Dis Ther*. 2015;4:365–390

Mathes E, Oza V, Frieden I, et al. "Eczema coxsackium" and unusual cutaneous findings in an enterovirus outbreak. *Pediatrics*. 2013;132:149–157.

Mulholland EK, Giffiths UK, Biellik R. Measles in the 21st century. *N Engl J Med*. 2012;366:1755–1757.

National Center for Biotechnology Information. Epstein Barr virus. https://www.ncbi.nlm.nih.gov/

National Center for Emerging and Zoonotic Infectious Diseases. Ebola. https://www.cdc.gov/

National Center for Emerging and Zoonotic Infectious Diseases. West Nile Virus. https://www.cdc.gov/

National Center for Emerging and Zoonotic Infectious Diseases. Zika. https://www.cdc.gov/

National Center for Immunization and Respiratory Disease. Rubella. https://www.cdc.gov/

Oğuz F, Akdeniz C, Unüvar E, et al. Parvovirus B19 in the acute arthropathies and juvenile rheumatoid arthritis. *J Paediatr Child Health*. 2002;38:358.

Panning M, Grywna K, van Esbroeck M, et al. Chikungunya fever in travelers returning to Europe from the Indian Ocean region, 2006. *Emerg Infect Dis*. 2008;14:416.

Peterson L. Epidemiology and pathogenesis of West Nile virus infection. In Post T, ed. UpToDate. 2018. www.uptodate.com

Pichler W, Yawalkar N, Schmid S, Helbling A. Pathogenesis of drug-induced exanthems. *Allergy*. 2002;57: 884–893.

Pickering LK, ed. *Red Book: Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

Rajapakse S, Rodrigo C, Rajapakse A. Atypical manifestations of chikungunya infection. *Trans R Soc Trop Med Hyg*. 2010;104:89.

Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haeomophagocytic syndrome. *Lancet*. 2014;383: 1503.

Reef SE, Cochi SL. The evidence for the elimination of rubella and congenital rubella syndrome in the United States: A public health achievement. *Clin Infect Dis*. 2006;43:S123–S125.

Reynolds M, Jones A, Peterson E, et al. Vital signs: Update on zika virus–associated birth defects and evaluation of all US infants with congenital zika virus exposure: US zika pregnancy registry, 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66:366–373.

Robinson CR, Doane FW, Rhodes AJ. Report of an outbreak of febrile illness with pharyngeal lesions and exanthem: Toronto, summer 1957: Isolation of group A Coxsackie virus. *Can Med Assoc J*. 1958;79:615.

Romero J. Hand, foot and mouth disease and herpangina. In Post T, ed. UpToDate. 2018. Www.uptodate.com

Rossi S, Ross T, Evans J. West Nile virus. *Clin Lab Med*. 2010;30:47–65.

Servey J, Reamy B, Hodge J. Clinical presentations of parvovirus B19 infection. *Am Fam Physician*. 2007;75:373–376.

Schieffelin JS, Shaffer JG, Goba A, et al. Clinical illness and outcomes in patients with Ebola in Sierra Leone. *N Engl J Med*. 2014;371:2092.

Scroggie DA, Carpenter MT, Cooper RI, Higgs JB. Parvovirus arthropathy outbreak in southwestern United States. *J Rheumatol*. 2000;27:2444.

Seddon JH, Duff MF. Hand-foot-and-mouth disease: Coxsackie virus types A 5, A 10, and A 16 infections. *N Z Med J*. 1971;74:368.

Sinclair C, Gaunt E, Simmonds P, et al. Atypical hand, foot, and mouth disease associated with coxsackievirus A6 infection, Edinburgh, United Kingdom, January to February 2014. *Euro Surveill*. 2014;19:20745.

US Department of Health and Human Services. HIV Prevention. https://aidsinfo.nih.gov/

Vouloumanou E, Rafailidis P, Falagas M. Current diagnosis and management of infectious mononucleosis. *Curr Opin Hematol*. 2012;19:14–20.

Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. *N Engl J Med*. 2015;372:1231.

Woolf AD, Campion GV, Chishick A, et al. Clinical manifestations of human parvovirus B19 in adults. *Arch Intern Med*. 1989;149:1153.

World Health Organization. At one-month mark in Ebola outbreak, focus shifts to remote areas. https://www.who.int/

World Health Organization. West Nile virus. http://www.who.int/

20

Skin ulcer and pyoderma

Joanne T. Maffei

Skin lesions are important clues to systemic diseases, and, conversely, host factors make patients susceptible to skin infections caused by certain organisms. The skin has a limited response to insults from the microbial world, forming vesicles and pustules that eventually rupture and leave exposed dermis. Accurate diagnosis and appropriate treatment depend on a detailed history that includes systemic complaints, history of exposure and travel, and the initial appearance of the skin lesions. Sound diagnosis of difficult cases also depends on appropriate cultures and histopathology. When possible, cultures should be obtained by aspirating pus or blister fluid from under intact skin; cultures from ulcerated skin are less reliable because of colonization by nonpathogenic skin flora. A Gram stain and routine culture should be done first; if the ulcer persists despite a course of antibiotics, a skin biopsy with histopathology and cultures for routine agents, acid-fast organisms, and fungal pathogens is appropriate. If the lesion has multiple thin-walled vesicles with interspersed shallow ulcers and crusts or is on a mucous membrane, a herpes polymerase chain reaction (PCR), direct fluorescent antibody (DFA) test, or viral culture should be considered.

Most superficial skin infections and ulcers can be treated empirically according to the typical clinical presentation of the lesions. A workup is required for lesions that do not respond to routine therapy, that are rapidly progressive, or that occur in an immunocompromised host.

Skin ulcers

Skin ulcers are superficial defects in the tissues of the epidermis and dermis, with surrounding inflammation. Infection, collagen vascular diseases, and malignancy can cause cutaneous ulcerations. Information on host factors, exposure history, and the clinical course of the lesions is critical to narrowing the differential diagnosis. The lesion's anatomic location also may offer clues to the cause. Facial ulcers may be caused by syphilis, herpes, or blastomycosis, whereas ulcers of the arms or hands may be caused by sporotrichosis, nocardia, atypical mycobacteria, herpetic whitlow, or cutaneous anthrax. Ulcers on the chest wall from underlying pulmonary involvement or associated with intravenous (IV) catheters may be caused by aspergillosis. Ulcers in the groin or perineum may result from sexually transmitted infections such as syphilis, chancroid, and herpes, as well as from Behçet's disease or fixed drug eruption.

Ulcers on the lower extremities result from venous insufficiency in 70% to 90% of cases and occur below the knee but never on the bottom of the foot. The patient with venous stasis ulcers has good peripheral pulses and no peripheral neuropathy. Ulcers in patients with poor peripheral pulses, an ankle/brachial pressure index <0.9, or sensory loss must be investigated further because venous stasis is not the cause. Any ulcer on the leg that does not respond to treatment for venous stasis ulcers should be further investigated by biopsy and culture, as should any ulcer that is rapidly progressive or appears on an immunocompromised host. Figure 20.1 outlines the steps in evaluating and treating leg ulcers.

A history of unusual occupation, hobby, or exposure can suggest causes of skin ulcers such as tularemia in rabbit hunters, *Mycobacterium marinum* in aquarium enthusiasts, and leishmaniasis in travelers to endemic areas of the Middle East, North Africa, and Central and South America. Host factors also may

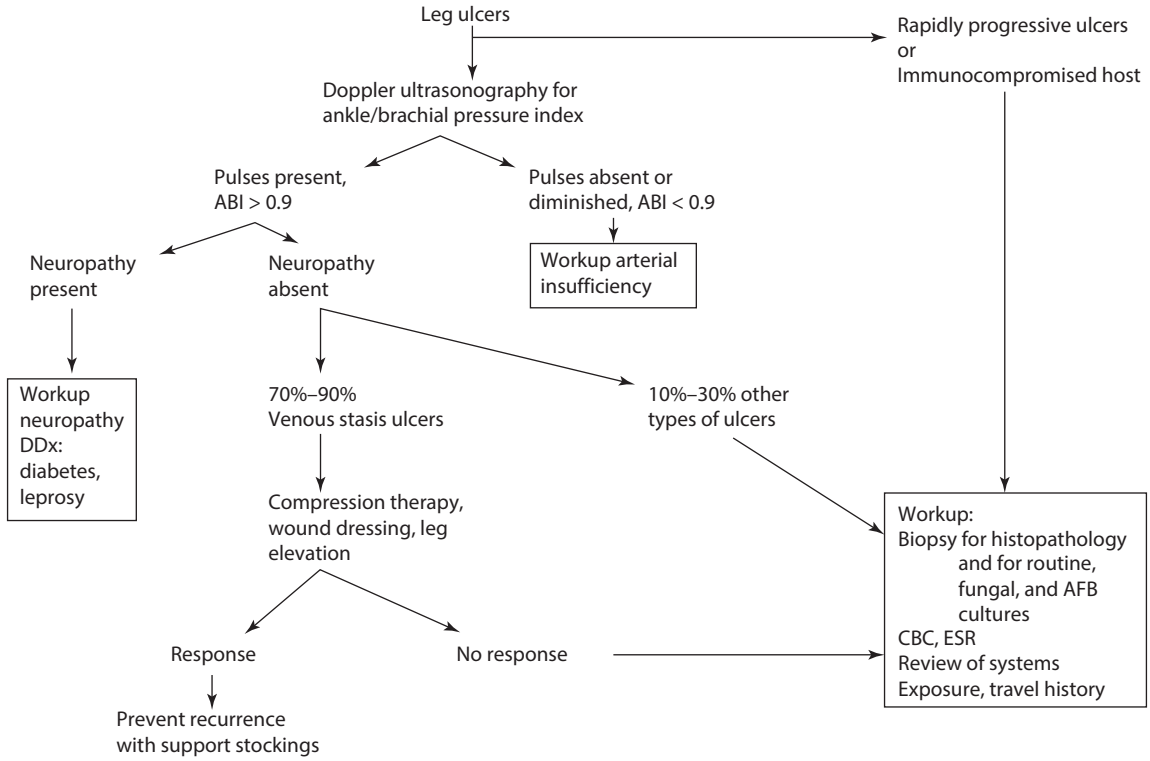

FIGURE 20.1 Algorithm for the evaluation of leg ulcers. ABI, ankle/brachial index; AFB, acid-fast bacilli; CBC, complete blood count; DDX, differential diagnosis; ESR, erythrocyte sedimentation rate.

predispose individuals to any of several types of ulcers. Patients with malignancies can be at risk for ecthyma gangrenosum caused by *Pseudomonas aeruginosa* or dense neutrophilic infiltration of the dermis that is noninfectious but responds to steroids (Sweet's syndrome, discussed later). Ecthyma gangrenosum caused by *P. aeruginosa* is a rapidly progressive (12–24 hours), necrotic ulceration with hemorrhagic bullae and skin sloughing in the setting of gram-negative sepsis and neutropenia. Empiric agents for ecthyma gangrenosum should include piperacillin-tazobactam, cefepime, imipenem, or meropenem plus an aminoglycoside such as tobramycin for high-risk cases.

Treatment of skin ulcers depends on the cause of the lesion. For venous stasis ulcers, local care with occlusive dressings on the wounds and compression bandages to aid venous return is necessary. If cellulitis or folliculitis is present, antibiotics to cover *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), streptococci, and gram-negatives should be administered empirically pending cultures. After the ulcer has healed, compression stockings should be worn to prevent new ulcers. Therapy for other types of ulcers should address their cause; Table 20.1 outlines the clinical presentation and epidemiology of infectious ulcers.

Noninfectious ulcers

Noninfectious causes of cutaneous ulcers include drug reactions, collagen vascular diseases, and malignancy. Drugs reported to cause ulcerations include methotrexate, etretinate, and warfarin. Granulomatosis with polyangiitis (GPA) formerly known as Wegener's granulomatosis, a systemic disease with involvement of the respiratory tract and kidneys, can form necrotizing ulcerations of the skin. Biopsy of these lesions may be positive for leukocytoclastic vasculitis, granuloma, and inflammatory infiltrates. Serology for immunoglobulin G (IgG) antibodies against neutrophilic cytoplasmic components (c-ANCA) is highly specific for granulomatosis with polyangiitis. Treatment includes corticosteroids and cyclophosphamide. Behçet's disease is another systemic condition that involves recurrent oral and genital aphthous ulcerations, arthritis, and uveitis; in some cases it attacks the central nervous system. Treatment includes corticosteroids, colchicine, interferon-α, tumor necrosis factor-α (TNF-α) inhibitors, or azathioprine. Malignancy should always be considered as a possible cause of ulcers that have not responded to antimicrobial therapy because basal cell carcinoma, hematologic malignancies, and metastatic cancers may form skin ulcers.

Pyoderma

Pyoderma is a general term used to describe superficial disruption of the skin with pus formation in response to a bacterial infection. Generally caused by a single organism, pyoderma can be primary or secondary. Similar lesions can be produced by neutrophilic dermatoses such as pyoderma gangrenosum and Sweet's syndrome. Table 20.2 outlines the clinical presentation of pyoderma and suggested treatment.

TABLE 20.1 **CLINICAL PRESENTATION OF SKIN ULCERS CAUSED BY INFECTIOUS AGENTS**

Cause	Laboratory workup	Epidemiology	Clinical clues to diagnosis
Bacterial	Routine culture and Gram stain		
Bacillus anthracis (anthrax)	Gram-positive rod, biopsy for immunohistochemistry and PCR	Wool handler; Western Asia, West Africa, Eastern Europe; injection drug users (heroin); potential bioweapon	Lesions on face and arms; painless papule develops into vesicle that dries, forming black eschar that then separates from the base to form an ulcer with marked surrounding gelatinous edema; LN common; injectional anthrax—higher mortality and shock, significant edema
Corynebacterium diphtheriae (diphtheria)	Gram-positive rod	Tropical climates; rare in the United States	Ulcer with sharp margins and clean base; preexisting skin lesions may become infected
Francisella tularensis (tularemia)	Gram-negative coccobacillus, serology	Rabbits, muskrats, beavers; North America, Japan, Europe, former Soviet Union; potential bioweapon	Systemic febrile illness; tender ulcer with painful LN
Nocardia spp.	Branching, beaded gram-positive rod, modified AFB-positive	Immunocompromised patients, soil exposure	Ulcer with purulent drainage, nodular lymphangitis
Pseudomonas aeruginosa (ecthyma gangrenosum)	Gram-negative rod, may have associated bacteremia	Neutropenic or immunocompromised patients	Rapidly progressive eruption from papules to hemorrhagic vesicles or bullae that undergo central necrosis and ulceration
Polymicrobial	Mixed gram-positive and gram-negative, and anaerobes	Debilitated, immunocompromised, diabetic patients	Pressure sores, decubitus ulcers, foot ulcers
Yersinia pestis (plague)	Gram-negative coccobacillus, bipolar-staining "safety pin" morphology, serology	Rodent zoonosis transmitted to humans via fleas; Far East, India, Africa, Central and South America, potential bioweapon	Bubonic plague with classic inguinal painful LN; may have skin lesions on lower extremities; pustule, papule, vesicle, or eschar may occur at inoculation site
Spirochetes			
Treponema pallidum (syphilis)	Serology	Sexually transmitted infection	Tertiary syphilis; nodular, ulceronodular, gummas; punched-out ulcer with gummy discharge
Fungal	Fungal smear, culture		
Aspergillus spp.	Septate hyphae; serum galactomannan assay in high-risk patients	Immunocompromised, HIV-positive	Ulcers, plaques, nodules, pustules; may be associated with trauma, IV catheter sites, secondary colonization of existing wounds, or direct extension from lung to chest wall
Blastomyces dermatitidis, B. gilchristii	Broad-based budding yeast, dimorphic fungus	Sugar cane worker, HIV-positive, immunocompromised; North America, Africa	Subcutaneous nodule that enlarges and ulcerates forming a crusted, verrucous plaque; may resemble squamous cell carcinoma
Coccidioides immitis, C. posadasii	Dimorphic fungus, serology	Soil exposure, HIV-positive; Southwestern United States, Mexico, Central and South America	Usually single nodule or plaque; may form pustules, subcutaneous nodules, or abscesses
Cryptococcus neoformans, C. gattii	India ink, encapsulated yeast, mucicarmine-positive capsule, cryptococcal antigen (serum and CSF)	Exposure to pigeons, soil exposure, HIV-positive, immunocompromised	Papule with crust resembling molluscum contagiosum; also forms ulcers on skin, mouth, and genitalia; may have lung or CNS involvement

TABLE 20.1 CONTINUED

Cause	Laboratory workup	Epidemiology	Clinical clues to diagnosis
Histoplasma capsulatum	Dimorphic fungus, histoplasma antigen (urine and serum)	Bats, birds, and soil exposure; HIV-positive, immunocompromised; Eastern and Central United States in Ohio/Mississippi River Valleys, Central and South America, West Indies, Africa, Madagascar	Papule with crust resembling molluscum contagiosum; ulcerative plaques and oral ulcerations
Sporothrix schenckii	Dimorphic fungus	Rose gardening, soil exposure	Papule or pustule at inoculation site develops into subcutaneous nodules or ragged-edged ulcer with proximal nodular lymphangitis; usually on upper extremities
Mycobacterial	AFB smear, culture		
Mycobacterium marinum	AFB-positive, growth at 30°C/86°F–32°C/90°F	Water, aquarium enthusiasts	Ulcer with thin seropurulent drainage, nodular lymphangitis
Mycobacterium ulcerans (Buruli ulcer)	AFB-positive, PCR for the insertion sequence IS*2404* in swabs or tissue samples	Africa, Australia, South East Asia, South America, North America (Mexico); 2- to 3-month incubation period, usually associated with trauma	Subcutaneous nodule that ulcerates with extensive scarring and contracture formation; edematous lesion rapidly progresses to extensive ulceration, may have osteomyelitis contiguous to ulcer
Mycobacterium avium complex	AFB-positive	HIV-positive, immunocompromised; soil, water	Multiple subcutaneous nodules or ulcers; may be associated with cervical lymphadenitis drainage to skin or direct inoculation
Mycobacterium haemophilum	AFB-positive, requires iron-supplemented culture medium and incubation at 28°C/82°F–30°C/86°F	Australia, United States, Canada, France, Germany, Singapore; HIV-positive, transplantation	Papules develop into pustules which form deep ulcers, usually on extremities overlying joints; may have septic arthritis ± osteomyelitis, may have LN
Mycobacterium tuberculosis	AFB-positive, TST or interferon-γ release assay helpful if positive	Worldwide	Nodules or ulcers especially in HIV-positive patients, scrofuloderma, plaques
Viral			
Herpes simplex	PCR, DFA, viral culture	Sexually transmitted infection	Oral, perineal, genital ulcers; whitlow on hands; lesions with thin-walled vesicles; shallow painful ulcers
Parasitic			
Leishmaniasis	Punch biopsy, aspirates, or scrapings of skin for culture, histopathology, and touch prep using Wright's and Giemsa stains looking for amastigotes at base of lesion; serology; PCR of tissue aspirates, or peripheral blood	Sandfly bites, travel to endemic area (military or civilian); incubation period weeks to months, HIV-positive, immunocompromised; *Old World*: Mediterranean, Middle East, Africa, Southern Asia, India; *New World*: Latin America, Central and South America	Papule at the site of insect bite enlarges to form a nodule, which then develops into a punched-out ulcer; may have associated LN; rarely nodules form without ulceration; may involve nasal or oral mucosa (mucocutaneous); visceral involvement possible

Abbreviations: LN = lymphadenopathy; AFB = acid-fast bacilli; CNS = central nervous system; DFA = direct fluorescent antibody; PCR = polymerase chain reaction; TST = tuberculin skin test; CSF = cerebrospinal fluid.

TABLE 20.2 **CLINICAL PRESENTATION AND THERAPY OF PYODERMA**

Type of disease	Distinguishing features	Causative organism	Treatment
Primary pyoderma			
Impetigo Nonbullous impetigo Bullous impetigo	Superficial honey-colored crusts Thin vesicles and bullae, when ruptured produce varnish-like crust	*Streptococcus pyogenes, Staphylococcus aureus* Toxin-producing strains of *S. aureus*	For patients with few lesions may use topical agents for 5 days: Mupirocin topical ointment 2% TID (MSSA or MRSA) *Or* Retapamulin topical ointment 1% BID (note—for MSSA lesions only, not MRSA) For patients with many lesions or in outbreak setting use oral agents for 7 days: *For MSSA:* Amoxicillin–clavulanate 875/125 mg PO BID *Or* Dicloxacillin 250 mg PO QID *Or* Cephalexin 250 mg PO QID *Or* Clindamycin 300–450 mg PO QID *For MRSA:* Minocycline 100 mg PO BID *Or* Trimethoprim-sulfamethoxazole (TMP–SMX) 1–2 double-strength tablets (TMP 160 mg) PO BID *Or* Clindamycin 300–450 mg PO QID
Ecthyma	Ulcer with crust	*Streptococcus pyogenes*, *S. aureus*	Treat as impetigo with oral agents for 7 days
Folliculitis	Hair follicle with pustules, erythema	*S. aureus*	*Topical*: Clindamycin topical gel 1% BID *Or* Erythromycin topical solution 2% BID *Or* Mupirocin topical ointment 2% TID *Or* Benzoyl peroxide lotion *Unresponsive:* Treat as impetigo with oral agents
Gram-negative folliculitis	Usually on face in patients with acne vulgaris on chronic suppressive antibiotic therapy	*Klebsiella, Enterobacter, Proteus* species	Amoxicillin–clavulanate 875/125 mg PO BID *Or* TMP–SMX one double-strength tablet (TMP 160 mg) PO BID
Hot-tub folliculitis	Pustules and vesicles on an erythematous base in bathing-suit distribution	*Pseudomonas aeruginosa*	Self-limited in normal hosts; decontaminate and chlorinate hot tub

TABLE 20.2 CONTINUED

Type of disease	Distinguishing features	Causative organism	Treatment
Furuncle/carbuncle	Abscess formation in dermis, subcutaneous tissue that may coalesce and drain; if cellulitis or sepsis associated, needs IV antibiotics; patients may have recurrences; suggest culture to rule out MRSA or gram-negative organisms	*S. aureus* both MSSA and MRSA, now many community-acquired strains are MRSA	Careful incision and drainage, and warm compresses; for lesions >5 cm and patients with fever, add antistaphylococcal antibiotics targeting MRSA including: TMP–SMX 1–2 double-strength (TMP 160 mg) PO BID *Or* Minocycline 100 mg PO BID If associated with cellulitis or systemic inflammatory response syndrome: Vancomycin 15 mg/kg IV q12h *Or* Daptomycin 4 mg/kg IV q24h (dosed for skin/soft tissue only, not bacteremia) If recurrent, eradicate nasal carriage of *S. aureus* by: Mupirocin nasal ointment 2% BID × 7 days and Chlorhexidine 2% daily wash × 7 days Along with either: Rifampin 300 mg PO BID plus Doxycycline 100 mg PO BID × 7 days *Or* Rifampin 300 mg PO BID plus TMP–SMX 1 tab PO BID × 7 days
Neutrophilic dermatoses			
Pyoderma gangrenosum	Rapidly progressive painful ulcers, ragged violaceous edges with necrotic centers, usually on lower legs; Underlying IBD, malignancy, arthritis, monoclonal gammopathy *Biopsy:* PMN, lymphocytic infiltration, ± vasculitis	No organisms seen, culture negative	Prednisone 0.5–1 mg/kg/d *Or* Cyclosporine 4 mg/kg/d For PG associated with Crohn's disease: Infliximab Other agents used include: mycophenolate mofetil, clofazimine, azathioprine, methotrexate, tacrolimus, thalidomide, dapsone (contraindicated in G6PD-deficient patients) Localized PG: topical or intralesional corticosteroids, or tacrolimus ointment
Sweet's syndrome	Fever, neutrophilia, prompt response to steroids, painful erythematous plaques, may form bullae and ulcerate; located on head, neck, arms; 20% have associated malignancy, usually AML, elevated sedimentation rate *Biopsy*: Dense PMN infiltration of the dermis, no vasculitis	No organisms seen, culture negative	Prednisone 1 mg/kg/d, slow taper over 4–6 wk *Or* Colchicine 1.5 mg/d PO *Or* Dapsone 100–200 mg/d PO (contraindicated in G6PD-deficient patients) *Or* Potassium iodide 900 mg/d PO Alternative agents: indomethacin, clofazimine, cyclosporine
Secondary pyoderma	Preexisting lesions of dermatitis such as eczema, psoriasis, or surgical/traumatic wounds		Based on culture data. Note increasing rates of community-acquired MRSA

Abbreviations: AML = acute myelogenous leukemia; G6PD = glucose-6-phosphate dehydrogenase; IBD = inflammatory bowel disease; MSSA = methicillin-sensitive *S. aureus*; MRSA = methicillin-resistant *S. aureus*; PG = pyoderma gangrenosum; PMN = polymorphonuclear leukocytes.

Primary pyoderma

Primary pyoderma is an infection of previously healthy skin, usually caused by *S. aureus* or *Streptococcus pyogenes*.

Impetigo

Impetigo is a superficial infection of the skin involving only the epidermis (see Figure 20.2). Impetigo is highly contagious and usually occurs in young children following minor skin trauma. Nonbullous impetigo, the classic honey-colored crusts on the face or extremities, is caused by *S. pyogenes* or *S. aureus*; toxin-producing strains of *S. aureus* cause bullous impetigo (varnish-like crust). Treatment of bullous and nonbullous impetigo requires coverage of methicillin-sensitive *S. aureus* (MSSA): dicloxacillin 250 mg orally four times a day (QID), or first-generation cephalosporins such as cephalexin 250 mg orally QID for 7 days; note that the oral cephalosporins cefixime and ceftibuten have no activity against MSSA. For penicillin-allergic patients, clindamycin 300 to 450 mg orally QID is appropriate. Because most areas have seen the emergence of community-acquired MRSA, empiric therapy targeting MRSA with trimethoprim-sulfamethoxazole (TMP-SMX), one to two double-strength tablets orally twice a day (BID), or minocycline 100 mg orally BID is warranted. For patients with few lesions, topical mupirocin ointment 2% applied to the lesion three times a day (TID) for 5 days is an equally effective alternative to systemic therapy. Topical retapamulin ointment 1% applied to the lesion twice a day for 5 days is an option for MSSA lesions (not for MRSA).

Ecthyma

Ecthyma (Figure 20.3) is impetigo that extends through the epidermis, forming shallow ulcers with crusts. It occurs in immunocompromised patients and is caused by *S. pyogenes* or *S. aureus*. Gram stain and culture of the lesion must be performed to rule out MRSA or ecthyma gangrenosum, which is caused by *P. aeruginosa* sepsis. Treatment of ecthyma due to streptococci or staphylococci is the same as that for impetigo, with oral agents for 7 days. Unlike impetigo, ecthyma may heal with scarring.

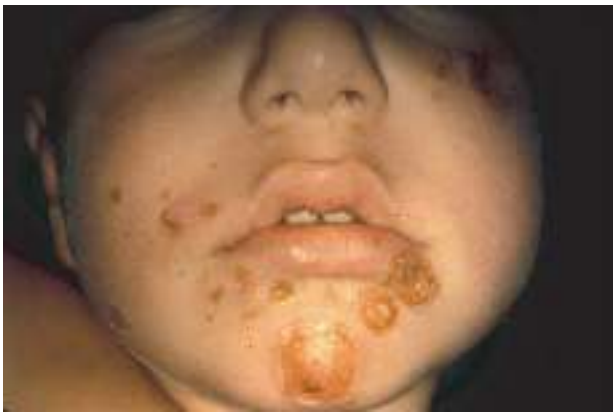

FIGURE 20.2 Impetigo. This is a superficial streptococcal or staphylococcal infection that occurs just beneath the stratum corneum. It generally occurs in the paranasal or perioral area in young people. Note typical honey-colored crusts, which heal without scarring.

Reproduced with permission from Sanders CV, Nesbitt LT, eds. *The skin and infection: A color atlas and text*. Baltimore: Williams & Wilkins; 1995: 35.

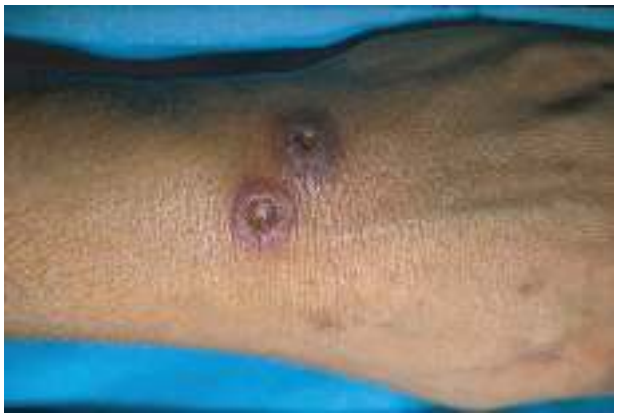

FIGURE 20.3 Ecthyma. This is a more serious form of impetigo in which the infection penetrates to the dermis. Scarring is common.

Reproduced with permission from Dr. Charles V Sanders from Sanders CV, Nesbitt LT, eds. *The skin and infection: A color atlas and text*. Baltimore: Williams & Wilkins; 1995: 35.

Folliculitis

Folliculitis is an inflammation of the hair follicles, usually caused by *S. aureus*. Topical therapy with mupirocin three times daily for 7 days is usually adequate. If the infection does not respond, oral therapy with agents used for impetigo should be adequate. Lesions that do not respond to antistaphylococcal antibiotics should be cultured because they may be caused by MRSA or other pathogens. Therapy should be tailored to antimicrobial sensitivities. On rare occasions, gram-negative organisms cause folliculitis, typically in association with either superinfection in patients taking long-term antibiotics for acne vulgaris or hot-tub bathing. Gram-negative folliculitis in acne patients is caused by *Klebsiella, Enterobacter*, and *Proteus* species and usually occurs on the face. Treatment depends on susceptibilities, but amoxicillin-clavulanate or TMP-SMX may be used empirically. Hot-tub folliculitis caused by *P. aeruginosa* is usually self-limiting in a normal host, and no action is necessary beyond decontaminating the water and ensuring proper chlorination.

Furuncles and carbuncles

Furuncles are skin abscesses caused by *S. aureus*; they may begin as folliculitis that extends into the surrounding dermis and subcutaneous tissue. Carbuncles comprise several furuncles that coalesce to form loculated abscesses with draining pus. If the patient is afebrile and the abscess is <5 cm in diameter, incision and drainage and warm compresses without oral antimicrobials should suffice. If the patient has fever or other components of systemic inflammatory response syndrome, or if the lesion is >5 cm, oral anti-staphylococcal antibiotics targeting MRSA should be prescribed in addition to careful incision and drainage of the abscess. In either case, cultures

of the abscess should be obtained to guide therapy in the event there is no response to the initial treatment. Some patients with recurrent furuncles and carbuncles may require elimination of nasal *S. aureus* carriage with nasal applications of mupirocin, bathing with chlorhexidine, and either oral rifampin plus doxycycline, or rifampin plus TMP-SMX.

Neutrophilic dermatoses

Pyoderma caused by neutrophilic infiltrates usually is associated with underlying disease such as cancer or inflammatory bowel disease (IBD). The main entities are pyoderma gangrenosum and Sweet's syndrome.

Pyoderma gangrenosum

The diagnosis of pyoderma gangrenosum is clinical. The lesion begins as a small erythematous papule, rapidly progressing to tender pustules that undergo central necrosis and ulceration. The border of the ulcers is ragged, violaceous, and surrounded by erythema. Distinguishing characteristics include severe pain at the ulcer site, lesions at the site of minor trauma, parchment scarring, and an associated systemic disease such as IBD, rheumatologic disease, or malignancy. Biopsy of the lesions is done to exclude infection, vasculitis, malignancy, and vascular occlusive disease because histopathologic findings are nonspecific. Central necrosis and lymphocytic and neutrophilic infiltrates with or without vasculitic changes are seen on histopathology of pyoderma gangrenosum lesions; lymphocytes and plasma cells around vessels are common findings. Pyoderma gangrenosum usually occurs on the lower extremities over bony prominences, where repeated trauma aggravates the condition (pathergy); its cause is unknown. Treatment for disseminated pyoderma gangrenosum includes prednisone 0.5 to 1 mg/kg by mouth daily or cyclosporine 4 mg/kg/d. For pyoderma gangrenosum associated with Crohn's disease, the TNF-α inhibitor infliximab is recommended as first-line therapy. Mycophenolate mofetil, clofazimine, azathioprine, methotrexate, tacrolimus, thalidomide, dapsone, and many other drugs and modalities have been used to treat pyoderma gangrenosum; response to therapy varies.

Sweet's syndrome

Sweet's syndrome is an acute febrile neutrophilic dermatosis that may be associated with a malignancy, infection (upper respiratory or gastrointestinal), IBD, pregnancy, medications, or vaccinations (BCG and influenza), or is idiopathic. Lesions are painful erythematous plaques usually on the upper extremities, head, and neck. These lesions are classically associated with fever and neutrophilia, but some patients have myalgia, arthralgia, proteinuria, and conjunctivitis. Nearly all patients with Sweet's syndrome have an elevated erythrocyte sedimentation rate. Dense neutrophilic infiltration of the dermis without vasculitis is the classic finding on biopsy, and it is important to exclude bacteria, mycobacteria, and fungi because steroids are the appropriate therapy for Sweet's syndrome. The response to prednisone 1 mg/kg/d is dramatic; constitutional symptoms improve within hours, and skin lesions improve over 1 to 2 days. Steroids should be tapered slowly over 4 to 6 weeks. Other first-line agents used to treat Sweet's syndrome include potassium iodide, colchicine, or dapsone. Alternative treatments for Sweet's syndrome include clofazimine, indomethacin, and cyclosporine.

Secondary pyoderma

Secondary pyoderma is a bacterial superinfection of skin previously disrupted by trauma, surgery, or chronic skin conditions such as eczema or psoriasis. The usual organism is *S. aureus,* which can be methicillin-resistant whether community-acquired or healthcare-associated. Empiric treatment for serious wound infections is IV vancomycin pending culture results. Mild to moderate infections can be treated with oral TMP-SMX (± rifampin) or minocycline. Secondary pyoderma caused by pressure sores and diabetic foot ulcers is usually polymicrobial and requires broad-spectrum therapy with vancomycin until MRSA is ruled out, plus piperacillin–tazobactam or a carbapenem, or a combination of ciprofloxacin and clindamycin. Table 20.2 summarizes suggested therapy for pyoderma.

Herpetic whitlow

Herpetic whitlow, a herpes simplex infection of the pulp of the finger, may occur in anyone who has mucocutaneous herpes or who comes in contact with herpetic lesions (i.e., healthcare workers). The initial lesion is a tender vesicle filled with turbid fluid. Lesions may be multiple and may ulcerate and become secondarily infected, developing purulent drainage. Axillary and epitrochlear lymphadenopathy with erythema of the proximal forearm also may occur. Diagnosis can be made by aspirating a vesicle and sending the fluid for PCR, viral culture, or performing a DFA test on the blister fluid. Treatment includes acyclovir, and surgery should be avoided.

Suggested reading

Alavi A, Sibbald RG, Phillips TJ, et al. What's new: Management of venous leg ulcers: Approach to venous leg ulcers. *J Am Acad Dermatol*. 2016;74:627–640.

Alavi A, Sibbald RG, Phillips TJ, et al. What's new: Management of venous leg ulcers: Treating venous leg ulcers. *J Am Acad Dermatol*. 2016;74:643–664.

Aronson N, Herwaldt BL, Libman M, et al. Diagnosis and treatment of leishmaniasis: Clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). *Clin Infect Dis*. 2016;63(12):e202–e264.

Ashchyan HJ, Nelson CA, Stephen S, et al. Neutrophilic dermatoses: Pyoderma gangrenosum and other bowel- and arthritis-associated neutrophilic dermatoses. *J Am Acad Dermatol*. 2018;79:1009–1022.

Burke VE, Lopez FA. Approach to skin and soft tissue infections in non-HIV immunocompromised hosts. *Curr Opin Infect Dis*. 2017;30:354–363.

Carrasco-Zuber JE, Navarrete-Dechent C, Bonifaz A, et al. Cutaneous involvement in the deep mycoses: A literature review. Part I—Subcutaneous mycoses. *Actas Dermosifiliogr*. 2016;107:806–815.

Carrasco-Zuber JE, Navarrete-Dechent C, Bonifaz A, et al. Cutaneous involvement in the deep mycoses: A review. Part II—Systemic mycoses. *Actas Dermosifiliogr*. 2016;107:816–822.

Gonzalez-Santiago TM, Drage LA. Nontuberculous mycobacteria: Skin and soft tissue infections. *Dermatol Clin*. 2015;33:563–577.

Narayanan N, Lacy CR, Cruz JE, et al. Disaster preparedness: Biological threats and treatment options. *Pharmacotherapy* 2018;38(2):217–234.

Nel JS, Bartelt LA, van Duin D, et al. Endemic mycoses in solid organ transplant recipients. *Infect Dis Clin N Am*. 2018;32:667–685.

Nelson CA, Stephen S, Ashchyan HJ, et al. Neutrophilic dermatoses: Pathogenesis, Sweet syndrome, neutrophilic eccrine hidradenitis, and Behçet disease. *J Am Acad Dermatol*. 2018;79:987–1006.

Ramdass P, Mullick S, Farber HF. Viral skin diseases. *Prim Care Clin Office Pract*. 2015;42:517–567.

Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10–e52.

Zingue D, Bouam A, Tian RBD, et al. Buruli ulcer, a prototype for ecosystem-related infection, caused by *Mycobacterium ulcerans*. *Clin Microbiol Rev*. 2017;31(1):e00045–17.

21

Cellulitis and erysipelas

Katherine S. Glaser and Kenneth J. Tomecki

Skin and soft-tissue infections (SSTIs) are routinely encountered in both outpatient and inpatient settings. In 2013, the US Food and Drug Administration (FDA) redefined SSTIs as acute bacterial skin and skin-structure infections (ABSSSIs), which include cellulitis/erysipelas, major skin abscesses, and wound infections with a surface area of at least 75 cm^2. In this chapter, we focus on the clinical presentation, microbiology, and treatment of cellulitis/erysipelas. Although there are notable differences between erysipelas and cellulitis, the treatment is similar and typically based on disease severity and presence of purulence.

Erysipelas

Clinical manifestations

Erysipelas is a superficial skin infection limited to the upper dermis and superficial lymphatics; it has a distinct clinical presentation. The legs are the most commonly affected site, but erysipelas can occur anywhere on the body. Young, elderly, and immunocompromised patients are particularly susceptible to erysipelas. Conditions such as obesity, venous insufficiency, lymphedema, and defects in the skin barrier (e.g., ulcers, surgical or traumatic wounds, preexisting inflammation) are all predisposing factors that increase the likelihood of a microbial breach through the epidermis leading to development of erysipelas.

Classically, erysipelas exhibits a sharply demarcated, tender, bright red edematous plaque with raised, indurated borders (Figure 21.1). The initial insult is often clinically undetectable but can be obvious, as in cases of postoperative or traumatic wounds. Regional lymphadenopathy, lymphatic streaking, and surrounding edema can occur. Systemic symptoms such as fevers, chills, and malaise may develop abruptly and precede skin disease by hours.

Recurrence is common, especially when an underlying comorbidity such as edema is present. Other complications include bullae formation, skin sloughing, sepsis, and organ dysfunction. Overall these sequelae are uncommon in the general population and are nearly exclusive to the immunocompromised patient.

Microbiology

Most cases of erysipelas are caused by *Streptococcus* spp., predominantly group A β-hemolytic streptococci (GAS) such as *S. pyogenes*. Less often, groups B, C, D, and G are implicated. Less commonly *Staphylococcus aureus* is involved, including methicillin-sensitive (MSSA) and methicillin-resistant strains (MRSA). Gram-negative organisms, anaerobic species, and polymicrobial infections also occur, although rarely.

The bacterial source is frequently unknown, but the interdigital toe spaces can be a nidus, especially in cases of lower extremity erysipelas. In neonates and postpartum women, the vaginal canal is often the reservoir of group B streptococci. Special circumstances like intravenous (IV) drug abuse, penetrating traumas, and open wounds increase the likelihood of staphylococcal, gram-negative, and anaerobic organisms, and polymicrobial infections.

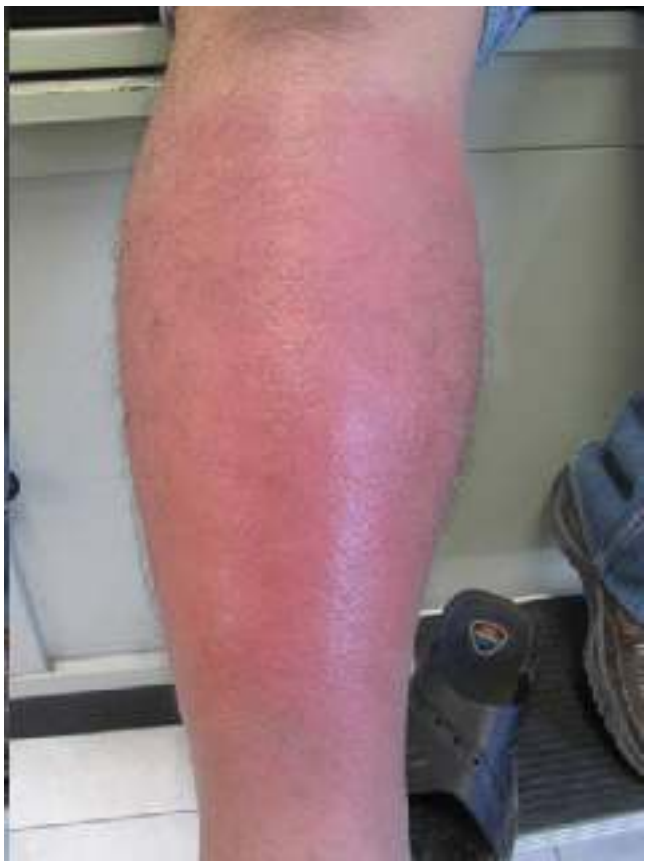

FIGURE 21.1 Erysipelas, right leg. Note the discrete, well-demarcated, raised edge of the erythematous plaque.

Courtesy of Jose Dario Martinez, MD, Monterrey, Mexico

Diagnosis and differential diagnosis

Physical exam alone is typically sufficient to establish a diagnosis. Routine lab tests, CBC, and basic metabolic panel may reveal a leukocytosis or organ dysfunction in severe cases. Swabs for Gram stain and wound cultures are usually unnecessary and generally low yield. Skin biopsy for tissue culture and tissue aspirates are more invasive testing methods which have similarly low-yield results. Blood cultures are positive in <5% of cases, but cultures (blood, tissue aspirate, or skin biopsy) should strongly be considered in those patients with an underlying malignancy, severe systemic symptoms, or immunosuppression for whom the physical exam and implicated organisms may be atypical.

The differential diagnosis, especially in facial erysipelas, includes allergic contact dermatitis and photoallergic reactions. If present, fevers, pain, leukocytosis, and a positive culture would favor the diagnosis of erysipelas. The facial rash in systemic lupus erythematosus and dermatomyositis can appear similar but bilateral, less well-demarcated, and associated with other systemic features. Other infectious etiologies (i.e., erysipeloid) should be considered, though the location on the hands, occupation, and history of animal exposure should help to distinguish the two conditions.

Cellulitis

Clinical manifestations

Cellulitis is a type of ABSSSI that involves the deep dermis and extends into the subcutaneous tissue. Factors that predispose an individual to erysipelas can increase the likelihood of cellulitis, including peripheral vascular disease, edema, obesity, diabetes, malignancy, ulceration, trauma, IV drug abuse, and inflammatory skin disorders. In healthy patients, antecedent trauma or inflammation often produces the opportunity for microbial entry via direct inoculation. In contrast, hematogenous seeding should be suspected in immunocompromised patients.

Clinically, cellulitis presents as a unilateral, ill-defined, erythematous, firm plaque in conjunction with the four cardinal signs of inflammation: rubor, calor, dolor, and tumor (Figure 21.2). Skin manifestations are often preceded by fever, chills, and malaise. Regional lymphadenopathy and lymphangitis may also occur

Complications include focal abscess and pustule and bullae formation within the cellulitis, as well as necrosis of the skin and subcutaneous tissue. Recurrence is common and often secondary to the aforementioned predisposing conditions. Sepsis, an infrequent complication, typically occurs in children or immunocompromised individuals. Severe disease and signs of sepsis should prompt the clinician to search for systemic infection. Rarely, acute glomerulonephritis and toxic shock–like syndrome can be seen in the setting of a GAS cellulitis.

Microbiology

The most frequent causative organisms in cellulitis are *Streptococcus pyogenes* and *Staphylococcus aureus*. MRSA strains are more often implicated in purulent cellulitis, abscesses, open wounds, penetrating traumas, and IV drug abusers, in which case empiric antibiotics should include MRSA coverage. Otherwise, in uncomplicated cellulitis, MRSA incidence is low and does not necessitate specific antimicrobial coverage. Gram-negative, anaerobic, and polymicrobial infections can be seen in immunocompromised individuals. Particular clinical situations can sometimes suggest atypical causative organisms, some such examples are listed in Table 21.1.

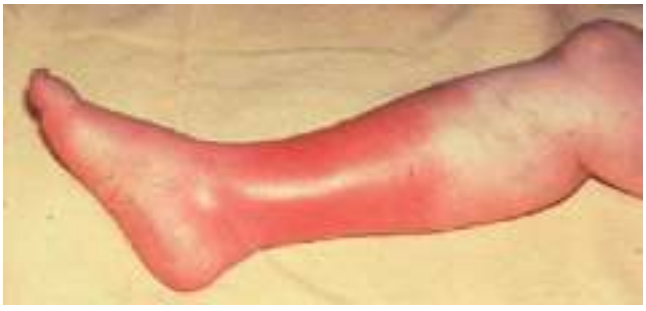

FIGURE 21.2 Cellulitis, right leg. Note the more irregular, less defined margin of the erythematous plaque.

TABLE 21.1 **CAUSES OF CELLULITIS SPECIFIC CLINICAL SITUATIONS OR EXPOSURES**

Clinical Scenario	Likely Organism
Postsurgical cellulitis	*Staph. Aureus*
Perianal cellulitis	*Strep. Pyogenes*
Preseptal cellulitis	Staph. aureus, Strep. Pyogenes
Orbital cellulitis	*Staph. aureus, Strep. Pneumonia*
Facial cellulitis	*Haemophilus influenzae*[a,b]
Neonatal cellulitis	Strep. Agalactiae (Group B Strep)
Crepitant cellulitis	*Clostridium species*
Salt water exposure	*Vibrio vulnificus*[b]
Freswater exposure	*Aeromonas hydrophilia*[b]
Hot-tub exposure	*Pseudomonas aeruginosa*[b]
Neutropenia	*Pseudomonas aeruginosa*[b]
Soil exposure	*Clostridium species*
Dog/cat bite	*Pasteurella multocida*[b], *Capnocytophaga canimorsus*[b]
Human bite	*Eikenella corrodens*[b]

[a] Less common since the advent of caccines
[b]Denotes gram negative organisms

Diagnosis and differential diagnosis

Like erysipelas, the clinical presentation of cellulitis should be sufficient to make a diagnosis. Swabs for wound culture from exudates, erosions, ulcerations, abscesses, and surgical wounds can help to confirm the diagnosis and direct antimicrobial therapy. However, the results may not always identify an organism and may be difficult to interpret if pathogenic or a contaminant. Skin biopsy for tissue culture and tissue aspirates has a lower yield than do swabs. Additional laboratory studies including CBCs, anti-DNase antibody, antistreptolysin titers, and blood cultures may be helpful but none is sensitive or specific. In cases of severe sepsis or immunosuppression, cultures should be performed and interpreted cautiously.

Imaging studies may be helpful in certain patients. Conventional radiography can delineate pockets of gas in anaerobic cellulitis or suspected necrotizing fasciitis, especially with *Clostridium* spp. as the cause. This should be considered when pain is disproportionate to exam findings, skin is anesthetic, skin color is gray or dusky, palpation reveals crepitus, or disease progresses despite conventional antibiotic therapy. In the setting of periorbital cellulitis, CT helps differentiate preseptal cellulitis from orbital cellulitis, an ophthalmologic emergency. In all other cases, if the diagnosis of cellulitis is questionable, MRI with T2-weighted images can highlight skin and soft-tissue edema but is largely unnecessary.

The differential diagnosis of cellulitis, especially on the legs, includes inflammatory diseases like stasis dermatitis or atopic dermatitis or contact dermatitis, arthropod assault, erythema migrans (Lyme disease), superficial thrombophlebitis, deep venous thrombosis, lipodermatosclerosis, and vasculitides. Importantly, cellulitis virtually never occurs bilaterally, which helps distinguish it from its many mimickers.

Therapy

Systemic antimicrobial therapy is the treatment of choice for cellulitis/erysipelas. Several appropriate antimicrobial therapeutic options exist, but selection should be based on the patient population and regional variations in bacterial susceptibility. See Table 21.2 for antimicrobial options for specific organisms. In addition to antimicrobial therapy, local measures including immobilization and elevation as well as supportive measures such as warm compresses can hasten recovery and alleviate symptoms.

In 2014, the Infectious Disease Society of America (ISDA) published updated practice guidelines for the diagnosis and management of ABSSSIs. The ISDA recommended management based on

TABLE 21.2 **ANTIMICROBIAL THERAPY FOR SPECIFIC ORGANISMS**

Organism	First Line Treatment	Second Line Treatments
Strep. Pyogenes	Penicillin	Clinidamycin, Cephalosporin
Straph. Aureus (MSSA)	Nafcillin / Oxacillin (IV), Dicloxacillin (PO)	Clinidamycin, Cefazolin, Doxcycline, SMS-TMP
Staph. aureus (MRSA)	Vancomycin (IV)	Doxycycline, Clindamycin, SMX-TMP
Clostridium species	Clindamycin + Penicillin	Fluoroquinolone + Metronidazole
Haemophilus influenza	Amoxicillin, Ceftriaxone	Azithromycin, Fluoroquinolone
Vibrio vulnificus	Doxycycline + Cefotaxime	Fluoroquinolone
Aeromonas hydrophillia	Fluoroquinolone	SMX-TMP
Pseudomonas aeruginosa	Ciprofloxacin	Piperacillin-tazobactam, Ceftazidime, Carbapenem
Pasteurella multocida	Amoxicillin-Clavulanate	Cefuroxime + Clindamycin, Doxycycline
Eikenella corrodens	Amoxicillin-Clavulanate	Fluoroquinolone + Metronidazole

Abbreviations used: MSSA, methicillin sensitive staph aureus; MRSA, methicillin resistant staph aureus; IV, intravenous; PO, oral; SMX-TMP, trimethoprirm-sulfamethoxazole

the degree of severity and presence of purulence. Purulent diseases include abscesses, furuncles, and carbuncles, which are categorized separately based on the need for incision and drainage as the primary therapy. In comparison, cellulitis and erysipelas are typically nonpurulent and treated with systemic antibiotics. Mild cases include cellulitis/erysipelas without purulence or systemic symptoms. Moderate cases are typical cellulitis/erysipelas with systemic signs of infection. Severe cases are those that have progressed despite treatment with antibiotics, have ≥2 systemic signs of infection (fever, tachycardia, tachypnea, hypotension, delirium, leukocytosis), are found in immunocompromised patients, or have signs of deeper infection such as bullae, skin sloughing, or organ dysfunction.

In mild cases, oral antibiotics should be adequate treatment, whereas moderate and severe cases usually require hospitalization for IV antibiotics. In hospitalized patients, cultures with susceptibilities should be obtained and, when finalized, antibiotics de-escalated to prevent resistance. If treatment is implemented on an outpatient basis, as in the majority of cases, follow-up appointment and patient counseling on the signs of treatment failures are essential for good care. Treatment failures may occur with organism resistance, atypical bacteria, inadequate antibiotic dosing, or noncompliance. Therapeutic success including reduction in lesion size and resolution of fever, if present, should occur within 48 to 72 hours of treatment initiation. If clinical improvement does not occur in a timely fashion, physicians should obtain cultures with susceptibilities, extend the duration of antimicrobial therapy, and reassess antibiotic selection.

Most patients with typical mild cellulitis/erysipelas will respond completely to a 7-day course of empiric therapy that covers *Streptococcus* and *Staphylococcus* spp. (see Table 21.3 for oral dosing regimens). Agents targeting streptococci species include clindamycin and β-lactams (e.g., penicillin, amoxicillin, cephalexin). When MRSA coverage is indicated, as in purulent cellulitis, penetrating trauma, known MRSA colonization, or IV drug use, systemic options include doxycycline, clindamycin, or trimethoprim-sulfamethoxazole (TMP-SMX). To cover both streptococci and MRSA empirically, clindamycin is the preferred drug as monotherapy or a combination of a β-lactam with either TMP-SMX or doxycycline. For penicillin-allergic patients who are not considered to have a type 1 immunoglobulin (IgE)-mediated hypersensitivity reaction, alternative therapies include cephalosporins, tetracyclines, or TMP-SMX.

Hospitalization for IV antibiotics is uncommon but, in this setting, vancomycin is typically the treatment of choice (Table 21.4). It offers excellent coverage of gram-positive organisms including MRSA. Polymicrobial infections may occur in immunocompromised patients, and thus broader coverage for gram-negative organisms may be required. In such cases, combined treatment with vancomycin plus an extended-spectrum antipseudomonal penicillin, an extended-spectrum cephalosporin, or clindamycin plus a fluoroquinolone would be appropriate.

Though not recommended as first-line therapy, other appropriate antibiotics for use in the hospital setting with MRSA coverage include linezolid, daptomycin, tigecycline, or telavancin. Several new antibiotics have also been approved for the treatment of ABSSSIs, with the benefit of MRSA coverage: dalbavancin, oritavancin, tedizolid, and delafloxacin (see Table 21.4).

The oxazolidinones linezolid and tedizolid are excellent options for gram-positive organisms, MRSA, and vancomycin-resistant enterococci (VRE), and they are available in both IV and oral formulations that offer an opportunity for early conversion to oral therapy. Daptomycin, a cyclic lipopeptide, is bactericidal against gram-positive organisms, MRSA, and VRE and allows for daily dosing. Tigecycline offers additional coverage against gram-positive, gram-negative, anaerobic, and multidrug resistant organisms. The lipoglycopeptides dalbavancin and oritavancin have a long half-life, which allows for single-dose infusions. Telavancin, another member of the lipoglycopeptide class, is a semi-synthetic derivative of vancomycin with a similar spectrum of coverage plus activity against VRE. The new fluoroquinolone delafloxacin is available in IV and oral formulations and provides coverage against gram-positive, MRSA, and gram-negative organisms, thus permitting its use as monotherapy.

In addition to antibiotic treatment, systemic corticosteroids or nonsteroidal anti-inflammatory agents can be used to help reduce inflammation and mitigate symptoms. The degree of local

TABLE 21.3 **ORAL ANTIMICROBIAL OPTIONS FOR MIL NON-PURULENT CELLULITIS/ERYSIPELAS CASES**

Class	Medication	Dosage (Adult)*
Pencillins	Penicillin V	500 mg every 6 hours
	Amoxicillin	500 mg every 8 hours
	Amoxicillin/ Clavulante	875/125 mg every 12 hours
	Dicloxacillin	500 mg every 6 hours
Cephalosporins	Cephalexin[a]	500 mg every 6 hours
	Cefaclor[b]	250-500 mg every 8 hours
	Cefuroxime[b]	250-500 mg every 12 hours
	Cefprozil[b]	250 mg every 12 hours
	Cefdinir[c]	300 mg every 12 hours
	Cefpodoxime[c]	400 mg every 12 hours
Macrolides	Erythromycin	500 mg every 6-12 hours
	Azithromycin	500 mg on day 1, 250 mg on days 2-5
	Clarithromycin	500 mg every 12-24 hours
Tetracyclines	Tetracycline	500 mg every 6-12 hours
	Doxycycline	100 mg every 12 hours
	Minocycline	100 mg every 12 hours
Lincosamide	Clindamycin	300 mg every 6 hours
Fluoroquinolones	Ciprofloxacin	500 mg every 12 hours
	Levofloxacin	500 mg every 24 hours
Sulfonamide	Trimethoprim-Sulfamethoxazole	160-800 mg every 12 hours

Abbreviations: mg, milligrams
* All dosages for 7-14 days unless otherwise specified
[a] First generation cephalosporin
[b] Second generation cephalosporin
[c] Third generation cephalosporin

TABLE 21.4 **DOSING REGIMENS FOR SEVERE CELLULITIS/ERYSIPELAS WITH MRSA COVERAGE**

Class	Medication	Route	Dosage (Adult)
Glycopeptide	Vancomycin	Vancomycin	15 mg/kg every 12 hours
Tetracycline	Doxycycline	Oral	100 mg twice daily
Lincosamide	Clindamycin	IV/oral	IV: 600 mg every 8 hours Oral: 300-450 mg four times daily
Oxazolidinones	Linezolid[a]	IV/oral	600 mg every 12 hours
	Tedizolid[a]	IV/oral	200 mg once daily
Cyclic Lipopeptide	Daptomycin	IV	4 mg/kg every 24 hours
Cephalosporin	Ceftaroline	IV	600 mg every 12 hours
Sulfonamide	Trimethoprime-Sulfamethoxazole	Oral	1-2 double strength tablets twice daily
Glycylcycline	Tigecycline[b]	IV	100 mg loading dose then 50 mg over 1 hour every 12 hours
Lipoglycopeptides	Telavancin[c]	IV	10 mg/kg over 1 hour every 24 hours
	Dalbavancin	Iv	Single dose: 1500 mg over 30 min Two dose: 1000 mg over 30 min then 1 Week later 500 mg over 30 min
	Oritavancin	IV	Single dose: 1200 mg over 3 hours
Fluoroquinolone	Delafloxacin	IV/oral	IV: 300 mg over 1 hour every 12 hours Oral: 450 mg twice daily

Abbreviations: MRSA, methicillin resistant staph aureus; IV, intravenous; Mg, milligrams; kg, kilograms; min, minutes
[a] IV and oral dosing are the same
[b] Requires dosing are the same
[c] Requires dose adjustments in severe hepatic impairment

inflammation may worsen when antibiotics are initiated, due to the sudden destruction of organisms and an enzymatic cascade. Quicker clinical improvements occur when systemic corticosteroids are used in combination with antibiotics compared to antimicrobial monotherapy. Long-term follow-up showed no difference in recurrence rates. For this reason, anti-inflammatory agents may be very helpful adjunctive therapy in nondiabetic patients with cellulitis/erysipelas without signs of deeper infection.

When tissue necrosis is present, antimicrobial therapy alone is insufficient; immediate surgical evaluation is necessary, with early and complete surgical debridement extending beyond the areas of necrosis to reach healthy tissue. Signs of deep infection warranting debridement include gangrenous changes, severe pain or anesthetic skin, crepitus, or abscess formation with multiple sinus tracts (for additional information see Chapter 22, "Deep soft-tissue infections: Necrotizing fasciitis and gas gangrene").

Recurrence is especially common in patients with ABSSSIs of the legs who have impaired circulation or ongoing skin breakdown. In such instances, continuous antimicrobial prophylaxis may be necessary, coupled with weight reduction, leg elevation, support stockings to reduce edema, and good skin hygiene with emollients and possibly topical antifungal therapy. In general, optimizing those comorbidities that are considered predisposing factors is paramount to prevent recurrences and minimize bacterial colonization.

Suggested reading

Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. *N Engl J Med*. 1996 Jan 25;334(4):240–245. PMID: 8532002.

Golan Y. Current treatment options for acute skin and skin-structure infections. *Clin Infect Dis*. 2019 Apr 8;68(Suppl 3):S206–S212. PMID: 30957166.

Halilovic J, Heintz BH, Brown J. Risk factors for clinical failure in patients hospitalized with cellulitis and cutaneous abscess. *J Infect*. 2012 Aug;65(2):128–134. PMID: 22445732.

Keller EC, Tomecki KJ, Alraies MC. Distinguishing cellulitis from its mimics. *Cleve Clin J Med*. 2012 Aug;79(8):547–552. PMID: 22854433.

Russo A, Concia E, Cristini F, et al. Current and future trends in antibiotic therapy of acute bacterial skin and skin-structure infections. *Clin Microbiol Infect*. 2016 Apr;22(Suppl 2):S27–36. PMID: 27125562.

Stevens DL, Bisno AL, Chambers HF, et al; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59:e10–52.

Tognetti L, Martinelli C, Berti S, et al. Bacterial skin and soft tissue infections: Review of the epidemiology, microbiology, aetiopathogenesis and treatment: a collaboration between dermatologists and infectivologists. *J Eur Acad Dermatol Venereol*. 2012 Aug;26(8):931–941. PMID: 22214317.

22

Deep soft-tissue infections

Necrotizing fasciitis and gas gangrene

Stephen Ash and Louis E. Kennedy

Necrotizing fasciitis (NF) and gas gangrene (GG) are serious infections of the deep soft tissue. They both carry a high morbidity and mortality. Early diagnosis and treatment is important and is the key to improving outcome. Broadly speaking, NF is an infection primarily of the fascia and deep soft tissue of the skin, whereas GG is usually an infection of the skeletal muscle.

The incidence of NF in the western world is approximately 4:100 000 with a mortality rate of 15% to 20%.

Previously, NF has been subdivided into different categories based on anatomical site, etc., but such classification is unhelpful with regards to the diagnosis and management of these dangerous conditions. More recently, NF has been classified into three etiologic types (Table 22.1).

Type I is polymicrobial with usually at least one anaerobic species present. This is more common in patients with a strong predisposition for NF, such as intravenous drug users and postoperative patients. It is more likely to be present on the trunk, abdomen, perineum, or perianally.

Type II is monomicrobial and caused by group A streptococci and is less often associated with a predisposing factor. It is more common on the head and neck, and arms and legs. Thirty percent of cases are complicated by streptococcal toxic shock syndrome.

Type III occurs in the extremities and is caused by marine vibrio or aeromonas organisms following injury in sea water.

Various other forms of NF have been described including that caused by Panton-Valentine leukocidin (PVL) staphylococcus, *Klebsiella pneumoniae*, and also a number of cases of necrotizing cutaneous mucormycosis following injuries incurred during a tornado.

Both GG and, particularly, NF are strongly associated with numerous underlying, premorbid risk factors (Box 22.1), each of which requires medical management in order to improve the prognosis of an individual patient.

Again, both conditions may be caused by one bacterial organism, or commonly, they may be polymicrobial and require treatment with broad-spectrum or multiple antibiotics.

Necrotizing fasciitis (NF)

Diagnosis of NF

NF is an uncommon, but severe infection with a fulminant course and high mortality often following a history of trauma or surgery. The patient may go into rapid decline with necrosis of soft tissue and multisystem

TABLE 22.1 **NECROTIZING FASCIITIS: CLASSIFICATION**

Type I	Polymicrobial, including anaerobes
Type II	Group A β-hemolytic streptococci
Type III	Marine vibrios and aeromonas

organ failure. The latter would appear to result from superantigenic overstimulation of the immune system and excessive production of cytokines.

NF can affect any part of the body, but has a predilection for the limbs, abdominal wall, perineum, and occasionally the neck and periorbital area. Although to begin with, there may be only slight redness, or other discoloration, and swelling, the clue to the patient having NF is often the disproportionate severity of pain as well as systemic upset. The condition is rapidly progressive, with systemic inflammatory responses, shock, and multiorgan failure. Early diagnosis is crucial in optimizing outcome. The diagnosis is predominantly clinical with surgical confirmation, but noncontrast CT and ultrasound may be of use in supporting such a diagnosis. These tests as well as plain x-ray may sometimes show gas or a localized abscess in the soft tissue. Differentiating early NF from the more common cellulitis may be difficult; one clue may be the severe pain that often accompanies early NF. Occasionally, one may find an area of anesthetic skin overlying the inflamed and indurated area, although this is usually a late feature. One report suggests tissue oxygen saturation of the affected limb may help distinguish between cellulitis and NF.

If left untreated, there is progressive discoloration and darkening of the tissue with subcutaneous hemorrhage accompanied by tachycardia, hypotension, acidosis, and fever or occasionally a fall in body temperature.

Some authorities have used a laboratory scoring system: the *L*aboratory *R*isk *I*ndicator for *NEC*rotizing fasciitis (LRINEC) to determine and assist in the diagnosis of NF. This uses a panel of hematologic and biochemical test results (C-reactive protein [CRP], serum creatinine, total white cell count, hemoglobin, blood glucose, and serum sodium) to provide a scoring system for the risk for having NF. However, recent studies strongly suggest that this system has a high specificity and high negative predictive value but limited sensitivity.

BOX 22.1

Factors predisposing to deep soft-tissue infection (necrotizing fasciitis and gas gangrene)

- Trauma, sometimes trivial and including insect bites
- Recent surgery
- Malignancy, particularly intra-abdominal and carcinoma of colon
- Diabetes mellitus
- Intra-abdominal sepsis
- Alcoholism
- Injecting drug use
- Obesity
- Malnutrition
- Recent chickenpox
- Immunocompromised states
- Chronic renal failure
- Systemic steroid use
- Peripheral vascular disease
- Old age

Treatment of NF

The principles of management of NF are outlined in Figure 22.1. Rapid *resuscitation* takes precedent, followed by the empiric administration of *broad-spectrum antibiotics.* The choice of antibiotic is further discussed below and summarized in Box 22.2. *Surgery* with exploration and excision of necrotic tissue should not be delayed. Surgery should involve thorough debridement of all nonviable and affected tissue; there is no role for an "incision and drainage" approach to surgery. Repeat surgical explorations on subsequent days should be considered.

Samples for microbiology such as blood cultures should be taken at presentation and also at the time of surgery. Administration of antibiotics should not be delayed whilst waiting for results. Treatment of *comorbidities* such as diabetes and malnutrition is important.

Some clinicians suggest considering the following three adjuvant measures to try to improve outcome, although their usefulness remains controversial:

1. The use of *hyperbaric oxygen* has been tried in many cases of NF. The current consensus is that it is of little or no value.
2. *Topical negative pressure-* or *vacuum-assisted wound* healing has been tried in patients after surgical excision to promote efficient wound healing of what is often a large surface area of tissue.
3. Because it is thought that some of the systemic proinflammatory effects of NF, mediated by cytokines, are a result of superantigenic effects of bacteria such as group A streptococci there is a hypothesis that the administration of pooled, polyvalent *intravenous immunoglobulin* (IVIG) may be beneficial in modifying this response. There is a growing amount of evidence that this is of value.

Choice of antibiotic

Possible choices of antibiotic are given in Box 22.2, and may be modified according to local policies and the circumstances around individual patients. The initial choice of antibiotic is likely to be empiric and should cover gram-positive and -negative organisms as well as anaerobic bacteria, and should be administered intravenously, as absorption from the gut is likely to be unreliable in patients with severe systemic upset. It is widely accepted that clindamycin should

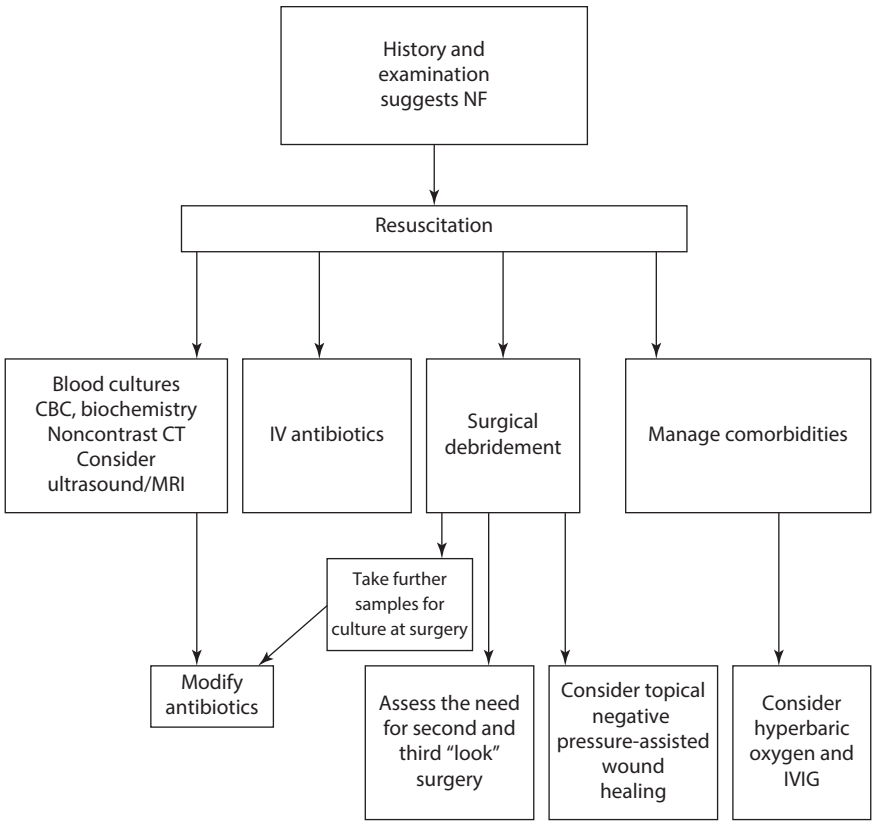

FIGURE 22.1 Management of necrotizing fasciitis. CBC, complete blood count; IV, intravenous; IVIG, intravenous immunoglobulin.

be included in any antibiotic regimen to treat NF because of its immunomodulatory effects. These effects are thought to include stimulation of opsonization and phagocytosis of bacteria, as well as reducing the production of M proteins and exotoxins from group A streptococci bacteria.

Over the past few years there have been reports of methicillin-resistant *Staphylococcus aureus* (MRSA) as the causative agent in some cases of NF, both in patients with infections acquired nosocomially and from the community. Some of the newer antibiotic agents with activity against MRSA may have use in this scenario, such as linezolid, tigecycline, and daptomycin.

BOX 22.2

Empiric antibiotic choices for necrotizing fasciitis

- Benzyl penicillin + nafcillin + metronidazole + quinolone
- Clindamycin + quinolone
- Carbapenem, eg. Meropenem (+/− fluconazole)
- Piperacillin with tazobactam
- Consider vancomycin or linezolid or daptomycin or tigecycline for possible MRSA
- *Clindamycin should be considered for inclusion in all antibiotic regimens because of its special immunomodulatory mechanisms.*

Gas gangrene (GG) (clostridial myonecrosis)

GG is most often caused by the anaerobic spore-forming bacillus *Clostridium perfringens*, an organism that causes infection of skeletal muscle following surgery or trauma. Necrosis and gas formation are characteristic features of the infection. There is rapid advancement of infection and muscle necrosis over just a few hours, if untreated.

Myonecrosis can also occur spontaneously, caused in this case by *Clostridium septicum*. This occurrence may be associated with underlying colonic abnormalities, or leukemia.

The first symptom of post-traumatic or post-surgical gas gangrene is the sudden onset of pain at the infected site. The area becomes tender and discolored, although it may be pale to begin with. Gas may be detected in the muscle on plain x-rays and also on both CT and MRI scans. However, with all but deep-seated infections, crepitus is palpable, demonstrating the presence of gas in the muscle tissue. The patient will become systemically unwell, with a bacteremia in many instances. Hemolysis may ensue, and renal failure may follow as a consequence.

Urgent surgical debridement, and antibiotic therapy are the essential mainstays of treatment and the prognosis may well be improved with the additional use of hyperbaric oxygen. Antibiotic therapy may be chosen from penicillins, clindamycin, and metronidazole. Tetracyclines and chloramphenicol can also be used. Antitoxin is no longer available.

Suggested reading

Huang K, Hung M, Lin Y, *et al*. Independent predictors of mortality for necrotising fasciitis: a retrospective analysis in a single institution. *J Trauma*. 2011;71:467–473.

Lancerotto L, Tocco H, Salmaso R, *et a*l. Necrotising fasciitis: classification, diagnosis, and management. *J Trauma*. 2012;72:560–566.

Sarkar B, Napolitano L. Necrotising soft tissue infections. *Minerva Chir*. 2010;65:347–362.

Wong CH, Khin LW, Heng KS, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotising Fasciitis) score: a tool for distinguishing necrotising fasciitis from other soft tissue infections. *Crit Care Med*. 2004;32:1535–1541.

Zacharias N, Velmahos G, Salama A, *et al*. Diagnosis of necrotising soft tissue infections by computed tomography. *Arch Surg*. 2010;145:452–454.

23

Human and animal bites

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Animal and human bites are common injuries. Patients may seek care at a hospital's emergency department, primary care physician's office, or with a specialist (e.g., orthopedics, plastic/hand surgery, infectious diseases). The bacteriology of these wounds is diverse and comprises both aerobic and anaerobic organisms originating from the oral flora of biting animal, the victim's skin flora, and occasionally environmental isolates.

Animal bites

Microbiology

An extensive number of bacterial species are isolated from infected animal bite wounds. *Pasteurella* spp., especially *P. multocida* and *P. septica*, will be present in 50% and 75% of dog and cat bite wounds, respectively. Anaerobes will be present in 50% of dog bite wounds and 67% of cat bite wounds. Streptococci are present in 46% of dog and cat bite wounds, whereas staphylococci are present in 46% of dog and 35% of cat bite wounds. *Streptococcus pyogenes*, if present, most likely is from the victim's skin flora as it is rarely isolated from dog and even less commonly from cat oral flora. *Staphylococcus aureus* is most likely also a secondary invader originating from skin flora as it is present in 20% of dog bites and only 4% of cat bites. We are not aware of dog and cat bite wound infection reports in humans due to methicillin-resistant *S. aureus*. *Capnocytophaga canimorsus* is an uncommon isolate from dog and cat bite wounds, but cases have been reported with fulminant infections often encountered in patients with asplenia, liver cirrhosis, and other immunocompromising conditions.

Wound evaluation and care

The elements of wound care are outlined in Box 23.1. If possible, wash the wound with soap and water as soon as possible after the injury. This will potentially reduce any bacterial or viral (e.g., rabies virus) inoculum. The addition of topical antiseptics or other similar remedies does not appear to affect the outcome or the incidence of infection. Washing the wound and keeping it clean and dry is sufficient for minor wounds.

If possible, the wound should be irrigated with sterile normal saline (no added iodine or antimicrobials) using an 18-gauge needle or catheter tip with a 20 mL syringe. This system functions as a high-pressure jet and reduces bacterial inoculum, whereas surface cleansing may not work as well. Tears or avulsion should be copiously irrigated, any debris removed, and necrotic tissue cautiously debrided.

Injuries to compromised hosts (Box 23.2) may lead to more extensive infections. Nerves and tendons may be injured or severed, especially when wounds involve the hand. If edema is present, develops, or is

BOX 23.1

Components of care for patients with animal and human bite injuries

History
- Circumstances of the event
- Type and extent of injury
- Patient's tetanus immunization history
- Animal rabies immunization history

Examination
- Musculoskeletal and neurovascular examination

Wound care
- Irrigation; debridement, if necessary
- Elevation

Antimicrobials
- Preemptive, 5–7 days (orally)
- Therapy for established infection

Culture (if infected)
Baseline radiograph (if suspect bony injury)
Tetanus immunization if required
Rabies prophylaxis if needed
Health department report (if required)
Decision regarding the need for hospitalization

BOX 23.2

Examples of conditions compromising natural host defences

Local defense defects
- Preexisting edema
- Prior lymph node dissection
- Prior radiation therapy

Medications
- Systemic steroids (chronic)
- Immunosuppressives

Diseases/conditions
- AIDS
- Alcoholism (chronic)
- Asplenia
- Cirrhosis
- Leukemia
- Lymphoma
- Myeloma
- Neutropenia
- Systemic lupus erythematosus

preexisting, elevation to reduce the edema is an important component of primary therapy. The use of a sling can be helpful, and this should be worn at the level of the heart when hand injury results in edema.

Preemptive antimicrobial therapy is often initiated for bite wounds that are extensive or located on the hands, or are associated with severe crush injury, the presence of preexisting edema, or have penetrated a joint or bony structure.

Closure of infected wounds is generally not recommended. Due to cosmetic and functional reasons, wounds to the head and neck and those overlying the joints may require primary closure. Major defects may require repair with subsequent surgeries.

Extremity elevation is vital to decreasing edema. If there is a need, tetanus immunization should be updated. Rabies prophylaxis will depend on local patterns of infection among the animals, the circumstance leading to the bite, mode of contact, and the patient's prior history of rabies immunization.

Antimicrobial selection

The preemptive selection of antimicrobials should take into account the microbiology of these wounds. Fortunately, most dog and cat bite isolates are susceptible to penicillin and ampicillin. Antimicrobial selections are outlined in Table 23.1. Of note is the relatively poor activity of cephalexin, cefaclor, cefadroxil, and erythromycin against *P. multocida*.

Patients who present >24 hours after injury without clinical signs of infection rarely require antibiotics. Patients who present for care <8 hours after injury and without signs of established infection can be given preemptive antibiotics for 5 to 7 days if they have moderate to severe wounds, especially if edema or extensive crush injury is present; are immunocompromised (including those with splenectomy, severe liver dysfunction, or chronic steroid use); have multiple deep puncture wounds, especially to the hands; have bone or joint space penetration; or have wounds adjacent to a prosthetic joint.

Follow-up is recommended within 48 hours or sooner, and the patient should be instructed to seek medical care sooner if the condition worsens.

The most common complications are septic arthritis, osteomyelitis, and residual joint stiffness. Long-standing pain should raise suspicion for complications such as septic arthritis or osteomyelitis. Although difficult to assess during the initial encounter, pain out of proportion to the injury when in proximity to a bone or joint should raise the issue of periosteum penetration.

The decision to hospitalize a patient should follow the items in Box 23.3. The course of antimicrobial therapy for cellulitis is typically 7 to 14 days, for septic arthritis 3 to 4 weeks, and for osteomyelitis 4 to 6 weeks. Abscesses should be drained, and infected wounds should be cultured. Therapeutic failure of outpatient therapy, including those listed in Box 23.4, should lead to hospitalization.

TABLE 23.1 **ACTIVITY OF SELECTED ANTIMICROBIALS AGAINST ANIMAL BITE ISOLATES**

	Pasteurella multocida	*Staphylococcus aureus*[a]	Streptococci	Capnocytophaga	Anaerobes
Penicillin	+	–	+	+	V
Ampicillin	+	–	+	+	V
Amoxicillin-clavulanate	+	+	+	+	+
Ampicillin-sulbactam	+	+	+	+	+
Dicloxacillin	–	+	+	–	–
Ertapenem/carbapenems	+	+	+	+	+
Cephalexin	–	+	+	–	–
Cefuroxime	+	+	+	+	–
Cefoxitin	+	+	+	+	+
Tetracyclines	+	V	–	V	V
Moxifloxacin	+	+	+	+	+
Erythromycin	–	+	+	+	–
Azithromycin	+	+	+	+	–
Clarithromycin	V	+	+	+	–
Trimethoprim-sulfamethoxazole	+	+	V	+	–
Clindamycin	–	+	+	–	+

Abbreviations: +, active; –, poor or no activity; V, variable activity against listed pathogen.
[a] β-lactams (with the exception of ceftaroline), fluoroquinolones, and macrolides do not have adequate activity against methicillin-resistant *Staphylococcus aureus* (MRSA); clindamycin and tetracyclines (doxycycline, minocycline) have variable but often adequate activity against MRSA.

Human bites

Human bites are either occlusional, where the teeth bite directly into flesh, or clenched-fist (closed-fist) injuries (CFIs). Most occur during fights, and the patient typically has a delayed presentation often resulting in infection.

Occlusional bites may be to any part of the body and include "love nips." Bites to children or the elderly may be the result of abuse. The most severe form of human bite wound is the CFI. Hand injuries can be severe and may result in abscess or osteomyelitis.

BOX 23.3

Hospitalization criteria for patients with bite wound infections

Signs and symptoms of systemic toxicity
Worsening infection
Septic arthritis
Osteomyelitis
Tenosynovitis

The bacteria associated with these infections include *Streptococcus anginosus*, *Streptococcus pyogenes*, *Staphylococcus aureus, Haemophilus* spp., *Eikenella corrodens*, and, in >55% of cases, oral anaerobes. Antimicrobial therapy is outlined in Table 23.2. Of note is the poor activity of cephalexin and erythromycin against *E. corrodens* and anaerobes.

CFIs injuries can be complicated by septic arthritis and osteomyelitis. Elevation and splinting are usually required, as are antimicrobials.

BOX 23.4

Causes of therapeutic failure for bite wound infections

Incorrect antimicrobial selection
Resistant isolates
Delay in seeking follow-up care
Noncompliance with medications or wound care
Failure to elevate the extremity
Underlying abscess or joint/bone involvement

TABLE 23.2 **ACTIVITY OF SELECTED ANTIMICROBIALS AGAINST HUMAN BITE WOUND ISOLATES**

	Eikenella corrodens	*Staphylococcus aureus*[a]	Streptococci	*Haemophilus* species	Anaerobes
Penicillin	+	–	+	–	–
Ampicillin	+	–	+	V	–
Amoxicillin-clavulanate	+	+	+	+	+
Ampicillin-sulbactam	+	+	+	+	+
Dicloxacillin	–	+	+	–	–
Cephalexin	–	+	+	–	–
Cefuroxime	+	+	+	+	–
Cefoxitin	+	+	+	+	+
Carbapenems	+	+	+	+	+
Tetracyclines	+	V	–	V	V
Moxifloxacin	+	+	+	+	+
Erythromycin	–	+	+	–	–
Azithromycin	+	+	+	–	–
Clarithromycin	V	+	+	–	–
Trimethoprim-sulfamethoxazole	+	+	V	+	–
Clindamycin	–	+	+	–	+

Abbreviations: +, Adequate activity; –, poor or no activity; V, variable activity against listed pathogen.
[a] β-lactams (with the exception of ceftaroline), fluoroquinolones, and macrolides do not have adequate activity against methicillin-resistant *Staphylococcus aureus* (MRSA); clindamycin and tetracyclines (doxycycline, minocycline) have variable but often adequate activity against MRSA.

Suggested reading

Abrahamian FM, Goldstein EJC. Microbiology of animal bite wounds. *Clin Microbiol Rev*. 2011;24:231–246.

Centers for Disease Control and Prevention (CDC). Nonfatal dog-bite injuries treated in emergency departments: United States–2001. *MMWR Morb Mortal Wkly Rep*. 2003;52:605–610.

Goldstein EJ. New horizons in the bacteriology, antimicrobial susceptibility, and therapy of animal bite wounds. *J Med Microbiol*. 1998;47:95–97.

Goldstein EJC, Citron DM, Merriam CV, et al. Comparative in vitro activity of ertapenem and 11 other antimicrobial agents against aerobic and anaerobic pathogens isolated from skin and soft tissue animal and human bite wound infections. *J Antimicrob Chemother*. 2001;48:641–651.

Langley RL. Animal-related fatalities in the United States-an update. *Wilderness Environ Med*. 2005;16:67–74.

Medeiros I, Saconato H. Antibiotic prophylaxis for mammalian bites. *Cochrane Database Syst Rev*. 2001;2:CD001738.

Merriam CV, Fernandez HT, Citron DM, et al. Bacteriology of human bite wound infections. *Anaerobe*. 2003;9:83–86.

Talan DA, Abrahamian FM, Moran GJ, et al. Clinical presentation and bacteriologic analysis of infected human bites in patients presenting to emergency departments. *Clin Infect Dis*. 2003;37:1481–1489.

Talan DA, Citron DM, Abrahamian FM, et al. Bacteriologic analysis of infected dog and cat bites. *N Engl J Med*. 1999;340:85–92.

24

Lice, scabies, and myiasis

Charlotte Bernigaud, Gentiane Monsel, and Olivier Chosidow

Arthropod infestations of humans are most commonly caused by mites, head or body lice (pediculosis), pubic lice (pthiriasis), or fly larvae (myiasis). Although many mite species may feed on human tissue, scabies are the most common mites living on human hosts. All of these arthropods can cause irritation and inflammation of the skin, but fly larvae may penetrate more deeply into the body. Diagnosis of each of these parasitic problems is dependent on accurate identification of the infesting arthropod. Lice and scabies mites are readily transmitted between close contacts, whereas myiasis is not a contagious condition.

Scabies

Scabies is a common parasitic infection caused by the mite *Sarcoptes scabiei* var. *hominis*, an arthropod of the order Acarina (Figure 24.1). The worldwide prevalence has been estimated to be about 100 to 200 million cases annually. Scabies has recently been recognized as a public health issue in the low- and middle-income countries and was added in 2017 to the list of neglected tropical disease by the World Health Organization. Tropical regions are the most affected, and young children, mostly under the age of 2, are often at risk. The morbidity of the disease is mainly due to scabies-secondary bacterial pyodermas. Scratching the skin disrupts the skin barrier, thereby providing an entry point for bacteria which can become invasive or cause post-infection complications such as post-streptococcal glomerulonephritis, acute rheumatic fever, or rheumatic heart disease. Worldwide, the risk of scabies outbreaks is particularly high in institutions (e.g., child and elderly care centers or hospitals), in underprivileged populations (e.g., refugees, homeless), and in immunocompromised individuals (e.g., HIV- or HTLV1-infected patients).

Scabies is an obligate parasite. The female mite burrows into the upper part of the epidermis and lays eggs that hatch into a larvae, which develops into a nymph that reach adulthood in 10 to 14 days. In general, transmission occurs by direct skin-to-skin contact. In severe form, such as profuse or crusted scabies, transmission may also occur through infected clothing or bedding. Skin eruption with classical scabies is attributable to both infestation and hypersensitivity reaction to the mite. Moreover, because the eruption is usually itchy, prurigo and superinfection are common. The main symptom is pruritus that typically worsens at night, and it is often associated with itching experienced by other family members in the household or among people in close physical contact with an infested individual. The lesions are commonly located in the finger webs, on the flexor surfaces of the wrists, on the elbows, in the axillae, and on the buttocks and genitalia. The elementary lesions are papules, vesicles, burrows, and nodules. In crusted scabies, clinical signs include hyperkeratotic plaques, papules, and nodules, particularly on the palms of the hands and the soles of the feet, although areas such as the axillae, buttocks, scalp, and genitalia in men and breasts in women may also be affected.

Diagnosis is based on patient history and physical examination. Recent criteria have been published for the diagnosis of scabies with three levels of diagnosis: Certainty-Confirmed Scabies, Clinical Scabies, and Suspected Scabies. The definitive diagnosis relies on the identification of the mite by light microscopy. Multiple superficial skin samples should be obtained from characteristic lesions by scraping with a

FIGURE 24.1 Scabies mite (*Sarcoptes scabiei*) female.

scalpel. The specimens are examined under a microscope, looking for mites (adults or immature forms), eggs, empty eggs, or scybala. Dermoscopy may also help diagnosing scabies in vivo. It is a useful tool that is as sensitive as skin scraping examination, and it permits the identification of a triangular or V-shaped structure corresponding to the fore portion of the mite (head and anterior legs), called the "delta-sign" (Figure 24.2). The confirmation of the diagnosis can be challenging in classic scabies as only 5 to 15 adult mites live simultaneously on the host; whereas hundreds, thousands, or even millions do in crusted scabies.

Therapy

People with scabies and their close physical contacts, even those without symptoms, should receive treatment at the same time. There are a variety of treatments available for human scabies. They can be administered either topically or orally. Topical treatment includes 5% permethrin, 10% to 25% benzyl benzoate, esdepalletrine, crotamiton, precipitated sulfur, and lindane (withdrawn from the market in most Western countries). Topical scabicides have neurotoxic effects on mites and larvae. Oral ivermectin interrupts the γ-aminobutyric acid-induced neurotransmission of many parasites, including mites. However, oral ivermectin is not approved by the US Food and Drug Administration (FDA) for scabies indication and is only licensed for scabies in some countries (e.g., Australia, Brazil, Germany, France). It is prescribed at 200 μg/kg as a single dose in patients >15 kg in weight, ideally during a meal (see below). A second dose is mandatory 7 to 10 days later due to the lack of ovicidal action of the drug. Despite the weak level of evidence (i.e., relevant and powered randomized controlled trials [RCTs]), the most recent Cochrane meta-analysis published in 2018 suggested that there was no difference in the efficacy of topical 5% permethrin compared with 200 μg/kg systemic or 1% topical ivermectin given twice and that both drugs should be considered as the most efficient treatments. The choice of agents is mostly based on the age of the patient, the presence and extent of eczematization or superinfection of the skin, the potential toxicity of the drug, and its cost and availability. Ivermectin should be routine therapy for patients who have no response to a topical scabicide, and it may be the appropriate first choice for the elderly, patients with generalized eczema or superinfection of the skin, other patients who may be unable to tolerate or comply with topical therapy, and patients included in mass drug administration programs (whether they have impetigo or not). New drugs with long plasma and skin half-lives that can be given once orally are currently under development. Drugs used in veterinary clinics, such as moxidectin, a member of the macrocyclic lactones family, or afoxolaner, a member of the isoxazolines family, are considered potential new alternatives for scabies treatment in humans.

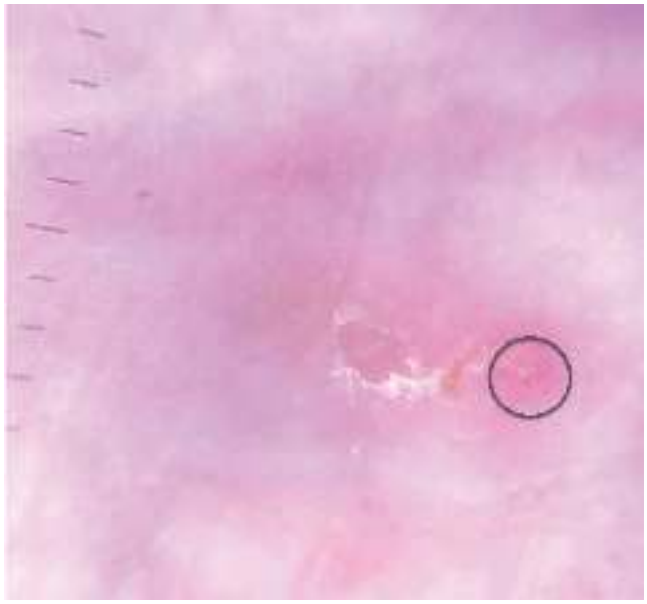

FIGURE 24.2 Visualization of scabies mite using dermatoscopy.

Patients should receive detailed information about scabies infestation and therapeutic options, including the amount of drug to be used and proper administration. Topical treatment should be applied to the entire skin surface, including the scalp, face (especially in children), all folds, groin, navel, and external genitalia, as well as the skin under the nails and reapplied again 7 to 10 days after the first treatment. Hands should not be washed during therapy (protection mandatory in infants), otherwise the treatment should be reapplied. Opinions diverge on whether the ivermectin tablets should be given with food or on an empty stomach. However, since ingestion of food increases the bioavailability of ivermectin in pharmacokinetics studies, taking the drug with food may enhance plasma concentration and penetration of the drug into the skin. The use of emollients to restore the skin barrier impaired by the infestation should be intensive, especially to reduce the itch sensation. Antihistamines (anti-H1) may help in the short term, mainly sedative antihistamines that help patients to sleep, even if histamine is not considered the main mediator implicated in scabies itch. After completion of treatment, patients should use clean clothing and bedding. If possible, potentially contaminated items should be washed at high temperature (50°C/122°F at least), kept in a plastic bag for up to 2 to 4 days in temperate climates, or frozen for at least 5 hours because mites that are separated from their human host will die within this time period. The use of insecticidal products should be restricted to unwashable

materials. Patients should be informed that itching may persist, especially in atopic individuals. After 4 weeks, the cause of itching should be reinvestigated.

Pediculosis capitis

The most common form of louse infestation is caused by the head louse, *Pediculus humanus* (designated *Pediculus humanus capitis* in the past to differentiate it from the body louse, formerly designated *Pediculus humanus humanus*, which has now been found to be genetically identical to the head louse). Since the 1970s, the prevalence has increased in many countries. Head lice predominantly infest schoolchildren (and their family close contacts) of all socioeconomic groups; transmission occurs through head-to-head contact, with the classroom being the main source of infestation. Active infestation is based on the finding of live lice. The stage of the louse most commonly seen is the nit. Each nit is oval, opaque, and white (about 0.8 × 0.3 mm) and is firmly attached individually to a single hair by the female louse. Nymphs or viable-appearing nits (louse eggs) are located about 1 mm from the scalp surface. Three immature stages (nymphs) precede the formation of the adult louse. Adult and immature lice are wingless and, as in all insects, have six legs. Each leg ends in a claw used for gripping hair. The adult lice are about 2 to 3.5 mm long and are white or cream in color (Figure 24.3).

Infested individuals may first notice itching of the scalp, most often in the postauricular and occipital regions, but pruritus occurs in a variable proportion of children. All immatures and adults require blood and, as a result of feeding, usually produce erythematous, papular lesions that are the cause of the pruritus. Some patients react to louse saliva with urticaria or lymphadenopathy. Secondary bacterial infection may occur as a result of scratching, and concomitant head louse infestation should always be considered in cases of scalp impetigo, neck or scalp eczematization, or posterior cervical lymph node enlargement in the absence of other lymphadenopathy.

FIGURE 24.3 Adult human louse (*Pediculus humanus*).

Courtesy of Dr. Arezki Izri, Université Paris 13 and Department of Parasitology, Hôpital Avicenne, Bobigny, France.

Therapy

Management of head louse infestation is difficult because good comparative-effectiveness research is still lacking, and louse resistance to pyrethroid and malathion has emerged. A systematic review is in process. DNA sequencing showed that "knockdown resistance" (*kdr*) to permethrin was linked to a three-point mutation (M815I-T917I-L920F) in the louse voltage-gated sodium channel α-subunit gene, conferring nerve insensitivity. However, genetic resistance might not be predictive of clinical or parasitologic failure. It is recommended to use 1% permethrin or pyrethrin insecticide as first-line therapy. If resistance in the community has been proved or live lice are present 1 day after the completion of treatment, a switch to malathion (if available) may be necessary. Other options include wet combing, also called "bug busting," or treatment with dimethicone or other topical agents (see Table 24.1), depending on the availability of the agents in the country. All treatments should be applied twice, at a week apart, because of insufficient ovicidal activity of most drugs. Topical ivermectin has shown greater efficacy than placebo in an RCT and has been approved by FDA in 2012. An RCT published in 2010 showed that a single oral dose of ivermectin (400 μg/kg of body weight) repeated within 7 days achieved higher louse-free rates on day 15 than 0.5% malathion lotion among patients with difficult to treat head lice. The safety of such dosage of ivermectin in patients with head louse infestation remains unknown and subsequently should only be used in the case of failure of all available topical treatments (off-label).

All family members and close contacts should be screened, and only those with active signs of infestation should be treated. Dead nits may be removed with a fine-toothed comb. All materials that touched the heads of infested persons, such as hats, scarves, bedding, and cushions, should be thoroughly washed in hot water (50°C/122°F at least). Any infested materials kept in plastic bags for 3 days may be safely used. Hair grooming aids, such as brushes, combs, and curlers, should be discarded or decontaminated with an insecticidal powder.

Pediculosis pubis (pthiriasis)

Pubic louse infestation is caused by the crab louse (*Pthirus pubis*), named for its crablike appearance caused by the enlargement of the second two pairs of legs. Adult crab lice are 1 to 2 mm long and equally wide and are gray, yellow, or brown. Extreme pruritus in the inguinal region is usually the first sign of infestation. Dried serous fluid, blood, or louse feces in the pubic hair are indicative of an infestation. Heavily infested individuals may have blue or gray macules that do not blanch under pressure. Nits are usually laid on the pubic and perianal hair, but infestations of facial hair, including eyebrows, eyelashes, mustache, and beard, may occur, as do less frequent infestations of the axilla. Transmission occurs most often during sexual contact. Definitive diagnosis requires identification of the nits or lice. As with head lice, pubic lice are not known to transmit any pathogens to humans, so the sole aim of therapy is removal of the insect parasite infestation.

TABLE 24.1 **THERAPEUTIC REGIMENS FOR SCABIES, LICE, AND MYIASIS**

Infestation	Therapies of choice	Alternative therapies	Additional measures
Classical scabies	Two applications of permethrin 5% or two doses of oral ivermectin, 200 μg/kg (at day 1 and day 7–10)	Two applications of benzyl benzoate 10–25%	People in close physical contact, even without symptoms, should receive treatment (two applications/doses) at the same time Decontamination of clothes and bedding
Head lice	Two applications of topical permethrin 1% or malathion 0.5%*	Bug busting Dimethicone Topical ivermectin Two doses of oral ivermectin (failure of all available treatments, not FDA-approved) 400 μg/kg (at day 1 and day 7)	Remove nits with lice combs Wash of clothes and hats
Body lice	Decontamination of clothes and bed linen Application of permethrin 1% or malathion 0.5% for 8–24 h	Oral ivermectin 200/400 μg/kg used in indigent population to reduce reinfestation, or body lice transmitted infectious disease epidemics —not approved	Decontamination of furniture and mattresses
Pubic lice	Two applications of permethrin 1% or malathion 0.5% Shaving	Two doses of oral ivermectin, 200/400 μg/kg (repeat at 7 days)—not approved	Treatment of all hairy area of the body and all sexual contacts when necessary Decontamination of clothes and bedding
Myiasis	Mechanical or surgical removal of the maggots	One dose of oral ivermectin 200 μg/kg —not approved	Disinfection to prevent secondary infection

* Withdrawn from some western-country markets

Therapy

Pubic lice are treated with the same insecticidal creams or lotion as pediculosis capitis, with a second application after 1 week because the products have poor ovicidal activity. Resistance to pyrethrins has been shown. All hairy areas of the body should be treated at the same time (see Table 24.1). Shaving is sometimes useful when nits are plentiful. Infestations of the eyelashes should be treated with permethrin 5% cream (wash off after 10 minutes) or only with petrolatum (applied twice a day for 8–10 days), followed by mechanical removal of the nits. Oral ivermectin at the dosage of 200/400 μg/kg (repeat at 7 days) has been anecdotally used in profuse cases.

As in other louse infestations, all sexual contacts should be examined and treated when necessary. Bedding and clothes should be washed in hot water (50°C/122°F). Prepubertal children presenting with pubic louse infestations should be evaluated with regard to possible child abuse. Treatment failure is usually a result of an untreated hairy area or reinfestation from an untreated sexual contact. In addition, patients should also be screened for associated sexually transmitted diseases.

Pediculosis corporis

Body louse infestation is caused by *Pediculus humanus* (sometimes incorrectly called *Pediculus corporis*), a louse species virtually identical in morphology to the head louse, except that it is usually slightly larger, about 2 to 4 mm long. Body lice feed on blood but retreat to hide in clothing on which the nits are laid. Infestations are most commonly found in homeless individuals, refugees, and victims of war and natural disasters. Infestations are recognized by extreme pruritus in conjunction with observation of nits firmly attached to clothing fibers. The erythematous, maculopapular feeding lesions are often scratched beyond recognition, leaving only serous or bloody crusts or secondary infection. Postinflammatory pigmentation is seen in chronic cases.

Unlike head and pubic lice, body lice may act as vectors of human bacterial pathogens in those areas of the world where these organisms are endemic. Trench fever, caused by *Bartonella quintana*, is rarely fatal but may cause endocarditis. As the name implies, it was most common during World War I and re-emerged in epidemic form in Europe during World War II. The recent emergence of trench fever has been confirmed in France, the United States, and Burundi, and more recently with refugees population from the Middle East. It is becoming more prevalent in populations of alcoholic homeless and displaced persons. Symptoms include fever, myalgias, headache, meningoencephalitis, chronic adenopathies, and transient maculopapular exanthema, but it may be asymptomatic. Louse-borne (epidemic) typhus, caused by *Rickettsia prowazekii*, still occurs in parts of Africa and Central and South America. It is a serious and sometimes fatal disease that may become epidemic in crowded, unsanitary living conditions. Symptoms include fever, headache, rash, and confusion. Louse-borne relapsing fever, caused by *Borrelia recurrentis*, is also sometimes fatal but has been rarely seen in recent years, except in Ethiopia.

Therapy

Bed linen and clothes must be systematically decontaminated, and this action suffices for some physicians. Others recommend thorough washing of the body with soap followed by application of pyrethrins/pyrethroids or malathion for 8 to 24 hours (see Table 24.1). Ivermectin, used at a regimen of three doses of 200 μg/kg each, given at 7-day intervals, greatly reduced the number of body lice infesting a population of homeless men. Such treatment may be effective in limiting the viability of body lice in patients living in an institution or routinely returning to a treatment center or shelter. Depending on the geographic location of the infested individual and his or her contact with other similarly infested individuals, the physician should consider the possibility of louse-borne disease. Infested furniture, mattresses, and box springs should be discarded or fumigated to destroy lice and nits. Infested materials sealed in plastic bags for 3 days or washed at temperatures hotter than 50°C/122°F may be used safely. Antibiotics are used to treat louse-borne infectious transmitted disease.

Myiasis

Myiasis is the invasion of living vertebrate (including human) tissue by fly larvae. Various species of flies that normally deposit eggs or larvae on garbage, carrion, or corpses may occasionally deposit these stages on wounds or skin adjacent to draining infections. Other fly species deposit eggs that hatch into larvae that penetrate intact skin. Flies in the former group include various house flies, blow flies (greenbottles and bluebottles), and flesh flies. The true myiasis producers in the second group are bot flies and warble flies. Although bot fly and warble fly larvae usually infest nonhuman hosts, these larvae occasionally invade human tissues. Myiasis is most often cutaneous, but fly larvae may also invade the nose and throat, eye, ear, and intestinal and genitourinary tracts.

Dermal (furuncular) myiasis, arising in intact skin, as caused by the human bot fly (*Dermatobia hominis*) in Central and South America and the tumbu fly (*Cordylobia anthropophaga*) in Africa, appears as a painful or itchy swelling with an opening at the skin surface. Observation of the opening under low magnification will reveal the posterior end of a moving larva, on which will be two dark circular areas, the respiratory openings (spiracular plates), which allow the larva to breathe while it is feeding with its anterior end embedded in the skin. If the larva is left in the skin, it will continue to feed just below the skin surface for several days to weeks and eventually back out and drop to the ground to complete development.

Therapy

Myiasis of the nose and throat, eye, ear, or internal organs may require surgical intervention or at least the use of anesthetics for manual removal of the larvae with forceps. Invasive rhino-orbital myiasis has been treated successfully with one dose of oral ivermectin prior to surgery. However, the use of ivermectin at the dosage of 200 μg/kg is an off-label treatment in many countries and should be reserved for selected cases.

In dermal myiasis, early diagnosis and removal of the larva will relieve the irritation and discomfort caused by its movements and feeding under the skin. Direct removal involves application of a local anesthetic, followed by grasping the larva with a forceps and pulling with constant pressure to dislodge its hold, which may be strong because of the teeth or spines surrounding the anterior part of its body. Indirect methods of removal involve application of an occlusive dressing containing petrolatum or even a piece of meat or animal fat if medical supplies are not readily available. Within a few hours, the suffocating larva will back out of the opening into the dressing or embed itself in the occlusive tissue. Secondary infections are rare, and little further treatment beyond disinfection is usually needed. To prevent cutaneous myasis in an endemic area, it is necessary to use insect repellents (*Dermatobia hominis*) and not to wear clothes dried outside or to rest in sandy areas (*Cordylobia anthropophaga*). Wound myiasis, which may even occur in modern medical facilities, can be prevented by frequent changes of dressings and isolation of patients, especially immobile ones, within screened rooms. Myiasis of wounds is treated by removal of the feeding maggots, irrigation, and disinfection. Because fly larvae feed on dead tissue, secrete antibiotic chemicals, and may even expedite healing, sterile maggot therapy (with greenbottle fly larvae) has been used successfully in the treatment of persistent surgical wounds or ulcers.

Suggested reading

Bernigaud C, Fang F, Fischer K, et al. Preclinical study of single-dose moxidectin, a new oral treatment for scabies: efficacy, safety, and pharmacokinetics compared to two-dose ivermectin in a porcine model. *PLoS Negl Trop Dis*. 2016;10:e0005030.

Bernigaud C, Fernando DD, Lu H, et al. How to eliminate scabies parasites from fomites: A high-throughput ex vivo experimental study. *J Am Acad Dermatol*. 2020;83:241–245.

Chosidow O. Scabies and pediculosis. *Lancet*. 2000;355:819–826.

Chosidow O. Clinical practice. Scabies. *N Engl J Med*. 2006;354:1718–1727.

Chosidow O, Giraudeau B, Cottrell J, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *N Engl J Med*. 2010;362:896–905.

Chosidow O, Giraudeau B. Topical ivermectin: A step toward making head lice dead lice. *N Engl J Med*. 2012;367:1750–1752.

Chosidow O, Fuller LC. Scratching the itch: Is scabies a truly neglected disease? *Lancet Infect Dis*. 2017;17:1220–1221.

Coates SJ, Thomas C, Chosidow O, el al. Ectoparasites: Pediculosis and tungiasis. *J Am Acad Dermatol*. 2020;82:551–569.

Currie BJ, McCarthy JS. Permethrin and ivermectin for scabies. *N Engl J Med*, 2010;362:717–725.

Engelman D, Yoshizumi J, Hay RJ, et al. The 2020 International Alliance for the Control of Scabies Consensus Criteria for the Diagnosis of Scabies. *Br J Dermatol*. 2020;183:808–820.

Foucault C, Ranque S, Badiaga S, et al. Oral ivermectin in the treatment of body lice. *J Infect Dis*. 2006;193:474–476.

Francesconi F, Lupi O. Myiasis. *Clin Microbiol Rev*. 2012;25:79–105.

Frankowski BL, Bocchini JA Jr. Council on School Health and Committee on Infectious Diseases. Head lice. *Pediatrics*. 2010;126:392–403.

Karimkhani C, Colombara DV, Drucker AM, et al. The global burden of scabies: A cross-sectional analysis from the Global Burden of Disease Study 2015. *Lancet Infect Dis*. 2017;17:1247–1254.

McGraw TA, Turiansky GW. Cutaneous myiasis. *J Am Acad Dermatol*. 2012;58:907–926.

Micali G, Lacarrubba F, Verzì AE, et al. Scabies: Advances in noninvasive diagnosis. *PLoS Negl Trop* Dis. 2016;10:e0004691.

Pariser DM, Meinking TL, Bell M, Ryan WG. Topical 0.5% ivermectin lotion for treatment of head lice. *N Engl J Med*. 2012;367:1687–1693.

Roberts RJ. Clinical practice. Head lice. *N Engl J Med*. 2002;346:1645–1650.

Romani L, Whitfeld MJ, Koroivueta J, et al. *N Engl J Med*. 2015;373:2305–2313.

Rosumeck S, Nast A, Dressler C. Ivermectin and permethrin for treating scabies. *Cochrane Database Syst Rev*. 2018;4:CD012994.

Thomas C, Coates SJ, Engelman D, et al. Ectoparasites: Scabies. *J Am Acad Dermatol*. 2020;82:533–548.

Weill A, Bernigaud C, Mokni M, et al. Scabies-infested pregnant women: A critical therapeutic challenge. *PLoS Negl Trop Dis*. 2021;15:e0008929.

25

Tungiasis and bed bugs

Tania F. Cestari and Simone Pessato

Tungiasis

In recent years, increased ecotourism and international travel to tropical countries has produced a growing incidence of infestations formerly limited to certain regions.

Tungiasis is a common ectoparasitic infestation that occurs mainly in the tropics, particularly where poverty and poor standards of basic hygiene exist. Despite recent progress in the treatment and prevention of tungiasis, diagnosis can present a challenge to those unfamiliar with the disorder, especially when it occurs in nonendemic countries.

Tungiasis is caused by the penetration of the female sand flea, *Tunga penetrans*, a hematophagous ectoparasite, into the epidermis of the host. The infestation is usually self-limited and presents few complications. It is known by several popular designations, including *chigoe flea, jigger flea, pico, nigua* (Mexico, Caribbean islands, Peru), *pique* (Argentina), *bicho dos pés, pulga da areia* (Brazil), *moukardan* (Sudan), *puce chique,* and *ogri eye* (South America).

In addition to humans, a wide spectrum of animal species is susceptible to an infection by *T. penetrans*. Pigs have been considered the main reservoir for human infections, but the parasite has been reported to affect cows, dogs, cats, goats, and rats as well. Recognition of infected animals and their treatment is mandatory to ensure control of outbreaks.

Epidemiology

T. penetrans is one of the few parasites that has spread from the Western to the Eastern hemisphere. Sand flea disease is common in resource-poor communities in South America and sub-Saharan Africa, with a prevalence of up to 60% in the general population. The parasite originally lived only on the American continent and came to Angola with the sand carried by travelers from Brazil. Within a few decades, it spread from Angola to sub-Saharan Africa, East Africa, and Madagascar. At present, tungiasis is endemic in many countries in Latin America (from Mexico to Northern Argentina), in the Caribbean islands, and in sub-Saharan Africa. Recent studies in Nigeria, Cameroon, and Brazil reported a similar high prevalence of tungiasis, from 45% to 51%; the higher rates occur in some communities of Brazil, Nigeria, and Trinidad and Tobago. The infestation happens mostly in underdeveloped communities in the rural hinterland, in secluded fishing villages along the coast, and in the slums of urban centers. The seasonal variation of tungiasis in endemic communities shows a highest incidence that corresponds to the peak of the dry season in the tropics.

In nonendemic areas, tungiasis is rare and usually appears on travelers returning from endemic countries. There are isolated reports of infection acquired in nonendemic regions, most likely by fleas that were imported from contaminated areas and completed their free-living life cycle at sites such as sandy beaches. Tungiasis is more common in adults. Considering the thinness of their stratum corneum and epidermis, children ought to be more susceptible; however, the infestation is rare in children living in nonendemic regions. There is no statistically significant difference between the prevalence of tungiasis in males and females considering the same chance of exposure and disease-related behavior.

Etiology

T. penetrans belongs to the genus *Tunga* of the order *Siphonaptera*; it is the smallest flea, measuring around 1 mm in length, and the only species of the genus that affect humans. The parasite development requires dry and warm soil with an optimal temperature ranging between 22°C/72°F and 31°C/88°F in the upper level of the soil. Male and female *T. penetrans* are bloodsuckers, but the male leaves its host after feeding, whereas the female burrows into soft skin regions of the body. Here, it remains for up to 5 weeks, completing its life cycle. Besides humans, various animals (domestic or wild mammals) may act as hosts for *T. penetrans.*

Clinical manifestations

About 90% of all lesions occur on the feet, and areas of soft skin, such as the interdigital spaces, the periungual regions, under the toenails, and along the medial border of the feet, are the favored sites for flea embedding. Occasionally, genital and perianal areas, thighs, hands, and other sites may be affected, especially when the infestation is massive.

The female flea burrows into the skin of its host, starting a complex five-stage sequence of structural and morphologic changes; the cycle is accompanied by different degrees of inflammatory reaction, known as the *Fortaleza classification* (Table 25.1). The clinical diagnosis of tungiasis is based on the presence of papular or nodular lesions, either single or multiple, white, gray, or yellowish in color, with a small brown-black central opening, usually localized to the feet, in a patient who recently visited endemic areas (Figure 25.1).

Dermoscopy has been shown to be helpful in confirming the clinical diagnosis of *Tunga* infestation. The exam in vivo shows an annular brown ring with a central black pore corresponding to the opening of the flea. In the central area (the abdomen), it is possible to visualize gray-blue blotches and a large number of whitish oval structures linked together forming a chain-like picture, matching the image of the eggs contained in the distended "jelly sac" and consistent with the late stage 3B of the parasite's development (Figure 25.2). After extraction of the intact parasite, ex vivo, the diagnosis is confirmed by visualization of the flea head and the abdomen full of eggs.

The histopathology of a typical lesion shows hyperkeratosis, parakeratosis, and acanthosis. The body of the flea locates in the upper dermis, and it is surrounded by a pseudocystic cavity. Inside the cavity, annular-shaped digestive and respiratory organs as well as ovaries rich in eggs may be observed. Eggs are oval or, less frequently, round, with a thickened wall and pale center. A peri-lesional, inflammatory infiltrate, mainly consisting of lymphocytes, neutrophils, and numerous eosinophils, is also present.

The differential diagnoses of tungiasis include *talon noir*, plantar or subungual warts, subungual exostoses, myiasis, abscesses, verrucae, ecthyma, tick bite, and melanocytic and nonmelanocytic skin tumors, especially melanoma.

Tungiasis is usually a self-limited condition, resolving in 4 to 6 weeks, with few complications consequent to the infestation. Colonial documents and travel reports from the early twentieth century indicate that the disease used to cause severe morbidity among the indigenous populations, such as grave inflammation in the feet, deep ulcers, gangrene, lymphangitis, and septicemia. Nowadays, the degree of morbidity depends on the intensity of infestation, hygiene conditions, and associated clinical disorders.

In economically depressed urban neighborhoods, however, poor housing conditions and inadequate healthcare lead to a high transmission potential, resulting in high parasite loads and secondary

TABLE 25.1 **BIOLOGIC CYCLE AND DEVELOPMENT OF *TUNGA PENETRANS* INFESTATION IN HUMANS**[A]

Stage/phase	Time after onset of penetration	Clinical findings: parasite	Clinical findings: host
Stage 1 Penetration	30 min–7 h (average 3 h	Penetration of the gravid flea; the abdominal segments 1–3 separate toward the cephalic direction	Penetration at an angle of 45–90 degrees; slight erythema; mild stink; tiny reddish spot
Stage 2 Hypertrophy	1–2 days	The abdominal segment enlarges and the parasite is visible	Itching and painful nodule with a central black dot; erythematous inflammatory area
Stage 3 White halo	4 days	Correspond to the maximum growth of the parasite; the lesion resembles a white pearl with a central opening from which the enlarged flea eliminates feces and eggs	Painful foreign-body reaction
Stage 4 Involution	3–4 weeks	Dark crust containing the parasite remains	The lesions may be numerous and close-set like a honeycomb; secondary infection is frequent
Stage 5 Residual scar	Days after the involution phase		Reorganization of the epidermis continued; the site occupied by the parasite is flattened and becomes indistinguishable from normal skin

[a] Fortaleza Classification, based on Eisele M, Heukelbach J, Marck EV, et al., 2003.

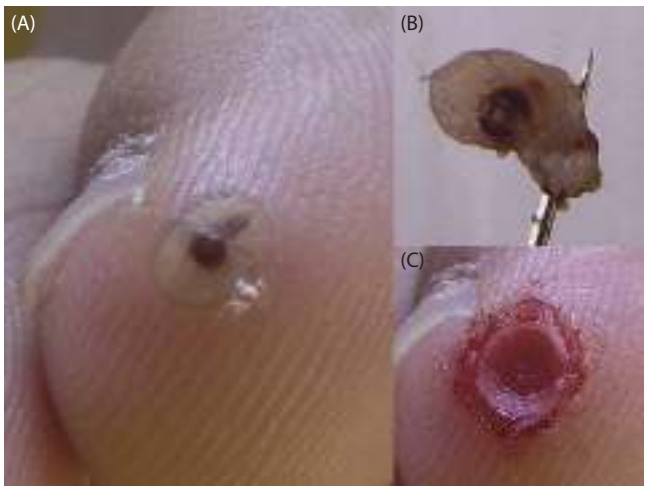

FIGURE 25.1 Tungiasis. (A) Isolated lesion on the first toe, corresponding to the parasite in its maximum growing stage and presenting as a white nodule with central opening. (B) Parasite removed with a needle after gentle debridment, showing the intact abdomen full of eggs. (C) Circular ulceration, with clean walls, after removing the female *Tunga*.

complications. The most common problems associated with tungiasis infestation are acute painful inflammation and edema, abscess formation, lymphangitis, fissures, ulcers, sepsis, tissue necrosis or gangrene, erysipelas, or even contamination by other infectious agents such as fungi, causing atrophy or loss of nails, toe deformations, and difficulty in walking and gripping. As an additional risk, clinical and epidemiologic evidence suggests that the possibility of bacterial superinfection is constant. In populations with low vaccination coverage, untreated tungiasis may provide a port of entrance for *Clostridium tetani* or *C. perfringens* bacilli, being a risk factor for tetanus.

FIGURE 25.2 Tungiasis. Dermoscopy of an isolated lesion showing the annular brown ring with a central black pore. In the surrounding area, it is possible to visualize whitish oval structures in a linear distribution corresponding to the intra-abdominal eggs (20×).

Courtesy Prof. Renato Bakos, Federal University of Rio Grande do Sul, Hospital de Clinicas de Porto Alegre, Brazil.

Treatment and control

Standard therapy for tungiasis consists of surgical extraction of the embedded parasite under sterile conditions, followed by appropriate care of the resulting wound. During the excision, care should be taken to prevent tearing of the flea and to avoid parts of the flea being left behind due to the risk of severe inflammation.

Topical application of kerosene, plant extracts, chlorophenothane, chloroform, 4% formaldehyde solution, turpentine, and yellow mercury oxide has been used but without controlled studies. Chemotherapeutic approaches to attempt to kill embedded fleas without mechanical extraction include administration of oral niridazole, thiabendazole, and ivermectin, none of which is completely effective.

Superinfection of the lesions may lead to pustule formation, suppuration, and ulceration. In this case, oral antibiotics should be prescribed and appropriate local care administered. Tetanus prophylaxis is recommended, especially for those individuals living in endemic areas.

The reduction of prevalence and intensity of tungiasis is possible through regular treatment of infested humans, elimination of animal reservoirs, and environmental changes. Prevention measures include paving of public areas and house floors and implementing basic hygiene measures. Animals living close to humans should also be treated using insecticidal compounds, such as collars, sprays, shampoos, or topical products. The early and late stages of the flea could be eliminated by spraying environmental insecticide on sandy areas, on beaches, and close to animal housing facilities. Biologic repellents, composed of coconut and jojoba oils (Zanzarin), may be recommended. A regular twice-daily application of Zanzarin for a period of 3 weeks reduced the rate of newly embedded fleas by 92% and reversed tungiasis-associated clinical pathology almost completely. Sanitary disposal of domestic garbage, proper vector control, correct housing of animals, wearing of protective shoes, and periodic self-examination in endemic areas are also mandatory.

Cimicidae infestation: Bedbugs

Bedbugs and their relatives belong to the family *Cimicidae* and are all blood-sucking ectoparasites of mammals or birds. The species *Cimex lectularius* is the most common. They are cosmopolitan and may be found in homes, in poultry houses, and around small caged pets or near bird and bat nests and roosts, parasitizing humans and also bats, chickens, and other domestic animals. In houses, they live in tufts, seams, and folds of mattresses, bed covers, bed frames, windows and door casings, bird nests, floor cracks, under carpets, behind loose wallpaper or wall pictures, and in furniture and luggage. Infestations of bedbugs can often be detected by their offensive odor, caused by an oily secretion produced by special glands.

Laboratory techniques have demonstrated that bedbugs could harbor some pathogenic microorganisms, including hepatitis B and hepatitis C viruses, HIV, and methicillin-resistant *Staphylococcus aureus*. However, the capacity of bedbugs to act as disease vectors is

debatable, and it appears unlikely that these insects could be a significant risk for HIV transmission. After World War II, bedbugs became uncommon. However, an increase has been observed recently and may be associated with international trade and traveling.

Epidemiology and etiology

The common bedbug is a wingless, ovoid, flat, reddish-brown, blood-sucking insect that grows up to 7 mm in length and has a lifespan from 4 months to 1 year (Figure 25.3).

Bedbugs respond to aggregation pheromones, resulting in clustering behavior, although solitary bedbugs may be found. They are nocturnal insects with chemo- and thermosensorial abilities that orient them toward human odors, being attracted by warmth and carbon dioxide. They feed on sleeping humans and hide during the day. When feeding, the insect grasps the skin with its forelegs and injects saliva containing anticoagulant, vasodilator, and anesthetic fluids. After a blood meal, female bugs lay between one and five eggs that hatch in 4 to 5 days. The female deposits eggs on rough surfaces of cracks and crevices, where nymphs could survive >260 days in case of starvation.

Clinical features

Bedbug bites are often observed in linear groups of three, the so-called "breakfast, lunch, dinner" pattern. Lesions usually occur on the face, neck, hands, and arms and can be noticed upon waking or one to several days later. The bite itself is painless and feeding is facilitated by a salivary apyrase, an anticoagulant enzyme. Lesions range from erythematous pruritic macules in previously unexposed patients, to pruritic papules, wheals, vesicles, or bullae in sensitized individuals. Exaggerated local responses occur in patients with a high degree of immunity, those sensitive to other insects, and after repeated bites. Type I hypersensitivity allergic cutaneous and asthmatic reactions have also been observed, as well as widespread bullous eruption with urticated hemorrhagic papules due to multiple bedbug bites.

The differential diagnosis of bedbug bites includes scabies, flea bites, and urticarial prurigo reactions.

FIGURE 25.3 Bedbug (*Cimex lectularius*) nymph in the process of ingesting a blood meal from the arm of a "voluntary" human host, showing the partially filled insect abdomen.

From Centers for Disease Control and Prevention, Public Health Image Library. http://phil.cdc.gov/phil/quicksearch.asp.

Treatment and control

Many physicians are unfamiliar with bedbugs and their bites. Awareness of the possibility of infestation is important to institute correct medication and parasite control measures. Treatment of the reaction secondary to the contact with bedbugs involves the use of antihistamine or corticosteroids and topical antimicrobials for secondary bacterial infection, if necessary. Cleaning out bedbugs' hiding places and eliminating cracks and crevices, as well as the use of insecticides, will decrease the infestation of houses. Pesticides containing dichlorvos, malathion, and pyrethrins are effective, taking into account the surface being treated. Bedbug control by repellents or permethrin-impregnated bed nets has proved its effectiveness in actual use in spite of sporadic reports of resistance to pyrethroids and decrease of DEET repellency

Suggested reading

Bakos RM, Bakos L. "Whitish chains": A remarkable in vivo dermoscopic finding of tungiasis. *Br J Dermatol*. 2008;159:991–992.

Cestari TF, Pessato S, Ramos-e-Silva M. Tungiasis and myiasis. *Clin Dermatol*. 2007;25:158–164.

DeVries ZC, Saveer AM, Mick R, Schal C. Bed bug (Hemiptera: Cimicidae) attraction to human odors: Validation of a two-choice olfactometer. *J Med Entomol*. 2018 Nov 12. doi:10.1093/jme/tjy202

Doggett SL, Dwyer DE, Peñas PF, Russell RC. Bed bugs: Clinical relevance and control options. *Clin Microbiol Rev*. 2012;25:164–192.

Eisele M, Heukelbach J, Marck EV, et al. Investigations on the biology, epidemiology, pathology and control of Tunga penetrans in Brazil: I. Natural history of tungiasis in man. *Parasitol Res*. 2003;90:87–99.

Haddad V Jr, Cardoso JL, Lupi O, Tyring SK. Tropical dermatology: Venomous arthropods and human skin: Part I. Insecta. *J Am Acad Dermatol*. 2012;67:331.e1–331.e14

Heukelbach J, Costa AML, Wilcke T, Mencke N, Feldemeier H. The animal reservoir of *Tunga penetrans* in severely affected communities of north-east Brazil. *Med Vet Entomol*. 2004;18:329–335.

Heukelbach J, Frank S, Feldemeier H. Therapy of tungiasis: A double randomized controlled trial with oral ivermectin. *Mem Inst Oswaldo Cruz*. 2004;99:873–876.

Mutebi F, Krücken J, von Samson-Himmelstjerna G, et al. Animal and human tungiasis-related knowledge and treatment practices among animal keeping households in Bugiri District, South-Eastern Uganda. *Acta Trop*. 2018;177:81–88.

Peccerillo F, Zambito Spadaro F, Fabrizi G, et al. Not a simple plantar wart: A case of tungiasis. *J Eur Acad Dermatol Venereol*. 2018;32:e113–e114.

Peres G, Yugar LBT, Haddad Junior V. Breakfast, lunch, and dinner sign: A hallmark of flea and bedbug bites. *An Bras Dermatol*. 2018;93:759–760.

Schwalfenberg S, Witt LH, Kehr JD, Feldmeier H, Heukelbach J. Prevention of tungiasis using a biological repellent: A small case series. *Ann Trop Med Parasitol*. 2004;98:89–94.

Vassena CV, Cáceres M, Santo-Orihuela PL. Pyrethroid resistance associated with a decreased DEET repellency in the common bed bug (Hemiptera: Cimicidae). *J Econ Entomol*. 2018 Dec 19. doi:10.1093/jee/toy387

Vasievich MP, Villarreal JD, Tomecki KJ. Got the travel bug? A review of common infections, infestations, bites, and stings among returning travelers. *Am J Clin Dermatol*. 2016;17:451–462.

Woloski JR, Burman D, Adebona O. Mite and bed bug infections. *Prim Care*. 2018; 45:409–421.

26

Superficial fungal infection of skin and nails

Evelyn K. Koestenblatt and Jeffrey M. Weinberg

The vast majority of fungal infections of the skin, hair, and nails are caused by the dermatophytes and yeasts including *Candida* spp. and *Malassezia furfur*. Proper diagnosis of these conditions is essential as they can present in a fashion similar to nonfungal disease. Moreover, some fungi causing systemic infections may begin as cutaneous lesions. In most cases, potassium hydroxide (KOH) preparation, culture, and/or biopsy can provide a definitive diagnosis. Treatment of these conditions may include topical and/or systemic antifungal therapy.

The dermatophytes

The dermatophytes are organisms that are found in specific ecologic niches and consume the structural protein keratin. Those found in the soil are referred to as *geophilic* while those that are transmitted from human to human, resulting in primarily infections of the hair, skin, and nails, are termed *anthropophilic*. *Zoophilic* organisms are those that are mainly found in fur, feathers, skin, and nails of animals. Zoophilic and geophilic organisms, when transmitted to humans, tend to be much more inflammatory than anthropophilic organisms. Factors precluding a dermatophyte infection or dermatophycosis include inoculum size, host immune status, the particular organism, a suitable environment, fungal growth rate exceeding epidermal turnover, and, in certain instances, the host genetics.

The term "tinea" refers to a dermatophycosis due to one of the following genera: *Epidermophyton, Trichophyton*, or *Microsporum*. Dermatophyte infections are described by their location on the body: tinea capitis (scalp), tinea corporis (glabrous skin), tinea faciei (face), tinea cruris (groin), tinea manuum (hand), tinea pedis (feet), tinea barbae (facial hair), and tinea unguium (nails). "Onychomycosis" refers to any fungal infection (dermatophytes and nondermatophyte organisms) of the nails. Most infections in the United States are due to five species: *Trichophyton rubrum, T. tonsurans, T. mentagrophytes, Microsporum canis,* and *Epidermophyton floccosum*.

Tinea capitis

In the United States, tinea capitis (scalp ringworm) is most commonly due to *T. tonsurans* and most often seen in children. Clinically, this form of tinea capitis begins with the appearance of papules and progresses to a scaly area of irregular or well-demarcated alopecia with black dots (Figure 26.1). The black dots are due to spore-filled hairs (endothrix invasion) breaking at the surface of the scalp. This type of infection is the most common form of tinea capitis and is seen more frequently in African American and Hispanic children. An inflammatory boggy, tender, purulent mass called a *kerion* may be present, often in African American children. A short course of systemic steroids along with antifungal treatment will reduce the inflammation

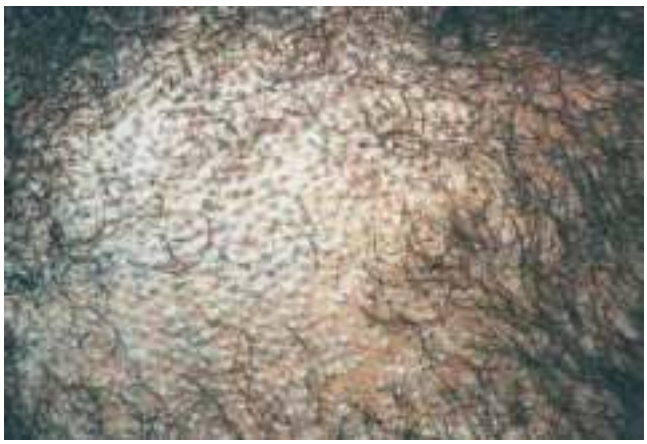

FIGURE 26.1 "Black dot tinea capitis" due to *T. tonsurans*.
Courtesy of Evelyn Koestenblatt.

and discomfort as well as the chance of scarring alopecia. Other organisms causing black dot tinea, including *T. soudanense* and *T. violaceum*, are being recovered with greater frequency in the United States.

Gray patch ringworm is another form of tinea capitis, caused by the organisms *Microsporum canis* and *M. audouinii*. In this case the fungus is on the outside of the hair shaft (ectothrix invasion), causing it to have a grayish appearance. Some of these organisms produce a yellow-green fluorescence visible with a Wood's (UV) lamp. Favus or tinea favosa is generally associated with malnutrition and poor hygiene; it is rarely seen in the United States and is most frequently due to *T. schoenleinii*. Clinically, favus appears as diffuse alopecia with yellow crusts or scutula, which are made up of hyphae, neutrophils, and skin debris. Microscopically, hyphae and air spaces are seen within the hair shaft.

The most common methods for diagnosing tinea capitis are KOH preparation and fungal culture. Collection of infected hair

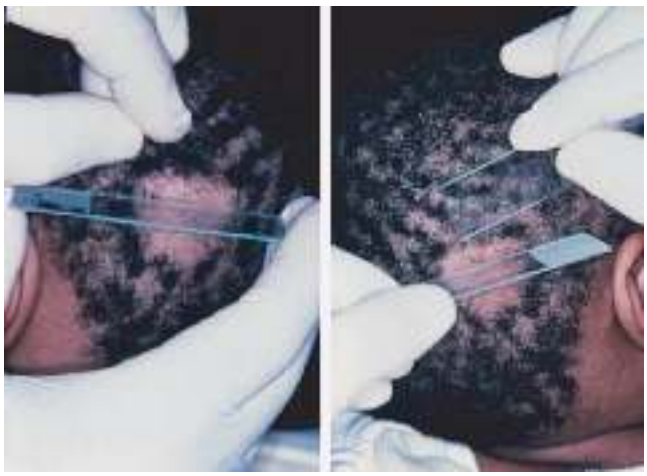

FIGURE 26.2 Tinea capitis techniques for collecting hair for KOH and culture.
Courtesy of Evelyn Koestenblatt.

TABLE 26.1 **TREATMENT FOR TINEA CAPITIS**

Griseofulvin	Terbinafine	Itraconazole	Fluconazole
20–25 mg/kg/d for 6–8 weeks (liquid microsize)	62.5 mg/d ≤20 kg 125 mg/d 20–40 kg 250 mg/d >40 kg For 2–4 weeks	5 mg/kg/d for 4–8 weeks	6 mg/kg/d for 3–6 weeks

is necessary for diagnosis of tinea capitis. The hairs may be obtained for both KOH prep and culture in two ways: a scalpel blade or glass slide may be used to scrape the area or a soft toothbrush or moist gauze can be firmly rubbed over the involved scalp (Figure 26.2). The hairs are placed onto a glass slide and mixed with 10% to 20% KOH, a coverslip is applied, and the sample is then examined under a microscope. The hairs are inspected for evidence of fungal infection with spores either inside (endothrix) or outside (ectothrix) of the hair shaft. For culture, the hairs are gently placed on the surface of the fungal media for a period of several weeks. Only the specimen should be placed inside of the media tube.

The gold standard of therapy for tinea capitis is oral griseofulvin. Topical therapy is most often unsuccessful because the medication cannot penetrate the hair follicle. Griseofulvin is usually given to children in conjunction with a fatty meal which stabilizes the gastric pH. The use of a warm compress to induce sweating and ultimately cutaneous excretion of the drug may also improve efficacy.

For patients who fail therapy with griseofulvin or cannot tolerate the medication, treatment with itraconazole (Sporanox), fluconazole (Diflucan), or terbinafine (Lamisil) is an option (Table 26.1). Terbinafine is an accepted alternative first-line agent for patients suffering from tinea capitas which is suspected or found to be caused by *Trichophyton*. Terbinafine may also be used for *Microsporum* infections but requires higher and longer dosing. In addition, brushes, combs, hats, hair ribbons, barrettes, and bed linen should be thoroughly washed. Children and caretakers of patients may be asymptomatic carriers of infection and ultimately sources for reinfection, which necessitates further evaluation and the use of 2.5% selenium sulfide or 2% ketoconazole shampoo three times a week for at least 5 minutes by all family members to reduce the spread of infectious spores.

Tinea corporis

Tinea corporis (Figures 26.3 and 26.4) refers to dermatophycosis of the glabrous skin. The infection may present as sharply demarcated annular lesions with a scaly border, bullous lesions, granulomatous eruptions, pustular lesions, psoriasiform plaques, and/or verrucous lesions. The disease is most prevalent in tropical areas but may be found across the world. In the United States, *T. rubrum* is the most common etiologic agent of tinea corporis. *T. mentagrophytes* and *M. canis* are also common. Infections caused by *M. canis* and some strains *of T. mentagrophytes* typically present with multiple lesions

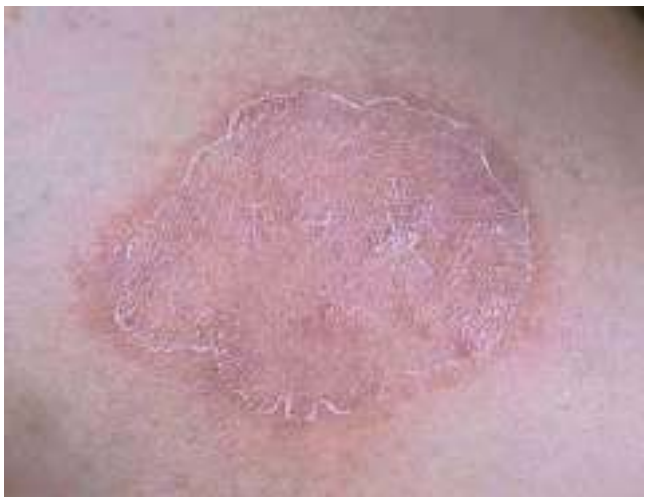

FIGURE 26.3 Tinea corporis.
Courtesy of Evelyn Koestenblatt.

and are often more inflammatory and symptomatic than those caused by *T. rubrum*. Tinea corporis may also be seen in caretakers of children suffering from black dot tinea capitis due to *T. tonsurans*.

Tinea cruris

Tinea cruris refers to a dermatophyte infection of the groin, including the suprapubic areas, proximal medial thighs, perineum, gluteal cleft, and buttocks. Infection is more often seen in men than women and is commonly caused by *T. rubrum, T. mentagrophytes*, and *E. floccosum*. Women more often suffer from candidiasis than tinea cruris.

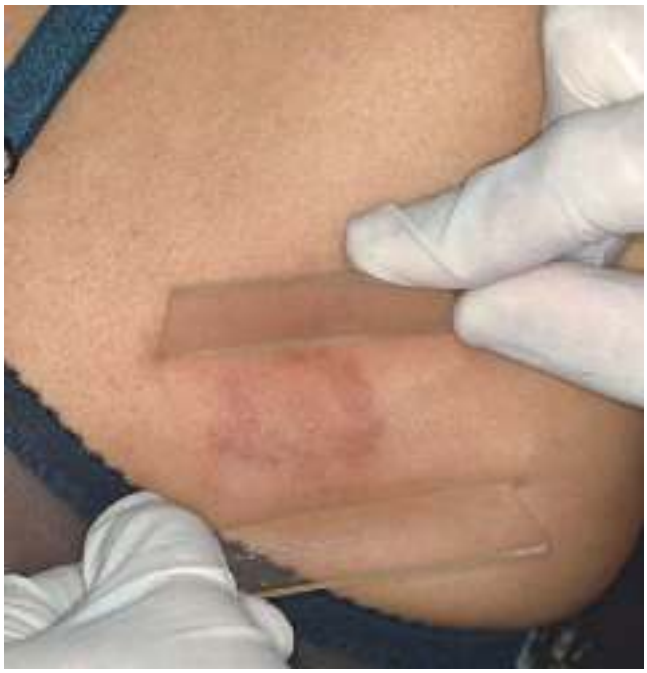

FIGURE 26.4 Erythematous tinea corporis with small pustules.
Courtesy of Evelyn Koestenblatt.

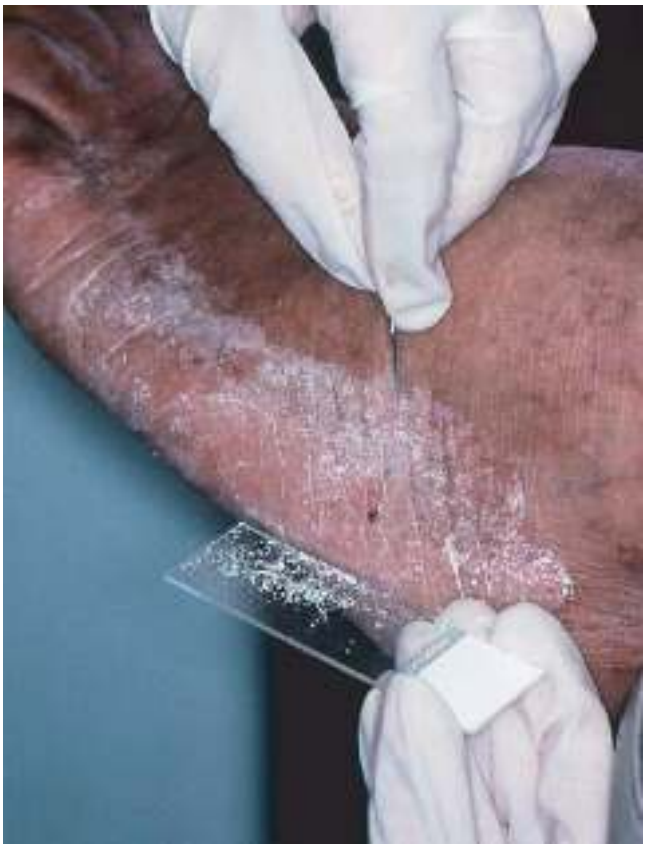

FIGURE 26.5 Moccasin type tinea pedis. Scrape the active border with a no. 15 blade for KOH preparation and culture.
Courtesy of Evelyn Koestenblatt.

Tinea pedis

Athlete's foot or tinea pedis is the most common fungal infection (Figure 26.5). The moisture, friction, maceration, heat, darkness, and occlusion present in the feet are perfect for fungal growth. *T. rubrum* is the most common etiologic agent and causes a "moccasin" distribution of scale and erythema. *T. rubrum* is associated with a familial autosomal-dominant predisposition to this type of infection. Dermatophytosis occurring between the toes is referred to as *interdigital tinea pedis*. *T. mentagrophytes*, *T. rubrum*, or *E. floccosum* may be recovered with or without bacterial organisms and/or yeast. *T. mentagrophytes* may also cause a vesicular-type tinea pedis characterized by vesicles with serous exudate on the plantar surface.

Tinea manuum

The patients commonly have dermatophycosis of both feet and one hand. Tinea manuum presents as a fine scale, with some erythema covering the surface of the palm, like the feet; *T. rubrum* is usually recovered.

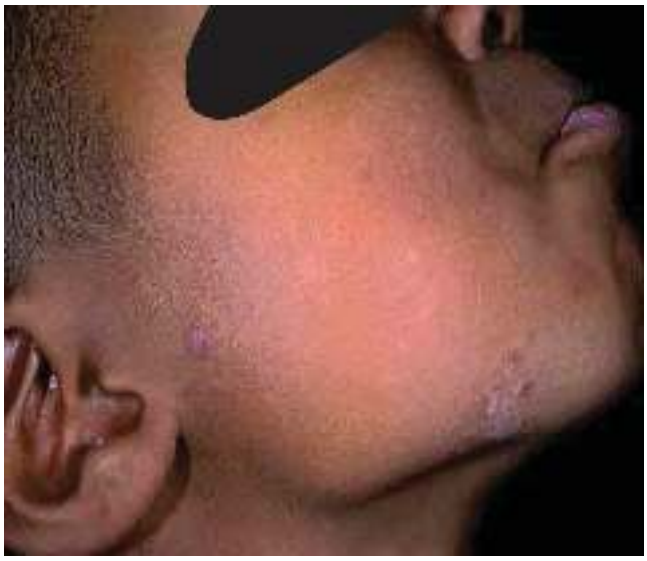

FIGURE 26.6 Tinea faciei.
Courtesy of Evelyn Koestenblatt.

Tinea faciei and tinea barbae

Tinea faciei occurs in women and children generally on the upper lip and chin (involvement of similar area in men is termed tinea barbae) and is frequently acquired from pets (Figure 26.6). *T. rubrum, T. mentagrophytes*, and *M. canis* are typically recovered.

Tinea barbae or ringworm of the beard is seen in men and associated with exposure to animals (cattle, horses, cats, and dogs). The inflammatory type causes a deep, nodular, pyogenic reaction. *T. mentagrophytes* and *T. verrucosum* tend to cause this kerion-like response, whereas *T. violaceum* and *T. rubrum* usually cause a more superficial infection with scaling and alopecia. Extracted hairs are necessary for diagnosis by KOH preparation and culture. In some instances biopsy may be necessary to rule out other dermatoses. Given that the organisms affect the hair, oral antifungal therapy is necessary as topical therapies will not adequately penetrate the hair follicle.

Dermatophytid (id) reactions

The *id reaction*, or autoeczematization, is a pruritic, disseminated, papulovesicular eruption secondary to a variety of inflammatory and infectious skin disorders. Dermatophytid reactions can be seen following infections of tinea capitis, tinea corporis, tinea cruris, tinea pedis, and tinea manuum, but no fungal forms are recovered from dermatophytid lesions. Treatment involves eradication of the underlying infection with topical corticosteroids and oral antihistamines to provide symptom relief.

Treatment

The first-line therapy for tinea corporis, cruris, manuum, faciei, and pedis consists of topical antifungals. Topical antifungal agents utilized in the treatment of dermatophytosis include several classes: allylamines, benzylamines, hydroxpyridones, and imidazoles (Table 26.2).

Commonly used imidazoles include clotrimazole (Lotrimin, Mycelex), miconazole (Desenex, Micatin, Monistat), econazole (Ecostatin, Spectazole), ketoconazole (Nizoral), oxiconazole (Oxistat), sertaconazole (Ertaczo), and sulconazole (Exelderm). The allylamines are fungicidal and include terbinafine (Lamisil AT), naftifine (Naftin), and butenafine (Lotrimin Ultra, Mentax). Ciclopirox (Loprox) is fungicidal and has antibacterial, anti-inflammatory, and antifungal properties. Treatment regimens for topical medication are generally for 2 to 4 weeks twice a day. Treatment with oral antifungals may be necessary, especially when the infection is deeper, more widespread, or involves hair-bearing areas.

Onychomycosis

Onychomycosis is more than an embarrassing cosmetic problem as it can be exquisitely painful and lead to serious infections, especially in diabetic and immunocompromised populations. The dermatophytes account for approximately 90% of toenail infections, whereas yeasts account for the majority of infections affecting the fingernails. Up to 50% of nail dystrophy is due to fungal infections. There are four types of onychomycosis: (1) distal subungual onychomycosis, (2) white superficial onychomycosis, (3) proximal subungual onychomycosis, and (4) candida onychomycosis.

The most common form is distal subungual onychomycosis, most frequently caused by *T. rubrum*. The nail of the toe or the finger appears thickened, with subungual debris, discoloration, and onycholysis (separation of the nail plate from the nail bed). The infection begins at the distal and/or lateral nail fold and involves the nail bed and hyponychium.

White superficial onychomycosis involves the surface of the toenail, imparting a chalky white appearance. The most common etiologic agents are *T. mentagrophytes* or nondermatophytes such as *Acremonium, Aspergillus, Cephalosporium, Fusarium*, or *Scopulariopsis*. *T. rubrum* is most often recovered in the HIV population. For diagnosis of white superficial onychomycosis, a curette can be used to scrape the white chalky material off the surface of the nail (Figure 26.7).

Proximal subungual onychomycosis is the least common form and may be a sign of HIV infection; it begins at the proximal nail fold, causing an opaque white area near the lunula. The opaque areas grow distally along with the nail. *T. rubrum* and occasionally *T.*

TABLE 26.2 **ANTIFUNGAL TOPICAL AGENTS**

Name	Concentration/ Vehicle	Formulation/ Class	Antibacterial activity	Anti-inflammatory activity	Pregnancy category	Indications	Dosage	Activity
Ertaczo	2% cream	Sertaconazole Imidazole	Gram-positive Gram-negative	Yes	C	T. pedis	BID 4 wk	Efloc, Tment, Trub
Exelderm	1% cream 1% solution	Sulconazole Imidazole	No	No	C	T. pedis/cruris/ corporis TV	QD/BID 3–4 wk QD-BID 3 wk	Efloc, Mcanis, Tment, Trub Calb Mfur
Lamisil AT	1% cream, spray solution	Terbinafine topical Allylamine	Gram-positive	No	B	T. pedis/cruris/ corporis TV (solution only)	QD/BID 1–4 wk BID 2 wk	Efloc, Tment, Trub Mfur
Loprox	0.77% cream, gel, suspension, 1% shampoo	Ciclopirox Hydroxpyridone	Gram-positive Gram-negative	Yes	B	T. pedis/cruris/ corporis TV (cream or suspension)	BID 1–4 wk BID 2–4 wk	Efloc, Mcanis, Tment, Trub, Calb Mfur
Lotrimin	1% cream, lotion, solution	Clotrimazole Imidazole	Gram-positive	No	B	T. pedis/cruris/ corporis TV	BID 2–4 wk BID 2–4 wk	Efloc, Tment, Trub, Calb Mfur
Lotrisone	0.05%, 1%, cream, lotion	Betamethasone/ clotrimazole Imidazole	Gram-positive	Yes	C	T. pedis T. cruris/corporis	BID 4 wk BID 2 wk	Efloc, Mcanis, Trub, Calb
Mentax	1% cream	Butenafine HCl Benzylamine	No	Yes	B	T. pedis T. cruris/corporis TV	BID 7 days QD 14 days QD 14 days	Efloc, Tment, Trub, Tton Efloc, Tment, Trub, Tton Mfur
Mycelex	1% cream, solution	Clotrimazole Imidazole	No	No	B	T. pedis/cruris/ corporis TV	BID 2–4 wk	Efloc, Tment, Trub, Calb Mfur
Naftin	1% cream, gel	Naftifine Allylamine	Gram-positive Gram-negative	Yes	B	T. pedis/cruris corporis	BID 1–4 wk (gel) QD 1–4 wk (cream)	Efloc, Tment, Trub,
Nizoral	2% cream 2% shampoo	Ketoconazole Imidazole	Gram-positive	No	C	T. pedis T. cruris/corporis Cutaneous candidiasis TV	QD 6 wk QD 2 wk QD 2 wk QD 2 wk	Efloc, Tment, Trub Efloc, Tment, Trub Mfur
Oxistat	1% cream, lotion	Oxiconazole Imidazole	Gram-positive	Yes, weak activity	B	T. pedis T. cruris/corporis TV	QD/BID 4 wk QD/BID 2 wk QD 2 wk	Efloc, Tment, Trub Mfur
Penlac Nail Lacquer	8% solution	Ciclopirox Hydroxypyridone	No	No	B	T. unguium finger/toe nails	QD 48 wk	Trub
Spectazole	1% cream	Econazole Imidazole	Gram-positive Some gram-negative No Pseudomonas	No	C	T. pedis T. cruris/corporis Cutaneous Candidiasis TV	QD 4 wk QD 2 wk BID 2 wk QD 2 wk	Maud, Mcanis, Mgyp, Tment, Trub, Tton Maud, Mcanis, Mgyp, Tment, Trub, Tton

Abbreviations: TV = tinea versicolor; Maud = *Microsporum audounii*; Mcanis = *Microsporum canis*; Mgyp = *Microsporum gypseum*; Tment = *Trichophyton mentagrophytes*; Trub = *Trichophyton rubrum*; Tton = *Trichophyton tonsurans*; Calb = *Candida albicans*; Mfur = *Malassezia furfur*; QD = once a day; BID = twice a day.

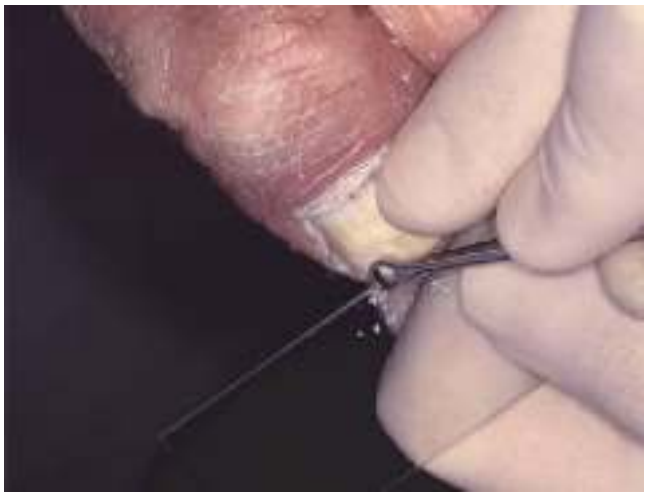

FIGURE 26.7 White superficial onychomycosis on the surface of the nail is scraped and small pieces are used for KOH preparations and culture.
Courtesy of Evelyn Koestenblatt.

megninii are the common etiologic agents. Material for KOH and culture from proximal subungual onychomycosis can be obtained by a punch biopsy into the affected area or after deep scraping below the surface of the nail.

Candida onychomycosis is mainly due to *Candida albicans* and causes yellowing of the nails with onycholysis. Before initiation of therapy, it is important to document the presence of fungi utilizing one or more diagnostic techniques including KOH preparation, fungal culture, and nail plate biopsy with periodic acid-Schiff (PAS) stain. However, lab results are only as good as the manner in which the specimen was taken. When managing distal and lateral onychomycosis (Figures 26.8 and 26.9), it is important to trim the nail back as close to the juncture of the nail plate and nail bed as

FIGURE 26.8 Clip back the nail as closely as possible to the juncture of the nail plate and nail bed.
Courtesy of Evelyn Koestenblatt.

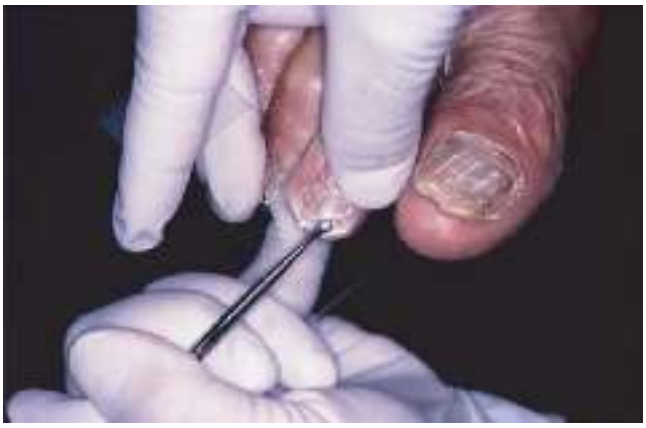

FIGURE 26.9 Curette small thin pieces of nail and debris for KOH preparation and culture.
Courtesy of Evelyn Koestenblatt.

possible. A curette can then be used to collect thin, small pieces of nail and debris for KOH and culture.

KOH preparation is a simple, inexpensive, and reliable way to diagnose fungal infections (Figures 26.10 and 26.11). The scraping is collected on a clean glass slide, and a couple of drops of 10% to 20% KOH are then added and mixed with the specimen. A coverslip is applied, and the slide is gently heated to promote breakdown of the keratin. The slide is microscopically examined for the presence of hyphal elements and yeast cells.

Material for culture should be gently placed on the surface of the agar using a wooden applicator stick that was premoistened with condensation from the tubed media (Figure 26.12). Sticks and blades should not come in contact with the inside of culture media tubes.

Proper diagnosis of onychomycosis is necessary because other disorders can present similarly, including psoriasis, irritant dermatitis, and trauma. Topical treatment of onychomycosis is generally insufficient to clear the infection. Naftin gel and 8% solution of ciclopirox have been used with moderate success. In the past, only 25% of patients treated with griseofulvin were disease-free after 1 year of therapy for toenail disease. Over the past several years, the emergence of itraconazole and terbinafine has allowed much shorter and more effective courses of therapy with fewer incidents of relapse.

Itraconazole has a broad spectrum of activity and shows activity against dermatophytes and nondermatophyte molds as well as yeasts and can be administered in a continuous or pulse fashion. In the continuous regimen, the dosage of itraconazole is 200 mg/d for 12 weeks for toenail disease and 8 weeks for fingernail disease. Pulse dosing of the medication involves a dosage of 200 mg twice daily for only 1 week of a given month. Toenails are treated for 3 months, whereas fingernails are treated for 2 months (Table 26.3). Unlike itraconazole, terbinafine is fungicidal, blocking cell membrane synthesis. This may account for terbinafine's higher efficacy for both mycologic and clinical cure rates as compared to other systemic antifungals. Terbinafine dosage is 250 mg/d for 12 weeks for toenails and 6 weeks for fingernails.

The combination of clipping and debridement of the affected nail with systemic antifungal therapy improves clearance of the

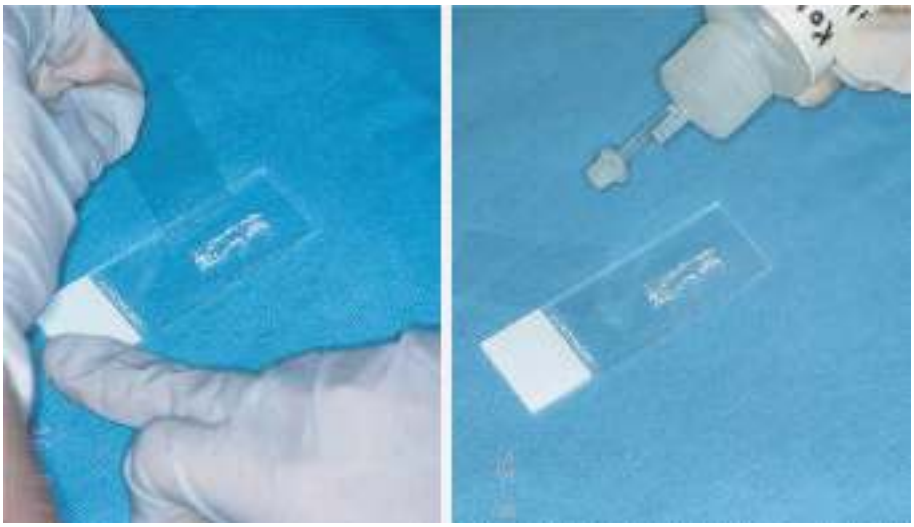

FIGURE 26.10 Method for KOH: Gather material on a clean glass slide and add a couple of drops of 10% to 20% KOH and mix with specimen. Add a coverslip.

Courtesy of Evelyn Koestenblatt.

infection. Other helpful measures include the use of white cotton socks and antifungal powder, properly fitting shoes, discarding prior fungus-laden shoes, and not walking around barefoot in public areas.

It is recommended for patients receiving either itraconazole or terbinafine to undergo liver function tests prior to and during treatment. Serious liver failure has been reported with the use of both therapies. Patients taking other medications metabolized by the cytochrome P450 pathway should not take itraconazole due to significant drug interactions. The use of itraconazole also carries a slight risk of developing congestive heart failure. Interactions have been reported in patients taking terbinafine and tricyclic antidepressants as well.

Although not approved by the US Food and Drug Administration, fluconazole is used to treat onychomycosis at a dose of 150 to 450 mg once a week for >3 months for fingernails and 6 to 12 months for toenails in those unable to tolerate other therapies.

Malassezia folliculitis

Malassezia folliculitis, previously called *Pityrosporum folliculitis*, presents with a chronic history of perifollicular erythematous and pruritic pustules and papules on the neck, torso, and upper arms. KOH preparation will reveal numerous spores and budding yeast forms. A confirmatory diagnosis in atypical locations can be made with the microscopic examination of a skin punch biopsy. Treatment is with topical antifungal therapies such as shampoos containing selenium sulfide or ketoconazole, propylene glycol 50% in water, or ciclopirox olamine cream. For more serious disease systemic oral therapies are warranted. For refractory cases, topical photodynamic therapy with methyl aminolevulinate has shown some efficacy.

FIGURE 26.11 Heat slide gently and press coverslip to flatten scale.

Courtesy of Evelyn Koestenblatt.

FIGURE 26.12 Specimen should be placed on the surface of the culture media with a wooden applicator stick.
Courtesy of Evelyn Koestenblatt.

Malassezia furfur (formerly *Pityrosporum ovale*) has also been associated with seborrheic dermatitis. Although the etiology of seborrhea is not known, *Malassezia*'s involvement may be due to its lipase degradation of sebum into inflammatory fatty acids such as arachidonic acid and to its activation of the alternative complement pathway. Whether its contribution is through immune response activation or as an irritant is still unknown. Indirect evidence supports its involvement in the pathogenesis because antifungal azole therapies have been shown effective in the treatment of seborrheic dermatitis.

Pityriasis versicolor

Pityriasis versicolor is also known as *tinea versicolor* but this is a misnomer as it is due to yeast, not a dermatophyte. The etiologic agent is *Malassezia furfur*. The skin lesions appear as sharply demarcated, superficial macules that may be hyper- or hypopigmented with fine scaling; they are located on the trunk, shoulders, neck, upper arms, back, abdomen, and, rarely, the face. Predisposing factors that cause the yeast form to convert to phialides (short hyphae with a fertile end) and spores include Cushing's disease, malnutrition, systemic steroid therapy, genetic predisposition, oral contraceptives, application of oils to the skin, immunosuppression, heat, and humidity.

Diagnosis is made by KOH preparation. Phialides and round short chains or clusters of budding thick-walled spores, commonly referred to as "spaghetti and meatballs," are seen microscopically. Culture is not generally performed as these organisms require an exogenous source of lipids for growth. Examination of the lesions with a Wood's lamp reveals a pale yellow fluorescence. A biopsy will show a thick basket-weave stratum corneum with phialides and spores.

Topical treatments are the most common therapy used. A 2.5% selenium sulfide lotion should be applied daily for 10 minutes, then washed off, for a week. To prevent recurrence the lotion may be used monthly for 3 months, and a shampoo with selenium sulfide can be used to prevent colonization of the scalp. Ketoconazole shampoo, imidazoles, triazoles, terbinafine spray, and propylene glycol are other useful topical treatments.

Oral therapies are effective but must also be continued to prevent recurrence. Itraconazole 200 mg/d for 5 to 7 days is effective, followed by 200 mg twice a day on a monthly basis for prophylaxis. Ketoconazole 200 mg/d for 10 days or single dose 400 mg repeated monthly can be effective. Fluconazole taken as a single dose of 300 to 400 mg has been shown to be effective as well.

Patients should be counseled that prophylaxis is necessary to avoid recurrence of infection and that the return to normal pigmentation takes time.

TABLE 26.3 **TREATMENT FOR ONYCHOMYCOSIS**

	Fingernails	Toenails
Itraconazole	200 mg/d for 8 consecutive weeks OR 200 mg twice a day for 1 week per month for 2–3 months	200 mg/d for 12 consecutive weeks OR 200 mg twice a day for 1 week per month for 3–4 months
Terbinafine	250 mg/d 6 weeks	250 mg/d 12 weeks
Fluconazole	150–200 mg/week for 6 months	150–200 mg/week 9–12 months

Candidiasis

Skin folds are the most common site of cutaneous candida infections. The lesions appear as erythematous, sometimes erosive, areas with satellite pustules. The intertriginous zones (submammary, inguinal creases, finger spaces) are often affected because of their predilection for moist conditions, as well as the nails, scrotum, and diaper area. Topical therapy including the azoles, nystatin, and clotrimazole are generally effective. It is also important to keep the area dry. Fluconazole and itraconazole are useful if systemic therapy is required.

Suggested reading

Elewski BE, Hazen PG. The superficial mycoses and the dermatophytes. *J Am Acad Dermatol*. 1989;21:655–673.
Finch JJ, Warshaw EM. Toenail onychomycosis: current and future treatment options. *Dermatol Ther*. 2007;20(1):31–46.
Kwong-Chung KJ, Bennett JE. *Medical Mycology*. Philadelphia: Lea and Febiger; 1992.
Rinaldi MG. Dermatophytosis: Epidemiological and microbiological update. *J Am Acad Dermatol*. 2000;43:S120–S124.
Rippon JW. *Medical Mycology: The Pathogenic Fungi and the Pathogenic Actinomycetes*, 3rd ed. Philadelphia: WB Saunders; 1988.

27

Eumycetoma

Ncoza C. Dlova, Anisa Mosam, and Antoinette Chateau

Epidemiology

Although eumycetomas are endemic worldwide, they are predominantly found in the tropical regions of the world.[1] The continents most affected are Asia and Africa, with India, Pakistan, and Sudan reporting the highest number of cases. Sporadic cases have been reported in Europe and the southwestern United States.[2] Eumycetomas are caused by organisms living in soil and plants; they are spread by direct contact or by traumatic implantation through, for example, wooden splinters into the skin. They occur most often in the feet of those walking barefoot but may also occur on the back and neck. There are reported cases of inoculation following contaminated intravenous cocaine injections.[3] The disease is noted in all age groups, but it is more often seen in the age range of 20 to 40 years, with males being more commonly affected than females.[2]

Etiology

At variety of causative agents have been associated with eumycetomas, but >90% of eumycetomas reported worldwide are due to four organisms[4]: *Madurella mycetomatis* (black grain), *M. grisea* (black grain), *Scedosporium apiospermum* (white grain), and *Leptosphaeria senegalensis*.

Pathophysiology

The pathophysiology is based on the interplay between the organism, host response, and the environment.[2] The patient's immune system plays a role, and those with poor cell-mediated immunity are predisposed to developing the disease.[5] Genetics also plays a role, and a polymorphism resulting in a reduction in activity of the chitotriosidase enzyme that is normally protective against the fungus has been identified.[2] HIV-infected patients have a more intense and faster progression of the disease.[6]

Clinical features

Eumycetomas are slow-growing, painless nodules that develop on the feet. As a result of the insidious and painless nature of the disease, patients delay seeking help. The implanted organisms set up an inflammatory reaction which involves the subcutaneous tissues and causes disfigurement (Figure 27.1) The characteristic clinical diagnostic features include a triad of nodules, sinuses, and grains. The color of the grains depends on the causative organism, and this is usually black or gray-white when it is due to a fungal infection.

FIGURE 27.1 Eumycetoma in a 35-year-old black male, showing a deformed foot with multiple nodules and sinuses.

With chronicity, the foot tends to become a large mass, and resultant spread of the infection to underlying bone results in osteomyelitis.[7] Eumycetomas have the tendency of forming cysts which can be walled off, thereby preventing distant spread and thus creating a therapeutic challenge. Although the most common site is the foot, with usually unilateral involvement, the legs, hands, neck, and back may be affected. If mycetoma affects the back, it may result in vertebral collapse and resultant neurological deficit. Lymphatic spread is rare.[7]

Differential diagnosis

Several other conditions need to be taken into account because they can mimic eumycetoma (hence the need for biopsy and culture). These are

- Foreign-body granulomas
- Soft-tissue neoplasms
- Tumors (e.g., Kaposi's sarcoma)
- Other deep fungal infections (e.g., sporotrichosis; chromomycosis, conidiobolomycosis)
- Cysts
- Botryomycosis
- Leishmaniasis
- Tuberculosis

Diagnosis

Histopathology

Histologically the lesions are characterized by granulomatous inflammation with organisms within the center of the abscesses.[4] Occasionally maze-shaped structures called *clubs* are found in the vicinity of the granules.[4] The clinical presentation of mycetoma remains the same irrespective of the implicated organism, although the histologic features—namely the size, shape, and color of the granules—can be suggestive of the causative agent. Using special stains (Grocott, periodic acid-Schiff, and hematoxylin and eosin) assists in ascertaining the various types of grain. Fine-needle aspiration is an alternative to obtaining samples for cytology.[8]

Laboratory diagnosis

Direct examination, culture, and histopathology are the various methods used to identify the causative species and genus.[3] Suggestions of the etiologic agent can be drawn from the size, form, and presence or absence of clubs or pseudo-clubs. The most commonly isolated organism in eumycetoma in the world is *M. mycetomatis*, with countries like Sudan reporting up to 70% of cases.[9]

Contamination of cultures with bacteria, as well as challenges in identifying the morphology of the organism when cultures are positive, can sometimes pose a problem in diagnosing the genus and species when studying pathology specimens.[3] This has led to the introduction of various methods of molecular diagnostic techniques, such as polymerase chain reaction (PCR), including PCR restriction fragment length polymorphism (RFLP), real-time PCR, and DNA sequencing, and these have been used to identify the species of eumycetoma from lesional biopsies and environment.[10]

In the next sections, we describe a few of the common organisms.

Madurella mycetomatis

Inspection reveals oval, spherical, or lobulated black grains measuring 0.5 to 1 mm which sometimes coalesce to form 5 mm oval grains. Hyphae are light brown, ranging from 1 to 5 mm in diameter and showing reddish-brown grains on microscopy.

Culture: Initially the hyphae look white and membranous, and then later change to yellow-brown with a dark pigment that spreads into the culture medium. Growth is at 26°C/79°F to 30°C/86°F. Oval conidia (3.5–5 μm) are produced, and these are derived from the simple or branched conidiophores.

Madurella grisea

These have spherical or multilobed black grains ranging between 0.5 and 1 mm in diameter. These are soft and then develop into hard and brittle grains. Microscopically, a clear center surrounded by brown, pigmented hyphae is seen.

Culture: Slow growing gray-green hyphae with peripheral folds and short hyphae are observed with growth at temperatures between 26°C/79°F and 30°C/86°F. Occasionally a reddish-brown pigment is detected. A pigmented wall is seen around septate hyphae (1–3 μm), and there are no spores, although numerous pycnidia and chlamydoconidia are seen sometimes.

Imaging

Ultrasound and MRI have been used to determine the extent of disease and bone involvement,[11] with an increase in soft-tissue volume (93%), bone sclerosis (56%), bone cavities (32%), periosteal reaction (27%), and osteoporosis (19%) often seen.[3] Ultrasound usually reveals the "dot in circle" sign, which is considered to be typical of mycetoma.[3] CT appears to be more sensitive in picking up early bone changes in contrast to MRI.[3]

Management of Madura foot

Management of *Mycetoma* is challenging, protracted, and sometimes disappointing. A combination of surgical and medical management is the gold standard of treatment in limited disease. There are no randomize controlled trials regarding the management of mycetoma, and treatment is based on case reports.[1]

Medical management

Azoles: Imidazoles and triazoles:

Treatment is protracted, from 9 to 12 months, but may extend to up to 18 to 24 months.

- Ketoconazole 400 mg/d has been shown to be effective. This drug is however limited by its side effects, the most important being hepatotoxicity and adrenal toxicity, and others being hyperpigmentation and gynecomastia.[1]
- Itraconazole 200 mg BID is better tolerated and is thought to have greater efficacy than ketoconazole.[12] Note that there is a drug interaction of itraconazole and ketoconazole with antiretroviral therapy.
- Posaconazole 200 mg QID has been used in recalcitrant cases of mycetoma with some success.
- Voriconazole 200 mg two to three times a day has shown to be effective. Voriconazole is contraindicated in patients taking rifampicin, ritonavir, and carbamazepine.[3] Side effects such as visual disturbances, skin rashes, and elevated liver function profile frequently result in discontinuation of the drug.[3]
- Fluconazole has shown poor results.
- Newer therapies such as isavuconazole and fosravuconazole have shown excellent in vitro results, and prospective studies are ongoing.[6]

Allylamines:

- Terbinafine at a dose of 500 to 1,000 mg/d has shown a cure rate of 50%.[13]

Polyenes:

- Amphotericin B has not been shown to be effective. However there have been isolated reports of efficacy at doses ranging from 0.5 to 1.25 mg/kg/d.

Griseofulvin, a fungistatic agent, has shown poor results.[2]

A study conducted in Brazil showed improvement in patients receiving a combination of itraconazole and trimethoprim-sulfamethoxazole. The latter was thought to exert an antibacterial effect against secondary bacterial infection as well as exerting an effect on the fungi itself.[14]

Surgery

Surgery is advocated in limited disease. Antifungal therapy is used to debulk the lesion, followed by surgery, and then continuation of oral therapy. Extensive disease with bone involvement may necessitate amputation in a subset of patients.

Topical negative pressure therapy following surgery has been shown to be effective.[6]

Conclusion

Eumycetomas are a neglected disease prevalent in the tropics, particularly in India, Pakistan, and Sudan. This is a chronic, smoldering disease in which diagnosis is delayed due to initial its painless nature and the difficulty in confirming the causative organism by microbiological culture. Therapy is prolonged due to the poor response rates attributed, in part, to encapsulation and depth of inflammation.

Hence treatment of this chronic condition is expensive, and efforts need to be directed to prevention. Due to chronicity and subsequent disfigurement, many are subjected to debulking surgery and amputation. This poses a challenge in young males, who are the most frequently affected and the most productive workforce. Further research and education should be directed toward prevention, awareness, improved noninvasive diagnostic techniques, and combination therapies.

References

1. Fahal AH. Management of mycetoma. *Exp Rev Dermatol*. 2010;5(1):87–93.
2. Emmanuel P, Dumre SP, John S, Karbwang J, Hirayama K. Mycetoma: A clinical dilemma in resource limited settings. *Ann Clin Microbiol Antimicrob*. 2018 Aug 10;17(1):35. PubMed PMID: 30097030. Pubmed Central PMCID: PMC6085652.
3. Castro LG, Valente NY, Germano JA, Vaccari EM, da Silva Lacaz C. Mycetoma in an HIV-infected patient. *Revista do Hospital das Clinicas*. 1999 Sep-Oct;54(5):169–171.
4. Estrada R, Chávez-López G, Estrada-Chávez G, López-Martínez R, Welsh O. Eumycetoma. *Clin Dermatol*. 2012–7;30(4):389–396.
5. Fasciana T, Colomba C, Cervo A, et al. Madura foot: An imported case of a non-common diagnosis. *Le infezioni in medicina*. 2018 Jun 1;26(2):167–170.
6. Reis CMS, Reis-Filho EGM. Mycetomas: An epidemiological, etiological, clinical, laboratory and therapeutic review. *Anais brasileiros de dermatologia*. 2018 Jan-Feb;93(1):8–18.
7. Verma P, Jha A. Mycetoma: Reviewing a neglected disease. *Clin Exper Dermatol*. 2018 May 28.
8. Gabhane SK, Gangane N, Anshu. Cytodiagnosis of eumycotic mycetoma: A case report. *Acta Cytologica*. 2008 May-Jun;52(3):354–356.
9. Ahmed AOA, van Leeuwen W, Fahal A, van de Sande W, Verbrugh H, van Belkum A. Mycetoma caused by Madurella mycetomatis: A neglected infectious burden. *Lancet Infect Dis*. 2004;4(9):566–574.
10. Ahmed AO, Desplaces N, Leonard P, et al. Molecular detection and identification of agents of eumycetoma: Detailed report of two cases. *J Clin Microbiol*. 2003 Dec;41(12):5813–5816.
11. Czechowski J, Nork M, Haas D, Lestringant G, Ekelund L. MR and other imaging methods in the investigation of mycetomas. *Acta radiologica* (Stockholm, Sweden: 1987). 2001 Jan;42(1):24–26.
12. Ameen M, Arenas R. Developments in the management of mycetomas. *Clin Exp Dermatol*. 2009 Jan;34(1):1–7.
13. Welsh O, Vera-Cabrera L, Salinas-Carmona MC. Mycetoma. *Clin Dermatol*. 2007 3;25(2):195–202.
14. Castro LGM, Piquero-Casals J. Clinical and mycologic findings and therapeutic outcome of 27 mycetoma patients from São Paulo, Brazil. *Intl J Dermatol*. 2008;47(2):160–163.

28

Lymphadenopathy/Lymphadenitis

Gerald Friedland and Sheela Shenoi

Fever and lymphadenopathy is a commonly encountered presentation in clinical practice. It is important to have a logical and systematic approach for the accurate diagnosis and treatment of patients with this syndrome (Figure 28.1). Careful history-taking and physical examination are essential in the initial patient evaluation, and the following questions are requisite:

1. Is the adenopathy local or generalized?
2. Is the process acute or chronic?
3. Is the cause infectious or noninfectious?
4. Is there a primary peripheral lesion?

Important elements of the history should also include the presence or absence of pain, occupational and animal exposures, geographic residence, travel history, sexual and drug use behavior, trauma, presence or absence of systemic symptoms, and/or history of underlying disease. A thorough examination must include the location of lymphadenopathy including an evaluation of all accessible lymph node–bearing areas, the size and consistency of palpated nodes, whether they are discrete or matted, and whether tenderness is present and, if so, at what level of severity.

As a general rule, a node >1 cm should be considered abnormal. Stony-hard nodes are usually a sign of malignancy. Very firm, rubbery nodes suggest lymphoma. Softer nodes are the result of infectious or inflammatory conditions, and, when suppuration is present, these nodes may tend to be fluctuant. The term *shotty* refers to small nodes that feel like "buckshot" under the skin, as found in the cervical nodes of children with viral illnesses. A group of nodes that feel connected and seem to move as a unit is said to be *matted* and can be either benign (e.g., tuberculosis [TB], sarcoidosis, lymphogranuloma venereum, and HIV) or malignant (e.g., metastatic carcinoma and lymphoma). Pain and tenderness is usually the result of an inflammatory process or suppuration within the nodes but may also represent hemorrhage into the necrotic center of a malignant node. The presence or absence of tenderness does not reliably differentiate benign from malignant nodes.

Localized lymphadenopathy

Lymphadenopathy is considered localized if no more than two contiguous lymph node groups are involved. Anatomically and clinically, the node-bearing areas are divided into five major groups: (1) the head and neck area, (2) the axilla, (3) the inguinal area, (4) the mediastinal-hilar areas, and (5) the retroperitoneal and paraaortic areas. Basic knowledge of the anatomy and areas drained by these lymph nodes can help in narrowing the differential diagnosis (see Table 28.1). Infectious local adenopathy may be acute or chronic. It is usually associated with a primary lesion. At times, the peripheral lesion may be subtle or inapparent. In patients with

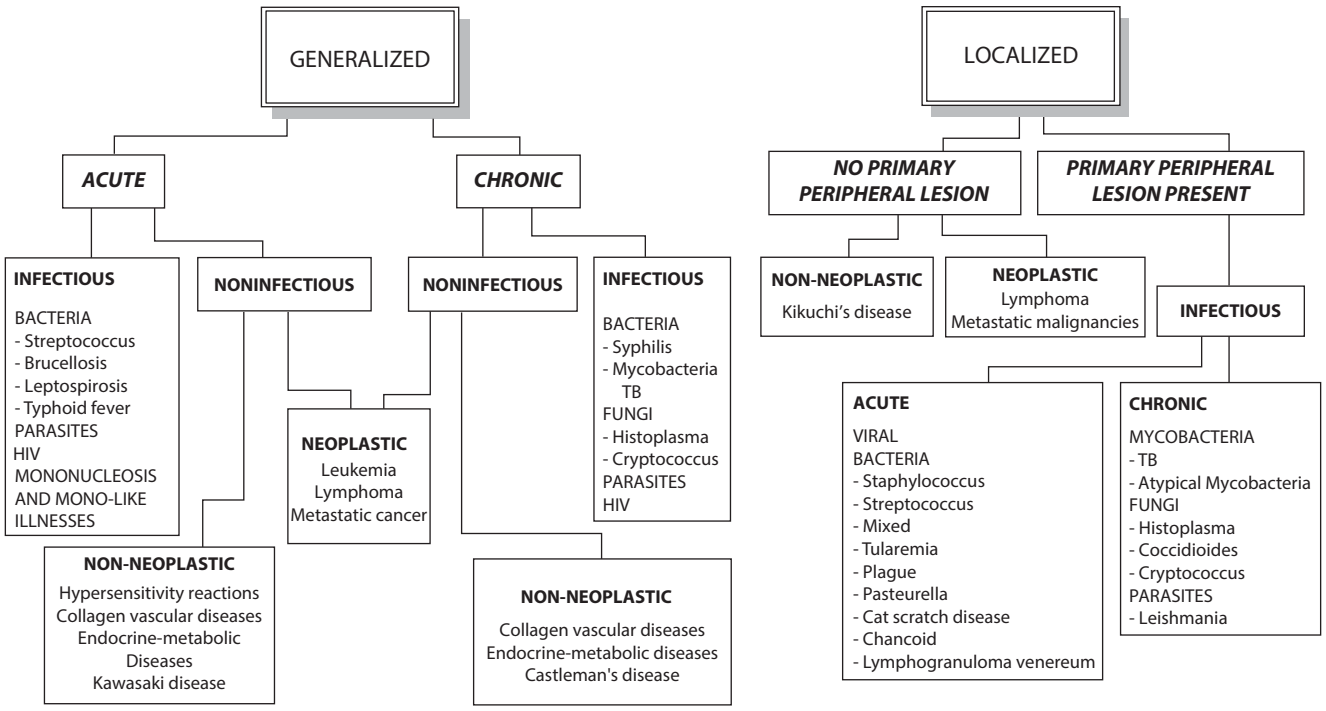

FIGURE 28.1 Differential diagnostic scheme for fever and lymphadenopathy.

TABLE 28.1 LOCALIZED LYMPHADENOPATHY: ANATOMIC AREAS DRAINED AND ASSOCIATED CONDITIONS

Lymph node area	Anatomic area	Areas drained	Associated conditions/comments
Head and neck	Occipital and posterior auricular	Scalp, face	Local infections with skin pathogens: *Staphylococcus, Streptococcus*, acute viral illnesses Children: secondarily infected insect, tick, or spider bites, dermatophyte infections (ringworm), viral infections
	Anterior auricular	Eyelids, palpebral conjunctivae, external auditory meatus, pinna	Conjunctivitis, oculoglandular syndrome (*Francisella tularensis*, *Neisseria gonorrhoeae*, *Bartonella henselae*), keratoconjunctivitis
	Tonsillar, submaxillary, submental	Pharynx, mouth, teeth, lips, tongue, and cheeks	Infections of the head, neck, sinuses, ears, scalp, pharynx, teeth, and oral mucosa
	Posterior cervical	Scalp and neck, skin of arms and pectorals, thorax, cervical, and axillary nodes	Mononucleosis, Kikuchi disease, tuberculosis, lymphoma, head and neck malignancies
Axillary		Upper extremity Thoracic wall, breasts, and back	Acute pyogenic infection, cat scratch disease, brucellosis, melanoma, breast malignancy
Inguinal		Lower extremities Abdominal wall Genitalia: penis, scrotum, vulva, vagina, perineum, and perianal region	Pyogenic infections of the lower extremities Sexually transmitted diseases: herpes simplex, syphilis, chancroid, lymphogranuloma venereum Pelvic and perianal malignancy
Mediastinal-hilar		Lungs, trachea, esophagus	Granulomatous disease (infectious and noninfectious) Malignancies
Abdominal retroperitoneal para-aortic		Abdominal viscera Retroperitoneal organs: kidneys Pelvic organs	Usually granulomatous disease: *Mycobacterium tuberculosis, Mycobacterium avium* complex Malignancies: lymphoma

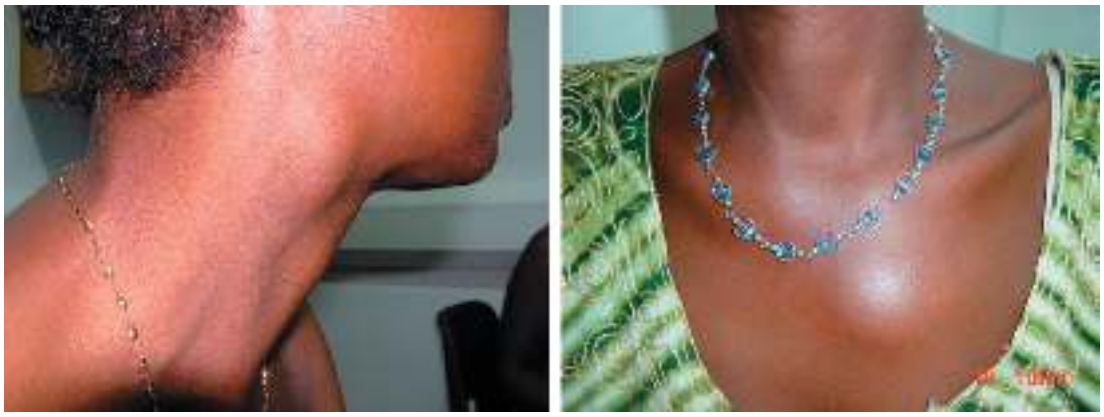

FIGURE 28.2 Palpable lymph nodes in the anterior cervical area (left image) and left parasternal areas (right image).

unexplained localized lymphadenopathy and a reassuring clinical picture, a 3- to 4-week period of observation may be appropriate before considering biopsy. It is important to bear in mind and examine carefully the areas of drainage of each nodal group as this will often reveal the primary site of infection or other pathology. The lymph nodes of the head and neck are collectively called *cervical nodes* and *occipital* and *auricular nodes* and are more accurately subdivided into several anatomic and clinical areas (see Figure 28.2). The occipital and posterior auricular nodes drain large areas of the scalp and face. Adenopathy of these groups may be associated with primary infectious lesions in these areas (usually from staphylococcal and streptococcal infections) but can be a common feature of acute viral illnesses as well. In children, secondarily infected wounds from insect bites and ringworm (dermatophyte infection) are common causes. The anterior auricular nodes drain the eyelids, palpebral conjunctivae, external auditory meatus, and pinna of the ear. Conjunctivitis and anterior auricular adenopathy (the oculoglandular syndrome) is classically associated with *Francisella tularensis* via direct inoculation of the conjunctival sac but may also be seen with conjunctival infection from *Neisseria gonorrhoeae*, *Bartonella henselae* (cat scratch disease), and epidemic keratoconjunctivitis. The sternocleidomastoid muscle divides the cervical nodes into anterior and posterior sections, each with different drainage areas and resultant clinical importance. The anterior nodes, including the tonsillar, submaxillary, and submental nodes, are most commonly involved because they drain the tonsils and other structures in the pharyngeal area, including the teeth and gums. Enlargement of these nodes should prompt careful inspection of the contents of the mouth. In addition, this group also drains the external structures of the medial face including the lips, chin, cheeks, and medial aspects of the conjunctivae. The posterior cervical nodes are in the occipital triangle of the neck, posterior to the sternocleidomastoid muscle and above the inferior belly of the omohyoid muscle. The drainage of these nodes is more limited, and, if enlarged, systemic disease should be considered including infectious mononucleosis and mononucleosis-like syndromes, including HIV infection.

Kikuchi disease, or histiocytic necrotizing lymphadenitis, is a rare self-limited disorder involving the cervical lymph nodes. This condition was first recognized in Japan and has been predominantly described in females of Asian and Middle Eastern origin, commonly <40 years of age. Clinical manifestations of this entity include fever or flu-like symptoms, rash, localized and sometimes tender cervical lymphadenopathy, elevated erythrocyte sedimentation rate (ESR), and leukopenia. The involved nodes are usually rubbery or firm, discrete, and rarely >2 cm in diameter. Its etiology is still obscure, but it has been associated with Kaposi's sarcoma–associated herpesvirus (KHSV-HHV-8). This condition does not respond to antibiotics but usually resolves spontaneously in 1 to 2 months. Because of its association with systemic lupus erythematosus (SLE) and Still's disease, it is also thought to be autoimmune in origin. Recognition of this disease is important because pathologists who are unfamiliar with it commonly mistake it for other conditions that require treatment, such as malignant lymphoma and Kawasaki disease.

The inferior deep cervical nodes lie below the level of the inferior belly of the omohyoid muscle and anteroposterior to the sternocleidomastoid muscle. These nodes receive drainage from the scalp; the superior deep cervical nodes; the axillary nodes; and the nodes of the hilum of the lung, the mediastinum, and abdominal viscera. Infectious and noninfectious entities that involve these structures should be considered when these nodes are involved. Adenopathy in this area is usually subtle and not recognized clinically but may be detected with the Valsalva maneuver.

While rarely representing coccidioidomycosis, supraclavicular lymphadenopathy has been associated with malignancy in the majority of patients >40 years. The left supraclavicular (Virchow) node receives lymphatic flow from the thorax and abdomen and may indicate pathology involving the testes, ovaries, kidneys, pancreas, prostate, stomach, or gallbladder. Mediastinal and hilar adenopathies are usually detected only on radiography. These nodes are infrequently involved in acute suppurative disease. Acute suppurative mediastinal lymphadenitis, if present, can be a fulminant process, typically a complication of progressive infections of the upper respiratory tract or perforation of the esophagus or bronchial tree as a result of trauma or surgery. A useful diagnostic criterion is whether the lymphadenopathy is unilateral or bilateral. Unilateral enlargement most frequently suggests granulomatous disease of both infectious (e.g., *Mycobacterium tuberculosis* and histoplasmosis) and noninfectious (e.g., sarcoidosis) origin (see Figure 28.3) and an ipsilateral malignant pulmonary process. Bilateral hilar adenopathy is seen in approximately three-fourths of patients with sarcoidosis. When

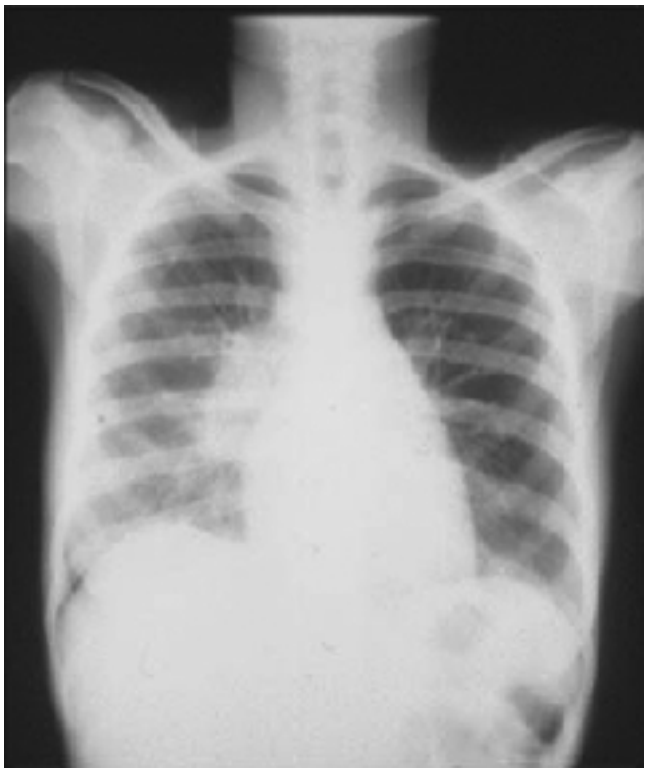

FIGURE 28.3 Chest x-ray depicts unilateral (right) hilar lymphadenopathy (as indicated by the arrow) in a patient with pulmonary tuberculosis.

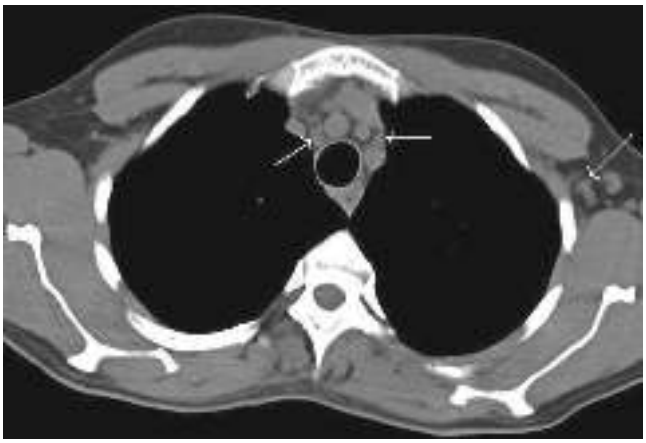

FIGURE 28.4 An example of chest CT in a patient with HIV and atypical mycobacterial pulmonary infection who presented with multiple hilar and left axillary lymphadenopathy (as indicated by the arrows).

dealing with mediastinal and hilar adenopathy, the diagnostic approach includes *M. tuberculosis* skin test (purified protein derivative [PPD]) or interferon-γ release assay (IGRA) blood test, sputum cultures (routine, fungal, acid-fast bacillus [AFB]), and lymph node culture (routine, AFB, anaerobic) as well as cytology. CT is useful in assessing the size and location of these lymph nodes. Biopsy should be considered in any node >1 cm in the absence of a primary diagnostic lesion. Tissue for histologic examination may be obtained through inferior cervical node biopsy, transbronchial lung biopsy, mediastinoscopy, or percutaneous or surgical biopsy of the hilar nodes (see Figure 28.4).

The axillary nodes drain the entire upper extremity as well as the lateral parts of the chest wall, back, and breasts. This cluster of nodes is most frequently involved in acute pyogenic infections of these drainage areas. By far, the most common etiologic organisms include staphylococci and streptococci, associated with furunculosis, cellulitis, or lymphangitis. The extremities are also often the site of zoonotic infections from other organisms acquired from the environment, including *F. tularensis* (tularemia), *Yersinia pestis* (plague), *Pasteurella multocida* (from dog or cat bites or scratches), *Erysipelothrix rhusiopathiae* (erysipeloid), and *B. henselae* (cat scratch disease). Lymphadenopathy can precede the ulcers seen with localized cutaneous leishmaniasis.

Inguinal lymphadenopathy is very common, partly due to frequency of trauma or prior infections in the lower extremities and the wide watershed drainage area. These nodes not only drain the lower extremities but also the lower abdominal wall, the genitalia, perineum, and perianal areas. Acute pyogenic bacterial infection caused by the same organisms encountered in axillary adenopathy are the usual culprits. The drainage of the perineum and the perianal area suggests that enteric aerobic and anaerobic gram-negative organisms as well as gram-positive organisms are present. Because of the drainage of the genitalia and perianal area, sexually transmitted infections often involve the inguinal nodes as well. Those most likely to present with prominent inguinal adenopathy are syphilis (secondary), lymphogranuloma venereum, chancroid, and genital herpes simplex. Initial inguinal lymphadenopathy can progress to the buboes seen with bubonic plague, although they can also be seen in the axillary, cervical, crural, and submaxillary nodes.

The abdominal and retroperitoneal nodes drain the abdominal viscera and the retroperitoneal and pelvic organs. They may receive drainage from the inguinal nodes as well. Because they are not directly accessible by physical examination, their recognition and characterization usually requires CT or MRI (see Figure 28.5).

Generalized lymphadenopathy

Generalized lymphadenopathy is present if nodes in two or more noncontiguous major lymph node–bearing areas are enlarged. It is frequently a manifestation of disseminated infection. Clues may be provided by the age of the patient, presence or absence of rash, geographic factors (e.g., dengue fever, filariasis, localized leishmania lymphadenitis, histoplasmosis, TB), occupation and dietary history (brucellosis, toxoplasmosis), and exposure to animals and their excreta or standing water (leptospirosis). Acute generalized infectious lymphadenopathy, which is most often viral, is a common feature of many childhood viral infections, including rubella, measles, and varicella. Generalized lymph node enlargement may also be seen in the prodromal period of hepatitis A and B, Epstein–Barr virus (EBV), cytomegalovirus (CMV), HIV, and toxoplasmosis. These conditions initially present with the mononucleosis-like syndrome and generalized lymphadenopathy. Bacterial pathogens are much less often the cause of generalized lymphadenopathy, except in

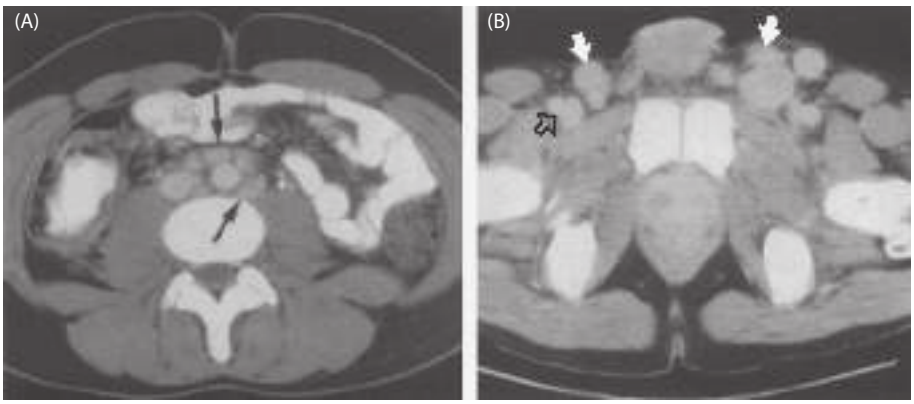

FIGURE 28.5 An example of high-attenuation lymph nodes (*solid arrows*) in the (A) retroperitoneum and (B) inguinal areas of patients with AIDS and Kaposi's sarcoma. Contrast-enhanced femoral vessels are seen on the right (*open arrow*).

brucellosis and leptospirosis. In all these infections, the nodes are typically tender, discrete, firm to touch, and without fluctuance. Acute generalized noninfectious lymphadenopathy is frequently due to hypersensitivity reactions, most commonly drug-induced. Sulfonamides, hydralazine, carbamazepine, and phenytoin are among the agents that have been most commonly implicated in such reactions. This condition rapidly disappears on withdrawal of the offending drug. Other offending medications include allopurinol, atenolol, captopril, quinine, primidone, and sulindac. Collagen vascular diseases, including rheumatoid arthritis and SLE, may also cause acute generalized lymphadenopathy and fever. Kawasaki syndrome (acute febrile mucocutaneous lymph node syndrome) is a disease of uncertain origin that is seen almost exclusively in infants and young children, and it also presents with nonsuppurative cervical lymphadenopathy that may be unilateral.

Chronic generalized infectious lymphadenopathy is less likely to be viral, except for HIV. Its presence suggests more serious diagnostic possibilities. Disseminated bacterial and fungal diseases, including TB, syphilis, histoplasmosis, and cryptococcosis, should be considered. In children, persistent lymphadenopathy and fever may suggest an immunodeficiency state, including chronic granulomatous disease. Castleman's disease, associated with HHV-8, the same etiologic agent as for Kaposi's sarcoma, also presents with fever and chronic lymphadenopathy and is discussed later in this chapter.

Chronic generalized noninfectious lymphadenopathy is most often neoplastic. Lymphoreticular neoplasms (e.g., Hodgkin's disease, non-Hodgkin's lymphoma, chronic lymphocytic leukemia) predominate. Fever, when present, may be due to the underlying malignant disease or to secondary infection. Non-neoplastic diseases (with variable frequency) cause chronic generalized lymphadenopathy and fever, and these include sarcoidosis, Still's disease, and hyperthyroidism. In patients receiving immunosuppressive therapy following a solid organ or bone marrow transplant, one should consider the diagnosis of posttransplant lymphoproliferative disorder (PTLD), which is a heterogeneous group of lymphoid proliferations, most of which are of B-cell lineage and associated with EBV. These disorders can occur months to years after transplantation and would require reduction in immunosuppressive therapy with or without antiviral therapy.

Lymphadenopathy and HIV infection

Lymphadenopathy is a common and important finding in people with HIV infection. Acute retroviral infection is a mononucleosis-like syndrome that occurs 2 to 10 weeks after exposure to HIV. Acute bilateral generalized lymphadenopathy, which may be accompanied by fever, sore throat, maculopapular rash, headache, mucosal ulcerations, myalgias, and malaise, is a common feature; occasionally signs and symptoms of meningitis are seen due to early neural invasion of the virus. Since HIV antibody tests are negative during the first 6 weeks and sometimes longer, during the early stage of HIV primary infection, the diagnosis is best made by testing for HIV RNA in plasma (viral load). Titers are extremely high during the acute infection and may be assayed by the reverse transcription-polymerase chain reaction (RT-PCR) method. The mean interval between the onset and resolution of symptoms during primary HIV infection is approximately 25 days, after which patients may remain asymptomatic for years. During this time, many infected individuals exhibit persistent generalized lymphadenopathy (PGL) which may last for several years. The nodes are typically nontender and firm to rubbery in consistency. In the untreated patient, as immunodeficiency worsens, symptoms may include fevers, night sweats, weight loss, and diarrhea and herald the presence of more severe complications including opportunistic infections and malignancies, thus defining AIDS. In contrast to earlier stages in the natural history of HIV disease, lymphadenopathy is a less common finding in those with AIDS, and its presence suggests an infectious or neoplastic process involving the reticuloendothelial system. Of infectious causes, disseminated *Mycobacterium avium-intracellulare* infection, *M. tuberculosis*, histoplasmosis, CMV infection, toxoplasmosis, syphilis, and cryptococcosis are most common. Although high-grade B-cell lymphomas are common in AIDS, they are often extranodal. Kaposi's sarcoma may involve lymph nodes, occasionally without apparent skin lesions. The diagnosis of lymphadenopathy in people living with HIV is highly dependent on the geographic and social setting. In high-prevalence TB settings, TB is usually the most frequent finding, occurring in up to 60% of cases. In contrast,

in a recent retrospective, multicentered biopsy study among people living with HIV in a non-TB endemic setting, 42.9% of peripheral lymphadenopathy was attributable to malignancy, 49.5% to reactive changes, and 7.5% to infections, with only 2.8% of all cases secondary to TB. Fevers, weight loss, antiretroviral use, and lower viral loads were significantly associated with nonreactive (malignant or infectious) lymphadenopathy. Multicentric Castleman's disease, associated with HHV-8, presents with persistent fever, marked splenomegaly, generalized lymphadenopathy in >90% of patients, weight loss in 70%, and pancytopenia in 35%. These symptoms usually last >6 months and may represent acute infection with HHV-8 or reactivation of HHV-8 in the setting of immune suppression in AIDS. For more details on HIV and AIDS, please refer to Chapter 101, "Differential diagnosis and management of HIV-associated opportunistic infections."

General diagnostic approaches

In most cases of infectious lymphadenopathy, clinical and laboratory findings short of biopsy often suggest the causative agent responsible for the enlarged nodes. Some of these findings are as follows:

1. Primary site of infection (e.g., streptococcal cellulitis, staphylococcal furuncle, syphilitic chancre)
2. Associated symptoms: "B" symptoms with lymphomas, rash, serositis with SLE; arthritis with Still's disease, or rheumatoid arthritis
3. Characteristic rash (e.g., rubella, rubeola, drug eruption, acute HIV infection)
4. Characteristic physical findings (e.g., splenomegaly in mononucleosis, lymphoma)
5. Typical hematologic findings (e.g., eosinophilia [drug reactions], atypical lymphocytosis [mononucleosis syndrome], high ESR and/or C-reactive protein [CRP] [rheumatologic diseases])
6. Skin tests or IGRA (e.g., TB [though unreliable in immunocompromised hosts])
7. Serologic tests (e.g., EBV, hepatitis, syphilis, HIV, tularemia)
8. Stains, cultures, and histologic examination of material from peripheral primary lesions and pulmonary lesions (atypical mycobacteria, tuberculosis, plague, lymphoma).

Lymph node biopsy versus fine-needle aspiration biopsy

The simplicity, safety, and cost-effectiveness of fine-needle aspiration (FNA) make it a useful test for the evaluation of persistent lymphadenopathy. The advent of radiologically guided FNA makes biopsy of the nodes of the hilum and retroperitoneum accessible, thus avoiding extensive surgical procedures. The presence of a cytopathologist on site to determine the adequacy of the specimen has been shown to increase the yield of FNA considerably. However, there are limitations to the procedure. FNA is useful in the diagnosis of benign reactive processes, certain infections, or metastatic disease, yet its accuracy in the diagnosis of lymphoma and primary malignancies as well as granulomatous infections remains controversial. Technical difficulties pose an obstacle for the effective differentiation of certain malignancies. Because the chemotherapeutic agents used for treatment of patients with lymphoma are selected on the basis of the specific type of lymphoma, excisional biopsy remains necessary for definitive subclassification of lymphoma in the majority of patients. Another limitation of FNA is insufficient material for histology, special stains, and culture, particularly when mycobacterial disease or other granulomatous infections are under consideration. These additional tests are often necessary to establish the diagnosis and select appropriate therapy. This is especially important for *M. tuberculosis* and nontuberculous mycobacteria, when establishing the species and the antitubercular medication resistance pattern is critical.

The following general guidelines are intended to suggest to the clinician circumstances in which excisional biopsy is appropriate:

1. Undiagnosed chronic lymphadenopathy of 1 month in adults, 3 months in children
2. Localized nonsuppurative lymphadenopathy without an accessible or apparent peripheral lesion
3. Enlarging undiagnosed lymphadenopathy after 2 weeks of observation
4. Nontender, matted to hard lymphadenopathy or a high clinical suspicion of neoplastic disease
5. Radiologic findings or systemic signs and symptoms suggesting granulomatous or lymphoproliferative disease when noninvasive tests are unrevealing
6. Positive tuberculin test in the absence of diagnostic pulmonary TB
7. New adenopathy in immunocompromised patients; otherwise, asymptomatic patients with HIV and PGL do not need biopsies
8. Lymphadenopathy in the setting of fever of undetermined origin
9. Persistently nondiagnostic or inconclusive FNA results.

Technique

Approximately half of all lymph node biopsies lead to a specific diagnosis. Careful attention to several rules maximizes the usefulness of the invasive diagnostic procedure.

1. Discuss the differential diagnosis with the surgeon, pathologist, and the microbiology laboratory ahead of time so that any special considerations (e.g., fixation, staining, and special culture media) can be identified.
2. Select the best site. Lymph nodes frequently involved in minor inflammatory processes, such as the inguinal and submandibular nodes, should be avoided. In the presence of generalized lymphadenopathy, the inferior or posterior cervical nodes are preferred. The second choice is the axillary node.
3. The largest node in a cluster of enlarged nodes should be removed.

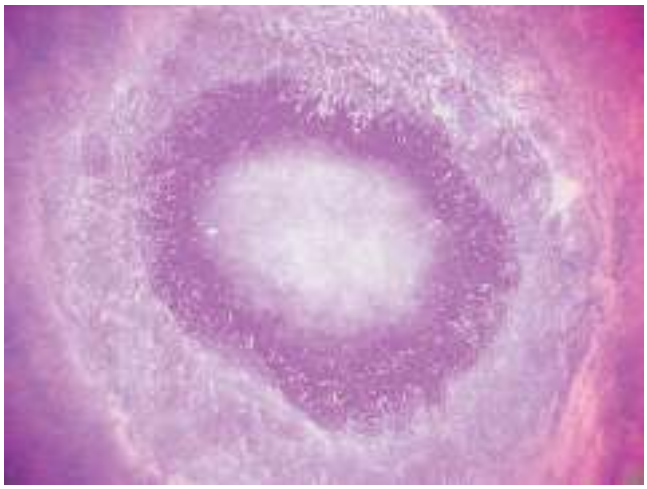

FIGURE 28.6 An example of a supraclavicular lymph node biopsy stained by hematoxylin and eosin (H&E). This is a granuloma, with extensive necrosis in the center, caused by *Mycobacterium tuberculosis*.

Courtesy of Theresa Liu-Dumlao, MD.

4. Remove nodes in their entirety with capsules intact. Dissect them, sending half of the specimen to the pathology laboratory and the other half to the microbiology laboratory for stains and culture of common pathogens, including mycobacteria, fungi, and other suspected organisms (see Figure 28.6).
5. Request that the pathologist make additional sections of the excised tissue if the node is abnormal but not diagnostic.
6. Consider a repeat biopsy and the excision of more tissue if the node is abnormal but not diagnostic and the clinical picture is unclear.

Interpretation

Entities discussed in this chapter that have a characteristic histologic pattern and for which a specific or strongly suggestive diagnosis can be made histologically are lymphoma, other neoplasms, TB, fungal disease, sarcoidosis, toxoplasmosis, and cat-scratch disease. Most noninfectious non-neoplastic disorders and most acute viral infections show nonspecific lymphadenitis or hyperplasia only. However, a significant number of patients with initially nondiagnostic lymph node biopsies and persistent lymphadenopathy will ultimately prove to have a serious underlying disease. If the biopsy is not initially diagnostic, it is essential to follow the patient carefully and consider repeat biopsy if adenopathy persists.

Suggested reading

Bogoch II, Andrews JR, Nagami EH, et al. Clinical predictors for the aetiology of peripheral lymphadenopathy in HIV-infected adults. *HIV Med*. 2013;14(3):182–186.

Ferrer R. Lymphadenopathy: Differential diagnosis and evaluation. *Am Fam Physician*. 1998;58(6):1313–1320.

Fijten GH, Blijham GH. Unexplained lymphadenopathy in family practice: An evaluation of the probability of malignant causes and the effectiveness of physicians' workup. *J Fam Pract*. 1988;27:373–376.

Libman H. Generalized lymphadenopathy. *J Gen Intern Med*. 1987;2:48–58.

Mason WH, Takahashi M. Kawasaki syndrome. *Clin Infect Dis*. 1999;28:169–185.

Morgenstern L. The Virchow-Troisier node: A historical note. *Am J Surg*. 1979;138:703.

Oksenhandler E, Duarte M, Soulier J, et al. Multicentric Castleman's disease in HIV infection: A clinical and pathological study of 20 patients. *AIDS*. 1996;10:61–67.

Pasternack M, Swartz M. Lymphadenitis and lymphangitis. In Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005: 1205–1211.

Scadden D, Muse V, Hasserjian R, Case records of the Massachusetts General Hospital. Case 30-2006. A 41-year old man with dyspnea, fever and lymphadenopathy. *N Engl J Med*. 2006;355: 1358–1368.

Tsang WYW, Chan JKC, Ng CS. Kikuchi's lymphadenitis: a morphologic analysis of 75 cases with special reference to unusual features. *Am J Surg Pathol*. 1994;18:219–231.

Section 5

Clinical syndromes: Respiratory tract

29

Bronchitis

Phillippa Poole and Mark Hobbs

Bronchial infections with viral and bacterial microorganisms cause considerable morbidity as well as economic costs incurred through healthcare and loss of productivity. These infections affect all age groups. An important consideration is whether or not an individual has underlying chronic lung disease, as that alters the etiology, clinical presentation, laboratory findings, and indications for therapy. In this chapter, we discuss acute infectious bronchitis in individuals without underlying chronic lung disease before outlining approaches when an individual has an acute exacerbation of a chronic lung disease such as asthma, chronic obstructive pulmonary disease (COPD), or non-cystic fibrosis bronchiectasis. Idiopathic pulmonary fibrosis is outside the scope of this chapter.

Acute bronchitis

Acute bronchitis is a common condition in both children and adults. It has been defined as "an acute illness, occurring in a patient without chronic lung disease, with symptoms including cough, which may or may not be productive and associated with other symptoms or clinical signs that suggest LRTI [lower respiratory tract infection] and no alternative explanation (e.g., sinusitis or asthma)." Most people will experience this at some time during their lives, and, in most cases, it is self-limiting and will not result in those affected seeking medical attention.

Nonetheless, this condition is a frequent cause of attendance to primary care providers and has been identified as a potential target for reducing unnecessary antibiotic prescribing in the community. Additionally, those who seek medical care for acute bronchitis, especially if this is frequent, should be considered for investigation into whether they have an underlying chronic airways disease or an alternative explanation for chronic or recurrent cough.

Typical symptoms of acute bronchitis are the acute onset of cough with or without sputum production or discoloration, often preceded by or associated with upper respiratory tract symptoms such as sneezing, a runny nose, or a sore throat. The cough often lasts for 7 to 10 days but may persist for several weeks. Fever and wheezing are frequently associated, as is a burning sensation in the tracheal area. Some patients may have focal signs on chest auscultation. Abnormality of vital signs or the presence of focal chest signs suggesting consolidation should prompt consideration of a chest radiograph to exclude pneumonia.

Young children under 2 years of age may present with the similar syndrome of bronchiolitis. In addition to the previously described symptoms and signs they may have a reduced oral intake and, in severe cases, may develop cyanosis or apnea. Treatment may involve the use of nebulized adrenaline or hypertonic saline.

Acute bronchitis is usually a viral illness but it may also be caused by bacterial species including *Mycoplasma pneumoniae, Chlamydophila pneumoniae*, or *Bordetella pertussis* among others. The relative frequency of implicated viral species varies with time, place, and patient age, with agents circulating in the community with epidemic-like characteristics. Common viral causes include influenza, rhinovirus, coronavirus, respiratory syncytial virus (RSV), human metapneumovirus, and parainfluenza virus. In young children with bronchiolitis, RSV and rhinovirus are the most common pathogens.

Extensive investigation for a cause of acute bronchitis is not usually necessary or beneficial. While molecular testing (polymerase chain reaction [PCR]) of upper respiratory tract secretions will often identify a viral pathogen, this finding seldom alters management. However, a positive result for a viral pathogen can provide some reassurance to the patient and clinician that antibiotics are not required. Additionally, testing for specific pathogens may be of use in selected cases, such as for epidemiological monitoring, determining whether inpatients may be co-housed in shared rooms, or investigating occupational health exposures. If whooping cough (pertussis) is suspected then confirmation of this diagnosis should be sought as it carries significant public health implications.

Antibiotic treatment is commonly requested by patients with acute bronchitis, with wide variation in prescribing practice for this condition. There is observational evidence that antibiotic use may lead to a statistically significant but clinically nonsignificant reduction in symptom duration. Given the typically benign, self-limited course of the illness and increasing rates of antibiotic resistance in common bacterial pathogens, antibiotic use for this condition should be avoided. Unnecessary treatment exposes the patient to the risk of an allergic reaction or adverse drug reaction such as gastrointestinal upset, and undermines their ability to self-manage this common condition in the future. Several methods exist for dealing with patients' expectations of receiving antibiotics. These include education or printed information outlining the uncertainties involved or the use of delayed prescriptions. This is where a prescription is given but is to be used only under specific criteria which point to bacterial infection. Where antibiotics are thought to be necessary, a macrolide or doxycycline is a suitable choice. Agents with a low barrier to resistance, such as quinolones, should generally be avoided. Symptomatic treatment may be offered, but there is little evidence it alters any outcomes. The use of neuraminidase inhibitors for influenza has become controversial due to publication bias in early trials. The benefits of these medications are unclear, but they may be appropriate in some patients with a consistent illness during an epidemic if the circulating strain is known to be susceptible and the patient has presented early in their illness.

Postviral bacterial pneumonia may occur following an episode of bronchitis and may be severe. Investigation for this with a chest radiograph should be considered in patients who have deteriorated or failed to settle as expected. If pneumonia is confirmed, antibiotic treatment is appropriate and further microbiologic investigation may be required. Consideration should be given to specific cover for *Staphylococcus aureus* in patients with post-influenza pneumonia.

Acute exacerbations of chronic airways disease

Disease definitions

Asthma and COPD are relatively common, with each affecting 5% to 10% of people worldwide. By definition, asthma is a reversible airways disease characterized by steroid-responsive airways inflammation. It occurs in people with a genetic predisposition to develop allergic reactions to aeroallergens. In contrast, COPD is a progressive disease with an enhanced inflammatory response in the airways and the lungs to noxious particles and gases, such as smoke from cigarettes or fires. COPD as a disease entity encompasses patients with emphysema and/or chronic bronchitis. The latter term describes a clinical syndrome of chronic cough or sputum for 3 months in 2 consecutive years and should not be considered indicative of chronic infection. Instead, excess mucus is produced by goblet cells which have become hypertrophic due to the abnormal inflammatory response.

Bronchiectasis (BX) is a rarer condition which results in daily production of large amounts of sputum. It has a number of causes, including infection. BX is characterized by irreversible dilation of parts of the bronchial tree resulting from destruction of the muscle and elastic tissue. The damaged airways are in turn more susceptible to mucus build-up and infection. The prevalence of BX is unknown but the condition is increasingly recognized in part because of greater use of chest CT scans.

It is increasingly recognized that chronic airways diseases may occur together: bronchial hyperreactivity may be a risk factor for COPD; there is now a defined asthma–COPD overlap syndrome; and BX may complicate severe asthma or COPD.

Common features of acute exacerbations

The role of infection in chronic airways diseases is discussed further later. All three are characterized by the occurrence of acute exacerbations (AEs) which may or may not be infective in origin. There are various definitions of AEs, but most are clinical, such as an acute worsening in the patient's shortness of breath, and/or cough, and/or sputum beyond the baseline, sufficient to warrant a change in management. AEs are more frequent in the winter months, suggesting that viruses play an important role.

The frequency of AEs increases with disease severity and correlates with poorer quality of life. In turn, AEs may have a role in accelerating decline in lung function and thus contribute to morbidity and premature mortality. In economic terms, the cost of AEs, especially hospitalizations, far exceeds that of stable chronic disease management. Costs amount to billions of dollars annually in the United States alone.

The pathologic and physiologic abnormalities of airways that predispose patients with chronic airways disease to bacterial infection include impaired mucociliary clearance, bronchial obstruction by abnormal secretions, and bronchoconstriction. In patients with COPD or BX, there are colonizing bacteria in the bronchial epithelium which may become pathogenic, as well as impaired host defenses. For example, there is reduction in bacterial phagocytosis, intracellular bactericidal activity by polymorphonuclear neutrophils, macrophage recruitment, and sputum immunoglobulin levels.

Although purulence of sputum is often equated with infection, the characteristic yellow to green color is caused by myeloperoxidase released from polymorphonuclear neutrophils and eosinophils,

reflecting the stasis of secretions in the bronchial tree. Microscopic assessment of the sputum by Gram stain and simple wet preparation reveal the two essential characteristics of bacterial infection: first, increased numbers of bacteria; second, increased bronchial neutrophilic inflammation. To be significant, the Gram stain must have bacteria in numbers >10 to 20 per oil immersion field, which is significantly above the average of 2 when a patient is stable. In addition, the majority of the inflammatory cells are neutrophils. This, when accompanied by an increase in the volume of sputum expectorated, reflects the outpouring of neutrophils into the bronchial lumen in response to bacterial infection.

Reducing the impact of acute exacerbations

To reduce morbidity and unnecessary healthcare utilization, including hospitalization, all patients with chronic airways disease at risk of AEs should use preventive approaches. Smoking cessation and influenza vaccination are essential preventive strategies for every patient with chronic airways disease. Pneumococcal vaccination has less of an evidence base to support its use, but is recommended every 5 years for those with COPD.

In airways diseases with copious sputum (usually chronic bronchitis or BX), sputum clearance techniques such as postural drainage and active cycle of breathing are safe and improve symptoms and quality of life. Physiotherapists have a role in teaching these techniques as well as in clearance of secretions in severe AEs, although this lacks evidence of effectiveness.

Education is an important component in the management of all chronic airways diseases. Patients should be taught to recognize early symptoms and seek escalation of therapy, including antibiotics where appropriate. Maintenance of physical fitness is critical. Many of these aspects are covered in pulmonary rehabilitation programs which have been shown to improve symptoms, quality of life, and healthcare utilization at all stages of COPD.

Exacerbation frequency in COPD has become an important end point in clinical trials. These have shown a reduction in AE of COPD (AECOPD) with inhaled corticosteroids and long-acting bronchodilators (β-agonists and antimuscarinics) and possibly by oral phosphodiesterase inhibitors, mucolytics, and bacterial extract immunostimulants. Combining a long-acting inhaled bronchodilator and corticosteroid leads to an even greater reduction in exacerbations. The mechanism is unclear but is likely anti-inflammatory or immunomodulatory. A current controversy is the finding that, overall, inhaled corticosteroids reduce AECOPD, yet are associated with an increase in the risk of pneumonia. The role of prophylactic antibiotics is discussed further later.

Symptoms of acute exacerbations

Patients with AEs of chronic airways disease present with similar respiratory symptoms. Among these are increased dyspnea, increased frequency and severity of cough, increased volume or purulence of sputum, or chest tightness. More general symptoms include malaise, anorexia, fatigue, chills, or fevers. A viral cause may be suspected when the patient has antecedent coryzal symptoms. The presence of rigors, high fevers, or pleuritic pain suggest coexistent pneumonia. Physical examination may reveal wheeze, accessory muscle use, decreased breath sounds, tachypnea, or tachycardia. Measures of airflow such as forced expiratory volume (FEV_1) or peak flow will be reduced from usual values. Chest radiography may assist in determining the presence of pneumonia or other conditions such as heart failure. Increasingly, patients with chronic lung diseases have other comorbidities that need to be incorporated into the differential diagnosis, such as heart failure, cancer, or pulmonary emboli.

The goals of therapy for an infective AE of chronic airways disease are the expeditious resolution of the acute infection without significant early relapses followed by a long infection-free post-treatment period. Implicit in these goals is the avoidance of further damage to the airways and lungs along with maintenance of functional status and quality of life.

Role of infection in asthma

The role of infection in causing asthma is controversial. RSV and rhinovirus are found more commonly in the airways of children with asthma, but this is not thought causal. On the other hand, viruses cause about 75% of asthma exacerbations. Most commonly, infection is with rhinovirus, but other common viral pathogens are influenza, RSV, coronavirus, human metapneumovirus, parainfluenza, or adenovirus. Bacterial infections play only a minor role. Compared with nonasthmatic controls, people with asthma infected with a common cold–causing rhinovirus show more severe lower respiratory symptoms and changes in airway physiology. This suggests the presence of abnormal airways responses to infection, such as defective interferon responses to rhinovirus. The bacteria *C. pneumoniae* and *M. pneumoniae,* primarily recognized as causative agents in "atypical" community-acquired pneumonia, may play a role in asthma.

Current treatment options for AE of asthma are limited and have developed little in recent years. Generally they consist of increased inhaled bronchodilator therapy and anti-inflammatory treatment with inhaled or oral corticosteroids. Antibiotics are reserved for situations where there is strong evidence of a bacterial lung infection. Macrolides have been shown to have anti-inflammatory, bactericidal, and possibly antiviral activity, making them attractive agents in asthma. However, clinical trials of macrolides in either acute or chronic asthma have yielded inconsistent results. Newer antiviral approaches such as either vaccination against or enhancement of the host response to respiratory viruses are under consideration.

Role of infection in COPD

An AECOPD is thought to occur as a result of the increased inflammatory burden in the airways from interactions among host, viruses, bacteria, and/or air pollution. Infections (viral, bacterial, or other) account for the majority of AECOPD, with other causes being air pollution or comorbidities such as heart failure, pneumonia, or pulmonary embolism. In a third of AECOPD no cause is found. During an infective AECOPD, the airways exhibit an increase in neutrophils, products of neutrophil activation, and oxidative stress,

some of which may result in an increased systemic acute phase response.

Depending on the study, viruses account for 12% to 48% of AECOPD, with the common viral pathogens being influenza, parainfluenza, rhinovirus, adenovirus, coronavirus, and RSV. In some AECOPD, both viruses and bacteria are found. Where viruses are detected, the AECOPD is more severe and prolonged than when they are not detected.

The same bacteria seen in an AECOPD may colonize the airways of more than half of patients while they are in a stable state. Features that suggest pathogenicity include a pure, heavy growth of organism on sputum culture or a change in organism from one known to be present in the stable state. The four most common bacterial organisms found in COPD patients and in AECOPDs are *Streptococcus pneumoniae*, *Haemophilus influenzae, H. parainfluenzae,* and *Moraxella catarrhalis*. In very severe COPD, *Pseudomonas aeruginosa* is an important consideration, particularly in patients with frequent hospitalizations, more than four courses of antibiotics per year, recent oral steroid use, or who have not been vaccinated against influenza. The atypical organisms—*Chlamydophila*, *Legionella*, and *Mycoplasma*—do not play a specific causative role in AECOPD.

In principle, the identification of a specific bacterial etiology in AECOPD allows for selection of appropriate therapy and avoids the costs and adverse effects associated with the use of unnecessary medications, including the emergence of resistant strains. Obviously, antimicrobials are not indicated for any AECOPD that is not bacterial in nature. A Cochrane review of antibiotics for AECOPD found that currently available antibiotics, as a group, do not reduce treatment failure in mild exacerbations, whereas they do in severe AECOPD. There is no evidence of an effect on mortality or length of hospital stay, with almost no data on patient-reported outcomes.

In practice, the decision to treat with antibiotics is often based on clinical and not microbiologic grounds. Sputum cultures and antibiotic sensitivity testing are rarely indicated to guide empirical treatment for mild AECOPD in the community. In part this is due to the delay in getting a helpful result. Another problem is the difficulty in obtaining adequate sputum samples, free of saliva, that reflect the bronchial pathology. A final problem is the cost and availability of the test.

In contrast, a sputum culture and antibiotic sensitivity testing should be considered if the patient is having frequent AECOPDs treated with antibiotics; if the AECOPD is severe, especially where artificial ventilation is needed; or if the AECOPD does not respond to the initial choice of antibiotic. If gram-negative bacilli (other than *Haemophilus*-like organisms) or gram-positive cocci resembling staphylococci are noted on Gram stain, culture and sensitivity should be performed. There is increasing interest in procalcitonin-guided antibiotic therapy in AECOPD, but whether it offers clinical benefit is uncertain.

A useful heuristic is to treat empirically with antibiotics those AECOPDs which have no other cause and that have all three of the following: increased dyspnea, increased volume, and increased purulence of sputum. In addition, antibiotics are recommended for most exacerbations in those with severe COPD.

Antibiotics for AECOPD should be chosen with the following in mind:

- coverage of all common pathogens in AECOPD;
- local resistance patterns;
- risk factors for *P. aeruginosa;*
- route of delivery, with oral preferred where possible;
- a dosage regimen that favors compliance;
- minimization of undesirable side effects, interactions with other medications, and costs;
- duration appropriate to treat the infection. This is usually 5 to 7 days unless there is coexistent underlying disease such as bronchiectasis.

Empirical oral treatments for infective AECOPDs suggested by global guidelines come from most of the major antimicrobial classes (i.e., penicillins, tetracyclines, quinolones, macrolides, cephalosporins, and sulfonamides). Oral antibiotics should suffice in most cases without pneumonia. The increase in β-lactamase-producing *H. influenzae* and *M. catarrhalis* and the rising incidence of penicillin-resistant *S. pneumoniae* have forced a shift to newer antibiotics or combinations, such as a penicillin with a β-lactamase inhibitor such as clavulanic acid. Of the new quinolones, moxifloxacin appears to have the best efficacy and safety profile. If pseudomonas is suspected, a quinolone is the antibiotic of choice. In an AECOPD, parenteral therapy should only be needed if the patient is severely unwell. Switching from parenteral to oral therapy should be considered as early as possible as it is cost-effective and permits earlier discharge from hospital. Antiviral therapy is not indicated for usual AECOPD.

In the United States, by far the most commonly used antibiotic for bronchitis is azithromycin, followed by amoxicillin and clarithromycin. This is despite concerns about the cardiotoxicity of azithromycin in patients at high risk of QT prolongation. Macrolide resistance in *S. pneumoniae* is a growing concern, with prevalence proportional to the amount of macrolide use in the population.

Thirty years ago the use of prophylactic antibiotics for chronic bronchitis was common, including cyclical treatment, but concerns about effectiveness and antibiotic resistance led to a decline in the use of this approach. Recently there has been renewed interest in whether prophylactic antibiotics prevent AECOPD. In part this is due to the observation that, in addition to antibacterial effects, macrolides may be anti-inflammatory and immunomodulatory. Both continuous and pulsed approaches (several days per week or month) have been trialed. In one placebo-controlled study of 250 mg/d azithromycin for a year in more than 1,000 patients with at least moderate COPD, there was a 40% reduction in the number of patients with an AECOPD and a 20% reduction in the total number of AECOPDs. However, this benefit came at an increased risk of adverse effects including hearing impairment and an increase in antibiotic resistance in the colonizing organisms. A recent Cochrane systematic review found no data on efficacy of prophylactic antibiotics used for >1 year. Because of ongoing safety concerns to both individual patients and to society, prophylactic antibiotics in COPD should be reserved for the small portion of

patients with moderate to severe COPD and high morbidity from frequent bacterial AECOPD.

Role of infection in bronchiectasis

BX is the end result of a number of disease processes, several of which are noninfective, such as cystic fibrosis (CF), cilial or connective tissue diseases, immune deficiency syndromes, or abnormal immunologic responses to *Aspergillus* spp. Infection does play a role in the development of some cases of BX (e.g., recurrent respiratory infections in childhood including with respiratory viruses, *Bordetella pertussis,* or tuberculosis).

Regardless of the cause, few studies have assessed the microbiologic pattern of airway colonization in established BX. Bacteria found in the airways during stable BX include *S. pneumoniae*, *H. influenza*e, *M. catarrhalis, S. aureus*, gram-negative enteric bacilli, *Mycoplasma pneumoniae*, and nontuberculous mycobacteria. *P. aeruginosa* is particularly a problem in BX of early onset or where there is severely reduced lung function. Colonization with *P. aeruginosa* is associated with an increased rate of exacerbations and hospitalizations, and with an increased risk of death. Therefore some respiratory physicians will attempt to eradicate new *P. aeruginosa* colonization when detected.

Unfortunately, little is known about the microbiologic etiology of AE in BX (AEBX). Despite the lack of evidence, general recommendations for AEBX have been made, which include:

- considering periodic surveillance of colonization;
- providing antibiotic treatment for patients with exacerbations;
- obtaining a sputum sample for culture before starting antibiotic treatment in most cases and particularly in those requiring hospitalization;
- for empirical antibiotic treatment, stratifying patients according to the potential risk of *Pseudomonas* spp. infection;
- adjusting or modifying empirical antibiotics according to sputum culture results.

Prolonged antibiotic therapy has shown only a small benefit in modifying the outcome of purulent BX. Nebulized antibiotics are not recommended for non-CF BX, in contrast to the situation with CF BX.

As in COPD, there is interest in the use of prophylactic treatment of patients with BX using either continuous or pulsed regimens, with the main aim to reduce exacerbation frequency. While this approach does reduce exacerbations significantly in BX, it has no effect on lung function decline or quality of life. Moreover, there is the potential for harm through adverse effects and in terms of driving antibiotic resistance, as discussed earlier in the COPD section. At present, this approach is not recommended in routine practice.

The isolation of nontuberculous mycobacteria from the patient with bronchiectasis may reflect either colonization or active infection. Depending on the species identified and imaging appearances, further investigation and management may be required, but this topic is outside the scope of this chapter.

Suggested reading

Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365:689–698.

Arroll B, Kenealy T, Kerse N. Do delayed prescriptions reduce antibiotic use in respiratory tract infections? A systematic review. *Br J Gen Pract*. 2003;53:871–877.

Chodosh S. Treatment of acute exacerbations of chronic bronchitis: State of the art. *Am J Med*. 1991;91:87s–92s.

The Cochrane Database of Systematic Reviews. http://www.cochrane.org/cochrane-reviews/.

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. www.ginasthma.org.

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. https://goldcopd.org/.

Mathioudakis AG, Chatzimavridou-Grigoriadou V, Corlateanu A, Vestbo J. Procalcitonin to guide antibiotic administration in COPD exacerbations: A meta-analysis. *Eur Respir Rev*. 2017:26:143. doi:10.1183/16000617.0073-2016.

Singanayagam A, Joshi PV, Mallia P, Johnston SL. Viruses exacerbating chronic pulmonary disease: The role of immune modulation. *BMC Med*. 2012;10:27. doi:10.1186/1741-7015-10-27.

Wedzicha JA, Seemungal TAR. COPD exacerbations: Defining their cause and prevention. *Lancet*. 2007;370:786–796.

Wenzel RP, Fowler AA. Clinical practice: Acute bronchitis. *N Engl J Med*. 2006;355:2125–2130.

Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): A randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;380:660–667.

Woodhead M, Blasi F, Ewig S, et al.; Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections–full version. *Clin Microbiol Infect*. 2011;17(Suppl 6):E1–E59. doi:10.1111/j.1469-0691.2011.03672.x.

30

Croup, supraglottitis, and laryngitis

Irmgard Behlau

Croup

Croup is a clinical syndrome characterized by a seal-like barking cough, hoarseness, inspiratory stridor, and often some degree of respiratory distress. The term *croup* is usually used to refer to acute laryngotracheobronchitis. Other croup-like syndromes can include spasmodic croup and bacterial tracheitis (Table 30.1). Other potential infectious causes of stridor include supraglottitis (epiglottitis), peritonsillar abscess, retropharyngeal abscess, and rarely, diphtheria, whereas noninfectious etiologies include angioneurotic edema, foreign-body obstruction, hemangioma, trauma, neoplasm, subglottic stenosis, or extrinsic compression. Croup is primarily a disease of children between the ages of 1 to 6 with peak incidence between 6 months and 3 years. The parainfluenza viruses (1, 2, and 3) are the most frequent cause with outbreaks occurring predominantly in the winter months. Other occasional causes include respiratory syncytial virus (RSV), influenza, and adenovirus with rare cases secondary to *Mycoplasma*, *Corynebacterium diphtheriae*, and herpes simplex virus (HSV). In adults, the causes are also predominantly viral, including reported cases of influenza, parainfluenza, RSV, HSV, and cytomegalovirus (CMV). In either children or adults, most likely secondary bacterial infections with *Haemophilus influenzae* type b (Hib), staphylococci, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* can be seen.

Croup usually follows a relatively mild upper respiratory infection. Its onset is commonly abrupt and occurs in the late evening and night. Viral infection with associated inflammation of the nasopharynx spreads inferiorly to the respiratory epithelium of the larynx and trachea. The subglottic region in children is normally narrow and surrounded by a firm ring of cartilage. Small swelling of this narrow subglottic area will significantly restrict air flow and produce audible inspiratory stridor, while the impairment of the mobility of the vocal cords will produce hoarseness.

Rapid, objective, and calm assessment of severity must be done to determine management and without respiratory compromise. The presence of chest wall retractions and stridor at rest are most critical (Table 30.2). Anteroposterior radiologic examination of the soft tissues of the neck (with medical monitoring) may be useful when the diagnosis is in question. The classic steeple sign is produced by the cone-shaped narrowing of the proximal 1-cm subglottic area of the trachea, at the conus elasticus to the level of the true vocal cords. It is produced by edema with elevation of the tracheal mucosa and the loss of the normal lateral convexities (shoulders) of the air column (Figure 30.1). Direct visualization of the airway can be attempted if the symptoms are not typical and the child is stable. If intubation appears imminent or there is a strong suspicion of epiglottitis, this should be performed under anesthesia. In croup, the supraglottic region appears normal.

Therapy

Management includes corticosteroids, nebulized budesonide, and nebulized epinephrine. Oxygen or heliox are often used as supportive treatment. No clear data exist on the benefits of mist or humidified air.

TABLE 30.1 **COMPARISON OF CROUP-LIKE SYNDROMES**

Characteristic	Spasmodic croup	Laryngotracheobronchitis	Bacterial tracheitis	Supraglottitis
Age range	6 mo–3 yr	0–6 yr (peak, 6 mo–3 yr)	1 mo–6 yr	Infants ≤2 mo, older children, and adults
Etiology	? Viral ? Airway reactivity	Parainfluenza virus (1, 2, 3) Influenza Respiratory syncytial virus Adenovirus	*Staphylococcus aureus* *Haemophilus influenza* *Corynebacterium diphtheriae*	*Haemophilus influenzae* (Hib/non-b) *Streptococcus pneumonia* Group A streptococcus *Haemophilus parainfluenzae*
Onset	Sudden	Insidious	Rapid deterioration	Sudden
Clinical manifestations	Afebrile Nontoxic Barking cough Stridor Hoarse	Low-grade fever Nontoxic Barking cough Stridor Hoarse	High fever Toxic Barking cough Stridor Hoarse	High fever Toxic Nonbarking cough Muffled voice Drooling Dysphagia Sitting, leaning forward
Endoscopic findings	Pale mucosa Subglottic swelling	Deep-red mucosa Subglottic swelling	Deep-red mucosa Copious tracheal secretions	Cherry-red epiglottis Arytenoepiglottic swelling
Complete blood count, differential	Normal	Mild leukocytosis Lymphocytosis	Normal to mild leukocytosis Marked Bandemia	Marked leukocytosis Bandemia
Radiographic findings	Subglottic narrowing	Subglottic narrowing	Subglottic narrowing Irregular tracheal border	Large epiglottis Thick arytenoepiglottic folds
Therapy	Mist Calm ?Racemic epinephrine ?Steroids	Corticosteroids Racemic epinephrine Nebulized budesonide Intubation (if necessary)	Intubation Antibiotics	Intubation Antibiotics
Response	Rapid	Transient	Slow (1–2 wk)	Variable (hours–days)
Intubation	Rare	Occasional	Usual	Usual

Analgesics improve sore throat and overall comfort. Antitussives, decongestants, and "prophylactic" antibiotics are not beneficial.

Due to the sustained anti-inflammatory effects of corticosteroids, they have been shown to improve the status of not only severe croup but also mild to moderate croup. Dexamethasone in doses of 0.15 to 0.6 mg/ kg has been shown to be beneficial and decreases the need for hospitalizations and unscheduled medical visits even in mild croup. Oral, intramuscular, and intravenous routes of administration are all effective, with nebulized dexamethasone possibly less effective. Nebulized budesonide, 2 mg, has been shown to be as effective as dexamethasone but is often reserved for patients with intractable vomiting or for simultaneous administration with epinephrine in severe respiratory distress because it is substantially more expensive and more difficult to administer. The combination of oral dexamethasone and nebulized budesonide is no better than either alone. For the management of outpatient croup, oral prednisolone, 2 mg/kg/day as two divided doses per day, may be considered as an alternative, but comparison studies have been limited to oral dexamethasone.

Owing to the rapid onset of action, the use of nebulized racemic epinephrine has markedly reduced the need for intubation, even in hospitalized patients, to less than 2%. L-epinephrine (1:1000) is as effective as racemic epinephrine. Improvement occurs within minutes, but symptoms can recur within 2 hours; therefore, patients must be observed in the emergency room for 3 hours.

The administration of oxygen should be reserved for children with significant respiratory distress and hypoxia (oxygen saturation on room air ≤92%). Heliox, a lower density gas that is a mixture of oxygen (20%–30%) and helium (70%–80%), has been proposed to help reduce the need for intubation in the severely ill child by improving laminar gas flow through a narrowed airway. There remains insufficient evidence to advocate its general use.

If intubation is deemed necessary, an endotracheal tube one to two sizes smaller than would be used for the same-size healthy child will be needed to prevent pressure necrosis and resulting subglottic stenosis. For those children who appear to have a secondary bacterial infection, antibiotic therapy similar to that recommended for epiglottitis should be considered to treat the possibility of a secondary

TABLE 30.2 **RECOMMENDED TABLE ALGORITHM FOR THE MANAGEMENT OF CROUP (LARYNGOTRACHEOBRONCHITIS)**

Condition	Treatment
Mild	
No stridor	Analgesics, hydration as needed
No chest wall retractions	Single dose of oral dexamethasone (0.6 mg/kg body weight)
No respiratory distress at rest	Educate parents (illness, when to seek medical assessment)
Moderate	
Stridor at rest	Above including oral dexamethasone, 0.6 mg/kg
Mild chest wall retractions	Observe in emergency room
No agitation or significant respiratory distress	If improved with no stridor or retractions, educate, home If no or minimal improvement by 4 h, hospitalization
Severe	
Stridor may decrease with worsening airway obstruction	Nebulized racemic epinephrine 2.25% (0.5 mL/2.5 mL saline) or L-epinephrine 1:1000 (5 mL), may repeat
Significant respiratory distress	Oral or parenteral dexamethasone 0.6 mg/kg, may repeat
Severe chest wall retractions	If contraindications to oral medication, consider nebulized budesonide 2 mg with epinephrine
Agitation or lethargy	
Decreased air movement	Humidifed oxygen (≤92% room air 0_2 sat, consider heliox)
Possibly cyanosis	ICU care, intubation as necessary

bacterial process. Table 30.2 outlines therapy recommendations depending on the clinical state of the patient.

Acute Supraglottitis (Epiglottitis)

Supraglottitis is characterized by inflammation and edema of the supraglottic structures, including the epiglottis, arytenoepiglottic folds, arytenoids, and false vocal cords; paradoxically, the epiglottis may be spared.

In children, acute supraglottitis is typically characterized by a fulminating course of severe sore throat, high fever, dysphagia, drooling, low-pitched inspiratory stridor, and airway obstruction, which, if left untreated, can lead to death. The child appears toxic and prefers an airway-preserving posture—sitting upright, jaw protruding forward, while drooling. In adults, the presentation is more variable; most adults have mild illness with a prolonged prodrome. In immunocompromised patients, there may be a paucity of physical findings.

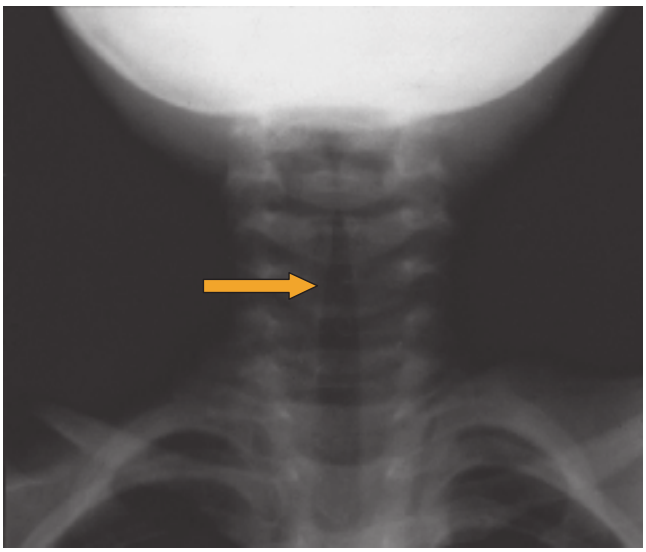

FIGURE 30.1 The "steeple sign" of croup. Anteroposterior radiograph of the upper airway (*arrow*) of a patient with croup.

Courtesy of Drs. A Weber and HD Curtin, Department of Radiology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

Definitive diagnosis is made by examination of the epiglottis and supraglottic structures. No attempt should be made to visualize the epiglottis in an awake child; therefore, a severely ill child must be examined in the operating room at the time of control of the airway. In children, the epiglottis is typically fiery red and extremely swollen, but occasionally the major inflammation involves the ventricular bands and arytenoepiglottic folds, and the epiglottis appears relatively normal. In adults, awake indirect laryngoscopy may be performed, but only when it is possible to establish an artificial airway. In adults, the supraglottic structures may appear pale with watery edema. If indirect laryngoscopy is unavailable, lateral neck radiographs are also useful for evaluating supraglottitis (Figure 30.2), but they are not as sensitive and should never delay protecting the airway. The classic appearance is of an enlarged epiglottis bulging from the anterior wall of the hypopharynx with straightening of the cervical spine from the usual mild lordosis. Computed tomography (CT) imaging may help to diagnose complicating conditions such as a parapharyngeal abscess (Figure 30.3).

The epidemiology of acute supraglottitis has changed dramatically since the introduction of the Hib vaccines in the mid to late 1980s. Supraglottitis, which most commonly had affected children 2 to 7 years of age, is now rarer in young children than adults, is primarily a disease of older children and adults, and is increasingly being caused by other microbial pathogens. The incidence of invasive Hib has decreased more than 99% compared to the pre-vaccine era. The organisms typically involved, in addition to Hib, are *S. pneumoniae*, *Staphylococcus aureus*, β-hemolytic streptococci, *H. influenzae* type non-b, *Haemophilus parainfluenzae*, rarely in adults *Pasteurella multocida*, and possibly increasing reports of *Neisseria meningitidis* since 1995. There are very rare reports of children developing Hib epiglottitis despite vaccination. The role respiratory tract viruses play as primary pathogens remains unclear. There have been reports of HSV type 1 and varicella as primary pathogens in immunocompromised

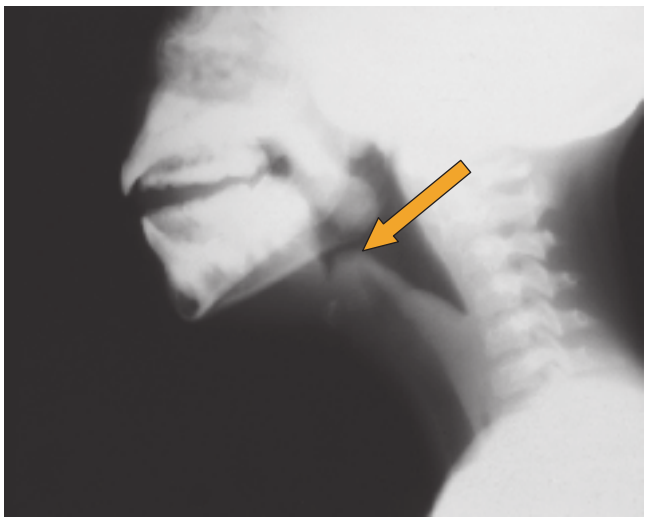

FIGURE 30.2 The "thumb sign" of supraglottitis. Lateral radiograph of the neck in a patient with supraglottitis; arrow indicates thickened epiglottitis.

Courtesy of Drs. A Weber and HD Curtin, Department of Radiology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

hosts. Noninfectious causes include thermal and corrosive injury, lymphoproliferative disorders, and graft-versus-host disease.

Therapy

Treatment of acute supraglottitis is directed at establishing an airway and administering appropriate antibiotics. Children with epiglottitis should routinely have an artificial airway established; observation cannot be routinely recommended because the mortality rate is 6% to 25% and increases to 30% to 80% for those who develop obstruction. Most deaths occur within the first hours after arrival. The use of a "prophylactic airway" has reduced the mortality rate to less than 1%. The management of the airway in adult supraglottitis reflects the greater variability of clinical presentation and course. It has a range of mortality rates from 10% to 32%. Vigilant airway monitoring and continuous staging are needed for adults whose disease may progress to respiratory compromise. A formal written "acute airway obstruction protocol" should be followed. Factors associated with airway obstruction include symptomatic respiratory difficulty, stridor, drooling, shorter duration of symptoms, enlarged epiglottis on radiograph, and *H. influenzae* bacteremia.

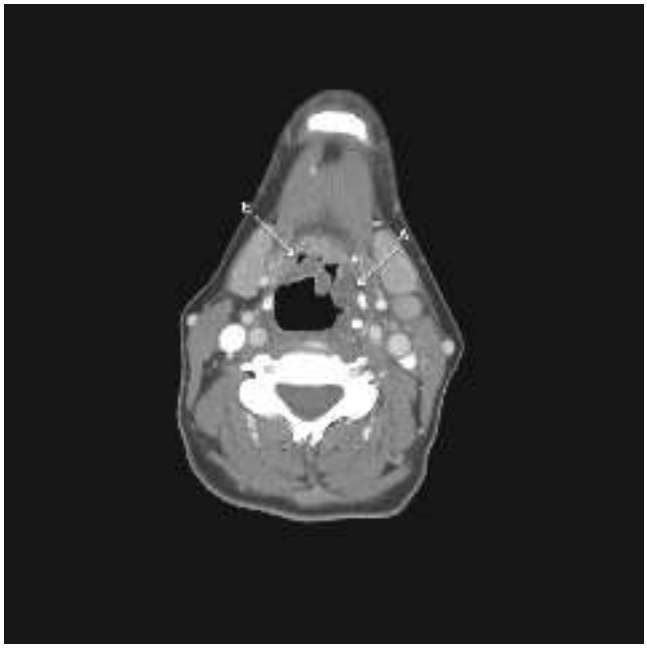

FIGURE 30.3 CT scan of the neck in an adult with acute supraglottitis due to group A β-hemolytic streptococci. Findings include an edematous epiglottis (E), narrowing of the larynx, and also a hypoattenuating area (A) at the level of the hyoid body suggestive of early abscess formation.

Courtesy of Drs. RL Reichle and PA Rogoff, Department of Radiology, Mount Auburn Hospital, Cambridge, Massachusetts.

An endotracheal tube is preferred over a tracheotomy for the following reasons: (1) ease of removal of the tube 2 to 3 days after the edema has subsided, thereby shortening the hospital stay; (2) no surgery; and (3) mortality and complication rates equal to or lower than those for tracheotomy.

Antibiotic therapy should include coverage for *H. influenzae*, *S. pneumoniae*, group A β-hemolytic streptococci, other streptococci, *H. parainfluenzae*, and *S. aureus*. Second- and third-generation cephalosporins are first-line agents. Pediatric dosages are intravenous cefuroxime, 150 mg/ kg, 3 doses per day; cefotaxime, 150 mg/ kg, 3 doses per day; ceftriaxone, 50 mg/ kg/day; or ampicillin–sulbactam, 200 to 400 mg/ kg, at 4 doses per day. The recommended adult dosages are intravenous ceftriaxone, 2 g/ day; cefotaxime, 2 g every 4 to 8 hours; or ampicillin/sulbactam 1.5 to 3 g every 6 hours. Antibiotic therapy should be continued for 10 to 14 days. In patient populations with a significant prevalence of community-acquired methicillin-resistant *S. aureus* (MRSA) or penicillin-resistant *S. pneumoniae*, clindamycin, 30 to 40 mg/kg divided in 3 doses (max 2400 mg/day) or vancomycin, 40 to 60 mg/kg/ day in 3 to 4 doses in children or 2 g/ day in adults adjusted for renal function should be considered. Duration of therapy is usually 7 to 14 days, depending on patient response.

Steroids are commonly used for supraglottitis to theoretically decrease inflammation. There has been no evidence for any significant benefit, and in adults, there is no indication that steroids prevent the need for airway intervention. With epiglottitis being so uncommon and therefore all studies being small, it will be difficult to evaluate any beneficial role. The use of steroids remains controversial.

Prevention

Prophylaxis is indicated for supraglottitis secondary to Hib. Rifampin, 20 mg/ kg, not to exceed 600 mg/day, daily for 4 days is recommended for: (1) all household contacts (except pregnant women) when there is a child younger than 12 months irrespective of vaccine status or there is a child younger than 4 years of age with incomplete vaccination; (2) day-care and nursery school classroom contacts (including adults) (a) if two or more cases of invasive disease have occurred within 60 days and unvaccinated or incompletely vaccinated children attend or (b) with one case and susceptible children 2 years or younger who attend for 25 hours or more per week (susceptible children should be vaccinated); if

children are older than 2 years, rifampin prophylaxis need not be given irrespective of vaccination status. (3) The patient should receive prophylaxis before discharge if treated with ampicillin or chloramphenicol to prevent reintroduction of the organism into the household. Prophylaxis is not needed for those treated with the aforementioned recommended cephalosporins because they eradicate Hib from the nasopharynx.

Since the introduction of conjugated vaccines for infants beginning at 2 months of age, the incidence of supraglottitis resulting from Hib in this age group has declined by 99%, along with other invasive forms of Hib. There have been isolated rare reports of supraglottitis in children who have been vaccinated, but in general, we are seeing a near-eradication of Hib supraglottitis in young children. Supraglottitis caused by Hib occurs now primarily in undervaccinated children, infants too young to have completed the primary series of vaccinations, and older children and adults who have never been immunized.

Laryngitis

The larynx rests in the hypopharynx and consists of: (1) the supraglottic larynx, which includes the laryngeal inlet formed by the epiglottis anteriorly and the arytenoepiglottic folds bilaterally merging inferiorly into false cords, and (2) the glottic larynx, which consists of the true vocal cords.

Acute laryngitis often presents with hoarseness, odynophagia, and localized pain, which may also be referred and manifests as otalgia. Obstruction of the airway is uncommon in adults but more common in young children, especially if associated with tracheal inflammation as in croup, and must be distinguished from acute supraglottitis. Examination of the larynx reveals erythema, edema, secretions, and occasionally superficial mucosal ulcerations. The presence of exudate or membrane on the pharyngeal or laryngeal mucosa should raise the suspicion of streptococcal infection, mononucleosis, or diphtheria; granulomatous infiltration may be compatible with tuberculosis, sarcoidosis, fungal infection, or syphilis.

The respiratory viruses such as influenza virus, parainfluenza virus, rhinovirus, and adenovirus are most often isolated in cases of laryngitis (90%). *M. catarrhalis* has been isolated from the nasopharynx of 50% to 55% and *H. influenzae* from 8% to 15% of adults with laryngitis. It remains unclear whether these may represent a secondary bacterial invasion. Group A and G streptococci, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* have also been associated with acute laryngitis. Laryngeal diphtheria is very rare and usually results from extension of pharyngeal involvement. It may occur in previously immunized persons.

Fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, and cryptococcosis may cause laryngitis. Candidiasis is most often seen in immunosuppressed patients. *Treponema pallidum*, HSV, and herpes zoster virus may also be causes of acute laryngitis. Laryngeal tuberculosis is very rarely seen in the United States since the advent of effective antimycobacterial therapy. It is associated with a large tuberculous load, and patients often have very active pulmonary involvement. Sarcoidosis, Wegener's granulomatosis, and rhinoscleroma may be considered causes of laryngitis.

Therapy

Because most cases of acute laryngitis are viral in etiology and self-limited, treatment usually consists of resting the voice and inhaling moistened air. The role of empiric antibiotic therapy of laryngitis has been examined by prospective double-blinded studies. Penicillin V had no effect on the clinical course. Patients treated with erythromycin (0.5 g twice a day for 5 days) had a marked reduction of *M. catarrhalis* carriage in the nasopharynx and reported a significant improvement of subjective voice disturbances after 1 week and cough after 2 weeks; however, there was no difference in laryngoscopic examination and voice evaluation. Because acute laryngitis in adults is self-limiting and subjective symptoms are spontaneously reduced after 1 week in most cases, empiric antibiotic treatment does not seem warranted as a general policy.

Antimicrobial therapy is indicated only in those patients with a bacterial infection or super-infection; therapy is directed toward the believed causative agent. Usual duration is for 10 to 14 days. The use of corticosteroids should be avoided due to their ability to mask vocal cord pathology.

Immunosuppressed patients who present with hoarseness or patients whose hoarseness has persisted longer than 10 to 14 days should have a laryngoscopic examination to exclude other more atypical causes such as HSV, bacterial, fungal, mycobacterial, and malignant etiologies of laryngitis.

Suggested Reading

Alberta Clinical Practice Guideline Working Group. Guideline for the diagnosis and management of croup. Alberta Medical Association (Canada). 2008 Update. Available at: www.topalbertadoctors.org/cpgs/?search=croup&x=0&y=0 (accessed November 4, 2013).

Cherry JD. Clinical practice. Croup. *N Engl J Med*. 2008;358(4):384–391.

Hartling L, Fernandes RM, Bialy L, *et al.* Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis. *BMJ*. 2011;342:d1714.

Ito K, Chitose H, Koganemaru M. Four cases of acute epiglottitis with a peritonsillar abscess. *Auris Nasus Larynx*. 2011;38(2): 284–288.

Mayo-Smith MF, Hirsch PJ, Wodzinski SF, *et al.* Acute epiglottitis. An 18-year experience in Rhode Island. *Chest*. 1995;108(6):1640–1647.

Riffat F, Jefferson N, Bari N, McGuinness J. Acute supraglottitis in adults. *Ann Otol Rhinol Laryngol*. 2011;120(5):296–299.

Russell KF, Liang Y, O'Georman K, *et al*. Glucocorticoids for croup. *Cochrane Database Syst Rev*. 2011;1(1):CD001955.

Shah RK, Roberson DW, Jones DT. Epiglottitis in the *Hemophilus influenzae* type B vaccine era: changing trends. *Laryngoscope*. 2004;114(3), 557–560.

31

Atypical pneumonia

Thomas M. File, Jr.

The term "atypical pneumonia" was first coined more than 60 years ago to describe cases of pneumonia caused by an unknown agent(s) and which appeared clinically different from pneumococcal pneumonia. It was initially characterized by constitutional symptoms often with upper and lower respiratory tract symptoms and signs, a protracted course with gradual resolution, the lack of typical findings of consolidation on chest radiograph, failure to isolate a pathogen on routine bacteriologic methods, and a lack of response to penicillin therapy. In the 1940s an agent that was believed to be the principal cause was identified as *Mycoplasma pneumoniae.* Subsequently other pathogens have been linked with "atypical pneumonia" because of similar clinical presentations, including a variety of respiratory viruses, *Chlamydia pneumoniae, C. psittaci,* and *Coxiella burnetii*. Less common etiologic agents associated with atypical pneumonia include *Francisella tularensis, Yersinia pestis* (plague), and the sin nombre virus (Hantavirus pulmonary syndrome), although these agents are often associated with a more acute clinical syndrome. In addition, although presently exceedingly rare, inhalation anthrax is included in part because of the concern for this pathogen as an agent of bioterrorism. Finally, pneumonia caused by *Legionella* spp., albeit often more characteristic of "pyogenic" pneumonia, is also included since it is not isolated using routine microbiologic methods.

Although the original classification of atypical and typical pneumonia arose from the perception that the clinical presentation of patients was different, recent studies have shown that there is excessive overlap of clinical manifestations of specific causes that does not permit empiric therapeutic decisions to be made solely on this basis. Thus, the designation of "atypical pneumonia" is controversial in relationship to scientific and clinical merit and many authorities have suggested that the term "atypical" be discontinued. However, the term remains popular among clinicians and investigators and remains prevalent in recent literature regardless of its clinical value. Moreover, options for appropriate antimicrobial therapy for the most common causes are similar, and this is considered by some to provide justification to lump these together.

M. pneumoniae, *C. pneumoniae,* and *Legionella pneumophila* are the most common causes of atypical pneumonia. Results of recent studies indicate they cause from 10% to 30% (depending on population assessed and methodology of diagnosis) of cases of community-acquired pneumonia (CAP). However, these pathogens have not been identified often in clinical practice because until recently there have not been specific, rapid, or standardized tests for their detection. The "other" causes of atypical pneumonia occur with much less frequency.

Treatment of atypical bacterial in the spectrum of CAP has been controversial and is related to several issues, including the relevance of terminology, imprecise diagnostic methods at present, and perceived contradictory results of published evidence. However, limitations of clinical trial methodology limit our interpretation of the actual benefit of providing coverage since many atypical pneumonias are eventually self-limited. Studies evaluating the time to clinical recovery and the use of earlier end points for evaluation suggest that appropriate therapy provides a benefit if an atypical pathogen is a pathogen. Recent critical reviews of the evidence for therapy of atypical pneumonia concluded that available evidence does support treatment.

Clinical manifestations

Although the diagnosis of these specific pathogens is difficult to establish on clinical manifestations alone, there are several generalizations which may be helpful.

Mycoplasma pneumoniae

M. pneumoniae is a common cause of respiratory infections that range from unapparent infection, URI, and, tracheobronchitis to pneumonia. Respiratory droplets with a usual incubation period of several weeks transmit infection from person to person. Only 3% to 10% of infected persons develop pneumonia. Although commonly perceived as a cause of CAP predominantly in young healthy patients, the incidence of *M. pneumoniae* pneumonia increases with age, highlighting the importance of this pathogen in the elderly as well. *M. pneumoniae* is primarily transmitted from person to person via respiratory droplets. The incubation period after exposure averages 2 to 3 weeks.

M. pneumoniae pneumonia is considered the "classic" atypica pneumonia. Many of the pathogenic features are believed to be immune-mediated rather than induced directly by the bacteria (antibodies produced against the glycolipid antigens of *M. pneumoniae* may cross-react with human red cells and brain cells). Constitutional symptoms including headache, malaise, myalgias, and sore throat are frequently present. Cough is typically initially dry, may be paroxysmal and frequently worse at night, and may become productive of mucopurulent sputum. The physical findings often are minimal, seemingly disproportionate to the patient's complaints. Auscultation of the lungs usually reveals variable scattered rales or wheezes. Bullous myringitis, first described in volunteer subjects infected with *M. pneumoniae*, has been infrequent in naturally occurring infection and is not a diagnostic sign. Chest radiograph findings are variable. Most common is peribronchial pneumonia.

The course of *M. pneumoniae* pneumonia is usually mild and self-limiting. However significant pulmonary complications may occur and include pleural effusion, pneumatocele, lung abscess, pneumothorax, bronchiectasis, chronic interstitial fibrosis, respiratory distress syndrome, and bronchiolitis obliterans. Extrapulmonary manifestations including mucocutaneous disease (including mild maculopapular rashes, erythema multiforme, and mucositis), neurological involvement (i.e., aseptic meningitis, meningoencephalitis, cerebral ataxia, Guillain–Barré syndrome, and transverse myelitis), hemolytic anemia (associated with cold agglutinins), myo-pericarditis, polyarthritis, hepatitis, and pancreatitis. A recent study of patients with *M. pneumoniae* requiring ICU care observed an ICU mortality of 11%.

Chlamydia pneumoniae

Pneumonia caused by *C. pneumoniae* may be sporadic or epidemic. *C. pneumoniae* infections are often acquired early in life. Transmission is by person to person via respiratory secretions, with an incubation period of several weeks. Reinfections or recrudescent processes, both referred to as *recurrent infection*, may occur throughout one's lifetime. Most adults who are hospitalized with *C. pneumoniae* pneumonia have recurrent infection.

The clinical manifestations of C. pneumoniae pneumonia remain somewhat unclear because of the lack of a gold standard of diagnosis and the contributing effect of co-pathogens. The majority of infections are asymptomatic. For symptomatic infection the onset is usually insidious. A biphasic pattern of illness has also been reported, with upper respiratory tract symptoms preceding the onset of pneumonia by 2 to 6 weeks. Infections often present initially with sore throat, hoarseness, and headache as important nonclassic pneumonic findings. A subacute course is common, and fever is low grade. Cough is prominent but unproductive and, if not treated early and effectively, may last for weeks or even months. Chest radiograph findings are nonspecific. Patients with primary infection are usually younger and tend to have higher fever. For older patients with reinfection, the presence of comorbid illness and the requirement for supplemental oxygen therapy are often the reason for hospital admission.

Legionella pneumophila

Legionellosis is primarily associated with two clinically distinct syndromes: *Legionnaires' disease* (LD), a potentially severe pneumonia, and *Pontiac fever*, a self-limited, non-pneumonic illness. Many of the clinical features of Legionnaires' disease are more typical of pyogenic (bacterial) pneumonias. However as LD has become increasingly recognized, less severely ill patients are seen earlier in the course of disease and thus clinical manifestations of unusual severity are now less specific. *Legionella* is not spread person to person but usually by exposure to water. Outbreaks may be associated with infected water sources. The incubation period is 2 to 10 days. Although there are many species, most prevalent is *L. pneumophila* serogroup 1.

The onset of LD is often acute, with high fever, myalgias, anorexia, and headache which often precedes the cough. Temperature often exceeds 40°C/104°F. Gastrointestinal symptoms are prominent, especially diarrhea. Hyponatremia and elevated lactate dehydrogenase levels (LDH) are common abnormal laboratory studies observed in our experience. Radiographic findings are varied and nonspecific; however, the most common findings are patchy unilobar infiltrates, which can progress to consolidations.

The index of suspicion for *Legionella* infection should be particularly high during known outbreaks, which are often associated with contamination of water supplies in large facilities such as hospitals, hotels, or apartment buildings. Other epidemiologic factors that should heighten suspicion for *Legionella* infection include known or potential exposure to a contaminated water source (e.g., hot tubs, birthing pools, fountains) and exposure to soil or potting mix in areas where the incidence of *L. longbeachae* is high.

Other causes of atypical pneumonia

Several of the less common causes of the atypical pneumonia syndrome are zoonotic infections transmitted from animals to humans. In such cases epidemiological clues may be very important, and, while specific manifestations cannot be considered "diagnostic" of a specific etiology, there are general findings that are characteristic of these diseases (Table 31.1).

TABLE 31.1 **COMMON CHARACTERISTICS AND THERAPY FOR THE "OTHER" ATYPICAL PNEUMONIAS**

Pathogen	Epidemiological or underlying condition	Clinical features	Recommended therapy
Chlamydia psittaci	Exposure to birds	HA, pharyngeal erythema, splenomegaly, Horder spots (see text)	Doxycycline *Alternatives*: Macrolide or respiratory fluoroquinolone (e.g., levofloxacin or moxifloxacin)
Coxiella burnetii (Q fever)	Exposure to farm animals (especially parturient)	HA prominent, liver involvement	Doxycycline (in combination with hydroxychloroquine if endocarditic) *Alternatives*: Macrolide or respiratory fluoroquinolone
Francisella tularensis[a] (Tularemia)	Exposure to rabbits	HA, chest pain prominent	Streptomycin or gentamicin (acceptable and preferred) considered as drug of choice Fluoroquinolone or doxycycline effect for most cases (especially if nonsevere)
Yersinia pestis[a] (Pneumonic plague)	Exposure to infected animals (rodents, cats, squirrels, chipmunks, prairie dogs)	For inhalation, acute onset with rapidly severe pneumonia; blood tinged sputum	Streptomycin, gentamicin (acceptable and preferred) Tetracycline, doxycycline
Bacillus anthracis[a]	Woolen mill worker	Biphasic (see text); hallmark radiographic finding-mediastinal widening	Ciprofloxacin plus one of the following for initial therapy: Meropenem, clindamycin, or linezolid; switch to monotherapy when clinically appropriate—see text and refer to Hendricks et al.
Viruses			
Influenza	Influenza in community (avian-poultry exposure)	Influenza pneumonia usually follows tracheo-bronchitis	Oseltamivir (orally), zanamivir (via inhalation), peramivir (IV); beloxavir (orally)
Adenovirus		Pharyngitis prominent	No approved antiviral
Respiratory Syncytial Virus	Adults: Cardiopulmonary disease, COPD	Bronchospasm	No antiviral agent currently recommended (ribavirin possibly for selected cases; see text)
Hantavirus Pulmonary Syndrome	Exposure to rodent excreta	Febrile prodrome/ followed by noncardiogenic pulmonary edema with shock; thrombocytopenia	Supportive care
MERS-CoV	Travel to Arabian peninsula	Severe respiratory syndrome	Supportive care

[a] Potential infectious agent for biological warfare.
Abbreviation: HA = Headache

Coxiella burnetii may be associated with exposure via any mammal, but most commonly cattle, goats, sheep, and pets, including cats and dogs. Infected mammals shed *C. burnetii* in their urine, feces, milk, and placenta. The mode of transmission is either aerosol or by tick bite. High concentrations of the organism can be found in birth products of infected animals. The incubation period is approximately 3 weeks. The acute disease (Q fever) is often a self-limiting "flu-like" illness characterized by fever, headache, myalgias, cough, and arthralgia. Pneumonia is commonly accompanied by granulomatous hepatitis. Radiological findings include lobar or segmental alveolar opacities, which may be multiple. Other manifestations may include maculopapular or purpuric rash, aseptic meningitis or encephalitis, hemolytic anemia, endocarditis, pericarditis, pancreatitis, or epididymo-orchitis. Occasionally *C. burnetii* is associated with chronic Q fever, which is defined as infection lasting for >6 months and in which endocarditis is the predominant manifestation.

Pneumonia due to *C. psittaci* usually occurs after exposure to infected birds. Infection in birds is usually asymptomatic or may cause illness associated with ruffled feathers or ocular or nasal discharge. The organism is shed in feces, urine, and respiratory secretions. Humans are usually infected by inhalation of organisms in dried feces or in bird feather dust, which may occur during cage cleaning. The onset is often insidious, with nonproductive cough, fever, and headache, but may be abrupt. Headache may be severe and associated with photophobia. The incubation period is usually 5 to 15 days. Clinical clues include pharyngeal erythema, splenomegaly (which tends to occur toward the end of the first week), and a rarely

seen specific rash (Horder's spots, a pink blanching maculopapular eruption resembling the rose spots of typhoid fever).

Francisella tularensis can cause primary tularemia pneumonia. Human infection occurs following contact with infected animals (hares or rabbits most common) or the bite of invertebrate vectors (most commonly ticks but also mosquitoes, horseflies, fleas, and lice). In one reported outbreak of tularemia pneumonia, a significant risk factor was grass mowing (presumably airborne transmission from close contact to rabbit habitats). Pneumonia may also occur from hematogenous spread after vector-borne (e.g., tick) infection. The incubation period following infection with *F. tularensis* is 3 to 5 days. The onset is usually abrupt, with high fever, chills, cough (usually nonproductive, occasionally with hemoptysis), pleuritic chest pain, and diaphoresis. Other than pneumonia *Tularemia* may also be associated with other clinical syndromes including ulceroglandular, oculoglandular, and typhoidal forms.

Hantaviruses comprise a genus of enveloped viruses within the family Bunyaviridae and are associated with two severe, acute febrile illnesses: *hemorrhagic fever* with renal syndrome and *hantavirus pulmonary syndrome* (HPS). Hantaviruses are shed in the urine, feces, or saliva of acutely infected reservoir rodents; transmission to humans occurs via the aerosol route. Many patients describe encountering living or dead rodents or visible evidence of rodent infestation prior to illness. Typically the incubation period is 3 weeks after exposure. The clinical illness of HPS typically begins with a prodromal phase characterized by nonspecific manifestations such as fever, myalgias, headache, nausea, vomiting, abdominal pain, and cough. This phase typically lasts 3 to 8 days and is followed by the cardiopulmonary phase, which starts suddenly with tachypnea and shortness of breath and is followed by respiratory failure and shock. Chest radiograph shows noncardiogenic bilateral interstitial edema during this phase. Characteristically, the patient is hemoconcentrated and manifests significant thrombocytopenia.

Yersinia pestis, which causes plague pneumonia, is primarily a zoonotic infection of rodents and wild and domestic animals (most often cats); humans are considered incidental hosts. Transmission occurs via bites of rodent fleas, scratches or bites from infected domestic cats, direct handling of infected animal tissues, or inhalation of respiratory secretions from infected animals. Infection is found in the United States mainly in the southwestern and Pacific coastal areas. Incubation is usually 2 to 3 days. The disease may have an abrupt onset and usually begins with a painless cough with shortness of breath. Untreated pneumonic plague has a 40% to 90% mortality.

In the natural setting, *inhalation anthrax* is exceedingly uncommon and is classically referred to as *wool sorters disease* because of the association with workers in woolen mills who may inhale *Bacillus anthracis* spores. However, its potential use as a biological weapon has brought increased interest to this pathogen. In the 2001 outbreak of probable bioterrorism-associated anthrax conducted through the US postal system, nine cases of inhalation anthrax were identified and resulted in four deaths. The incubation is variable, often less <1 week, but it can be 6 weeks or longer. Initial symptoms are nonspecific with fever, malaise, chest pain, and nonproductive cough. This may be followed by brief improvement and then severe respiratory distress, shock, and death. Widened mediastinum (associated with hemorrhagic mediastinitis) without parenchymal infiltrates found on radiographic imaging (CT scan is most sensitive) is characteristic of inhalation anthrax. The diagnosis is often established with positive blood cultures that may initially be dismissed as "contaminants."

In addition to inhalation anthrax syndrome, pneumonic plague and pneumonic tularemia are possible agents of bioterrorism. Clustered cases occurring without the expected epidemiologic exposures to animals, insects, or environmental activities should raise the possibility of a bioterrorism event. Specific epidemiological, clinical, and microbiological clues should lead to early suspicion and rapid activation of the health alert system since laboratory confirmation of the agent could be delayed.

Pneumonia caused by respiratory viruses

Viruses account for an important number of pneumonias in adults, especially during the winter months and among the elderly. Recent studies suggest that approximately one-quarter to one-third of adults hospitalized for pneumonia had a virus as sole etiology. Of interest, many of the emerging infections have been associated with newly identified viruses (many zoonotic): Middle East respiratory syndrome-novel coronavirus (MERS-CoV) and avian influenza A viruses (H5N1 and H7N9). Influenza and RSV are the most commonly identified viral pathogens; others include parainfluenza virus, rhinovirus, coronavirus, and human metapneumovirus. Influenza should be considered during periods of peak activity within a community and is often associated with sudden fever, myalgias, and cough. RSV is a more common cause of pneumonia in immunocompetent adults than previously appreciated. Characteristics include seasonal occurrence (winter) and association of bronchospasm. MERS-CoV is a novel coronavirus identified in the fall of 2012 in Saudi Arabia; it is different from the coronavirus previously associated with severe acute respiratory syndrome (SARS). Most persons infected developed a severe acute respiratory illness and about a third died. MERS-CoV is a zoonotic virus; available evidence suggests infection occurs through contact with camels, although transmission from person-to-person and to healthcare providers has occurred. A few cases from travelers have been reported in the United States. Clinicians are advised to consider this in patients with compatible illnesses who have traveled to the Arabian Peninsula or neighboring countries.

A strain of avian influenza (influenza A H7N9) was identified in China in 2013. Most people infected have had contact with poultry, and available evidence suggests there is no ongoing spread from person to person. Symptoms begin with high fever and cough. While mild cases have been seen, most patients have severe respiratory illness with a mortality rate of approximately 40%.

Diagnosis

Laboratory tests used for the diagnosis of the etiologic agents associated with atypical pneumonia are listed in Table 31.2. Until

TABLE 31.2 **DIAGNOSTIC STUDIES FOR PATHOGENS ASSOCIATED WITH ATYPICAL PNEUMONIA**

Pathogen	Rapid test	Standard culture or microbiologic test(s)	Serology,[c] other tests
M. pneumoniae	PCR [95]*	Throat or NP swab [90] (requires 7–10 days for preliminary growth)	ELISA, CF [75–80] (IgM may be present after 1 week but can persist 2–12 months) Diagnostic criteria: Definite: 4-fold titer rise Possible: IgG ≥1:64 (CF) IgM ≥1:16 (ELISA) Cold Agglutinin [50] [<50% specificity; takes weeks to develop)
C. pneumoniae	PCR [80–90]	Throat or NP swab-requires cell culture technique, rarely done [50–90]	CF or MIF (latter not as available) (IgM may take up to 4–6 weeks to appear in primary infection) Diagnostic criteria: Definite: 4-fold titer rise Possible: IgG ≥1:512 IgM ≥1:32
Legionella pneumophila	Urine Antigen (serogroup 1) [60–70] PCR[a]	Sputum, bronchoscopy [75–99] (selective media required, 2–6 days)	IFA[c] ELISA [40–75] Diagnostic criteria: Definite: 4-fold titer rise Possible: IgG or IgM ≥1:512 (titer of a:256 has positive predictive value of only 15%)
C. psittacosis	PCR[a]	Usually not done (considered laboratory hazard)	CF (Presumptive IgG ≥1:32) MIF for IgM
Coxiella burnetii	PCR[a]	Usually not done (considered laboratory hazard)	IFA (current reference method)
Viruses Influenza RSV Adenovirus	Rapid Antigen Detection (EIA)[b], PCR Antigen Detection (IF or EIA; mainstay of diagnosis), PCR PCR PCR	Virus isolation Virus isolation Virus isolation	CF or HAI, ELISA ELISA ELISA
Francisella tularensis	PCR (not available in general laboratories)	Culture (selective media; considered laboratory hazard)	ELISA preferred; passive hemagglutination
Yersinia pestis	Gram Stain, morphology, gram-negative coccobacillus exhibiting bipolar staining ["safety pin"]; PCR	Culture (considered laboratory hazard)	ELISA, IF
Bacillus anthracis (Inhalation Anthrax)	PCR	Culture (may be dismissed as *Bacillus* contaminant)	

Numbers in brackets ([ ]) indicate % sensitivity of test.
[a] In selected laboratories; reagents are not FDA-cleared.
[b] Low sensitivity for 2009 influenza A N1N1.
[c] Paired sera generally required.
Abbreviations: ELISA = enzyme-linked immunosorbent assay, CF = complement fixation, HAI = Hemaggluination inhibition; IF = Immunofluorescence; MIF = microimmunofluorescence, IFA = indirect fluorescence Ab

recently serologic tests were the most common means of laboratory diagnosis for most pathogens associated with atypical pneumonia but are less valuable given the requirement for measurement during acute and convalescent specimens. However, advancements in molecular testing methods have produced new potentials for diagnosis and more rapid identification of these pathogens. Nucleic acid amplification tests (NAATs), such as polymerase chain reaction (PCR), are becoming available with marked expansion of diagnostic capability for infectious diseases. There are several commercially available and/or institutionally developed NAATs for the atypical pathogens. Tests approved by the US Food and Drug Administration (FDA) are available for *Mycoplasma*, *Chlamydia*, and *Legionella* (as part of multiplex PCR) and most respiratory viruses. Present evidence suggests testing for atypical pathogens in patients admitted for CAP is poorly standardized in real life and does not mirror atypical prevalence in different settings.

Although the isolation of *M. pneumoniae* on specialized media is possible, culture requires 2 to 3 weeks and the organism is fastidious. As a result, most clinical laboratories do not attempt to culture this organism. Cold agglutinins, which are immune-mediated, are often positive in patients with *M. pneumoniae*. *C pneumoniae* can be cultured on cell lines, but this is rarely used by standard laboratories. *Legionella* can be readily isolated from respiratory specimens but requires specialized media-buffered charcoal yeast extract agar (BYCE). A urinary antigen test is available for *L. pneumophila* serogroup 1, which represents the most common cause of *Legionella* pneumonia in the United States; sensitivity for *L. pneumophila* serogroup 1 is approximately 70 to 80%, with a specificity close to 100%.

Several of the other causes of atypical pneumonia can be isolated by culture, including *Francisella, Yersinia, C. psittaci,* and *Bacillus anthracis*. Since these agents can be potentially transmitted from laboratory isolates, if there is a clinical suspicion the laboratory should be notified to optimize growth conditions and take proper precautions to reduce the risk of infection among laboratory personnel. Blood cultures are often positive for *Yersinia* infection. For *C. psittaci*, *Coxiella,* and *F. tularensis,* serology is the primary means of diagnosis.

For most respiratory viruses, PCR is now the most sensitive diagnostic approach. PCR was vital for epidemiology during the 2009 influenza H1N1 pandemic because commercially available rapid influenza detection tests (RIDTs) were found to be relatively insensitive (sensitivity ranging from 10% to 70% depending in part on the method used).

Antimicrobial therapy

Antimicrobial agents generally considered effective for these atypical pathogens are included in Tables 31.1, 31.3, and 31.4. Since most cases of atypical pneumonia are treated empirically, clinicians need also to consider the possibility of other standard pathogens (i.e., *S. pneumoniae, H. influenzae*) when deciding on antimicrobial therapy.

TABLE 31.3 **AUTHOR'S RECOMMENDATION FOR ANTIMICROBIAL THERAPY OF *M. PNEUMONIAE* AND *C. PNEUMONIA* (ADULT DOSES[a])**

Antimicrobial	Dose	Duration (days)
Clarithromycin (Biaxin)	500 mg BID	7
Azithromycin (Zithromax)[b]	500 mg initially then 250 mg/d (alternative 500 mg/d)	5 (3)
Dirithromycin (Dynabac)	500 mg/d	7
Doxycycline[b]	100 mg BID	7
Omadacycline	100 mg BID IV for 2 days then Daily; can switch to 300 mg PO	7
Levofloxacin (Levaquin)[b]	500 mg/d 750 mg/d	7 5 (data limited)
Moxifloxacin (Avelox) [b]	400 mg/d	7
Gemifloxacin (Factive)	320 mg/d	5
Delafoxacin[c]	300 mg IV, q12h for at least 6 doses with	5–7
Lefamulin[c]	potential to switch to 450 mg oral tablet 150 mg IV BID or 350 mg PO	5–7

[a] Oral except where noted.
[b] Also can be administered intravenously in equivalent dose.
[c] Completed phase 3 study.

Mycoplasma and *Chlamydia*

Appropriate treatment (especially for *M. pneumoniae*) reduces the morbidity of pneumonia and shortens duration of symptoms. Erythromycin and tetracyclines (e.g., doxycycline) have been considered effective therapy. The newer macrolides (clarithromycin and azithromycin) have good in vitro activity against these organisms, and have shown good results in clinical studies. Although resistance to the macrolides is relatively low in the United States (<10%), the prevalence of macrolide-resistant *Mycoplasma* in Asia is very high (up to 70–90% in some areas). The newer fluoroquinolones (i.e., levofloxacin, moxifloxacin, gemifloxacin) are bactericidal and have been shown to be effective in clinical trials.

Legionella

There is little debate concerning the need for therapy in *Legionella* pneumonia. Therefore, empirical therapy should be included in treatment of severe CAP. Macrolides initially have been considered the treatment of choice for Legionnaires' disease. However, intracellular models as well as animal models of *Legionella* infection indicate that the systemic fluoroquinolones and the newer macrolides (especially azithromycin) show superior activity compared with erythromycin. Several observational studies suggest that quinolones produce superior clinical responses compared with macrolides. The addition of rifampin to erythromycin has been suggested for patients who are severely ill; however, there is no convincing laboratory data to show that adding rifampin to fluoroquinolones or the more active macrolide therapy improves bacterial killing. I prefer the newer fluoroquinolones because of greater activity in vitro against *S. pneumoniae* (including drug-resistant strains) and other common causes of CAP that need to be considered for empirical therapy (Table 31.4). Doxycycline has also been shown to be effective in limited, well-documented cases for *L. pneumophila*, but *L. longbeachae* is often resistant. Oral therapy for less serious cases or for step-down from intravenous (IV) therapy includes the oral macrolides and fluoroquinolones as well as doxycycline.

More recently FDA-approved antimicrobials or those in late-stage development with activity against *Mycoplasma* and *Chlamydia* as well as *Legionella* include delafloxacin, omadacycline, and lefamulin.

The duration of therapy for optimal response of *C. pneumoniae* and *M. pneumoniae* has not been well established. In initial descriptions of *C. pneumoniae* pneumonia, observers found that respiratory symptoms frequently recurred or persisted after short courses (5–10 days) of erythromycin or tetracycline. In recent recommendations, the usual duration of therapy for *C. pneumoniae* or *M. pneumoniae* using more recently approved agents has been 7 to 10 days (shorter for azithromycin because of its longer half-life); however, recent studies (mostly with the fluoroquinolones) have suggested that a minimum of 5 days may be adequate for immunocompetent patients if the patient has had a good clinical response within 48 to 72 hours. Similarly, the usual duration of therapy for Legionnaires' disease of immunocompetent adults has been 7 to 14 days; one recent study showed good efficacy of 750 mg/d of levofloxacin for 5 days. For therapy of immunocompromised patients or more severe disease, longer duration is recommended.

Therapy for other pathogens associate with atypical pneumonia

For details, please see Table 31.1.

C. psittaci. The tetracyclines (e.g., doxycycline 100 mg orally twice daily) are generally considered the drugs of choice, with the macrolides as appropriate alternatives. The newer fluoroquinolones are active in vitro and in animal models but their efficacy for human infection is unknown.

C. burnetii. Doxycycline is the preferred agent; macrolides or fluoroquinolones are alternatives. Prolonged therapy (e.g., 18

TABLE 31.4 **PARENTERAL THERAPY FOR SERIOUS *LEGIONELLA* INFECTIONS**[a]

Preferred antimicrobial	Alternative antimicrobial
Fluoroquinolone Levofloxacin (Levaquin) 500 mg IV q24h [750 mg/d for 5 days possible for immunocompetent patients]	Doxycycline 100 mg IV q12h
Moxifloxacin (Avelox) 400 mg IV q24h	
Azithromycin (Zithromax) 500 mg IV q24h	-- -- -- -- -- -- -- -- -- -- -- -- -- -- -- --
-- -- -- -- -- -- -- -- -- -- -- -- -- -- -- --	
Newer Agents Delafloxacin** 300 mg IV, q12h Omadacycline 100 mg q12h IV for 2 days then daily Lefamulin[b] 150 mg IV q12h	

[a]Requiring hospitalization or in immunocompromised patients; can change to PO when clinically stable and can tolerate PO.
[b]Not FDA-approved at time of submission.

months) with hydroxychloroquine in combination with doxycycline is the preferred treatment regimen for Q fever endocarditis.

F. tularensis. Aminoglycosides are the drug of choice for severe infection. The traditional choice of therapy for pneumonic tularemia is streptomycin (10 mg/kg q12h up to 2 g/d for an adult); however, gentamicin (3–5 mg/kg/d) is more available and less toxic; treatment is for 7 to 14 days. An oral fluoroquinolone (ciprofloxacin, levofloxacin) or doxycycline (100 mg IV or PO BID) has often been used with good success in nonsevere ambulatory pneumonia and is easier to administer.

Hantavirus pulmonary syndrome. Treatment options are limited. Ribavirin has in vitro activity but clinical observations of efficacy are inconclusive. Optimal cardiopulmonary and fluid management is critical for appropriate management.

Y. pestis. Pneumonic plague has a mortality approximating 100% if untreated. Aminoglycosides are the preferred agents for plague, with doxycycline and tetracycline as alternatives. Streptomycin (similar dose/day as for tularemia) has been considered the drug of choice, with 10 days being the minimum recommended course of therapy; however, as with tularemia, gentamicin is now considered acceptable and preferred. Doxycycline is an alternative for those intolerant of gentamicin. Close contacts of patients with pneumonic plague should receive tetracycline (500 mg QID) or doxycycline (100 mg BID) for 5 to 7 days for prophylaxis.

Inhalation anthrax. The mortality rate remains high if treatment is not initiated prior to the development of clinical symptoms. Initial therapy of inhalation anthrax should include at least two agents effective against *B. anthracis,* which can be switched to monotherapy once the patient has stabilized and possible susceptibility test results are known. A commonly recommended initial regimen is ciprofloxacin (400 mg IV q8h) plus clindamycin (900 mg IV q8h) or linezolid (600 mg IV q12h). Adjunctive use of antitoxin should be administered as soon as possible. If anthrax is a concern as an agent of bioterrorism, it is important to provide prophylaxis to the population at risk. The preferred regimens are ciprofloxacin (500 mg PO BID), levofloxacin (500 mg/d), or doxycycline (100 mg PO BID). Amoxicillin 500 mg TID for an adult is acceptable if the associated *B. anthracis* strain has an amoxicillin MIC of 0.125 μg/mL or less. Prophylaxis should be continued for 60 days.

Influenza. Because of the high rates of resistance in the United States, amantadine and rimantadine are not recommended for treatment of seasonal influenza. A neuraminidase inhibitor (oseltamivir, zanamivir, or peramivir) is the recommended antiviral treatment. Peramivir is available for IV administration when oral therapy is unsuitable. Recently beloxavir, a selective inhibitor of influenza cap-dependent endonuclease, has been approved for seasonal influenza. Although there are no randomized clinical trials, oseltamivir is can be considered for the treatment of avian influenza A (including H5N1 and the newly described H7N9). There does appear to be a mortality benefit for H5N1 based on an analysis of a registry of 300 patients. While no data are available regarding treatment of persons with H7N9 influenza, laboratory testing indicates that most strains are susceptible to oseltamivir but resistant strains have been identified.

RSV. The routine use of ribavirin is not recommended for infants and children with RSV. The benefit of ribavirin therapy for adults has not been established; however, it has been shown to reduce morbidity and mortality in adult bone marrow transplant recipients who develop RSV infections.

MER-Cov. No specific antiviral therapy is presently available.

Suggested reading

Arnold FW, Summrsgill JT, LaJloie AS, et al. A worldwide perspective of atypical pathogens in community-acquired pneumonia. *Am J Respir Crit Care Med*. 2007;175:1086–1093. Observational study from a large international cohort showing patients with atypical pneumonia treated empirically with antimicrobials with coverage for atypical pathogens had faster time to clinical stability.

Centers for Disease Control and Prevention. Avian influenza. https://www.cdc.gov/flu/avianflu/. Excellent source for up-to-date information regarding this new viral infection.

Centers for Disease Control and Prevention. Middle East respiratory syndrome coronavirus (MERS-CoV) http://www.cdc.gov/coronavirus/mers/index.html. Excellent source for up-to-date information regarding this new viral infection.

Eljaaly K, Alshehri S, Aljabri A, et al. Clinical failure with and without atypical bacterial coverage in hospitalized adults with community-acquired pneumonia: Systemic review and meta-analysis. *BMC Infect Dis*. 2017;17:385. Empiric atypical coverage was associated with a significant reduction in clinical failure in hospitalized adults

File TM Jr., Marrie TJ. Does empiric therapy for atypical pathogens improve outcomes for patients with CAP? *Infect Dis Clin N Am*.2013;27:99–114. A critical review of the significance of empirical therapy of atypical pneumonia concluding that available evidence supports treatment for atypical pathogens empirically.

Gaydos CA. What is the role of newer molecular tests in the management of CAP? *Infect Dis Clin N Am*. 2013;27:49–49. Excellent review of newer molecular tests.

Gramegna A, Sltgiu G, Di Pasquale M, et al. atypical pathogens in hospitalized patients with community-acquired pneumonia: A worldwide perspective. *BMC Infect Dis*. 2018;18:677. Assessment of both testing for atypical pathogens and their prevalence in hospitalized patients with CAP worldwide, especially in relation with disease severity.

Hendricks KA, Wright ME, Shadomy SV, et al. Centers for disease control and prevention expert panel meetings on prevention and treatment of anthrax in adults. *Emerg Infect Dis*. 2014;20. Expert consensus statement on prevention and treatment of anthrax.

Infectious Diseases Society of America and the American Thoracic Society. Consensus Guidelines on the Management of Community-Acquired Pneumonia. *Clin Infect Dis*. 2007. Excellent review and updated, evidence-based guideline, which is a unified statement from both the IDSA and ATS (an update of the guideline is under review at the time of this writing).

Jain S, Self WH, Wunderink RG, et al.; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among US adults. *N Engl J Med*. 2015;358:415–427. A multicenter study of the etiology of CAP requiring hospitalization. Of note, viruses accounted for approximately 25% as sole identified pathogen.

Marrie TJ, Costain N, La Scola B, et al. The role of atypical pathogens in community-acquired pneumonia. *Semin Resp Crit Care Med*. 2012;33:244–256. Review of atypical pneumonia.

Pavia AT. What is the role of respiratory viruses in community-acquired pneumonia: What is the best therapy for influenza and other viral causes? *Infect Dis Clin N Am*. 2013;27:157–175. Review of viruses as causes of CAP.

Shefet D, Robenshtok E, Paul M, Leibovici. Empirical atypical coverage for inpatients with community-acquired pneumonia: A systematic review of randomized controlled trials. *Arch Intern Med*. 2005;165:1992–2000. One of a few meta-analyses that suggest no significant difference in mortality or clinical response using a standard endpoint (e.g., 7–10 days following end of therapy) for assessment. However, regimens with coverage of atypical pathogens showed a trend toward clinical success. Subgroup analysis in patients with *Legionella* spp. found a significantly lower failure rate in those who were treated with antibiotics active against atypical pathogens.

Valade S, Biard L, Lemiale V, et al. Severe atypical pneumonia in critically ill patients. *Ann Intens Care*. 2018; 8:81. Study observed a mortality rate of 11% for severe *M. pneumoniae* pneumonia.

32

Community-acquired pneumonia

Keyur S. Vyas

Community-acquired pneumonia (CAP) continues to cause significant morbidity and mortality worldwide. In developed countries, most episodes occur in those elderly who have one or more chronic underlying diseases. Children are more commonly affected in the developing world. Morbidity and mortality from CAP remains high worldwide despite advances in antibiotic and intensive care therapy. Making the clinical diagnosis of pneumonia is usually not difficult; deciding which patients should be admitted to the hospital and selecting appropriate therapy, however, can be challenging.

Diagnosis and treatment

Pneumonia is suspected when one or more of the following is present: cough, purulent sputum, dyspnea, pleuritic pain, fever, chest auscultation findings consistent with pneumonia, leukocytosis, or a new pulmonary infiltrate on imaging. Once the diagnosis is suspected, the physician must decide whether hospitalization is necessary and. if so, whether intensive care unit (ICU) admission is appropriate.

A number of risk factors predict a complicated course (Box 32.1). Multiple scoring systems have been proposed to assess disease severity and predict mortality to assist in determining if hospitalization is necessary; two such systems are the CURB-65 score from the British Thoracic Society and the Pneumonia Severity Index (PSI) from the Pneumonia Patient Outcomes Research Team (PORT). The PSI assigns points for 19 variables based on age and comorbidities similar to those listed in Box 32.1. Patients are then assigned to one of five risk categories. Patients in risk groups I and II can be managed as outpatients, whereas risk groups III–V should be hospitalized. The CURB-65 criteria include confusion, blood urea nitrogen (BUN) (>20 mg/dL), respiratory rate (>30 breaths/minute), blood pressure (systolic ≤90 mm Hg or diastolic ≤60), and age (≥65 years). Patients with 0 to 1 of these findings can be managed as outpatients. Those with a score of 2 should be admitted to hospital, whereas those with 3 or more should receive ICU care. The PSI gives a more accurate prediction of which patients can be safely managed outside the hospital. The CURB-65 is less cumbersome and easier to use in the outpatient setting. Various biomarkers have been proposed to assist in risk stratification, with procalcitonin (PCT) being the most widely studied and increasingly used in clinical practice. PCT is elevated in bacterial infections compared to nonbacterial processes. Its utility in determining the need for initiation of antibiotics is debatable; however, studies have shown it to be a useful adjunct in guiding de-escalation and discontinuation of antibiotics, especially as part of antibiotic stewardship efforts. Risk stratification guides and biomarker measurements are useful adjuncts to assist the clinician's judgment, which remains the ultimate decision-making tool.

Accurate history, including occupation; travel; exposure to animals, birds, and insects; sick contacts; recent dental work; and history of alcohol or drug abuse may suggest a causative agent (Table 32.1). Bacteria and respiratory viruses cause the majority of CAP, with a minority of cases caused by fungi, such as the endemic mycoses. Geographic variations affect the spectrum and proportion of causative agents. A significant

BOX 32.1

Predictors of a complicated course in patients with community-acquired pneumonia

Suspicion of high-risk cause (*Staphylococcus aureus*, gram-negative bacilli, aspiration, or postobstructive process)
Age >50 years
Prior episode of pneumonia
Consolidation, multilobe involvement, or pleural effusion on chest radiograph
Abnormalities on physical examination:
- Temperature ≤95°F (35°C) or >104°F (40°C)
- Systolic or diastolic blood pressures ≤90 mm Hg or ≤60 mm Hg,
- Respectively
- Respiratory rate ≥30 breaths/minute
- Heart rate >125 beats/minute
- Extrapulmonary areas of infection

Laboratory factors
- Abnormal renal function (BUN >20 mg/dL or serum creatinine >1.2 mg/dL)
- Sodium ≤130 mg/dL
- Glucose ≥250 mg/dL
- Hematocrit ≤30%
- WBC count ≤4,000/mm^3 or >30,000/mm^3
- Metabolic acidosis (pH ≤7.35)
- PaO_2 ≤60 mm Hg breathing room air

Comorbid conditions
- Renal insufficiency
- Congestive heart failure
- Liver disease
- Diabetes mellitus
- Altered mental state
- Neurologic disease
- Alcoholism
- Immunosuppression
- Malignancy
- Splenectomy
- No responsible person in the home to assist the patient

Abbreviations: BUN = blood urea nitrogen; WBC = white blood cell.

TABLE 32.1 **RELEVANT CLINICAL HISTORY RELATED TO SPECIFIC PATHOGENS**

Anaerobes (oral)	Alcoholism, aspiration, lung abscess, recent dental work, endobronchial obstruction
Bordetella pertussis	Cough ≥2 weeks with whoop or vomiting after cough
Burkholderia cepacia	Bronchiectasis
Chlamydia pneumoniae	COPD, smokers, biphasic illness
Chlamydia psittaci	Bird exposure
Coccidioides immitis	Travel to Southwest United States
Coronaviruses (SARS and MERS)	Travel to or residence in East Asia or the Middle East or with outbreak in other countries
Coxiella burnetii	Farm animal or pregnant cat exposure, hepatosplenomegaly
Francisella tularensis	Exposure to wild mammals, esp. rabbits and ticks in endemic areas
Haemophilus influenzae	COPD, smokers, HIV, postinfluenza
Hantavirus pulmonary syndrome	Pulmonary edema, hemoconcentration, thrombocytopenia esp. after travel to Southwest United States
Histoplasma capsulatum	Bat or bird droppings, cave exploration
Influenza	Seasonal outbreak. Travel to or residence in Asia: avian influenza
Klebsiella pneumoniae	Alcoholics
Legionella spp.	Hotel or cruise ship
Moraxella catarrhalis	COPD, smokers
Mycobacterium tuberculosis	Alcoholics, HIV, elderly, injection drug use
Mycoplasma pneumoniae	Prominent cough, hyperreactive airways, hemolytic anemia
Pneumocystis jirovecii	HIV, chronic corticosteroid use
Pseudomonas aeruginosa	COPD, bronchiectasis
Staphylococcus aureus	Postinfluenza, endobronchial obstruction, injection drug use
Streptococcus pneumoniae	Most common through all age groups, alcoholics, postinfluenza

Bacillus anthracis (anthrax), *Yersinia pestis* (plague), and *Francisella tularensis* (tularemia) would be the most likely bacterial bioterrorism agents to cause pneumonia.
Abbreviations: COPD = chronic obstructive pulmonary disease; SARS = severe acute respiratory syndrome; MERS = Middle East respiratory syndrome; HIV = human immunodeficiency virus.
Adapted from Infectious Diseases Society of America and American Thoracic Society Consensus Guidelines 2007.

proportion of cases may be polymicrobial, most commonly bacteria in combination with either atypical bacteria or respiratory viruses. A causative agent is identified in only about half of cases of CAP even with extensive testing. Most cases are treated empirically without identification of a specific cause, especially in the outpatient setting.

Streptococcus pneumoniae is the most commonly identified bacterial pathogen in all treatment settings, followed by atypical bacterial agents (*Chlamydia pneumoniae and Mycoplasma pneumoniae),* and *Haemophilus influenzae*. The incidence of pneumonia due to *S. pneumoniae* is falling in North America compared to Europe, likely due to increased use of pneumococcal vaccines and decreased rates of smoking. *Staphylococcus aureus* causes only 1% to 3% of cases of CAP but is associated with significant morbidity and mortality, especially in younger adults. Respiratory viruses are a significant cause of CAP in up to a third of cases. There are no unique clinical features of any pathogen that allow a specific identification by history alone.

HIV disease should be a diagnostic consideration in most patients hospitalized with CAP.

Laboratory studies (Box 32.2 and Table 32.2) may be useful in diagnosis and management. The extent of the evaluation should depend on the severity of illness and the likelihood that test results will influence therapy. Diagnostic studies are usually unnecessary for patients treated on an outpatient basis because empiric antimicrobial choices adequately treat most common bacterial etiologies. Hospitalized patients should have, at a minimum, routine laboratory studies including a CBC with differential, a chest radiograph, and arterial blood gases, especially if hypoxic. Blood cultures are diagnostic in up to 14% of patients hospitalized for CAP. They are most useful in patients with severe CAP (Table 32.2). The Gram stain and culture of expectorated sputum is most useful in patients with severe CAP (Table 32.2). The sputum specimen should be grossly purulent, obtained by deep cough (or tracheal aspirate), and processed in <2 hours. Minimum criteria for a specimen suitable for culture are <10 squamous epithelial cells or >25 polymorphonuclear neutrophils (PMNs) per low-power field. Sputum studies can be diagnostic for *Legionella*, mycobacteria, fungi, and *Pneumocystis jirovecii* (Box 32.2). Molecular diagnostic tests such as polymerase chain reaction amplification assays may be performed on nasopharyngeal or lower respiratory tract specimens for many pathogens including *S. pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Bordetella pertussis*, and respiratory viruses. A parapneumonic pleural effusion is a common complication of pneumonia, and cultures obtained by thoracentesis will often give a positive result. The incidence of pleural effusion with pneumonia depends on the etiologic agent, accompanying approximately 95% of *Streptococcus pyogenes* infections but only 10% of *S. pneumoniae* infections. Sampling of the lower respiratory tract via bronchoalveolar lavage, bronchoscopic protected specimen brushings, or quantitative endotracheal aspirates may be useful in cases of nonresolving pneumonia. Transthoracic needle aspiration and lung biopsy should only be considered in severely ill patients not responding to therapy for whom less invasive techniques are nondiagnostic.

Urinary antigen tests (UAT) may be useful in *Legionella* spp. and *S. pneumoniae* infections. Both tests have a >90% specificity. The *S. pneumoniae* UAT may yield a diagnosis even after starting antibiotics. The *Legionella* UAT is positive in 74% of cases due to serogroup I, which causes most cases of community-acquired Legionnaires' disease in the United States. Serologic studies may aid in the confirmation of atypical bacterial causes of CAP but are rarely helpful in antibiotic choice. A fourfold rise in serologic titer, which often takes several weeks, is necessary for confirmation. Cross-reactivity among some organisms lessens the specificity of serology. A definitive microbial cause is identified in only a minority of patients even after extensive testing.

BOX 32.2

Routine studies useful in the diagnosis and management of patients hospitalized with community-acquired pneumonia

Chest radiograph (posterior and lateral)
Arterial blood gas values (for hospitalized patients). Pulse oximetry should be obtained for patients judged suitable for outpatient therapy.
Complete blood count with differential
Chemistry panel, including electrolytes, glucose, blood urea nitrogen, and creatinine
Aminotransferases
Blood culture (2 sets drawn 10 minutes or more apart)
Not necessary for all patients. See Table 32.4.
Pleural fluid gram stain, culture, leukocyte count with differential, pH
Sputum studies (for pneumonia unresponsive to usual antibiotics, see Table 32.4):
- Acid-fast stain and culture
- Fungal stains and culture
- *Legionella* spp. Culture
- Immunofluorescent antibody, Gomori's methenamine silver, or
- Giemsa stain for *Pneumocystis jirovecii* (*carinii*)
- A Gram stain (from an appropriately obtained specimen, examined by an expert within 2 h of collection before the patient has received antibiotics)

Urinary antigen
- *Streptococcus pneumoniae*
- *Legionella* spp.

Serology (for patients with appropriate epidemiologic history)
- HIV serology
- *Legionella* spp.
- *Francisella tularensis*
- *Mycoplasma pneumoniae*
- *Chlamydia (pneumoniae and psittaci)* spp.
- *Coxiella burnetii*

Abbreviation: HIV = human immunodeficiency virus.

Recommendation for empiric selection of antimicrobial agents

Delay in antibiotic therapy for CAP increases morbidity and mortality. Empiric selection of antimicrobials is necessary in most cases. Selection of appropriate antibiotics is facilitated by categorizing patients by age and severity of illness, comorbidities, and epidemiologic factors. Some microbes cause disease in all ages and types of patients; others are common only in patients with certain comorbidities (Boxes 32.3 to 32.6).

Among patients with mild pneumonia not requiring hospitalization (Box 32.3), *S. pneumoniae* is the most common bacterial pathogen. The atypical pneumonias (*M. pneumoniae* and *C. pneumoniae*) are also common and are generally benign, with systemic complaints often more prominent than respiratory ones. Fever, headache, and myalgia are frequent. Leukocytosis is rare, and chest infiltrates consist primarily of segmental lower lobe or hilar infiltrates. *M. pneumoniae* is more common among patients

TABLE 32.2 **CLINICAL INDICATIONS FOR MORE EXTENSIVE DIAGNOSTIC TESTING**

Indication	Blood culture	Sputum culture[a]	*Legionella* UAT	Pneumococcal UAT
ICU admission	X	X	X	X
Failure of outpatient antibiotic therapy		X	X	X
Cavitary infiltrates	X	X[b]		
Leukopenia	X			X
Active alcohol use	X	X	X	X
Chronic severe liver disease	X			X
Severe obstructive/structural lung disease		X		
Asplenia (anatomic or functional)	X			X
Recent travel (within 2 weeks)			X	
Positive *Legionella* UAT result		X[c]	NA	
Positive pneumococcal UAT result	X	X		NA
Pleural effusion	X	X	X	X

Abbreviations: NA = not applicable; UAT = urinary antigen test.
[a] A Gram stain should be obtained as well.
[b] Fungal, tuberculosis, and bacterial cultures.
[c] Special media for *Legionella*.
Adapted from Table 5, IDSA/ATS Consensus Guidelines 2007.

<30 years of age but is recognized with increasing frequency in older persons. *M. pneumoniae* is characterized by a prominent cough, often occurs in slowly evolving epidemics, and can precipitate reactive airway disease, especially in children. *C. pneumoniae* is a common cause of mild, often biphasic illness, initially with upper respiratory symptoms and pharyngitis with development of pneumonia 2 or 3 weeks later. Reinfection is common. Macrolides such as azithromycin and clarithromycin are the drugs of choice for treating outpatient pneumonia in low-risk patients. However,

BOX 32.3

Guidelines for empiric antibiotic therapy for community-acquired pneumonia in outpatients younger than 50 years with no comorbid illness

Common pathogens

Streptococcus pneumoniae
Mycoplasma pneumoniae
Chlamydia pneumoniae
Respiratory viruses

Antibiotics

Macrolide[a]
Azithromycin, 500 mg PO day 1, then 250 mg/d
Clarithromycin, 250 mg PO BID
If macrolide intolerant:
Doxycycline 100 mg PO BID

[a] If >25% *S. pneumoniae* macrolide-resistant (minimal inhibitory concentration [MIC] ≥16 μg/mL) in a community: levofloxacin 750 mg PO daily, or moxifloxacin 400 mg PO daily.

BOX 32.4

Guidelines for empiric antibiotic therapy for community-acquired pneumonia in patients older than 50 years or with comorbid illness not requiring hospitalization

Common pathogens

Streptococcus pneumoniae
Legionella spp.
Haemophilus influenzae
Moraxella catarrhalis
Other gram-negative bacilli
Respiratory viruses

Antibiotics

Fluoroquinolone as a single agent
Levofloxacin 750 mg PO daily
Moxifloxacin 400 mg PO daily
Or
Macrolide[a]
Azithromycin, 500 mg PO day 1, then 250 mg/d
Clarithromycin, 250 mg BID
And
β-lactam
Amoxicillin 1 g TID
Amoxicillin-clavulanate 2 g BID
Ceftriaxone, cefpodoxime, cefuroxime

[a] Doxycyline 100 mg BID may be substituted in macrolide-intolerant patients.

BOX 32.5

Guidelines for empiric antibiotic therapy for community-acquired pneumonia in patients requiring hospitalization (not intensive care)

Common pathogens

Streptococcus pneumoniae
Mycoplasma pneumoniae
Chlamydia pneumoniae
Haemophilus influenzae
Legionella spp.
Aspiration
Respiratory viruses

Antibiotics

Fluoroquinolone[a]
Levofloxacin 750 mg IV/PO daily
Moxifloxacin 400 mg IV/PO daily
Or
Macrolide[b]
Azithromycin, 500 mg PO day 1, then 250 daily
Clarithromycin, 250 mg BID
And
β-lactam
Cefotaxime, ceftriaxone, ampicillin, ertapenem

[a] Second regimen should be substituted if fluoroquinolones have been used in the previous 3 months.

[b] Doxycyline 100 mg BID may be substituted in macrolide-intolerant patients.

BOX 32.6

Guidelines for empiric antibiotic therapy for community-acquired pneumonia in patients requiring intensive care hospitalization

Common pathogens

Streptococcus pneumoniae
Legionella spp.
Staphylococcus aureus[a]
Haemophilus influenzae
Pseudomonas aeruginosa
Enterobacteriacae spp.
Gram-negative bacilli
Aspiration
Respiratory viruses

Antibiotics[a]

β-lactam[b]
Ceftriaxone, cefotaxime, or ampicillin–sulbactam
And
Azithromycin or respiratory fluoroquinolone

[a] If *S. aureus* infection is suspected, either vancomycin or linezolid should be added to the preceding regimen.

[b] If *P. aeruginosa* is a likely organism, an antipseudomonal β-lactam (piperacillin–tazobactam, cefepime, imipenem, or meropenem) should be substituted for the β-lactams listed earlier. Either ciprofloxacin or levofloxacin should accompany the antipseudomonal β-lactam or the combination of an aminoglycoside with azithromycin.

mycoplasma resistance to macrolides is a growing problem, particularly in Asia. Doxycycline can be used for those who are macrolide intolerant.

Patients who are >50 or have comorbid illnesses (Box 32.4) are more likely to require hospitalization. Some can be managed as outpatients but will require close follow-up, preferably within 3 days. Gram-negative organisms, such as *Haemophilus influenzae* and *Moraxella catarrhalis*, are more common, particularly in persons who smoke or have chronic obstructive pulmonary disease (COPD). A respiratory fluoroquinolone, such as levofloxacin or moxifloxacin, is an acceptable choice for these patients unless they have received a fluoroquinolone in the previous 3 months or are allergic to them, in which case a macrolide plus a β-lactam should be given.

Patients hospitalized with pneumonia of moderate severity require empiric therapy to cover the organisms listed in Box 32.5. The first antibiotic dose should be given as soon as the diagnosis is made.

Empiric antimicrobial therapy for hospitalized patients should include either a respiratory fluoroquinolone alone or a macrolide combined with a β-lactam antibiotic. If fluoroquinolones have been used in the previous 3 months, the latter regimen is preferred. Ertapenem is as efficacious as ceftriaxone but has not been extensively studied. It is useful when a broader spectrum agent is necessary to cover anaerobes and gram-negative organisms, but it is not active against *Pseudomonas aeruginosa*. Ceftaroline, the first cephalosporin with methicillin-resistant *S. aureus* (MRSA) activity, is noninferior to ceftriaxone for CAP requiring hospitalization. Tigecycline, a glycylcycline with MRSA and anaerobic activity, is noninferior to levofloxacin in hospitalized patients with CAP. Neither ceftaroline nor tigecycline has activity against *Pseudomonas*. Given the efficacy and safety of current antibiotics for CAP, the use of these newer agents should be limited to specific circumstances when standard antibiotics are not appropriate. When the etiologic agent and its sensitivity are known, the antibiotic regimen should be as narrow and as cost-effective as possible.

Severe pneumonia causes increased mortality, ranging from 50% to 70% in some studies, especially during the first 7 days. Severe pneumonia manifests as hypoxia, tachypnea, multilobe involvement or consolidation, and signs of septic shock. These patients should receive ICU care. Organisms listed in Box 32.6 may cause more severe disease, although the severity of the pneumonia and ultimate outcome is more a function of the immune response of the host. Initial antimicrobial therapy should include either a macrolide or fluoroquinolone plus a β-lactam. Several retrospective studies indicate that the combination of a β-lactam plus macrolide may result in better outcomes especially in cases of severe CAP, although current guidelines do not include the obligatory addition of macrolides in this setting. Persons requiring ICU monitoring should have blood cultures drawn and sputum studies for Gram stain and culture. Empiric antibiotic choices should take into account organisms on

the Gram stain. Gram-positive cocci in clusters suggests *S. aureus,* which is often seen as a complication of influenza. MRSA is commonly found in the community and may cause a severe necrotizing pneumonia. For persons admitted to the ICU with severe pneumonia and clusters of gram-positive cocci in the sputum or cavitary lesions in the lung, initial therapy should include either vancomycin or linezolid. If vancomycin is used, strong consideration should be given to the addition of clindamycin. Linezolid and clindamycin have been shown in vitro to decrease bacterial toxin production. When a patient admitted to the ICU has severe structural defects of the lung (COPD or bronchiectasis) and gram-negative organisms in the sputum, initial antibiotics should have antipseudomonal activity (see Box 32.6).

Although rare, tularemic pneumonia should be considered in patients with exposure to wild mammals, especially rabbits, and ticks. Intravenous gentamicin should be given when tularemic pneumonia is considered. *Coxiella burnetii* causes an atypical pneumonia often accompanied by hepatosplenomegaly. It is endemic in many hot, dry areas. The most common reservoirs are sheep, goats, cattle, and ticks. Tetracycline or doxycycline is the recommended therapy. *Chlamydia psittaci* is an atypical pneumonia that should be considered in patients with exposure to birds, especially parrots. Splenomegaly and an atypical pneumonia suggests psittacosis, which is treated with tetracycline or doxycycline. *Mycobacterium tuberculosis* should be considered early when pneumonia does not respond to usual antibiotics. Fungal infections, such as blastomycosis, histoplasmosis, cryptococcosis, and coccidioidomycosis, may also present as a CAP and should be considered in persons with soil exposure or residence in or travel to endemic areas.

Viruses are responsible for up to one-third of the cases of CAP. Influenza A and B viruses are common worldwide and cause yearly seasonal epidemics. Influenza A viruses can also cause pandemics such as that caused by the 2009 novel H1N1 virus. Influenza can cause a primary viral pneumonia or predispose to secondary bacterial pneumonia, especially due to *S. aureus* or *S. pneumoniae*. Avian influenza virus infections such as H5N1 and H7N9, while limited in number, are important due to the very high case fatality rates (~50%), typically due to overwhelming pneumonia. Other viruses associated with CAP include parainfluenza, rhinoviruses, adenoviruses, and coronaviruses. Human metapneumovirus (hMPV) most commonly occurs in late winter or early spring in young children and adults >65 years, with symptoms ranging from mild disease to severe pneumonia. hMPV may cause exacerbations of asthma. Human bocavirus and parechovirus types 1, 2, and 3 cause lower respiratory tract infection in children. Respiratory syncytial virus (RSV) can cause CAP in adults, particularly those who are immunocompromised. Two novel human coronaviruses (CoV) have been implicated in severe respiratory infection. Severe acute respiratory syndrome (SARS) caused by the SARS CoV, was first identified in 2002, in China and Southeastern Asia, resulting in >8,000 infections worldwide with a 10% case fatality rate before the last cases were seen in the summer of 2003. In 2012, a severe respiratory illness with a high case fatality rate was identified in Saudi Arabia and Jordan. This Middle Eastern respiratory syndrome (MERS) is due to a novel coronavirus, MERS-CoV. As of April 2019, >2,400 cases with a case fatality rate of 34% have been identified, with the majority of cases occurring on the Arabian Peninsula. Treatment for all these viruses, except for influenza, is supportive. The neuraminidase inhibitors, oseltamivir, zanamivir, and peramivir decrease the duration of illness and may reduce complications seen with influenza and the spread of influenza to other patients. They should be given within the first 48 hours of symptom onset; however, patients requiring hospitalization or at high risk for complications from influenza, including pregnant women, persons with immunocompromise, or persons with underlying chronic medical illnesses, should be treated even if they present beyond 48 hours of symptom duration. Baloxavir is a cap-dependent endonuclease inhibitor used to treat influenza. Studies show similar efficacy to oseltamivir, but there are concerns for the development of resistance. The adamantanes, amantidine and rimantidine should not be used to treat influenza due to widespread resistance.

Therapeutic response

Antibiotic choices should generally not be altered during the first few days of therapy unless there is marked deterioration or cultures indicate the need for a change. Usually 48 to 72 hours are required for significant clinical improvement. Fever usually lasts 2 to 4 days but may last longer, especially in persons with bacteremia. The white blood cell count generally returns toward normal after 4 days, and blood cultures become negative 24 to 48 hours after starting treatment. Duration of therapy should be individualized according to the infecting organism, response to treatment, and the overall health of the patient. Antibiotic therapy for 5 to 7 days is generally sufficient, especially in persons treated as outpatients or those inpatients who have timely response to therapy. Routine prolongation of therapy beyond 8 days is not usually beneficial. Because of its long tissue half-life, azithromycin may be given for a shorter durations. Patients with pneumonia caused by *S. pneumoniae* should usually receive antibiotics for 72 hours after the resolution of fever. Persons who are bacteremic, immunocompromised, or develop lung abscess or empyema may require longer courses. When the patient is hemodynamically stable, improving clinically, and tolerating oral intake, transition to oral antimicrobials should be considered. It is not necessary that the patient be afebrile, but the fever curve should be improving. Persons with *S. aureus* pneumonia should receive at least 2 weeks of treatment unless a hematogenous source is suspected, in which case therapy should be continued for a minimum of 4 weeks.

Resolution of abnormal radiographic findings lags behind clinical improvement and is slower in elderly patients, smokers, and those with comorbidities or multilobe involvement. Multiple chest radiographs in the hospital are unnecessary except for intubated patents and those with clinical deterioration. Patients who are >40 years of age or are smokers should be followed until complete radiographic resolution of the infiltrate is demonstrated with follow-up chest radiographs obtained between 7 and 12 weeks after completion of therapy. If abnormalities have not resolved or greatly improved, the possibility of an occult neoplasm should be considered.

There are a number of reasons for failure in the treatment of CAP. The serum level of the chosen antibiotics may not be high enough. Some antibiotics, such as the aminoglycosides, may not achieve high

enough concentrations in the lung tissue. The etiologic agent may be resistant to the antibiotics, or less likely, resistance may develop during therapy. Initial improvement followed by recurrent fever may be due to the development of thrombophlebitis, empyema, lung abscess, or drug fever. Lack of clinical improvement should raise suspicion for alternative etiologies, such as viruses, mycobacteria, fungi, or parasites. Choice of antibiotic, dosage, and route of administration should be re-evaluated in this setting. Clinicians must always keep in mind the possibility of noninfectious mimics of pneumonia, such as pulmonary infarction, organizing pneumonia, carcinoma, pulmonary edema, atelectasis, sarcoidosis, hypersensitivity pneumonitis, and drug-induced pulmonary disease.

Suggested reading

Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.

Kaziani K, Sotiriou A, Dimopoulos G. Duration of pneumonia therapy and the role of biomarkers. *Current Opin Infect Dis*. 2017;30:221–225.

Lim WS, van der Eerden MM, Laing R, et al. Defining community-acquired pneumonia severity on presentation to hospital: An international derivation and validation study. *Thorax*. 2003;58:377–382.

Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(Suppl 2):S27–S72.

Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med*. 2014;371:1619–1628.

Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet*. 2015;386:1097–1108.

Ranzani OT, Taniguchi LU, Torres A. Severity scoring systems for pneumonia: Current understanding and next steps. *Curr Opin Infect Dis*. 2018;24:2227–2236.

Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. *Clin Microbiol Infect*. 2011;17 (Suppl 6):E1–E59.

Wunderink RG, Waterer G. Advances in the causes and management of community acquired pneumonia in adults. *BMJ*. 2017;358:j2471.

33

Nosocomial pneumonia

Cheston B. Cunha and Burke A. Cunha

Introduction

Nosocomial pneumonia (NP) may be defined as pneumonia that occurs after 5 or more days in hospital. NP is synonymous with hospital-acquired pneumonia (HAP). The subset of NP/HAP patients on ventilators are referred to as *ventilator-associated pneumonias* (VAP). NP occurring early (i.e., <5 days after admission) actually represents incubating community-acquired pneumonia (CAP) that has become clinically manifest early after hospital admission. For this reason, the respiratory pathogens causing "early NP" are the usual CAP pathogens (e.g., *Streptococcus pneumoniae*). With true NP (≥5 days after admission), the respiratory pathogens acquired in hospital are aerobic gram-negative bacilli (GNB). The most important, but not the most common, NP pathogen is *Pseudomonas aeruginosa*; some other GNB are also important NP pathogens (e.g., *Klebsiella pneumoniae*) (Box 33.1).

In this chapter, the term "NP" is used rather than a designation of the clinically meaningless healthcare-associated pneumonia (HCAP). Nursing home-acquired pneumonias (NHAP) are not the same as NP. First, the pathogens differ. NHAP pathogens are the same as CAP pathogens (e.g., *S. pneumoniae, Haemophilus influenzae*). Even though the respiratory secretion and urine/feces of nursing home/chronic care facility residents may be colonized by "hospital organisms" (e.g., GNB), these organisms are not NHAP pathogens (i.e., they do not cause NHAP). Pathogens aside, the NHAP mean length of stay (LOS) is approximately 7 days, which is the same LOS (~7 days) as for hospitalized CAP. This is in marked contrast to the NP LOS (~14 days). For these reasons, it is clinically important to differentiate NHAP from NP and not combine them as HCAP.

Mimics of nosocomial pneumonia

Because the definition of NP is based on epidemiologic rather than pathologic criteria, there are many noninfectious disorders that fit the epidemiologic definition of NP. In intensive care unit (ICU) patients, there are many mimics of NP with fever, leukocytosis, hypoxemia, and pulmonary infiltrates on chest x-ray (CXR). Many of these mimics of NP have pulmonary infiltrates but are disorders unassociated with fever/leukocytosis. In such patients with mimics of NP, the fever/leukocytosis are due to unrelated extrapulmonary processes (e.g., drug fever, phlebitis, cerebrovascular accidents, myocardial infarction, gastrointestinal bleed, adrenal insufficiency). Patients with acute respiratory distress syndrome (ARDS) often have fever/leukocytosis, hypoxemia, and pulmonary infiltrates that are unrelated to NP but rather are due to drug-induced pancreatitis mimicking NP. Other mimics of NP may have fever. In such cases, the diagnosis is usually suggested by associated extrapulmonary signs/symptoms (e.g., systemic lupus erythematosus [SLE] with pneumonitis. Before fever, leukocytosis, hypoxemia, and pulmonary infiltrates are ascribed to NP, the clinician should carefully rule out the many mimics of NP based on nonpulmonary

BOX 33.1

Clinical diagnosis of nosocomial pneumonia[a]

Appearance of new pulmonary infiltrates after 5 or more days in hospital with:

- Otherwise unexplained new fever (>38°C/100°F)
- Otherwise unexplained leukocytosis (± left shift)
- Otherwise unexplained pulmonary infiltrates (*consistent* with bacterial pneumonia)[b]

[a] Definition does *not* include positive respiratory secretion cultures in ventilated patients.

Positive blood cultures (excluding blood culture skin contaminants (e.g., methicillin-sensitive *Staphylococcus aureus* [MSSA], methicillin-resistant *S. aureus* [MRSA]) or secondary to extrapulmonary infections (e.g., central venous catheter infection, *P. aeruginosa*, *K. pneumoniae*, *Enterobacter* spp., *Acinetobacter baumannii.*

[b] See Table 33.2 (Mimics of nosocomial pneumonia).

findings from the history, physical examination, and relevant laboratory tests (Table 33.1). In ventilated patients, mimics of NP may also have positive respiratory secretion cultures. All too often, the clinical diagnosis of NP is based on "guilt by association" (e.g., fever/leukocytosis, hypoxemia, infiltrates on CXR, and positive respiratory secretion cultures).

Since a definitive diagnosis of NP is problematic (i.e., lung biopsy), some degree of overtreatment is unavoidable. If mimics of NP are excluded and the presumed diagnosis is NP, empiric monotherapy should be directed against the most important NP pathogens (e.g., *P. aeruginosa*) and not based on respiratory secretion cultures.

Respiratory secretion colonization versus infection

In intubated patients, respiratory secretions rapidly become colonized by nosocomial GNB. Nosocomial GNB colonization in the ICU occurs as a function of time. Antimicrobial therapy, if not chosen carefully, may not only promote colonization of respiratory secretions with GNB, but also colonization with *Staphylococcus aureus*, such as methicillin-sensitive *S. aureus* (MSSA) or methicillin-resistant *S. aureus* (MRSA). The common GNB colonizers of respiratory secretions (e.g., *Enterobacter* spp.*, Citrobacter freundii, Burkholderia cepacia, Stenotrophomonas maltophilia*) are relatively avirulent and rarely, if ever, cause NP. Until proved otherwise, if these organisms are cultured from respiratory secretions of ventilated patients, they should be considered as "colonizers" and not treated with antibiotics (Box 33.1). Respiratory secretions of ventilated patients are also commonly colonized by bona fide NP pathogens (e.g., *P. aeruginosa, K. pneumoniae*, *Serratia marcescens*). In contrast, *Acinetobacter baumannii* is a common colonizer of respiratory secretions but is rarely a cause of sporadic NP. Unless part of an outbreak/cluster, respiratory secretion cultures positive for *A. baumannii* should be regarded as colonization and the cause of NP until proved otherwise. Similarly, nosocomial Legionnaires'

TABLE 33.1 **RADIOGRAPHIC MIMICS OF NOSOCOMIAL PNEUMONIA**

Fever *plus* leukocytosis plus CXR infiltrates *plus* positive respiratory secretion cultures ≠ NP

Bronchiolitis obliterans organizing pneumonia (BOOP)[a]	Aspiration (chemical)[a]
Sarcoidosis[a]	Phantom tumor (localized CHF)[a]
SLE pneumonitis	Bronchogenic carcinoma[a]
Rheumatoid lung[a]	Metastatic carcinoma[a]
Pulmonary infarcts	Lymphoma
Goodpasture's syndrome	Radiation pneumonitis[a]
Wegener's granulomatosis	Lung contusion
Acute respiratory distress syndrome (ARDS)	Pulmonary hemorrhage
Drug-induced pulmonary disease	Mucus plug[a]
Noncardiogenic (neurogenic) pulmonary edema[a]	
Cardiogenic pulmonary edema (LVF)[a]	

Abbreviations: NP = nosocomial pneumonia; SLE = systemic lupus erythematosus; LVF = left ventricular failure; CHF = congestive heart failure.
[a] The disorders listed may mimic NP; many are afebrile disorders and may be associated with leukocytosis/left shift. Fever may be present with disorders listed, not typically afebrile infection, but search should prompt for a nonpulmonary cause of the fever. ARDS is in the ICU and commonly due to acute pancreatitis (drug-induced), and the patient is febrile secondary to pancreatitis not ARDS.
Diagnosis of NP should not be based on "guilt by association." Similarly, positive respiratory secretion's culture should be considered as colonization, not NP, until proved otherwise. Other clues to the clinical nonsignificance of positive respiratory secretion cultures are growth of non-NP pathogens, *Stenotrophomonas maltophilia, Burkholderia cepacia*, or colonizing pathogens (e.g., *Enterobacter* spp.*, S. aureus, Citrobacter* spp.) or multiple organisms, pathogens that are significant only if in a cluster/outbreak (e.g., *Acinetobacter* spp.).
Adapted from Cunha BA, ed. *Pneumonia Essentials*, 3rd ed. Sudbury, MA: Jones & Bartlett; 2007.

disease occurs in clusters/outbreaks and only rarely occurs as sporadic NP. Gram-positive cocci (e.g., enterococci) or *S. aureus* (either MSSA/MRSA) are common colonizers of respiratory secretions of ventilated patients receiving certain broad-spectrum antibiotics (e.g., ciprofloxacin, imipenem, ceftazidime). However, group D streptococci rarely, if ever, cause NP. In intubated patients with presumed NP, organisms cultured from respiratory secretion are often considered a cause of NP and are covered/treated. There is little to no relationship between respiratory secretion cultures and distal lung parenchymal NP pathogens. The clinical and pathologic features of *S. aureus* (MSSA/MRSA) CAP have well-described clinical parameters to evaluate potential MSSA/MRSA NP. *S. aureus* (MSSA/MRSA) CAP (virtually always associated with influenza or influenza-like illness) patients are critically ill, cyanotic, and have a fulminant necrotizing/hemorrhagic pneumonia with rapid cavitation in <72 hours (like *P. aeruginosa* NP). This is in contrast to the intubated patient with MSSA/MRSA cultured from respiratory secretions, without the clinical/radiologic characteristics of a necrotizing/hemorrhagic pneumonia. Unless the patient has MSSA/MRSA tracheobronchitis, MSSA/MRSA in respiratory secretions represents colonization and not MSSA/MRSA NP. Furthermore, adding MSSA/MRSA coverage in the empiric treatment of NP has no effect on outcomes (Table 33.2).

Without invasive diagnostic tests (e.g., lung biopsy), the definitive diagnosis of NP remains elusive. The epidemiologic diagnosis of NP is based on fever/leukocytosis, hypoxemia, and new-onset pulmonary infiltrates compatible with bacterial pneumonia. Obviously, there are many noninfectious mimics of NP with the same clinical presentations. *P. aeruginosa* and *S. aureus* in particular have readily recognizable clinical presentations (e.g., fulminant necrotizing/hemorrhagic pneumonias). When either of these two organisms is responsible for pneumonia (e.g., CAP due to *S. aureus* [+ influenza] or NP due to *P. aeruginosa*), such patients acutely deteriorate clinically with high spiking fevers accompanied by cyanosis and, on CXR, rapid cavitation (≤72 hours) after infiltrate appearance. Fulminant necrotizing/hemorrhagic pneumonia due to either *P. aeruginosa* NP or *S. aureus* (CAP + influenza) is frequently fatal. The clinical presentation of *P. aeruginosa* NP or *S. aureus* CAP (+ influenza) is distinctive and reflects the underlying lung pathology. The epidemiologic definition of NP is, but should not be, based on nonspecific clinical findings and respiratory secretion cultures. In intubated ICU patients in the United States with presumed NP, respiratory secretion cultures often are positive (>25%) for MSSA/MRSA. If MSSA/MRSA were actual pathogens in >25% of NP, this would be readily apparent in very high mortality/autopsy findings, which is not the case. MSSA/MRSA remains a rare cause of NP. In a ventilated patient, if either MSSA/MRSA or *P. aeruginosa* are cultured from respiratory secretions and the patient's clinical status has not dramatically deteriorated and there is no cyanosis and no rapid cavitation (≦72 hours) on CXR, then the pathogens represent colonization and not NP due to either of these pathogens. However, both *P. aeruginosa* or *S. aureus* may cause tracheobronchitis (purulent respiratory secretions with a negative CXR), which should be treated to preserve respiratory function.

TABLE 33.2 **NOSOCOMIAL PATHOGENS AND RESPIRATORY SECRETION COLONIZERS**

Nosocomial pneumonias: respiratory pathogens	Respiratory secretions: common colonizers
Common pathogens	**Common colonizers**
Pseudomonas aeruginosa	*Staphylococcus aureus* (MSSA/MRSA)
Klebsiella pneumoniae	*Pseudomonas aeruginosa*
Uncommon	*Acinetobacter baumannii*
Serratia marcescens	*Enterobacter* spp.
Escherichia coli	*Stenotrophomonas* (*Xanthomonas*) *maltophilia*
Rare	*Burkholderia* (*Pseudomonas*) *cepacia*
Acinetobacter baumannii [a]	*Citrobacter freundii*
Legionella spp.[a]	

[a] Nosocomial pneumonias due to these organisms are virtually always part of a cluster/outbreak.
Abbreviations: MRSA = methicillin-resistant *Staphylococcus aureus;* MSSA = methicillin-sensitive *Staphylococcus aureus.*

Optimal empiric monotherapy for nosocomial pneumonia

Until there are better methods to accurately diagnose NP, some overtreatment is understandable and clinically prudent. Because some overtreatment is unavoidable due to difficulties in diagnosis, clinicians use antibiotics as selectively as possible to empirically treat presumed NP. In ventilated patients optimal empiric monotherapy should have a high degree of anti-*P. aeruginosa* activity (e.g., meropenem, cefepime). In addition to an appropriate spectrum for NP (e.g., anti-*P. aeruginosa*), the antibiotic selected should have a "low resistance potential" to prevent the emergence of multidrug-resistant (MDR) GNBs as well as not promoting selection of *S. aureus* in respiratory secretions. The antibiotics often used in the therapy of NP that are most likely to result in the emergence of MDR GNBs are ceftazidime, imipenem, and ciprofloxacin. In addition, ceftazidime and ciprofloxacin are likely to select out MSSA/MRSA in respiratory secretions. Further proof of the unimportance of including MRSA coverage in NP empiric therapy is that MRSA coverage does not improve outcomes. MRSA coverage is not necessary for the empiric therapy of NP (Boxes 33.2 and 33.3).

For NP, well-selected monotherapy is optimal and double-drug therapy offers no advantage. When antibiotics had relatively little *P. aeruginosa* activity, double-drug therapy was used. Because currently available antibiotics have a high degree of anti-*P. aeruginosa* activity, optimal empiric monotherapy is effective. In bona fide *P. aeruginosa* NP, double-drug therapy is preferred.

If MDR *K. pneumoniae* or MDR *P. aeruginosa* strains are the cause of NP, meropenem remains useful against most non–metallo

BOX 33.2

Nosocomial pneumonia: selection of antibiotic empiric therapy

Key factors in empiric antibiotic selection for NP

1. High degree of activity against *Pseudomonas aeruginosa* (and other GNB NP pathogens). MSSA/MRSA coverage unnecessary.
2. Penetrates lung parenchyma in therapeutic concentrations
3. "Low resistance" potential (avoid ciprofloxacin, ceftazidime, imipenem)
   Carefully selected antibiotics that:
   - Do not increase **prevalence** of MSSA/MRSA
   - Do not increase **prevalence** of VRE
   - Do not increase **potential** for *Clostridium difficile* diarrhea/colitis
4. Good safety profile

Unimportant factors in NP antibiotic selection for NP

1. MSSA/MRSA coverage
2. Penetration into epithelial cells, alveolar macrophages (except for *Legionella* spp.)

Abbreviations: NP = nosocomial pneumonia; GNB = gram-negative bacteria; MSSA = methicillin-sensitive *Staphylococcus aureus*, MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

β-lactamase-producing GNBs. For meropenem-resistant strains, effective antimicrobial therapy is relatively limited (e.g., colistin).

Nosocomial pneumonia unresponsive to appropriate antibiotic therapy

Empiric therapy of NP is usually given for 1 to 2 weeks. After 2 weeks of therapy, lack of CXR improvement suggests an alternate diagnosis rather than ineffective antimicrobial therapy or the development of antibiotic resistance.

After 2 weeks of optimal anti-*P. aeruginosa* NP therapy, ventilated patients with fever, leukocytosis, hypoxemia, and persistent pulmonary infiltrates on CXR may have herpes simplex virus-1 (HSV-1) NP. In a patient without preexisting cardiopulmonary disease, otherwise unexplained "failure to wean" off a ventilator after 2 weeks of appropriate antimicrobial therapy for NP should suggest the possibility of HSV-1 NP. HSV-1 NP is an underrecognized clinical entity. If HSV-1 NP is suspected, diagnostic bronchoscopy should be performed. Herpetic vesicles in the oropharynx/airways are indicative of NP severity rather than lower respiratory tract infection (i.e., HSV-1 NP). HSV-1 cultured from respiratory secretions suggests colonization, not infection. Bronchoalveolar lavage (BAL) fluid should be obtained for cytologic diagnosis. Viral cytopathic effects in distal respiratory epithelial cells are diagnostic of active infection (not viral colonization/reactivation). Cowdry type A inclusion bodies (CPEs) in respiratory epithelial cells from BAL specimens are diagnostic of HSV-1 NP. If HSV-1 CPEs are present in BAL specimens, empiric therapy with acyclovir should be initiated (Box 33.4). Rapid improvement in oxygenation (e.g., decreased FiO_2/decreased A-a gradient) follows after 3 to 5 days of acyclovir therapy. Patients can then be weaned off the ventilator over the next several days.

Importantly, cytomegalovirus (CMV) in normal hosts, unlike HSV-1, is not a common cause of NP. The diagnosis of CMV NP is based on demonstrating CMV CPEs in BAL cellular specimens. Elevated CMV immunoglobulin M (IgM) titers/positive CMV PCR are not diagnostic of CMV NP. CMV PCR positivity reflects CMV reactivation in peripheral white blood cells, not infection in the lungs or elsewhere.

BOX 33.3

Empiric therapy of nosocomial pneumonia

Gram-negative nosocomial pneumonia

Preferred empiric therapy[a]

Nosocomial pneumonia
Preferred therapy coverage directed primarily against *P. aeruginosa* (MRSA coverage unnecessary)
Meropenem 1 g (IV) q8h × 2 weeks
Levofloxacin 750 mg (IV) q24h × 2 weeks
Cefepime 2 g (IV) q8h ± amikacin 1 g (IV) q24h × 2 weeks[b]

Alternative therapy
Piperacillin/tazobactam 4.5 g (IV) q6h *plus* amikacin 1 g (IV) q24h × 2 weeks

Specific therapy

MDR *Klebsiella pneumoniae*
Tigecycline 200–400 mg (IV) × 1 dose, then 100–200 mg (IV) q24h × 2 weeks
Colistin 1.7 mg/kg (IV) q8h × 2 weeks ± rifampin 600 mg (IV) q24h × 2 weeks
Polymyxin B 1.25 mg/kg (IV) q12h × 2 weeks

MDR *Acinetobacter baumannii*
Tigecycline 200–400 mg (IV) × 1 dose, then 100–200 mg (IV) q24h × 2 weeks
Ampicillin/sulbactam 3 g (IV) q6h × 2 weeks
Colistin 1.7 mg/kg (IV) q8h ± rifampin 600 mg (IV) q24h × 2 weeks
Polymyxin B 1.25 mg/kg (IV) q12h × 2 weeks

MDR *Pseudomonas aeruginosa*
Colistin 1.7 mg/kg (IV) q8h ± rifampin 600 mg (IV) q24h × 2 weeks
Polymyxin B 1.25 mg/kg (IV) q12h × 2 weeks

Abbreviation: MDR = multidrug resistant.

[a] Doses are for adults with normal renal function.

[b] Note that therapy of NP with piperacillin–tazobactam requires a higher than usual dose plus a second drug (e.g., amikacin). Do not use piperacillin–tazobactam at the usual dose 3.375 mg (IV) q6h or as monotherapy for NP.

Adapted from Cunha BA, ed. *Antibiotic Essentials*, 12th ed. Sudbury, MA: Jones & Bartlett; 2013.

BOX 33.4

Nosocomial HSV-1 pneumonia

Symptoms

"Failure to wean" off respirator (in patients *without preexisting lung disease*)
In immunocompetent hosts

Signs

Low-grade fevers
Unexplained hypoxemia (*with normal/near normal CXR*)
CXR unchanged after 2 weeks of optimal NP antibiotic therapy

Laboratory tests

Leukocytosis (± left shift)
Otherwise unexplained ↓ pO_2 or ↑ A-a gradient (>30)
HSV serology: unhelpful
Diagnostic bronchoscopy:
HSV vesicles:
Usually no HSV vesicles in respiratory passages
If present, HSV vesicles in respiratory tract (reflective of HSV severity/reactivation) not HSV
NP
Viral culture:
± HSV-1 virus cultured from respiratory secretions (Dx of colonization *not* infection)
Cytology:
HVS-1 intranuclear inclusion bodies (Cowdry type A). CPEs are Dx of infection not colonization/reactivation.

Empiric therapy

Acyclovir 10 mg/kg (IV) q8h × 7–10 days
(Results in clinical improvement in 3–5 days) (↓ FiO_2, ↓ A-a gradient)

Abbreviations: CSX = chest x-ray, HSV = herpes simplex virus.

Cunha BA, ed. *Pneumonia Essentials*, 3rd ed. Sudbury, MA: Jones & Bartlett; 2007.

Suggested reading

Berman SJ, Fogarty CM, Fabian T, et al. Meropenem monotherapy for the treatment of hospital-acquired pneumonia: Results of a multicenter trial. *J Chemother*. 2004;16:362–371.

Bouza E, Barillo A. Nosocomial pneumonia. In Cunha BA, ed. *Infectious Diseases in Critical Care*, 3rd ed. New York: Informa Healthcare; 2007: 178–207.

Bouza E, Giannella M, Torres M, et al. Herpes simplex virus: A marker of severity in bacterial ventilator-associated pneumonia. *J Crit Care*. 2011;26:432.e1–432.e6.

Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2002;165:867–903.

Cunha BA. Effective antibiotic resistance and control strategies. *Lancet*. 2001;357:1307–1308.

Cunha BA. Nosocomial Pneumonia in the Critical Care Unit. In Cunha CB, Cunha BA, eds. Infectious Diseases and Antimicrobial Stewardship in Critical Care Medicine, 4th ed., CRC Press, 2020:231–242.

Cunha BA. Nosocomial pneumonia: Diagnostic and therapeutic considerations. *Med Clin North Am*. 2001;85:79–114.

Cunha BA. Nosocomial pneumonia. In Cunha BA, ed. *Pneumonia Essentials*, 3rd ed. Sudbury, MA: Jones & Bartlett; 2010: 111–123.

Cunha BA. Cytomegalovirus (CMV) reactivation in the ICU: Not a cause of late ventilator associated pneumonia (VAP). *Crit Care Med*. 2010;38:341–342.

Eisenstein L, Cunha BA. Herpes simplex virus type 1 (HSV-1) pneumonia presenting as failure to wean. *Heart Lung*. 2003;32:65–66.

Ewig S, Welte T, Torres A. Is healthcare-associated pneumonia a distinct entity needing specific therapy? *Curr Opin Inf Dis*. 2012;25:166–175.

Griffin AT, Peyrani P, Wiemken TL, et al. Empiric therapy directed against MRSA in patients admitted to the intensive care unit does not improve outcomes in community-acquired pneumonia. *Infection*. 2013;41:517–523.

Laforce FM. Systemic antimicrobial therapy of nosocomial pneumonia: Monotherapy versus combination therapy. *Eur J Clin Microbiol Infect Dis*. 1989;8:61–68.

Limaye A, Boeckh M. CMV in critically ill patients: Pathogen or bystander? *Rev Med Virol*. 2010;20:372–379.

Lode HM, Raffenberg M, Erbes R, et al. Nosocomial pneumonia: Epidemiology, pathogenesis, diagnosis, treatment and prevention. *Curr Opin Infect Dis*. 2000;13:377–384.

Lopez A, Amaro R, Polverino E. Does health care associated pneumonia really exist? *Eur J Intern Med*. 2012;23:407–411.

Merrer J, Santoli F, Appere de Vecchi C, et al. "Colonization pressure"; and risk of acquisition of methicillin-resistant *Staphylococcus aureus* in a medical intensive care unit. *Infect Control Hosp Epidemiol*. 2000;21:718–723.

Novosel T, Hodge L, Weireter L, et al. Ventilator-associated pneumonia: depends on your definition. *Am Surg*. 2012;16:851–854.

Schreiber MP, Chan CM, Shorr AF. Resistant pathogens in nosocomial pneumonia and respiratory failure: Is it time to refine the definition of health care associated pneumonia? *Chest*. 2010;137:1283–1288.

Simoons-Smit AM, Kraan EM, Beishuizen A, et al. Herpes simplex virus type 1 and respiratory disease in critically-ill patients: Real pathogen or innocent bystander? *Clin Microbiol Infect*. 2006;12:1050–1059.

34

Aspiration pneumonia

Jean Gibb and Matthew Bidwell Goetz

Introduction

Aspiration is the inhalation of oropharyngeal or gastric contents into the respiratory tract. Three major syndromes may develop as a consequence of aspiration: chemical pneumonitis, bronchial obstruction secondary to aspiration of particulate matter, and bacterial aspiration pneumonia. Less commonly, interstitial lung disease occurs in persons with chronic aspiration. Which of these consequences emerges is determined by the amount and nature of the aspirated material as well as by the integrity of host defense mechanisms. Aspiration is the main means of bacterial contamination of the lower airways.

The term "aspiration pneumonia" is used to refer to the infectious consequences of inhalation of relatively large volumes of material (macro-aspiration). Although healthy persons frequently aspirate small volumes of pharyngeal secretions during sleep, the development of pneumonia after such micro-aspiration is normally prevented by mechanical (e.g., cough and mucociliary transport) and immunological responses. Pneumonia arises when these host defenses fail to limit bacterial proliferation either because of micro-aspiration of highly virulent pathogens to which the host lacks specific immunity (e.g., *Streptococcus pneumoniae* or enteric gram-negative bacteria) or because of macro-aspiration of lower or higher virulence organisms.

Aspiration may be clinically obvious, as when acute pulmonary complications follow inhalation of vomited gastric contents. Such acute chemical pneumonitis is often referred to as *Mendelson's syndrome*. On the other extreme, so-called *silent aspiration*, as occurs in persons with neurological impairment who lack cough responses, is often followed by the indolent onset of infectious pneumonia consequent to the inhalation of the composite of aerobic and anaerobic microorganisms normally resident in the oropharynx.

In evaluating patients who have aspirated, it is important to bear in mind that there are considerable variations in the subsequent clinical course. Although aspiration of gastric contents is inevitably accompanied by aspiration of the oropharyngeal flora, the initial chemical pneumonitis may resolve without further consequences. In the setting of risk factors for the development of aspiration pneumonia, it may result in the emergence of infection within several days if high-virulence organisms have colonized the oropharynx, or in the delayed emergence of mixed aerobic/anaerobic pneumonia caused by normal oral flora.

Risk factors

The risk for aspiration pneumonia is mediated by anatomic, microbiologic, immunologic, age-related, and comorbidity-related risk factors. First, inability to mechanically clear airways with cough and normal oropharyngeal reflexes provides extended incubation time for proliferation of bacteria in the large and small airways. This loss in structural control affects patients with cerebrovascular and other neurologic disorders, alcoholism, substance use disorders that result in sedation, general anesthesia, seizures, disorders of the gastrointestinal tract, and uncontrolled postoperative pain (see Box 34.1). Because these factors contribute to the risk of pneumonia in both hospitalized and community dwelling patients, such risk factors should be

BOX 34.1

Risk factors for aspiration

Altered level of consciousness
- General anesthesia
- Narcotic and sedative drugs
- Drug overdose and ethanol toxicity
- Metabolic encephalopathies (electrolyte imbalances, liver failure, uremia, sepsis)
- Hypoxia and hypercapnia
- CNS infections
- Dementia
- Seizure

Abnormal glottic closure
- Anesthetic induction or postanesthetic recovery
- Postextubation
- Structural lesions of the central nervous system (tumors, cerebrovascular accident, head trauma)
- Seizures
- Infection (e.g., diphtheria, pharyngeal abscess)

Gastroesophageal dysfunction
- Alkaline gastric pH
- Gastrointestinal tract dysmotility
- Esophagitis (infectious, postradiation)
- Hiatal hernia
- Scleroderma
- Esophageal motility disorders (achalasia, megaesophagus)
- Tracheoesophageal fistula
- Ascites (increased intra-abdominal pressure)
- Intestinal obstruction or ileus
- Diabetes (functional gastric outlet obstruction)

Neuromuscular diseases
- Guillain-Barré syndrome
- Botulism
- Muscular dystrophy
- Parkinson's disease
- Polymyositis
- Amyotrophic lateral sclerosis
- Multiple sclerosis
- Myasthenia gravis
- Poliomyelitis
- Tardive dyskinesia

Mechanical factors
- Nasogastric or enteral feeding tubes
- Upper endoscopy
- Emergency and routine airway manipulation
- Surgery or trauma to the neck and pharynx
- Tumors of the upper airway
- Tracheostomy
- Endotracheal tube
- Zenker's diverticulum

Other factors
- Obesity
- Pregnancy

considered for presentations of aspiration pneumonia in both outpatient and inpatient settings.

Second, disturbance of the normal oropharyngeal or gastric flora contributes to the risk for pneumonia following an aspiration event by increasing colonization of the oropharynx by relatively low-virulence bacteria. The presence of gingivitis, dental plaque, and decayed teeth combined with poor oral hygiene or decreased salivary flow (e.g., due to tube feedings or anticholinergic medications) are associated with this altered oropharyngeal microbiome.

Other iatrogenic interventions or sequelae, including enteral feeding, gastroparesis, or small bowel obstruction, increase colonization of gastric contents by pathogenic microorganisms and contribute to the risk of hospital-acquired pneumonia, especially in patients with altered consciousness, impaired swallowing, and similar comorbid risk factors. While some studies indicate that decreased gastric acidity increases the risk of aspiration pneumonia, recent studies in ICU patients have not demonstrated this association. Moreover, replacement of normal oral flora by more virulent microorganisms such as *Staphylococcus aureus, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* as a consequence of alcoholism, malnutrition, diabetes, and other severe comorbidities or prior antimicrobial therapy also increases the risk of pneumonia following an aspiration event.

Pulmonary clearance defects at the mucociliary level (e.g., secondary to tobacco smoking or influenza) and impairment of normal humoral and cellular host defenses, particularly those conditions that decrease immunoglobulin production (e.g., hematological malignancies) or result in severe neutropenia also increase the risk of developing pneumonia after aspiration. Not surprisingly, risk factors for aspiration leading to pneumonia are often cumulative.

Clinical epidemiology

Between 2002 and 2012, >1.5 million patients were admitted with a diagnosis of aspiration pneumonia to hospitals in the United States (ICD-9-CM procedure code 86.70, 96.71, or 86.72). These hospitalizations accounted for >55,000 deaths over a 10-year period, with a total cost of more than $9 billion. Aspiration syndromes predominantly affected those older than age 65, and >75% of patients hospitalized with sequelae of aspiration had two or more identified risk factors. Swallowing disorders due to neurologic diseases affect 300,000 to 600,000 people each year in the United States. Nearly 40% of stroke patients with dysphagia aspirate and develop pneumonia. Overall, aspiration accounts for approximately 0.5% of all hospitalizations, 3% to 4% of inpatient mortality, and 5% to 23% of all cases of community-acquired pneumonia. As a corollary, aspiration pneumonia is the second most frequent principal cause of pneumonia among US Medicare patients hospitalized for pneumonia.

Among nursing home patients, aspiration pneumonia accounts for up to 30% of cases of pneumonia, occurs at a rate three times that of age-matched patients in the community, and markedly increases the risk of death. Among such patients, difficulty swallowing food, use of tube feedings, requiring assistance with feeding, delirium, and use of sedative medications are the most frequent risk factors for aspiration pneumonia. While the debilitated elderly are at particularly high risk, prior silent aspiration is also common in apparently healthy elderly patients with community-acquired pneumonia.

Aspiration complicates the course of approximately 10% of persons admitted to hospitals for overdosage with sedative or hypnotic agents. Aspiration is the greatest contributor to airway-related mortality in anesthesia-associated airway events; in 2014, the rate of anesthesia-associated fatal aspiration in the United Kingdom was 1 in 350,000. Patient characteristics independently associated with an increased risk of aspiration following general anesthesia include male sex, nonwhite race, age >60 years, dementia, chronic obstructive pulmonary disease, renal disease, malignancy, moderate to severe liver disease, and emergency surgery.

Clinical course and diagnosis

Aspiration of gastric contents results in acute inflammation of the major airways and lung parenchyma. Animal models demonstrate maximal hypoxemia within 10 minutes of aspiration. In these models, the severity of lung injury is greatest when the pH is <2.5, but gastric materials can cause severe pulmonary injury even at higher pH. Local injury results in complement activation as well as release of tumor necrosis factor (TNF-α), interleukin (IL-8), and other pro-inflammatory cytokines which in turn are primarily responsible for the acute nonobstructive complications of chemical aspiration.

Acute clinical symptoms and signs of chemical pneumonitis following aspiration of gastric contents include respiratory distress, fever, cough, reflex bronchospasm, leukocytosis, and pulmonary infiltrates; up to a third of patients who experience aspiration develop acute lung injury or acute respiratory distress syndrome (ARDS), manifested by capillary permeability, proteinaceous edema, hypoxemia, and loss of lung compliance. Life-threatening hypoxemia may develop as a consequence of atelectasis, pulmonary capillary leak, and direct alveolar damage. However, in contrast to the course of gastric aspiration, more modest aspiration of normal oral flora (i.e., mixed aerobic/anaerobic bacteria) may be clinically silent and only later recognized when pneumonia develops.

Following an aspiration event, acute respiratory symptoms often improve with supportive therapy alone. Alternatively, patients may initially improve for several days but then worsen with the onset of recurrent symptoms and signs; this saddleback pattern of illness following an aspiration event often indicates the development of a secondary bacterial pneumonia.

The distinction between progressive chemical lung injury and the presence of bacterial pneumonia is important to avoid unnecessary antibiotic use, especially because pneumonia fails to develop in approximately half of all aspiration events. Furthermore, given the differences in microbial etiology of aspiration pneumonia versus other cases of community-acquired pneumonia, it is important to consider aspiration in persons with pneumonia who have the risk factors listed in Box 34.1 even if an aspiration event has not been witnessed.

Many of the clinical and laboratory manifestations of aspiration pneumonitis overlap with those of bacterial pneumonia and challenge the clinician to distinguish the host response to proliferating microorganisms from host response to the noninfectious inflammatory cascade. Early acute findings are easily attributable to chemical pneumonitis rather than bacterial infection if they follow witnessed vomiting and aspiration of gastric acidic contents. Furthermore, as a general rule, the clinical manifestations of aspiration pneumonia, including fever and respiratory symptoms such as productive cough, dyspnea, and pleuritic pain, are much less dramatic than those of chemical pneumonitis. In elderly patients who are at greatest risk for aspiration, the signs and symptoms of pulmonary infection may be particularly muted and overshadowed by nonspecific complaints such as general weakness, decreased appetite, altered mental status, or decompensation of underlying diseases. Pneumonia following silent aspiration events is often indolent; patients often do not develop fever, malaise, weight loss, and cough for 1 to 2 weeks or more after aspiration. This is an especially common presentation for patients who present with mixed aerobic/anaerobic lung abscesses or empyemas after an aspiration event.

Routine laboratory studies do not distinguish between aspiration pneumonitis and pneumonia. If the event is not witnessed, detection of pepsin A in tracheal aspirate may be used as a marker for gastric aspiration pneumonitis; of note, pepsin C, a normal product of pneumocytes, is present in patients without aspiration. Although procalcitonin distinguishes bacterial pneumonia from viral lower respiratory infections, procalcitonin results have not been shown to discriminate between aspiration pneumonitis and bacterial aspiration pneumonia.

Radiographic evaluation is necessary to establish the diagnosis of pneumonia because there is no combination of historical data, physical findings, or laboratory results that reliably confirms the diagnosis. Limitations of chest radiography for the diagnosis of pneumonia include poor specificity in patients with the ARDS and decreased sensitivity in persons with previous structural lung disease, very early infection, severe dehydration, or profound granulocytopenia. Otherwise, the failure to detect an infiltrate essentially rules out the diagnosis of pneumonia. While spiral CT of the chest provides a more sensitive means of detecting infiltrates than chest radiography, such infiltrates may not actually represent pneumonia. Patients with chronic aspiration may exhibit atelectasis, bronchiectasis, consolidation, and ground-glass opacities in the absence of an acute aspiration or a clinical acute bacterial pneumonia. Esophagography and CT are especially useful in determining whether recurrent aspiration disease is due to a tracheoesophageal or tracheopulmonary fistula.

Radiologic findings do not distinguish between chemical pneumonitis and aspiration pneumonia save for the fact that radiological abnormalities have more rapid onset and resolution with chemical pneumonitis. Pneumonia complicating aspiration most often involves the posterior segment of the right upper lobe, the superior segment of the right lower lobe, or both, as well as the corresponding segments on the left. Manifestations of mixed aerobic/anaerobic infection include necrotizing pneumonia, lung abscess, and empyema (Figures 34.1–34.5). Foreign body aspiration typically occurs in children and manifests as obstructive lobar or segmental overinflation or atelectasis. An extensive, patchy bronchopneumonic pattern may be observed in patients following massive aspiration of gastric contents.

Although the utility of routine sputum examination in uncomplicated pneumonia is much debated, cultures of sputum and two

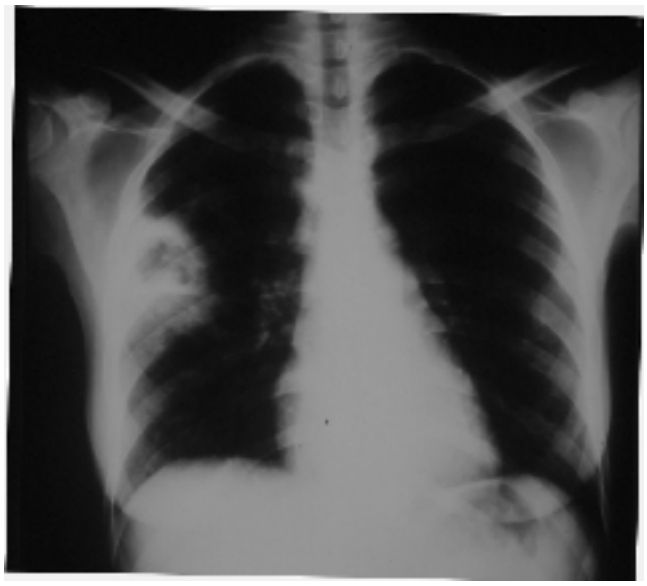

FIGURE 34.1 Mixed aerobic–anaerobic lung abscess following aspiration.

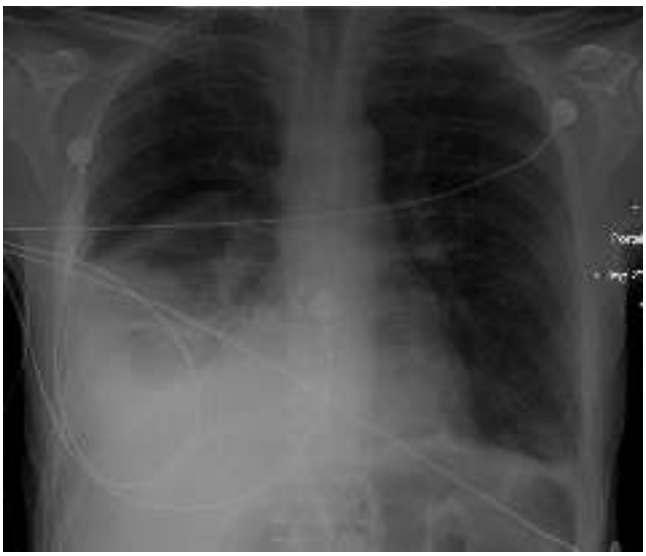

FIGURE 34.3 Chest x-ray showing increased parenchymal opacity in the right mid and lower lung field and bilateral pleural effusions in a patient presenting with progressive shortness of breath and a nonproductive cough for 1 month.

blood (two sets) should be obtained in patients who are medically unstable. Pleural fluid should also be cultured when present, and efforts to obtain sputum should be pursued before initiation of antimicrobial therapy in hospitalized patients who develop pneumonia after an aspiration event. Sputum samples must be carefully collected, transported, and processed in order to optimize the recovery of common aerobic bacterial pathogens such as *S. pneumoniae*. Since anaerobic cultures are not performed for sputum specimens, the presence of mixed bacterial flora on the sputum Gram stain should be used to diagnose polymicrobial infection typical of the mixed aerobic-anaerobic infections. Inspection of the sputum Gram stain is also necessary to ensure that materials being cultured are not unduly contaminated by saliva. Bronchoscopic sampling of the lower respiratory tract (with a protected specimen brush or by bronchoalveolar lavage) and quantitative culture are particularly useful in critically ill patients with hospital-acquired aspiration pneumonia. Such interventions are especially warranted in persons who do not respond to initial antimicrobial therapy.

Unfortunately, despite extensive evaluation, the microbial cause of pneumonia can be identified only 40% to 60% of hospitalized patients. In recent data, only 38% of patients with community-acquired pneumonia admitted to the hospital had an identifiable pathogen, and the incidence of viral pathogens was higher than that of bacterial pathogens. Pathogen detection has improved up to 89% in some studies with use of targeted polymerase chain reaction (PCR) for common bacterial and viral respiratory pathogens, but the utility of PCR for anaerobic flora or polymicrobial infection remains unclear. Nevertheless, identification of the infecting microorganism serves to verify the clinical diagnosis of infection and facilitates the use of specific therapy instead of unnecessarily broad-spectrum antimicrobial agents.

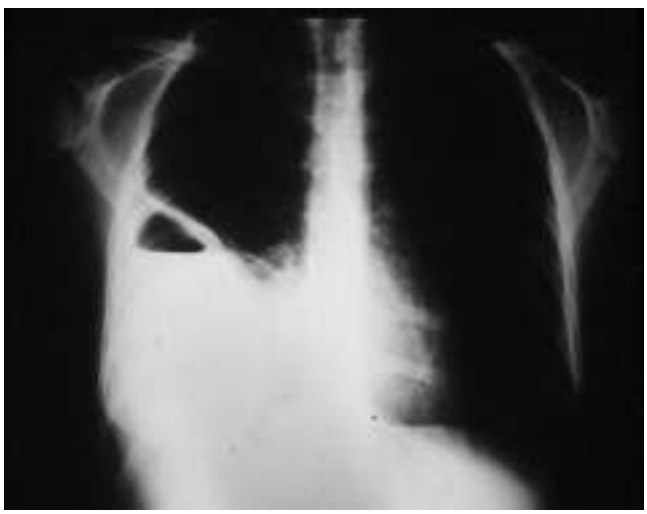

FIGURE 34.2 Mixed aerobic–anaerobic empyema following aspiration.

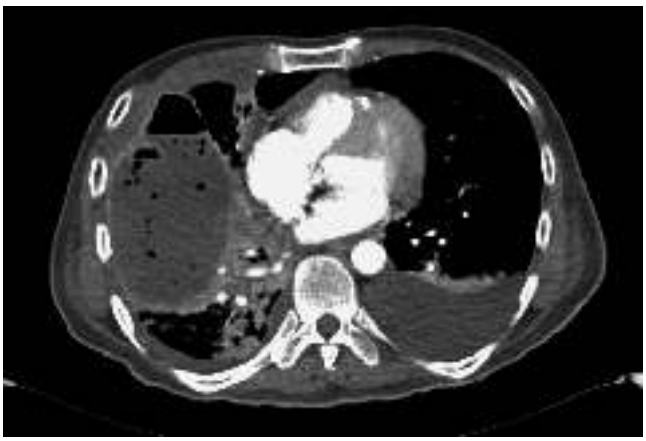

FIGURE 34.4 CT scan correlating with chest x-ray shown in Figure 34.5; interpreted as showing large loculated fluid and foci of gas in the right mid and lower hemithorax; interpreted as loculated fluid versus lung.

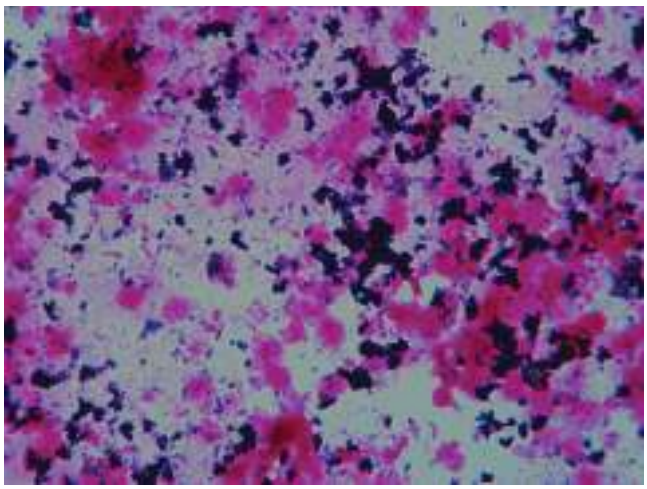

FIGURE 34.5 Gram stain of aspirated material from lung abscess shown in figure showing mixed bacteria flora with gram-positive cocci, gram-negative cocci, and gram-negative rods; the mixture of organisms is highly suggestive of a mixed aerobic–anaerobic infection.

Microbiology

The microbial etiology of aspiration pneumonia is complex and variable. The distribution of responsible pathogens differs in persons with community- versus hospital-acquired illness and varies with the presence or absence of previous antimicrobial exposure, comorbidities, or odontogenic disease.

While some studies show a decreased prevalence of anaerobic bacteria as causes of aspiration pneumonia, the adequacy of anaerobic culture techniques is often uncertain, leaving in doubt whether the true frequency of anaerobic infection has been underestimated. Methods to recover anaerobes in the laboratory are laborious and time-intensive; these are not performed in the majority of current clinical settings for routine sputum culture. In many studies performed during the 1970s, bacteriologic specimens were obtained by percutaneous transtracheal sampling or thoracentesis, and rigorous laboratory methods were used to optimize the recovery of anaerobic bacteria. Although typical causes of bacterial pneumonia such as *S. pneumoniae* were often recovered, these studies demonstrated that viridans streptococci and anaerobic organisms including *Peptostreptococcus, Bacteroides, Prevotella,* and *Fusobacteria* were the predominant pathogens in aspiration pneumonia.

Significant involvement of anaerobes in pulmonary infection is well described in patients with dysphagia or altered mental status and infection in dependent pulmonary anatomy—primarily lower, posterior lobes. Anaerobes are clinically recognized by the presence of purulent sputum and an identifiable odor, the product of volatile short-chain fatty acids by anaerobic microbes. These organisms are frequently implicated in lung abscesses and empyema. Even if viable organisms are not present, presence of *Bacteroides* capsular material alone may contribute to abscess formation. Well-performed studies continue to demonstrate anaerobes in up to 20% of nursing home patients with aspiration pneumonia; increased rates are found in patients with greater levels of debility. Conversely, the frequency of anaerobic infection is somewhat less in edentulous patients.

In communities with high rates of childhood or adult immunity to due to the use of protein-conjugate pneumococcal vaccines, viral etiologies of community-acquired pneumonia are more commonly identified than are bacterial etiologies. When bacterial pathogens are identified in patients with community-acquired pneumonia, *S. pneumoniae, L. pneumophila, M. pneumoniae*, and *C. pneumoniae* predominate and enteric gram-negative organisms are exceedingly rare.

Aerobic bacteria, particularly *S. aureus*, enteric gram-negative bacilli (i.e., *Enterobacteriaceae*) and occasionally *P. aeruginosa*, are more common causes of aspiration pneumonia in persons who develop disease after prior antibiotic exposure, while hospitalized, or in a nursing home setting. Studies in patients receiving care in intensive care units (ICUs) indicate that *S. aureus* and *Enterobacteriaceae* can be isolated from lower respiratory tract specimens from up to 40% of patients with hospital-associated pneumonias, many of which are due to aspiration. *P. aeruginosa* is most common in persons who have received prior intensive antimicrobial therapy or who have underlying bronchiectasis, cystic fibrosis, or severe immunological compromise. Data regarding the frequency of gram-negative pneumonia in patients with less severe aspiration pneumonia (i.e., those not requiring treatment in an ICU) are very sparse. Methicillin-resistant *S. aureus* nasal colonization in the nares carries a poor positive predictive value for the development of methicillin-resistant *S. aureus* (MRSA) pneumonia, but its absence has excellent negative predictive value and should be considered in the de-escalation of antibiotic therapy. Finally, polymicrobial infection, usually with a combination of aerobes and anaerobes, is common in patients with aspiration pneumonia.

Clinical management

Although corticosteroids have long been used in the treatment of acute chemical pneumonitis caused by aspiration, this treatment cannot be recommended. Prospective studies have failed to show a benefit in animal models of acid lung injury or in patients with either aspiration pneumonitis or the ARDS.

Antibiotic use is not warranted in most patients who acutely develop fever, leukocytosis, and pulmonary infiltrates following aspiration as these consequences are caused by chemical irritation and inflammation rather than by established infection. Many patients with chemical pneumonitis improve without any specific antimicrobial therapy. Retrospective data have demonstrated that in settings of witnessed macroaspiration, prophylactic antibiotics fail to decrease mortality or transfers to ICU-level care or prevent bacterial aspiration pneumonia. Prophylactic antibiotics carry the potential to select more resistant pathogens and generate a need for escalation in the spectrum of antibiotic therapy in those do develop aspiration pneumonia. While available studies do not preclude the possibility that there may be some benefit to early antibiotics in selected populations, such as persons with acute life-threatening complications of aspiration (i.e., patients requiring

invasive mechanical ventilation) or those who have aspirated heavily colonized gastric contents (e.g., in the setting of small bowel obstruction), neither are there any data showing that the benefits outweigh the harms. Antibiotics should generally be administered to patients whose symptoms do not improve within 48 to 72 hours or in whom new or progressive signs of pulmonary infection later emerge.

The need to select antibiotics with robust anaerobic activity in the treatment of aspiration pneumonia in patients with aspiration pneumonia is controversial. Vigorous anti-anaerobic therapy may not offer meaningful benefit to patients with simple pneumonia, especially if therapy is not unduly delayed. However, effective anti-anaerobic therapy should be given to persons with aspiration events manifesting as necrotizing pneumonias, lung abscesses, or empyemas. Because of the emergence of β-lactamase–mediated resistance among anaerobes, empirical treatment for complicated aspiration pneumonia likely to involve mixed aerobic-anaerobic flora requires the use of a β-lactam/β-lactamase inhibitor, clindamycin, or metronidazole combined with a penicillin, ampicillin, or an appropriate cephalosporin; if highly resistant aerobic gram-negative organisms are present, monotherapy with a carbapenem also provides excellent anti-anaerobic therapy (Table 34.1). Because of the very frequent concomitant presence of aerobes, metronidazole monotherapy should not be given.

Considering the range of pathogens and antimicrobial resistance, initial therapy of aspiration pneumonia that develops in nursing home or hospitalized patients must be carefully selected. Although monotherapy may be reasonable for immunocompetent patients with mild to moderate diseases who are known or likely to be infected by susceptible strains of *Proteus, Morganella*, *K. pneumoniae*, or *E. coli*, broad-spectrum multidrug therapy is often necessary to ensure coverage of drug-resistant pathogens. The choice of a particular combination must depend on the severity of infection, presence or absence of immunocompromise, and hospital-specific patterns of antimicrobial resistance and rates of isolation by specific microorganisms. Therapy should be made more specific when the pathogen(s) has been identified and susceptibilities are known. Again, the absence of MRSA in nasal surveillance specimens greatly reduces the risk of MRSA pneumonia being present.

With appropriate antimicrobial therapy, 50% of patients treated for aspiration pneumonia defervesce within 2 days of initiation of antibiotic therapy and 80% do so within 5 days. Prolonged fever is more common in patients with lung abscess or with infections by aggressive pathogens such as *P. aeruginosa*.

Prevention

Precautions should be taken to minimize the possibility of aspiration in hospitalized patients. Avoidance of the recumbent position and hypopharyngeal suctioning prevent aspiration by intubated patients. Guidelines from the American College of Chest Physicians and the American Gastroenterology Association provide specific recommendations regarding the evaluation of patients who are at risk for aspiration due to dysphagia. These guidelines recommend a multidisciplinary approach to patient evaluation and note the need to design and test therapy on an individual patient basis. Patients with documented aspiration during swallowing studies have a 4- to

TABLE 34.1 **SUGGESTED EMPIRIC THERAPY FOR INPATIENTS WITH ASPIRATION PNEUMONIA**

Suspected pathogens	Preferred agent	Alternative agents
Mixed aerobic/anaerobic flora	β-lactam plus metronidazole, β-lactam/β-lactamase inhibitor[a]	Clindamycin, moxifloxacin, ertapenem
Enterobacteriaceae	β-lactam/β-lactamase inhibitor[a], cefepime, carbapenem[b]	Third-generation cephalosporin[c] or fluoroquinolone[d], both ± aminoglycoside[e]
P. aeruginosa	Anti-pseudomonal β-lactam[f] ± aminoglycoside, carbapenem + aminoglycoside	Ciprofloxacin + aminoglycoside, ciprofloxacin + anti-pseudomonal β-lactam[e]
S. aureus, methicillin-sensitive	Anti-staphylococcal β-lactam[g] or first-generation cephalosporin[h]	Vancomycin, linezolid, trimethoprim-sulfamethoxazole
S. aureus, methicillin-resistant	Vancomycin	Linezolid, quinupristin/dalfopristin

Therapy should be modified when the identity and susceptibility of the responsible pathogen(s) is determined.
[a] Piperacillin/tazobactam is the preferred β-lactam/β-lactamase inhibitors for the treatment of nosocomial pneumonia due to Enterobacteriaceae. Ampicillin/sulbactam lacks adequate activity against many nosocomial enteric gram-negative bacilli.
[1b] Ertapenem, imipenem, and meropenem have equivalent activity against *Enterobacter* spp. mixed aerobic/anaerobic flora. Only imipenem and meropenem have activity against *P. aeruginosa*
[c] Third-generation cephalosporins: cefotaxime, ceftriaxone, and ceftazidime.
[d] Levofloxacin and ciprofloxacin generally have equivalent activity against *Enterobacter* spp. and *P. aeruginosa*. High resistance rates, particularly for nosocomial isolates, limit the empiric usefulness of these agents in many settings.
[e] Addition of an aminoglycoside should be strongly considered in seriously ill patients to ensure adequate breadth of antimicrobial therapy.
[f] Antipseudomonal β-lactams: ceftazidime, cefepime, imipenem, meropenem, or piperacillin-tazobactam.
[g] Antistaphylococcal β-lactams: nafcillin, oxacillin.
[h] Antistaphylococcal first-generation cephalosporins: cefazolin, cefadroxil, cephalexin.

10-fold increased risk of pneumonia depending on the magnitude of aspiration. Patients with risk factors for aspiration including neurologic disease, esophageal dysfunction, altered mental status, and known dysphagia have demonstrated higher 1-year mortality and higher risk for hospital readmissions compared to patients without risk factors; identifying and addressing risk factors has potential to reduce aspiration incidence.

Placement of gastrostomy tubes in persons with dysphagia is not superior to the use of a nasogastric tube for preventing aspiration. The failure of this intervention is likely related to ongoing aspiration of oral secretions and the observation that aspiration of gastric contents still occurs in persons fed by gastrostomy tubes. Nonetheless, decreased local irritation, fewer mechanical problems, and improved nutrition justify the use of gastrostomy tubes in selected patients. Monitoring the residual volume of tube feedings is often recommended as a measure to reduce incidence of aspiration in patients receiving tube feeds. However, in mechanically ventilated patients, the absence of gastric volume monitoring has not demonstrated an increase in ventilator-associated pneumonia.

Good periodontal care decreases the burden of pathogenic bacteria in oral secretions and thereby may prevent aspiration pneumonia. Studies have demonstrated direct correlation between implementation of oral hygiene initiatives and incidence of non–ventilator-associated hospital-acquired pneumonia. Data are mixed regarding the use of chlorhexidine oral care for the prevention of ventilator-associated pneumonia; there may be some benefit in short-term intubation (on the order of 2–3 days), but results for more critically ill patients intubated for longer periods are less obviously beneficial and in some instances trend toward harm. In contrast to the evidence to support good periodontal care, prophylactic antibiotic use is not recommended for patients in whom aspiration is suspected or witnessed.

Suggested reading

Bartlett JG. How important are anaerobic bacteria in aspiration pneumonia: When should they be treated and what is optimal therapy. *Infect Dis Clin. North Am*. 2013;**27**(1):149–155.

Dragan V, Wei Y, Elligson M, et al. Prophylactic antimicrobial therapy for acute aspiration pneumonitis. *Clin Infect Dis*. 2018;**67**(4):513–518.

Mark PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med*. 2001;344:665–671.

Raghavendran K, Nemnzek J, Napolitano LM, Knight PR. Aspiration-induced lung injury. *Crit Care Med*. 2011;**39**(4):818–826.

Smith Hammond CA, Goldstein LB. Cough and aspiration of food and liquids due to oral-pharyngeal dysphagia: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129:154S–68S.

35

Lung abscess

Amee Patrawalla and Lisa L. Dever

Lung abscess is a chronic or subacute lung infection initiated by the aspiration of contaminated oropharyngeal secretions. The result is an indolent, necrotizing infection in a segmental distribution, usually dependent and limited by the pleura. Except for infections with unusual organisms such as *Actinomyces*, the process does not cross interlobar fissures, and pleural effusion is uncommon. The resultant cavity is usually solitary, with a thick, fibrous reaction at its periphery. So defined, lung abscess is almost always associated with anaerobic bacteria, although the majority of infections are polymicrobial, with microaerophilic and aerobic bacteria present.

In contrast, *necrotizing pneumonia* is an acute, often fulminant, infection characterized by irregular destruction of alveolar walls and therefore multiple cavities. This infection spreads rapidly through lung tissue, frequently crossing interlobar fissures, and is often associated with pleural effusion and empyema. The duration of illness before recognition is usually only a few days. Causative organisms include *Staphylococcus aureus, Streptococcus pyogenes, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and, less commonly, other gram-negative bacilli, *Legionella* spp., *Nocardia* spp., and fungi.

Diagnosis

The focus of this discussion will be the diagnosis and therapy of anaerobic lung abscess. Diagnosis can usually be made from the clinical presentation and chest radiograph findings. Many patients have conditions such as seizure disorders, neuromuscular diseases, alcoholism, or other causes of impaired consciousness that predispose them to aspiration of oropharyngeal secretions. Obstructing tumors and foreign bodies may also predispose to lung abscess. Additionally, patients with impaired local and systemic host defenses are at greater risk. Gingival disease and poor dental hygiene, which promote higher concentrations of anaerobic organisms in the mouth, are common. Patients usually give a several-week history of fever and cough; putrid sputum occurs in fewer than 50% of patients. Hemoptysis may also occur. With chronic infection, patients will often experience weight loss and anemia, mimicking malignancy. Chest radiographs show consolidation in a segmental or lobar distribution with central cavitation, and air–fluid levels are often present (Figure 35.1 and 35.2). Chest tomography can further define the extent and location of the abscess (Figure 35.3). The lung segments most commonly involved are those that are dependent when the person is supine (i.e., posterior segments of the upper lobes and superior segments of the lower lobes).

The microbiologic diagnosis of lung abscess is hampered by contamination of specimens by the normal anaerobic flora of the mouth, prior antimicrobial therapy, and difficulties inherent in culturing and identifying anaerobic bacteria. Although the Gram stain of sputum may be helpful in suggesting an etiologic diagnosis, routine sputum cultures are of no value because all contain anaerobic organisms. Techniques that have been used to obtain uncontaminated lower airway specimens for anaerobic cultures include transtracheal needle aspiration, transthoracic needle aspiration, and open lung biopsy. Using these techniques, early investigators demonstrated anaerobic bacteria in virtually all untreated patients. These invasive techniques are seldom warranted in the clinical management of patients today. Quantitative cultures of bronchoalveolar lavage or

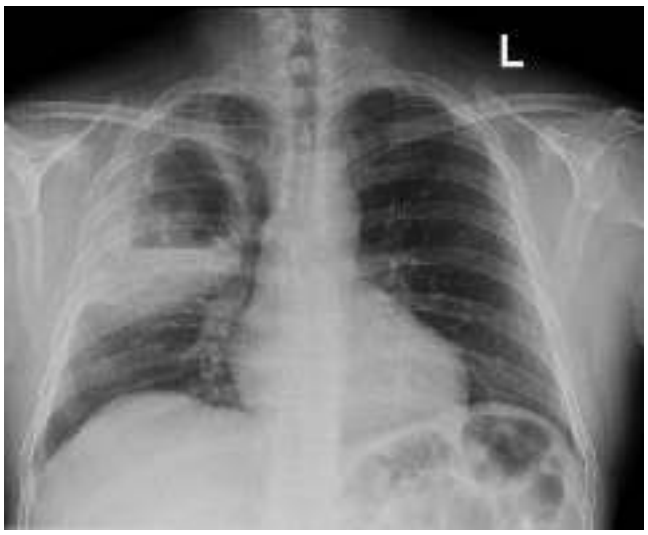

FIGURE 35.1 Chest radiograph showing a large lung abscess with air–fluid level in the right upper lobe.

other bronchoscopically obtained lower airway specimens, such as those obtained with a protected specimen brush, may prove useful in the occasional patient suspected of having lung abscess but are not needed in most. Transthoracic fine needle aspiration guided by either ultrasound or CT has been used increasingly for diagnostic purposes. Although generally safe in experienced hands, serious complications such as pneumothorax and bacterial contamination can result and greatly prolong the recovery period.

Anaerobic organisms most commonly recovered from lung abscesses are listed in Box 35.1. Multiple anaerobic organisms are commonly present along with aerobic or microaerophilic

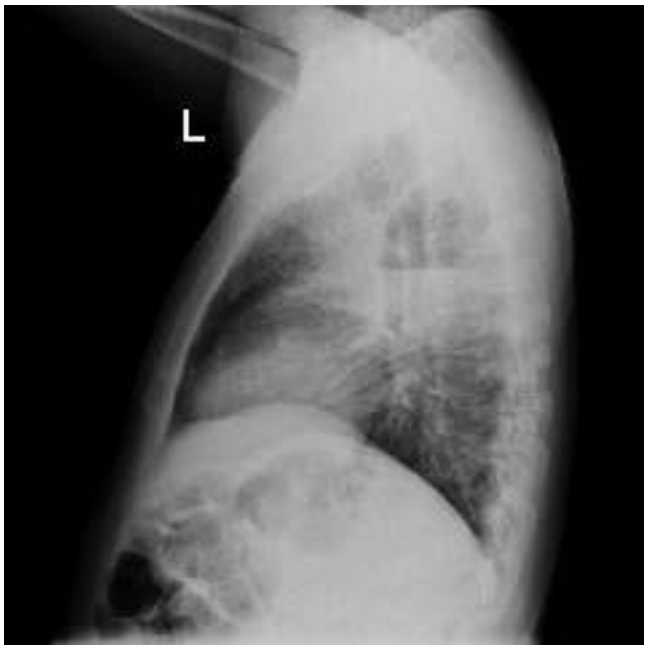

FIGURE 35.2 Corresponding lateral chest radiograph confirming that the large lung abscess with air–fluid level is located in the right upper lobe.

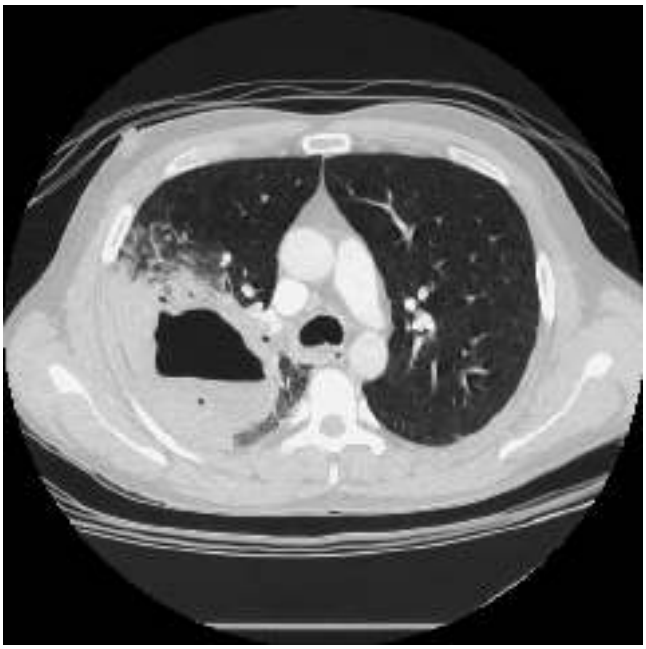

FIGURE 35.3 CT scan of the chest further defines the location and extent of the lung abscess measuring 8 × 6 cm.

organisms. The viridans streptococci, particularly the *Streptococcus milleri* group, appear to be significant pathogens. *K. pneumoniae* was the most common pathogen in a retrospective review of 90 cases of community-acquired lung abscess from Taiwan. *K. pneumoniae* was recovered from 30 patients (33%), compared to 28 patients with anaerobic organisms. In an observational hospital-based study

BOX 35.1

Anaerobes most commonly isolated in lung abscess

Organism

Gram-negative bacilli

Pigmented *Prevotella* spp.
Pigmented *Porphyromonas* spp.
Nonpigmented *Prevotella* spp.
Bacteroides spp.
Fusobacterium nucleatum
Fusobacterium spp.

Gram-positive cocci

Finegoldia magnus
Peptostreptococcus spp.
Peptococcus spp.

Gram-positive bacilli

Clostridium perfringens
Clostridium spp.
Actinomyces spp.

in India, *K. pneumoniae* was isolated from sputum cultures in 23 of 46 patients (50%) with lung abscess; anaerobic cultures were not obtained. In a retrospective single-center retrospective study of pediatric lung abscess, *S. aureus* and streptococcal species were the most common single pathogen identified, but in more than half of the patients no organism was recovered. The most likely explanation for these findings is lack of anaerobic cultures, prior antibiotic therapy, and geographic location. Other than determination of β-lactamase production, susceptibility testing of anaerobic organisms is usually not required.

Therapy

Most lung abscesses are treated empirically. Table 35.1 provides therapeutic options for intravenous treatment of lung abscess. Selection of agents should be guided by the spectrum of pathogens suspected or isolated from appropriately collected specimens. Historically, penicillin has been the antibiotic of choice because of its good in vitro activity against most anaerobic and microaerophilic bacteria present in the oral cavity. Two randomized clinical trials found that clindamycin is superior to penicillin, with time to resolution of symptoms and failure rate significantly lower in clindamycin-treated patients. Failure of penicillin therapy was associated with the isolation of penicillin-resistant *Bacteroides* spp. in one of these studies. Although increasing resistance of anaerobes and gram-positive bacteria to clindamycin has been reported, it is still preferred over penicillin for treatment of lung abscess when anaerobes or microaerophilic streptococci are likely to be predominant pathogens.

Although the combination of metronidazole and penicillin has been used successfully for the treatment of anaerobic pulmonary infections for decades, it should not be used if staphylococci or aerobic gram-negative bacilli may be part of the infectious process. Metronidazole has excellent bactericidal activity against virtually all gram-negative anaerobes but lacks activity against microaerophilic streptococci, as well as *Actinomyces* spp., and should not be used as a single drug agent in the treatment of lung abscess.

A number of other agents have good in vitro activity against anaerobic organisms, including β-lactamase producers, and may pose less risk for the development of *Clostridium difficile*-associated disease than clindamycin. These agents include second-generation cephalosporins, carbapenems, β-lactam/β-lactamase inhibitor combination drugs, and newer fluoroquinolones. In addition, these drugs are attractive for the treatment of lung abscess because of their activity against many of the aerobes that may be present in mixed infections. Ampicillin-sulbactam was found to be as effective as clindamycin with or without an added cephalosporin in the treatment of aspiration and lung abscess in a prospective trial. Drugs that have little or no anaerobic activity should not be used in the treatment of lung abscess. These include aminoglycosides, aztreonam, and the older fluoroquinolones, levofloxacin and ciprofloxacin. Although a number of newer antimicrobials have a suitable spectrum of activity in vitro, it is unlikely that any will ever prove to be more efficacious than current therapy in prospective clinical trials. This is because of the difficulties inherent in conducting trials in this condition—no single institution sees large numbers of patients with lung abscess, it is difficult to isolate anaerobic organisms from uncontaminated respiratory specimens for accurate diagnosis and susceptibility testing, and the patients' response to treatment varies widely but is often slow, which can lead to the erroneous conclusion of treatment failure if that decision is made too early.

TABLE 35.1 **INTRAVENOUS ANTIBIOTIC THERAPY OF ANAEROBIC LUNG ABSCESS**[a]

Antibiotic	Intravenous dosage	Frequency
Clindamycin	600 mg	q8h
Penicillin G plus	2–3 million U	q4h q6h
Metronidazole	500 mg	
Alternative regimens with broader-spectrum activity[b]		
Ampicillin–sulbactam	3 g	q6h
Piperacillin–tazobactam	3.375 g	q6h
Cefoxitin	2 g	q6h
Ertapenem	1 g	q24h
Imipenem	500 mg	q6h
Meropenem	1 g	q8h
Moxifloxacin	400 mg	q24h

[a] All dosages are for adults with normal renal function.
[b] Includes activity against gram-negative aerobic bacilli.

Duration of therapy

The duration of therapy for lung abscesses must be individualized, but extended therapy is usually required. Parenteral therapy is recommended initially in seriously ill patients and should be continued until the patient is afebrile and clinically improving. A prolonged course of oral antibiotics follows initial parenteral therapy. Less severely ill patients can be treated effectively with oral antibiotics alone. Options for oral therapy are provided in Table 35.2. Therapy should be continued until there is complete resolution or at least stabilization of chest radiographic lesions—this may require 6 to 8 weeks of therapy. Relapses may occur when therapy has been

TABLE 35.2 **ORAL ANTIBIOTIC THERAPY OF ANAEROBIC LUNG ABSCESS**

Antibiotic	Dosage (mg)	Frequency
Clindamycin	300	QID
Penicillin G plus	750	QID
Metronidazole	500	QID
Amoxicillin/clavulanate	875	BID
Moxifloxacin	400	Daily

All dosages are for adults with normal renal function.

discontinued before resolution of chest radiographic findings, even when patients are clinically asymptomatic.

Other therapy

The majority of patients with lung abscesses respond to appropriate antimicrobial therapy and spontaneous drainage of the abscess through the tracheobronchial tree. Bronchoscopy may be required in those who have unchanged or increasing air–fluid levels and who remain septic after 3 to 4 days of antibiotic therapy. However, it rarely results in direct drainage of the abscess cavity and may lead to spillage of purulent material into the airways. In patients failing to respond to medical therapy and in those with large abscess cavities (>6–8 cm diameter), drainage may be accomplished percutaneously, endoscopically, or surgically. Percutaneous catheter drainage, guided by CT or ultrasound, is the approach that has gained the most popularity in recent years. Although there are no controlled trials evaluating the role of this procedure in the treatment of lung abscess, a review of the literature suggests that in appropriately selected patients this approach is safe and effective. The safety of this approach, however, depends critically on the degree of synthesis of the two pleural surfaces. If the visceral pleura has not been firmly adhered to the chest wall, a pyopneumothorax results, often with bronchopleural fistula—a true disaster that is to be avoided. Successful drainage through pigtail catheters placed directly in abscess cavities using a flexible bronchoscope, in some instances with use of a laser to perforate the abscess cavity, has been described. Most recently endobronchial ultrasound has been used in endoscopic drainage of lung abscesses. It must be remembered that the gross appearance of the bronchial orifice and the results of cytological examinations may falsely suggest the presence of an underlying malignancy because of intense and long-lived inflammation. However, lung abscesses in adults >50 years of age are frequently associated with carcinoma of the lung, either because of cavitation of the neoplasm or cavitation behind a proximal bronchial obstruction. Such patients should be followed to resolution with great care. Thoracotomy or video-assisted thorascopic surgery for resection of lung abscess (most commonly a lobectomy), is required in fewer than 15% of patients. Surgery is generally reserved for patients who have failed medical therapy and other attempts at drainage and may have additional complications such as empyema, bronchopleural fistula, or suspicion of malignancy.

Suggested reading

Allewelt M, Schüler P, Bölcskei PL, *et al*. Ampicillin + sulbactam vs. clindamycin + cephalosporin for the treatment of aspiration pneumonia and primary lung abscess. *Clin Microbiol Infect*. 2004;10:163–170.

Bartlett JG. The role of anaerobic bacteria in lung abscess. *Clin Infect Dis*. 2005;40:923–925.

Bartlett JG. Lung abscess. In Calderwood SB, Bond S, eds. UptoDate. 2018. http://www.uptodate.com/home/index.html

Gudiol F, Manresa F, Pallares R, et al. Clindamycin vs. penicillin for anaerobic lung infections: High rate of penicillin failures associated with penicillin-resistant *Bacteroides melaninogenicus*. *Arch Intern Med*. 1990;150:2525–2529.

Herth F, Ernst A, Becker HD. Endoscopic drainage of lung abscesses: Technique and outcome. *Chest*. 2005;127:1378–1381.

Kuhajda I, Zarogoulidis K, Tsirgogianni K, et al. Lung abscess—etiology, diagnostic and treatment options. *Ann Transl Med*. 2015;3:183.

Madhani K, McGrath E, Guglani L. A 10-year review of pediatric lung abscesses from a single center. *Ann Thorac Med*. 2016:211:191–196.

Mohapatra MM, Rajaram M, Mallick A. Clinical, radiological and bacteriological profile of lung abscess: An observational hospital based study. *Open Access Maced J Med Sci*. 2018:6:1642–1646.

Wali SO, Shugaeri A, Samman YS, et al. Percutaneous drainage of pyogenic lung abscess. *Scand J Infect Dis*. 2002;34:673–679.

Wang JL, Chen KY, Hsueh PR, et al. Changing bacteriology of adult community-acquired lung abscess in Taiwan: *Klebsiella pneumoniae* versus anaerobes. *Clin Infect Dis*. 2005;40:915–922.

36

Empyema and bronchopleural fistula

Charlotte E. Bolton and Dennis J. Shale

Infection of the pleural space leading to empyema formation, and the importance of clearing infection and pus from this space, has been recognized since ancient times. Historically, empyema was associated with pneumococcal pneumonia, with *Streptococcus pneumoniae* causing up to 70% of pleural space infections. With effective antibiotic treatment for community-acquired pneumonia, the incidence of empyema due to pneumococcus has decreased and the spectrum of causative organisms has widened, with *S. pneumoniae*, *Streptococcus Milleri* group, and *Staphylococcus aureus* now accounting for up to approximately 65% and an increasing isolation rate for anaerobes and gram-negative organisms. However, parapneumonic effusions occur in 30% to 60% of pneumonia cases, and, when empyema occurs, it is associated with an overall mortality of 20% with a further 20% requiring surgical intervention. Importantly, a reported increase has occurred in recent times with the young and elderly at the greatest risk of empyema.

Parapneumonic effusions are classified as simple or uncomplicated, complicated, and empyema, based on the appearance and biochemical characteristics of aspirated fluid, which supports the clinical impression of a continuum of disease (Table 36.1).

This classification also has clinical utility in that, during the early acute phase, with free flowing fluid, treatment is simpler than in the more chronic fibropurulent stage associated with multiple loculations and the need for greater interventional therapy. Empyema may be defined as the presence of organisms and numerous host defense cells, neutrophils, in the pleural fluid, or, more narrowly, as pus apparent to the naked eye. Bronchopleural fistula (BPF) may be caused by an empyema or may be associated with empyema formation following surgery, penetrating lung injuries, or a lung abscess.

Etiology

Empyema occurs most commonly in association with bacterial pneumonia, either in a community-or hospital-acquired setting. In a study in 434 pleural infections in the United Kingdom using standard culture and nucleic acid amplification techniques a causative organism was identified in 74%. Of the 336 isolates in the community-acquired setting 52% were of the genus *Streptococcus*, approximately 20% were anaerobes, 10% were staphylococcal, and 10% were gram-negative organisms. In the hospital-acquired infections (60 isolates) *Staphylococcus* was the major genus isolated (35%) of which 71% were methicillin-resistant forms; 23% were gram-negative organisms; 18% were *Streptococcus*; and 8% were anaerobes. Other organisms isolated included *Actinomyces* spp., *Enterococcus* spp., and *Mycobacterium tuberculosis*. This large study supports smaller studies suggesting the spectrum of organisms in pleural infections differs from that in pneumonia. Local events such as thoracic surgery, rupture of the esophagus, hepatic or subphrenic abscesses, and all penetrating injuries may introduce organisms, especially gram-negative or anaerobic organisms, into the pleural space. Ameba may enter the pleural space from an amebic abscess in the liver. Tuberculous empyema is a modest problem in the developed world, but is still seen in reactivation of tuberculosis in the elderly. However, in developing countries, with rapid urbanization, continued population increase, and greater levels of human immunodeficiency virus infection, there is an increasing incidence of tuberculous empyema.

TABLE 36.1 **CLASSIFICATION OF PARAPNEUMONIC EFFUSIONS AND EMPYEMA**

	Appearance	Biochemistry and bacteriology	Risk category for poor outcome
Simple/uncomplicated parapneumonic	Clear fluid	pH >7.2	1 and 2
		LDH ≤1000 IU/L	Very low or low
		Glucose >3.3 mmol/L	
		Negative Gram smear or culture	
Complicated parapneumonic	Clear fluid or turbid	pH ≤7.2	3
		LDH >1000 IU/L	Moderate
		Glucose ≤3.3 mmol/L	
		Positive Gram smear or culture likely	
Empyema	Frank pus	Positive Gram smear or culture likely	4
		Biochemistry unnecessary	High

Pleural space infections may cause a BPF or may occur secondary to a BPF. Lung resection surgery remains the major cause of BPF, occurring in 3% to 5% of these operations.

Clinical features

There are no specific clinical features to differentiate simple from uncomplicated parapneumonic effusions. The main features are fever, chest pain, sputum production, appropriate physical signs of an effusion, and peripheral blood leukocytosis. Progression to an empyema is usually indicated clinically by the persistence or recurrence of fever and features of systemic upset with a lack of resolution of physical signs, because differentiation of consolidation from a small- to medium-volume effusion may not be possible. Other physical features include dyspnea with large effusions, rapid-onset finger clubbing, lethargy, and marked weight loss. Purulent sputum may indicate the development of a BPF. However, more insidious onset may occur with the presentation occurring over weeks to months after the original pneumonia or injury.

Investigations

A chest radiograph usually shows collection of fluid, although a localized, loculated collection may resemble an intrapulmonary mass. Differentiation between these possibilities may be resolved by the addition of a lateral chest radiograph to the standard posteroanterior film or by ultrasound or computed tomographic (CT) scanning. Ultrasonography is superior to CT in identifying septations in a loculated collection and also defines pleural thickening. Increasingly bedside ultrasound is used to guide a percutaneous diagnostic aspiration, increasing the diagnostic yield and patient safety. However, it is occasionally difficult to distinguish between empyema with a BPF and a lung abscess. In this setting, the use of CT scanning may guide both investigation and management approaches.

Aspirated material should be collected under anaerobic conditions and a portion submitted for anaerobic culture and a sample in a blood culture bottle can increase the anaerobic yield. Routine bacterial and mycobacterial culture should be undertaken with cytologic examination. If appropriate, fungi and parasites should be sought. Other investigations including pH, glucose concentration, and lactate dehydrogenase (LDH) activity of the fluid may be of use if there is little evidence of purulence to the naked eye. A meta-analysis of pleural fluid biochemistry, based on user characteristics, demonstrated that pH, especially ≤7.2, was a guide to the need for tube drainage and that glucose or LDH determination conferred no extra benefit; however, if pH assessment is unavailable, a glucose ≤60 mg/dL (3.3 mmol/L) is an alternative guide. Pleural fluid pH is measured in nonpurulent samples taken into a heparinized syringe and determined in a blood gas analyzer. There is no need to determine the pH of purulent samples. Litmus paper assessment is not an alternative. It should be remembered that lidocaine can lower the pH of samples and hence the sampling syringe should not be contaminated by this.

Generally, percutaneous pleural biopsy is not helpful and potentially harmful, although the diagnosis of tuberculosis is often made only from such material.

The literature on the value of individual investigations in guiding management is very limited. The American College of Chest Physicians (ACCP) analysis of risk of a poor outcome is based on pooled data, a small number of randomized controlled trials, and expert consensus but provides a framework to guide management of treatment (Table 36.1).

Therapy

There has been a paucity of evidence on which to base therapeutic decisions, which reflects the wide breadth of the condition in terms

TABLE 36.2 **MANAGEMENT OPTIONS FOR PLEURAL SPACE INFECTION**

Therapeutic option	Comment
Observation and antibiotics	Acceptable option for small-volume category 1 or 2 low-risk collections
Therapeutic thoracentesis	Repeated treatment used in complicated effusions and empyema. Small studies suggest benefits, but no comparison with tube drainage
Tube thoracostomy	Most commonly used drainage method. Combined with antibiotics can improve clinical and radiologic status in 24–36 hours
Fibrinolysis	Probably not of value in most complicated effusions. Can be used in patients unfit for required surgical intervention
Medical or surgical thoracoscopy	Allows complete drainage and inspection of the pleural space. Small studies suggest leads to more rapid resolution of effusion
Decortication	Allows removal of all pus, tissue debris, and connective tissue. Is major surgery and requires the patient to be fit for surgery. Appropriately used, will reduce management period. Not for routine management of residual pleural thickening
Open drainage	An alternative option to decortication for patients unfit for surgery, but leads to a prolonged recovery period

of clinical feature and pathology. However, the recent ACCP and the British Thoracic Society (BTS) UK guidelines have both reviewed evidence and graded it to develop management recommendations. These documents represent current good practice, but both emphasize the need for more robust studies in the area of the management of pleural space infections.

Management options are summarized in Table 36.2 with summary notes. All patients with a pleural effusion in the presence of sepsis or pneumonia require diagnostic aspiration. Patients with parapneumonic effusion or empyema require antibiotics, usually, commenced empirically and subsequently guided by culture results. Many will have received antibiotics already, and negative cultures do not indicate cessation of antimicrobial therapy.

Small or insignificant effusions, the maximal thickness of which is ≤10 mm on ultrasound scanning or decubitus radiograph, simple or uncomplicated (category 1), may not need thoracentesis and are unlikely to need tube drainage. However, if the volume increases up to 50% hemithorax, simple or uncomplicated (category 2), or a positive Gram stain or culture is reported, further thoracentesis is recommended, though in a very small effusion such results are often false positives. In these categories the risk of a poor outcome is low, and they equate to the former simple or uncomplicated parapneumonic effusions.

Larger effusions occupying more than 50% hemithorax with evidence of loculation or parietal pleural thickening or with a pH ≤7.2 or evidence of infection in the pleural space (category 3) require closed tube drainage and carry a moderately high risk of a poor outcome. Generally, such drainage is effective, though negative low-pressure high-volume suction may be needed if flow is slow and will hasten the obliteration of the pleural space. In the past large-bore tubes were recommended for drainage, but more recently narrow-bore tubes placed with imaging guidance have been shown to be just as effective and to be better tolerated by patients. Tube drainage is contraindicated in patients with a neoplasm causing airway obstruction, which is the only indication for bronchoscopy in empyema. Full characterization of this category, which corresponds to the complicated parapneumonic effusions in other classifications, requires more extensive investigation to develop an appropriate management plan (Table 36.2). Effective antibiotic choice and closed tube drainage should lead to radiologic and clinical improvement within 24 to 36 hours. Failure to respond requires further investigation, including imaging to assess tube position, any residual collection, or the formation of loculation, and should include either ultrasound or contrast-enhanced CT scanning as loculation and parietal pleural thickening are indicators of a poor outcome. A slow response to lack of improvement will allow an empyema to form and may require surgical intervention, while increasing the risk of prolonged morbidity and a higher mortality.

The presence of pus defines an empyema (category 4), which carries a high risk of a poor outcome and requires closed tube drainage and antibiotic treatment. Frequently in empyema, the chest tube can become blocked, requiring saline flushes to maintain patency. As many infections will be of mixed organisms, antibiotic coverage for both anaerobic and nonanaerobic organisms is required. Surgical options are likely to be needed in this group. It requires a cautious and balanced decision so that surgery is not contemplated too late, a widely reported problem, when the patient's condition may reduce the chance of a satisfactory outcome. Medical or surgical thoracoscopy has been reported to reduce the time to recovery and to be as effective as formal surgical intervention, but the design of comparisons is inadequate to make firm recommendations other than that surgical options should be pursued if there is evidence of continuing sepsis and a collection after 7 days of antibiotic treatment and drainage.

Decortication aims to remove pus and fibrous tissue lining the pleural cavity but is a major surgical procedure and is unsuitable for debilitated patients, who should be considered for fibrinolytic therapy or open drainage. Decortication has the benefit of a quicker resolution of the empyema over methods of open drainage, which have a median healing period of 6 to 12 months. In general, decortication is not needed for residual pleural thickening from the successful management of categories 3 or 4, unless it persists for longer than 6 months or where there is extensive pleural thickening or respiratory symptoms secondary to restrictive effects.

The evidence for using fibrinolytic agents has been inconclusive due to small, often open, studies. A recent double-blind study in 454 patients with complicated pleural infection and at category 3 or 4 risk compared streptokinase with placebo, with all other treatment options as per routine. The primary end point of death or surgical drainage at 3 months was no different between treatment groups, $p = 0.43$. Similarly, secondary end points of death rate, requirement for

BOX 36.1

Management of bronchopleural fistula (BPF)

Small BPF

- Some may close spontaneously:
- Without empyema
  - Transbronchoscopic fibrin glue
  - Transbronchoscopic tissue glue
  - Transbronchoscopic vascular occlusion coils/Amplatzer devices
  - Transbronchoscopic laser/tetracycline/gel foam
  - Thoracoscopic sealing
- With empyema
  - Antibiotic/tube drainage and attempted closure of BPF

Large BPF

- Typically associated with empyema:
  - Surgical options include decortication or open drainage of empyema and occlusion of the BPF by direct closure or well-vascularized muscle or omental flaps

surgery, radiographic outcome, and length of hospital stay were also no different between the streptokinase or placebo groups, whereas serious adverse events were increased in the streptokinase group, relative risk 2.49 (95% confidence interval 0.98–6.36). Important contraindications include BPF, coagulation disorders, and allergy.

Currently fibrinolytic therapy is not recommended for routine care of infected pleural effusions but remains an option for the patient unfit for surgery or in the absence of free flowing pus. Treatment with streptokinase 250 000 international units twice daily for 3 days or urokinase 100 000 international units daily for 3 days has been recommended. The latter is less likely to produce allergic side effects. Early clinical studies comparing the use of streptodornase (DNase) with tissue plasminogen activator and in combination in complicated parapneumonic effusions and empyema suggest this combination is effective and reduces the need for surgery and the length of hospital stay.

This classification of empyema has the value of matching a spectrum of clinical status to a plan of escalating therapeutic options but remains only a guide based on limited evidence. Patients may move in either direction along this spectrum, so careful and repeated assessment of the patient's status is required, particularly soon after a therapeutic intervention is made, to ensure a continuing appropriate management response.

The aim with BPF, whether in the setting of trauma, neoplasm, or empyema, is to deal with the air leak and any new or residual empyema. Air in the pleural cavity indicates the presence of a BPF and need for tube drainage. The air leak may be dealt with either by surgical or by nonsurgical intervention, largely depending on the size and duration of the BPF (Box 36.1).

Pleural space infections demand major management decisions of physicians. There are various approaches to the patient with empyema and BPF, and the heterogeneity of the response means that the management of this problem should be individualized to the patient. There is considerable literature relating to such problems, but most studies until recently have been too small to demonstrate clear beneficial options.

Suggested reading

Davies HE, Davies RJO, Davies CWH. Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010. *Thorax*. 2010;65(Suppl 2): ii41–ii53.

Fruchter O, Kramer MR, Dagan T, *et al*. Endobrochial closure of bronchipleural fistulae using Amplatzer devices. *Chest*. 2011;139(3):682–687.

Janda S, Swiston J. Intrapleural fibrinolytic therapy for treatment of adult parapneumonic effusions and empyemas. A systematic review and meta-analysis. *Chest*. 2012;142(2):401–411.

Light RW. Parapneumonic effusions and empyema. *Proc Am Thorac Soc*. 2006;3:75–80.

Maskell NA, Batt S, Hedley EL, *et al*. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. *Am J Respir Crit Care Med*. 2006;174:817–823.

Section 6

Clinical syndromes: Heart and blood vessels

37

Endocarditis

John L. Brusch

Definition and pathogenesis

The term *infective endocarditis* (IE) describes an infection of the endothelial surface of the heart, most commonly that of a valve. Cases may be categorized in several ways: as acute (ABE) or subacute (SBE) on the basis of the speed of their clinical progression, or by pathogenic organism (e.g., *Staphylococcus aureus*), or by location (e.g., right- or left-sided), or by the nature of the infected material (native tissue vs. prosthetic), or by the mechanism of acquisition, such as intravenous (IV) drug abuse. When approaching a case of possible IE, it is quite helpful to generate a profile of disease process using the preceding characteristics especially when it comes to empirically choosing the initial antibiotic regimen.

Pathogenesis

All varieties of IE share the same basic pathogenesis: a bloodstream infection that delivers the organisms to the surface of the valve. Then, they must be able to firmly adhere.

Most microorganisms cannot directly attach to normal endothelium. They require a preexistent platelet fibrin thrombus or nonbacterial thrombotic endocarditis (NBTE). This results from a variety of valvular abnormalities that cause turbulent blood flow across a high- to low-pressure gradient and denude epithelium from surfaces impacted by the turbulence. The damaged endothelium loses its anticoagulant properties. A sterile nidus of platelets and fibrin form over this area and gradually develop into NBTE.

Over time, the transient *Streptococcus viridans* bacteremias of daily living, which occur after injury to mucosal surfaces in the oropharynx, genitourinary tract, or gastrointestinal tract, stimulate the formation of agglutinating antibodies that cause the streptococcus to clump together; these are not bactericidal. When these antigen–antibody clumps reach a critical mass, they are able to adhere to the NBTE by means of their ability to produce an extracellular dextran, glucan, and adhesive matrix of molecules (MSCRAMMs) that attach to the fibronectin-platelet units found within the thrombus. There, they multiply and stimulate further deposition of platelets and fibrin. This is amplified by activation of the extrinsic clotting pathway as well as by cytokine and fibronectin production. Streptococci may actually produce biofilms within this vegetation. All of these factors quite effectively thwart the body's defenses as well as interfere with antibiotic effectiveness because of the reduced metabolic state of the pathogens and limited penetration into the thrombus itself. The concentration of bacteria within the thrombus may be $>10^{10}$ colony-forming units per gram of tissue.

Complications may arise through local bacterial spread or through embolization of fragments of the vegetation. The endovascular location of the lesions causes multiorgan bacterial seeding as well as organ damage through immune complex deposition.

S. aureus does not require any preexisting NBTE to initiate valvular infection. It has the ability to directly enter endothelial cells (endotheliosis). In doing, it shuts off the anticoagulation effect of the cells. Microthrombi appear on the valve surface and enlarge, as just described.

Epidemiology

Since the 1960s, the mean age of patients with IE has increased from 58.6 to 60.8 years (1998–2009). The overall incidence of IE in the United States increased from 11/100,000 population to 15/100,000 population from 2000 to 2011. These increases have been driven primarily by the proliferation of various types of intravascular devices as well as the aging of the population. Approximately 50% of the cases are seen in those >60 years of age. Males are disproportionately affected.

S. aureus, both methicillin-sensitive (MSSA) and methicillin-resistant (MRSA), have become the most common cause of acute IE, IV drug abuse IE (IVDAIE), prosthetic valve IE (PVIE), and intravascular device-associated valvular infections. Approximately 17% of these infections are caused by *S. viridans*. Coagulase-negative staphylococci (CoNS) and enterococci each account for 11% of cases.

Native valve endocarditis

In most cases of native valve endocarditis (NVE), there is an identifiable predisposing cardiac lesion. Mitral valve prolapse with regurgitation is the most common underlying cardiac abnormality in patients with IE in the United States. Rheumatic heart disease remains the most common underlying valvular abnormality in developing countries. Other recognized predisposing cardiac lesions are ventricular septal defects, subaortic and valvular aortic stenosis, tetralogy of Fallot, coarctation of the aorta, Marfan syndrome, and pulmonary stenosis.

As mentioned earlier, overall cases of IE have increased significantly since 2005. The rate of increase in prior years had been initially attributed to the "graying" of the population and, more recently, to the growth of intracardiac/intravascular device placement. In addition, it has become recognized that the increasing incidence may well be associated with 2005 recommendations to forego antibiotic prophylaxis in those at moderate risk of developing IE associated with various procedures. In response, there has been a significant growth of IE in moderate-risk individuals (75%) and a greater growth in those patients at high risk (177%). In part, this rise may be attributable to the decrease in recommended antibiotic prophylaxis. About 70% of cases of NVE are due to *S viridans*, *S. bovis,* and enterococci. *S. aureus* has surpassed the *S. viridans* group streptococci as the leading overall cause of SBE. In data published from the International Collaboration of Endocarditis-Prospective Cohort Study (ICE-PCS), *S. aureus* was the most commonly identifiable pathogen among the 1,779 cases of definitive IE (31.4%). *S. aureus* accounts for 25% of NVE. It is currently the most aggressive form of native valve infection with a higher mortality rate and greater incidence of embolic and/or central nervous system (CNS) events (Figures 37.1–37.3). Enterococcal IE accounts for 10% of cases. It typically occurs in elderly men and young women with underlying genitourinary disease. In recent years, both enterococci and staphylococci have become major pathogens in infections originating from intravascular catheters. HACEK group (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis,*

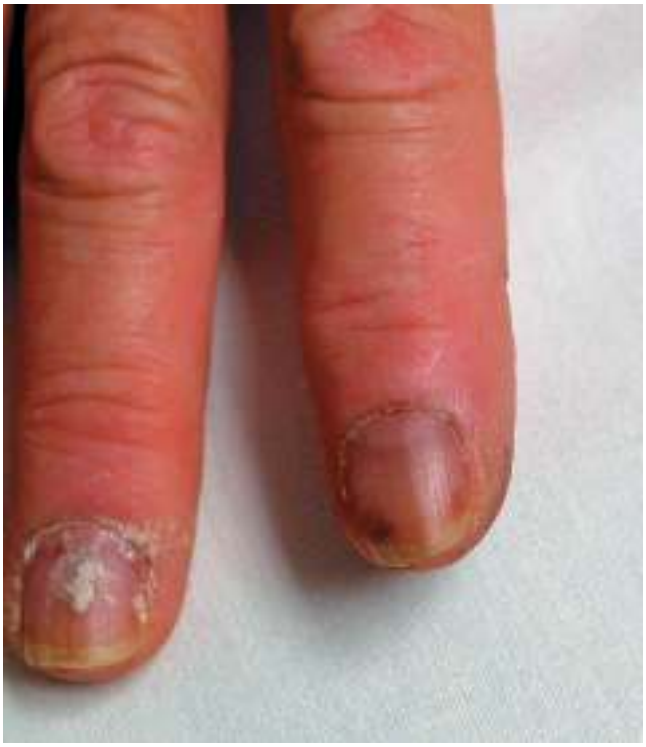

FIGURE 37.1 Splinter hemorrhage of nails in patient with *Staphylococcus aureus* infective endocarditis.

Eikenella corrodens, and *Kingella* species) gram-negatives account for <10% of community-acquired IE. Fungi rarely cause IE on a native valve (2%) except in IV drug abusers (13%).

Prosthetic valve endocarditis

The overall incidence of prosthetic valve endocarditis (PVE) is 1% to 4% during the first 12 months following valve surgery. PVE accounts for 20% to 30% of total cases of IE. The causative organisms

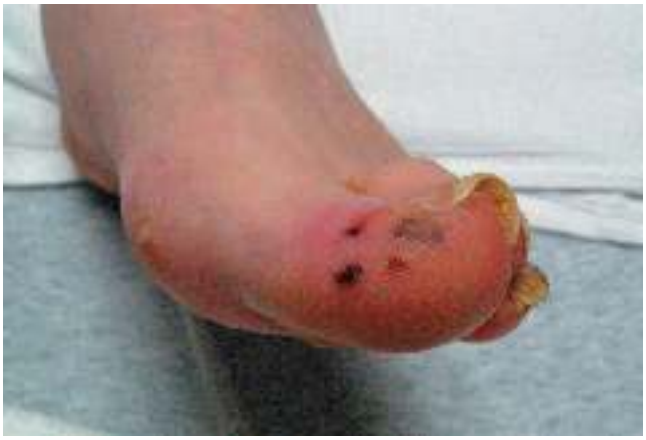

FIGURE 37.2 Embolic lesions in a patient with *Staphylococcus aureus* infective endocarditis.

FIGURE 37.3 Embolic lesions in a patient with *Staphylococcus aureus* infective endocarditis.

differ in early and late PVE. Infection within 60 days of valve insertion is considered to be early PVE that is usually caused by CoNS (25–30%) or *S. aureus* (15–20%). During this time, infection of the valve is caused by contamination of the operative field or through healthcare-associated bloodstream infection (HCBSI). Sites of bacterial adherence are the sutures, sewing ring, and cardiac annulus. As the implanted valve gradually becomes coated (conditioned) with tissue proteins, fibronectin, and fibrinogen, this facilitates microorganisms "sticking" to the valvular structures.

The intermediate postoperative phase occurs 60 to 365 days after implantation. The sewing ring has become "endothelialized" by cells that do not express the antithrombotic properties of normal endothelium, especially at the sewing cuff of the valve. During the intermediate period, the profile of pathogens becomes increasingly similar to that of NVE except that CoNS continues to be a significant cause of PVE.

The 1-year postoperative date marks the beginning of the late phase of PVE. At this time, the percentage of PVE caused by CoNS stabilizes at 10%.

In a prospective study of patients with prosthetic valves and *S. aureus* bacteremia conducted at Duke University Medical Center, 26 of 51 patients (51%) developed PVE. The risk of endocarditis in this study was independent of the type of valve (mechanical vs. bioprosthetic), location (mitral vs. aortic), or onset of bacteremia after prosthetic valve implantation. The remaining cases of PVE are caused by gram-negative aerobic organisms, enterococci, diphtheroids, and streptococci. Fungal endocarditis may develop in patients with prolonged hospitalization with indwelling central venous catheters and long-term antibiotic use. Organisms that cause late PVE closely resemble those of NVE, although staphylococci remain predominant.

Nosocomial endocarditis

Nosocomial infective endocarditis (NIE) describes IE diagnosed after 48 hours of hospitalization and up to 4 weeks following a hospital-based procedure. The term "healthcare-associated infective endocarditis" (HCIE) describes cases of IE acquired outside the hospital. Patients with either NIE or HCIE are more likely to be diabetic, to be on hemodialysis, or to have been subjected to intravascular catheters or inserted intracardiac devices, and are more likely to have persistent *S. aureus* bloodstream infection. IE can occur as a complication of nosocomial bacteremia.

Since the mid-1980s, the increased use of intravascular devices and invasive diagnostic procedures, with their consequent complications, has increased the risk of HCIE. Colonized intravascular catheters now account for up to two-thirds of HCIE. The most common pathogens isolated in this type of infection are CoNS (15%), enterococci (14%) streptococcal species (8%), gram-negatives (5.8%), culture-negative (4.7%), and *Candida* species. Only 25% of patients with NIE will have fever or chills.

The upsurge of intravascular catheter-related bloodstream infections (CRBSIs) is directly related to an increase in the acute IE caused by *S. aureus*. In the past two decades, CRBSIs have increased >100%. The risk for this type of infection significantly increases 3 to 4 days after the insertion of the catheter.

During the first 15 days after insertion, skin flora makes up the greatest source of infection for these devices. After this time, contamination of the upper portion of the catheter by healthcare providers is a major source and leads to colonization of the hub and resultant intraluminal contamination. The risk of contamination/infection of the system is directly related to the length of time that the catheter remains in place and to the degree of manipulation of the hub. Rarely is a contaminated infusate the source of infection. Shortly after insertion, the catheter's extraluminal wall becomes coated with a fibrin-platelet thrombus that becomes covered by endothelial cells. This structure essentially becomes an NBTE, which can become infected as skin bacteria, commonly *S. aureus*, migrate down the insertion tract. *S. aureus* in the infected thrombus may enter the bloodstream as well as the endothelium of the adjacent vein, multiply there, and then re-enter the bloodstream, resulting in a sustained *S. aureus* bacteremia. This may or may not lead to valvular infection. This process may explain persistent *S. aureus* bloodstream infection with negative transesophageal echocardiogram (TEE).

The Infectious Disease Society of America has updated its CRBSI guidelines with key recommendations regarding *S. aureus* bloodstream infection (Box 37.1). *S. aureus* in blood should rarely, if ever, be considered a contaminant, and a low threshold should be maintained regarding suspicion of IE in this setting.

Long-term catheters should be removed in the setting of endocarditis. TEE should be performed (at least 5–7 days after the onset of bacteremia or fungemia) for patients with CRBSI who have a prosthetic heart valve, pacemaker, or implantable defibrillator.

Infective endocarditis in the intravenous drug abuser

IVDAIE accounts for at least 25% of total cases of IE, and this number is rising. The incidence of hospitalization for IV drug abuse has reached 12%, and HIV infection is four times higher in this population (40–90%). Those with CD4 counts of less 350 are eight

BOX 37.1

Catheter-related bloodstream infections (CRBSIs) with *Staphylococcus aureus*

Catheter removal recommended

Long-term catheters should be removed from patients with CRBSI associated with any of the following conditions: endocarditis, severe sepsis, bloodstream infection that continues despite >72 h of appropriate antimicrobial therapy, suppurative thrombophlebitis, or infections due to S. aureus, Pseudomonas aeruginosa, fungi, or mycobacteria.

S. aureus specific recommendations

In addition to catheter removal, patients should receive 4–6 weeks of antimicrobial therapy, or a minimum of 14 days of therapy if they meet the following criteria: the patient is not diabetic or immunosuppressed; if the infected catheter is removed; if the patient has no prosthetic intravascular device (e.g., pacemaker or recently placed vascular graft); if there is no evidence of endocarditis or suppurative thrombophlebitis on TEE and ultrasound, respectively; if fever and bacteremia resolve within 72 h after initiation of appropriate antimicrobial therapy; and if there is no evidence of metastatic infection on physical examination and sign or symptom-directed diagnostic tests.

times more likely to develop IVDAIE. The tricuspid valve is involved in 30% to 70% of cases; 13% involve both right and left sides of the heart. *S. aureus* causes up to 70% of cases. The contributions of other pathogens are as follows: streptococcal species, 8%; enterococcal species, 2%; fungal species, 2%; gram-negative anaerobes, 5%; and polymicrobials, 9%. The polymicrobial infections include various combinations of *Pseudomonas* sp., *S. aureus,* and *S. pneumoniae.* Polymicrobial IE most likely reflects poor injection techniques such as using contaminated water, sharing needles, and licking needles for good luck before injection.

Endocarditis in IV drug abusers involves mainly normal valves. Only 20% to 30% of the patients have an underlying valvular abnormalities. As discussed, *S. aureus* can produce its own sterile valvular thrombus. It is postulated that organisms that cannot do so produce an NBTE through contaminant particulate matter contained within the injected material. The tricuspid valve is predominantly involved in IVDAIE, but aortic and mitral valves may also be damaged. Although *S. aureus* is known to be the most common causative organism in patients with IE associated with IV drug abuse, a variety of microorganisms and fungi, including unusual and fastidious organisms (e.g., the HACEK group) and gram-negative organisms (e.g., *Pseudomonas* spp. from water sources used), are not uncommon in IV drug abusers, particularly in the patients who are not meticulous in their injection practices.

Right-sided IV drug abusers will commonly present with pleuritic pain, hemoptysis, cough, or empyema caused by septic pulmonary emboli. Left-sided disease (30% of cases) may lead to cerebral mycotic aneurysms (especially with *P. aeruginosa*), renal failure, and septic arthritis.

Polymicrobial infections may also occur. Because of the higher incidence of right-sided lesions and the generally younger age of the affected group, prognosis for recovery in treated IVDAIE is better than in the general population. However, valvular damage sustained in the course of the infection confers an extremely high risk of recurrent IE in those patients who continue to use IV drugs.

Diagnosis of infective endocarditis

Recognizing the clinical presentations of valvular infection is the first step toward arriving at a successful diagnosis. SBE makes itself manifest in markedly different ways than does acute disease. Untreated subacute disease may extend over a year. It often presents with non–cardiac-related symptoms such as renal failure, musculoskeletal complaints, and peripheral stigmata that are primarily immune complex-mediated. Fevers may not be consistently present and are usually low-grade. Because of the need for underlying preexisting valvular abnormalities, a cardiac murmur is almost always present. Often, there will be no change in the nature of the murmur during the disease process.

ABE is a rapidly progressing disease with very high-grade fever course. Congestive heart failure (CHF) develops early on. Occasionally, patients will have a more extended course prior to the correct diagnosis when they have been given antibiotics aimed incorrectly at misdiagnosed infections. This can result in a state of "muted" disease. These antibiotics simply dampen the symptoms of ABE but do not have any significant effect on the valvular infection.

The diagnosis of IE has been become more challenging due to a variety of factors, including increasing numbers of cases among the immunosuppressed with attenuated signs and symptoms of the disease as well as an increase in "nonclassic" organisms" for IE, such as CoNS. In addition, rheumatological diseases and lymphomas are quite effective mimics. Among patients with *S. aureus* CRBSI, there is a growing challenge in determining the significance of a noncontinuous bacteremia, as well as the challenge of interpreting the significance of a continuous bacteremia in the setting of a negative TEE.

Documentation of a continuous bacteremia is the major criteria for diagnosing IE. Such a bloodstream infection denotes that the source is an endovascular one.

Blood culture caveats:

1. Drawing one set of blood cultures is worse than drawing none. One cannot determine whether a positive culture is a contaminant or represents a continuous bacteremia.
2. The venipuncture site must be appropriately prepared with application of chlorhexidine, which is allowed to dry before the venipuncture is performed. Failure to do so is the major cause of contamination of blood cultures with CoNS.
3. An adequate volume of blood must be obtained:10 mL of blood per blood culture bottle. Inadequate volumes are the major cause of false-negative blood cultures.

4. Blood cultures should not be drawn from an intravascular catheter except in the setting of ruling out catheter infection.
5. No patient is too ill to delay initiation of antibiotic therapy for a few minutes to obtain two or three sets of blood cultures. They can be drawn in quick succession as long as the skin is appropriately prepared and the appropriate blood is drawn through different venipunctures.
6. Unless the patient has recently been on antibiotics or there is concern for CoNS PVE, no more than three sets of blood cultures need to be drawn. This exception for CoNS recognizes the fact that IE with this pathogen does not always have a continuous bacteremia.

Therapy

A vegetation consists of microorganisms in high density (10^{10} organisms/g of tissue) and in a reduced metabolic state inside an acellular lesion with impaired host defenses. Eradication of IE is thus almost totally dependent on the efficacy of the antimicrobial therapy. To achieve this end, certain principles of therapy are critical:

1. Parenteral antibiotics are usually required to provide a predictably high serum antibiotic level and thus optimize penetration of the antibiotic into tissue. There is growing evidence that in patients who are responding to 2 weeks of IV therapy, oral administration of well-absorbed antibiotic such as linezolid or levofloxacin can be effective.
2. Bactericidal rather than bacteriostatic antibiotics should be used to compensate for impaired host defenses in the vegetation. A major exception to this rule is the bacteriostatic antibiotic, linezolid.
3. Prolonged therapy is required for complete eradication of microorganisms.

In a patient with suspected IE but in whom culture results are not available, empiric antimicrobial therapy should be directed against staphylococci, streptococci, and enterococci unless epidemiologic data points at alternative etiologies. Nafcillin or oxacillin, 2 g IV every 4 hours, and gentamicin, 1 mg/kg IV every 8 hours, may be used as initial therapy. Vancomycin, 15 mg/kg every 12 hours, should be used if the patient is allergic to penicillin. Vancomycin should also be the drug of choice in suspected nosocomial endocarditis because of the high incidence of MRSA and coagulase-negative *S. epidermidis* (CoNS) in such a setting (see Figures 37.4 and 37.5).

Viridans streptococci and *Streptococcus bovis*

Antibiotic selection for therapy of streptococcal endocarditis is based on the minimal inhibitory concentration (MIC) of the isolated organism to penicillin (Table 37.2). Viridans streptococci and *S. bovis* are generally highly susceptible to penicillin (MIC ≤0.12 μg/mL) and can be treated with aqueous penicillin G or ceftriaxone for 4 weeks. The addition of gentamicin can shorten therapy to 2 weeks, but such therapy should be reserved for patients with NVE of <3 weeks duration with normal renal function and without intracardiac or extracardiac complications. The same regimen applies to the therapy of streptococcal PVE, but the duration of treatment is prolonged to 6 weeks. For streptococci with moderate resistance to penicillin (MIC 0.12 to ≤0.5 μg/mL), the addition of gentamicin for the first 2 weeks is always recommended to prevent

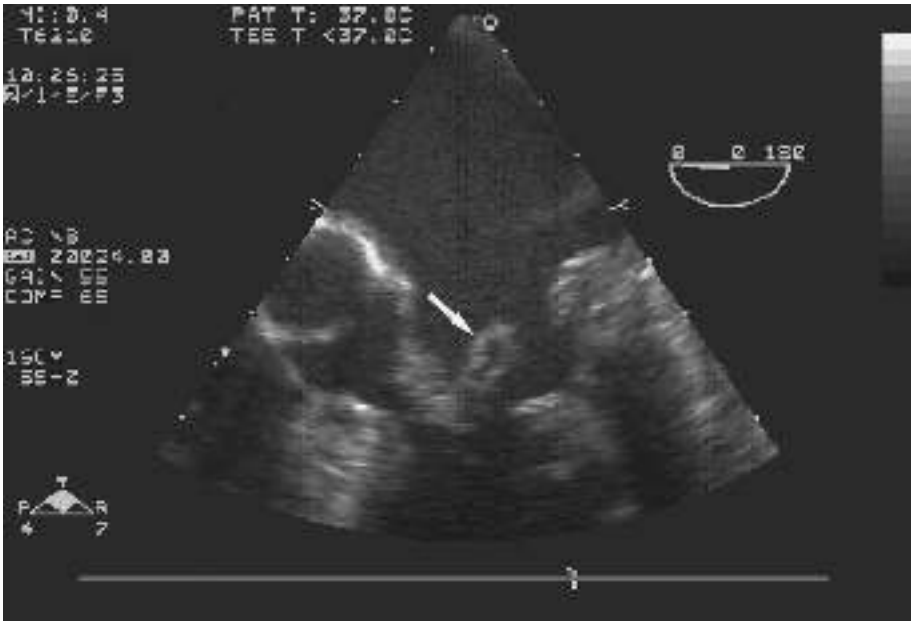

FIGURE 37.4 Transesophageal echocardiogram of a patient with *Haemophilus parainfluenzae* infective endocarditis showing large vegetation in mitral valve chordae apparatus (*arrow*).

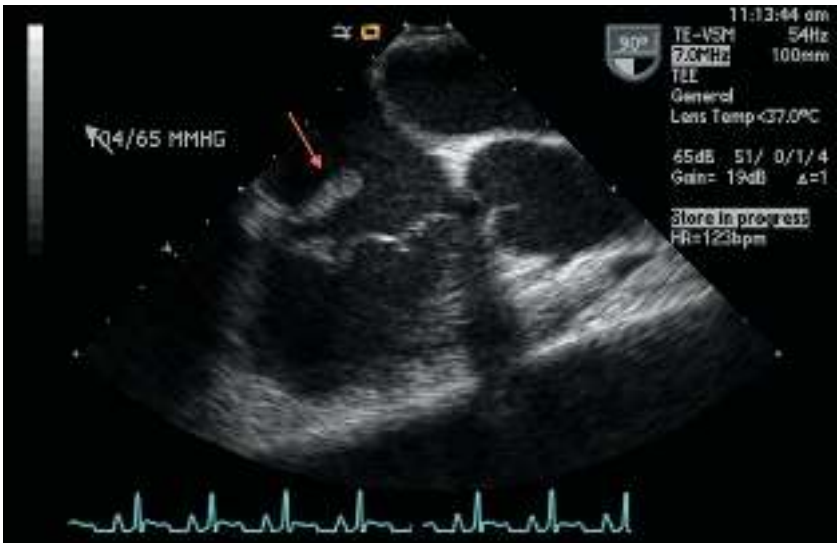

FIGURE 37.5 Transesophageal echocardiogram of an intravenous drug user with a large vegetation on the tricuspid valve (*arrow*).

TABLE 37.1 MODIFIED DUKE CRITERIA FOR DIAGNOSIS OF INFECTIVE ENDOCARDITIS

Definitive infective endocarditis

Pathologic criteria

Microorganism demonstrated by culture or histology of vegetation or emboli or intracardiac abscess

Histopathologically proven at autopsy or surgery

Clinical criteria

2 major; 1 major and 3 minor criteria; or 5 minor criteria

Possible infective endocarditis

1 major and 1 minor or 3 minor criteria[a]

Rejected

Alternative diagnosis, resolution of syndrome with ≤4 days of antibiotic; no histopathologic evidence with ≤4 days of antibiotic therapy; does not meet criteria for "possible" IE.

Major criteria	Minor criteria
Positive blood cultures	Predisposing heart condition or IV drug use
Typical microorganism for IE from 2 separate blood cultures, as follows:	Fever (38°C/100°F)
Viridans streptococci, *Streptococci bovis*, HACEK group, *Staphylococcus aureus*[a], or community-acquired enterococci with no primary focus	Vascular phenomena Immunologic phenomena
Persistently positive blood cultures with microorganism consistent with IE: At least 2 positive blood cultures drawn 12 h apart All of 3 or a majority of 4 or more separate blood cultures: first and last sample at least 1 h apart	Positive blood cultures but short of major criteria or serologic evidence of infection; excludes single positive blood cultures with coagulase-negative staphylococci and organism consistent with IE
Single blood culture positive for *Coxiella burnetii* or positive serology: antiphase 1 IgG ab titer 1:800[a]	Echocardiogram consistent with IE but short of major criteria was eliminated[a]
Endocardial involvement by showing vegetation; or abscess; or new prosthetic valve dehiscence; or *de novo* valvular regurgitation in echocardiogram. TEE recommended for prosthetic valve, "possible IE" cases, or complicated IE with intracardiac abscess[a]	

Abbreviations: TEE = transesophageal echocardiogram; IE = infective endocarditis; IgG = immunoglobulin G; ab = antibody.
[a] Modifications from the original Duke Criteria

TABLE 37.2 **ANTIBIOTIC THERAPY FOR STREPTOCOCCAL ENDOCARDITIS**

Viridans streptococci or *S. bovis* MIC ≤0.12 μg/mL	**Viridans streptococci or *S. bovis* MIC 0.12 μg/mL to ≤0.5 μg/mL**	**Viridans streptococci or *S. bovis* MIC 0.5 μg/mL**
Native valve		
		Ceftriaxone 2g/24h IV/IM for 6 wk additional weeks
Ceftriaxone, 2 g/24 h IV/IM 4 wk	Ceftriaxone, 2 g/24 h IV/IM 4 wk plus	
	Gentamicin 1 mg/kg IV/IM q8h for the first 2 wk	Gentamicin, 1 mg/kg q8h IV/IM 4–6 wk
Ceftriaxone, 2 g/24 h IV/IM 2 wk		
plus		
Gentamicin, 1 mg/kg q8h IV/IM for the first 2 wk		
Prosthetic valve		
PCN G, 24 mU/24 h IV 6 wk	PCN G, 24 mU/24 h IV 6 wk	PCN G, 24 mU/24 h IV 6 wk
Or	*Or*	*Or*
Ceftriaxone, 2 g/24 h IV/IM 4 wk with or without	Ceftriaxone, 2 g/24 h IV/IM 6 wk	Ceftriaxone, 2 g/24 h IV/IM 6 wk
Gentamicin 1 mg/kg IV/IM q8h for the first 2 wk[a]	*Plus*	*Plus*
	Gentamicin 1 mg/kg IV/IM q8h for 6 wk	Gentamicin 1 mg/kg IV/IM q8h for 6 wk
If patient is allergic to PCN		
Vancomycin, 30 mg/kg q24h IV divided in 2 doses, no more than 2 g/24 h unless concentration inappropriately low at 4 wk	Vancomycin, 30 mg/kg q24h IV divided in 2 doses, no more than 2 g/24 h unless concentration inappropriately low at 6 wk	Vancomycin, 30 mg/kg q24h IV divided in 2 doses, no more than 2 g/24 h unless concentration inappropriately low at 6 wk *plus* Gentamicin, 1 mg/kg q8h IV/IM 4–6 wk

Abbreviations: MIC = minimal inhibitory concentration; PCN = penicillin.
[a] Combination therapy has not demonstrated superior cure rates compared to monotherapy

relapse. IE caused by highly penicillin-resistant viridans streptococci (MIC 0.5 μg/mL) and by *Abiotrophia* and *Granulicatella* spp. (formally known as nutritionally variant streptococci) are difficult to treat and should be treated with the same regimen as recommended for enterococcal endocarditis. Vancomycin is to be administered only for patients with significant penicillin allergies. IV penicillin G and IV ampicillin are currently less frequently used because of their multiple dosing schedules(q4–6h).

It is important to make note of the possibility of surgical therapy for the treatment of *S. anginosus*. This is a group of *S. viridans* that behaves more like *S. aureus*. They may cause both intracardiac and extracardiac abscesses (brain abscesses). Frequently these sites require surgical drainage. Their antibiotic sensitivity pattern is like that of the other groups of *S. viridans.*

Staphylococci

Most penicillin resistant strains of *S. aureus* I don't produce beta-lactamases or are intrinsically methicillin resistant. Nafcillin or cefazolin should be administered for 6 weeks (Table 37.3). Vancomycin should be used only in cases of serious β-lactam allergy (immunoglobulin E [IgE]-mediated hypersensitivity) or if a MRSA isolate is suspected or documented; otherwise increasing rates of MRSA, both hospital and community isolates, obligate the use of vancomycin as empiric antibiotic therapy. In cases of vancomycin failure or difficulty achieving therapeutic levels due to fluctuating renal function, alternatives linezolid and daptomycin should be considered. In cases of uncomplicated right-sided endocarditis with MSSA, the treatment course of nafcillin/oxacillin may be limited to 2 weeks. It is important to be aware of the presence of *S. lugdunensis*. This is a coagulase-negative staphylococcus that is capable producing suppurative complications similar to those of *S. aureus*.

In PVE, the most common causative agents are *S. aureus* and coagulase-negative *S. epidermidis* (see Table 37.3). Both species are commonly resistant to β-lactam antibiotics; thus, until sensitivity to methicillin can be confirmed, vancomycin should be used as the primary therapy of endocarditis. Bacteriologic

TABLE 37.3 **ANTIBIOTIC THERAPY FOR STAPHYLOCOCCAL ENDOCARDITIS**

***S. aureus* or coagulase-negative staphylococcus native valves**	***S. aureus* or coagulase-negative staphylococcus prosthetic valves**
Methicillin sensitive	
Nafcillin, 12 g q24h IV 6 wk	Nafcillin, 12 g q24h IV ≥6 wk
	Plus
	Rifampin, 300 mg PO q8h ≥6 wk
	plus
Or	Gentamicin, 1 mg/kg q8h IV first
Cefazolin, 6 g q24h IV 6 wk	2 wk
Methicillin-resistant or PCN allergic	
Vancomycin, 30 mg/kg q24h IV divided in 2 doses, no more than 2 g/24 h unless concentration inappropriately low for 6 wk	Vancomycin, 30 mg/kg q24h IV divided in 2 doses ≥6 wk
Or	
Daptomycin 8–10 mg/kg per 24 for 6 wk	
Or	*Plus*
Linezolid 600 mg IV q12h for 6 wk	Rifampin, 300 mg PO q8h ≥6 wk
	Plus
	Gentamicin, 1 mg/kg q8h IV first 2 wk
Daptomycin, 12 mg/kg q24 IV 4–6 wk (for right-sided endocarditis only)	

failures are common, and surgical valve replacement may be necessary.

Enterococci and vancomycin-resistant enterococcus

Enterococci are intrinsically resistant to the bactericidal effect of penicillin or vancomycin. Therefore, for the treatment of endocarditis, the addition of aminoglycoside is needed to promote bactericidal effect. Cephalosporins are inactive against enterococci and cannot substitute for penicillin in this setting. The emergence of enterococci highly resistant to penicillin, aminoglycosides, and vancomycin has seriously compromised the efficacy of available treatment; therefore, all enterococcal isolates in cases of suspected IE should be subjected to in vitro sensitivity testing.

Patients with prosthetic valve infection should have therapy prolonged for a minimum of 6 weeks. Some gentamicin-resistant enterococcal strains are quite sensitive to streptomycin. There is a good deal of evidence that a combination of ampicillin (12 g per 24 hours) with ceftriaxone (2 g BID) is very effective in IE due to *Enterococcus faecalis* strains that are both susceptible to and highly resistant to gentamicin and in patients who cannot tolerate the potential side effects of an aminoglycoside. In my opinion, this combination is the preferred therapy for these patients. For enterococci that are highly resistant to ampicillin and highly resistant to aminoglycosides, treatment is based on vancomycin alone. In such cases, the input of an infectious disease consult is needed to arrive at an appropriate therapeutic choice.

Vancomycin-resistant enterococcus (VRE) now accounts for 15% of infections in critical care units; isolates of *Enterococcus faecium* are much more common than *E. faecalis*. There is no standard regimen for VRE endocarditis. From compassionate use data, linezolid resulted in a cure rate of 77% in VRE IE (Table 37.4).

Other treatment considerations

Gram-negative organisms of the HACEK group grow slowly on standard culture medium, although most will grow within 6 days. Because β-lactamase-producing HACEK organisms have emerged, ampicillin can no longer be recommended. At this time, third- or fourth-generation cephalosporins or ampicillin-sulbactam should be the regimen of choice. Fluoroquinolones (ciprofloxacin, levofloxacin, gatifloxacin, or moxifloxacin) may be used as an alternative regimen in patients who cannot tolerate β-lactam therapy (Box 37.2).

TABLE 37.4 **ANTIBIOTIC THERAPY FOR ENTEROCOCCAL AND PENICILLIN (PCN)-RESISTANT STRAIN STREPTOCOCCAL ENDOCARDITIS**

Enterococci and PCN-resistant strain streptococci, native valves or prosthetic valves[a]

Penicillin-sensitive

Ceftriaxone 2 g IV q12h
Plus
Ampicillin 2 g IV q4h for 6 wk

Ampicillin, 12 g q24h IV, plus gentamicin, 1 mg/kg IV q8h 4–6 wk

Penicillin-resistant or PCN-allergic (β-lactamase-producing strain)

Vancomycin, 30 mg/kg q24h IV divided in 2 doses 6 wk, plus gentamicin[b], 1 mg/kg q8h IV 6 wk

Enterococci PCN- and vancomycin-resistant, native valves or prosthetic valves

E. faecium	***E. faecalis***
	Ceftriaxone,2 g q24h IV/IM ≥8 wk, plus ampicillin 12 g q24h IV ≥8 wk (preferred)
	Or
Linezolid, 600 mg IV/PO q12h ≥8 wk	Imipenem–cilastatin, 2 g q24h IV ≥8 wk, plus ampicillin 12 g q24h IV ≥8 wk

[a] Prosthetic valve or intracardiac material; recommended therapy for 6 weeks.
[b] Substitute gentamicin with streptomycin, 15 mg/kg q24h IV/IM divided in 2 doses 4–6 wk, whenever enterococci are gentamicin-resistant but streptomycin-sensitive.

BOX 37.2

Antibiotic therapy for endocarditis caused by HACEK microorganisms[a]

Native and prosthetic valve

Ceftriaxone 2 g/24 h IV/IM 4 wk
Or
Ampicillin 12 g/24 h IV 4 wk
Or
Ciprofloxacin 500 mg/12 h PO or 400 mg q12h IV for 4 wk (need close monitoring)

[a] *Haemophilus parainfluenzae, H. influenzae, H. aphrophilus, H. paraphrophilus, A. actinomycetemcomitans, C. hominis, E. corrodens, K. kingae*, and *K. denitrificans*.

Most streptococci other than *S. viridans* or enterococci (pneumococcus, group A to G streptococci) remain susceptible to penicillin, but empiric therapy must allow for possible resistance. Although pneumococcal endocarditis is rare (≤1%), its aggressive fulminant course and the increasing incidence of penicillin and cephalosporin resistance have mandated vancomycin with or without ceftriaxone as the empiric regimen. Non–group A strains of streptococci may need gentamicin in addition to penicillin to achieve synergistic killing. Enterobacteriaceae and *Pseudomonas aeruginosa* are uncommon causes of endocarditis. Therapy should be determined by in vitro susceptibility testing.

Treatment of PVE is generally longer than that of NVE. If infection occurs within a year after surgery, empiric therapy should particularly target *S. epidermidis* and *S. aureus*. Animal models demonstrate rapid sterilization of vegetations with the addition of rifampin (Table 37.3). Thus, when PVE is clinically suspected, the combination of vancomycin, gentamicin, and rifampin should be initiated empirically. Rifampin is the key part of this combination since it is most likely the only one able to penetrate into the biofilm of the infected valve. The purpose of the other two antibiotics is to prevent resistance developing to the rifampin. For staphylococcal infection, nafcillin or oxacillin should be substituted for vancomycin if susceptibility results allow. If the pathogen is resistant to all available aminoglycosides, a fluoroquinolone may be used as an alternative. Duration of aminoglycoside use is similar to recommendations for infection of native valves.

Due to the higher mortality and valvular complications of PVE, especially when due to *S. aureus*, surgery is more frequently considered than in native valve infection.

Fungal endocarditis is poorly responsive even to standard-treatment amphotericin B or newer agents (for ≥6 weeks). Surgical valve replacement is usually necessary. In patients with hemodynamically stable valves and candida or aspergillus infections susceptible to imidazoles, long-term suppression with fluconazole (*Candida albicans*) or itraconazole (*Aspergillus* spp.) may be the preferred therapeutic choice. In PVE, valve replacement is usually mandatory regardless of the fungal organism.

Culture-negative endocarditis

The most common cause of culture-negative endocarditis (see NIE) currently is prior antimicrobial treatment before obtaining appropriate blood culture. In addition this condition is often caused by fastidious or difficult to culture organisms, including fungi, *Rickettsia*, *Mycobacteria*, *Chlamydia, Legionella*, *Coxiella burnetii*, and *Bartonella*.

Traditionally, serological studies have been the diagnostic modality of choice in CNIE but recent molecular advances (16S ribosomal RNA PCR) and epidemiology may also be helpful (Table 37.5).

Oral antibiotic regimens have seldom been used to treat IE because of concern about achieving adequate levels in the vegetation by the oral route and . I have employed linezolid orally to finish up the last 2 weeks of therapy in the situation where the patient was doing well but essentially "ran out" of venous access. With newer agents, such as the quinolones and linezolid, the serum concentration after oral administration is equivalent to that seen with parenteral dosing. These agents have been used for the oral treatment of highly susceptible gram-negative pathogens. A 4-week oral regimen of ciprofloxacin plus rifampin has been used to treat uncomplicated right-sided endocarditis in IV drug abusers. A recent study examined partial oral antibiotic treatment of left-sided endocarditis due to *Streptococcus* spp., enterococci, and CoNS. The criteria excluded any patients with ongoing signs of significant inflammation, fever, or

TABLE 37.5 **ANTIBIOTIC THERAPY FOR CULTURE-NEGATIVE ENDOCARDITIS**

Native valve	Prosthetic valve
Ampicillin–sulbactam 12 g/24h IV 4–6 wk	**Early infection (≤1 yr)**
Plus	Vancomycin 30 mg/kg q24h IV divided in 2 doses 6 wk
Gentamicin 1 mg/kg IV/IM q8h for 4–6 wk	*Plus*
Or	Gentamicin 1 mg/kg IV/IM q8h 2 wk
Vancomycin 30 mg/kg q24h IV divided in 2 doses 4–6 wk	*Plus* Cefepime 2 g q8h IV 6 wk
Plus	*Plus*
Gentamicin 1 mg/kg IV/IM q8h for 4–6 wk	Rifampin 300 mg q8h PO/IV 6 wk
Plus	
Ciprofloxacin 1 g/24h PO or 400 mg q12h IV 4–6 wk	
If *Bartonella* suspected,	
Ceftriaxone, 2 g/24 h IV/IM 6 wk *plus* gentamicin 1 mg/kg IV/IM q8h 2 wk with or without	
Doxycycline 100 mg PO/IV q12h 6 wk	

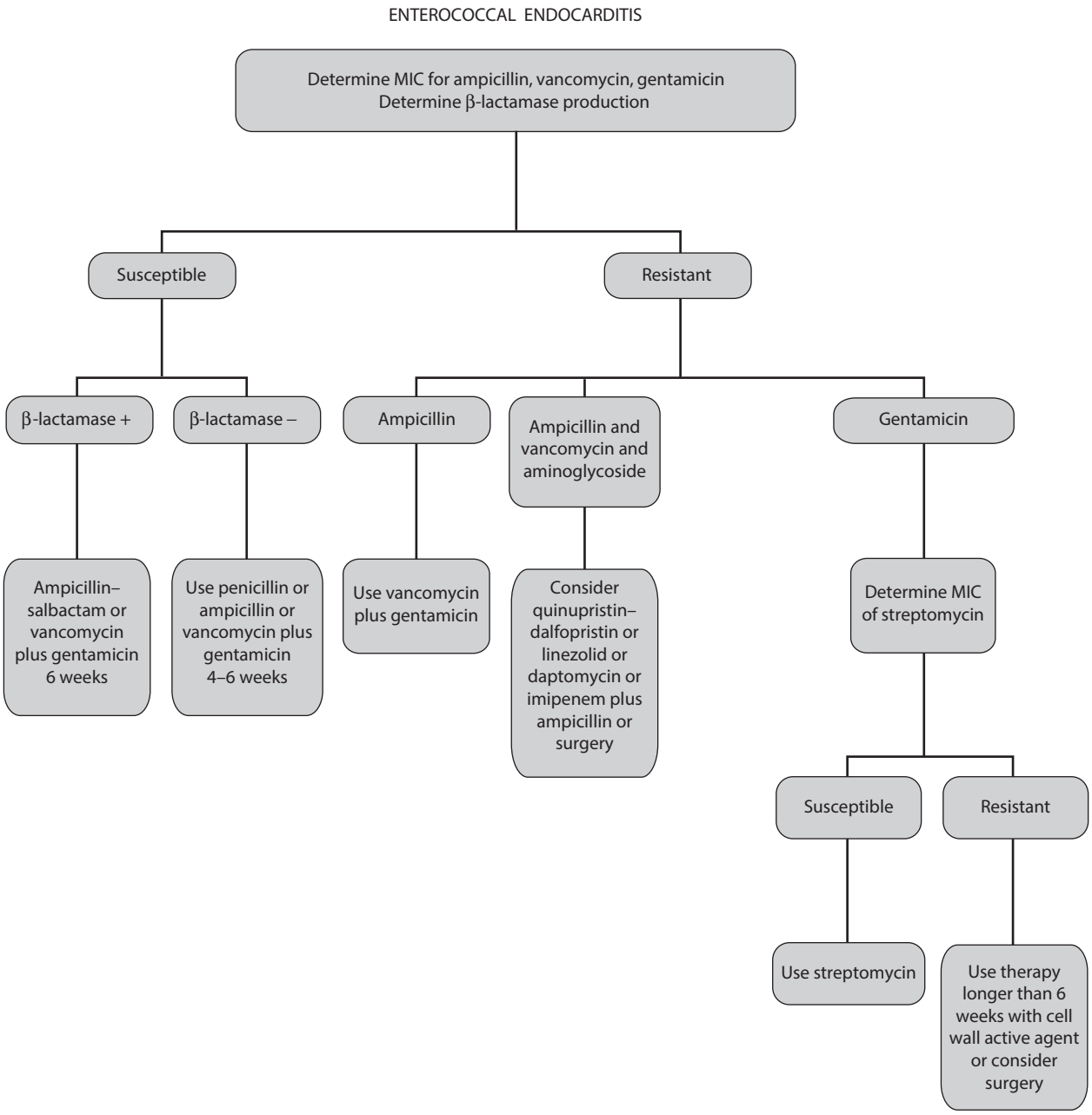

FIGURE 37.6 Algorithm for the treatment of HACEK endocarditis.

abscess formation, and the pharmacokinetics of the oral antibiotic matched those when it was given intravenously. Outcomes in the partially orally treated group were equivalent to those who remained continuously on IV-administered agents.

Prophylaxis

The American Heart Association's (AHA) most recent guideline in April 2007 made substantial changes in recommending preventive antibiotics. These recommendations were prompted by a growing amount of evidence that suggests that the risks of prophylactic antibiotics outweigh the benefits for most patients, especially those at low to moderate risk of developing procedure-related IE. (The risk of developing IE is very low, with 1 in 114,000 adults in the United States with prosthetic valves developing IE and 1 in 142,000 adults with rheumatic heart disease developing disease after dental procedures.) In addition, the data show that IE is much more likely to result from random bacteremias associated with daily activities than from dental, gastrointestinal, or genitourinary instrumentation. There is no compelling evidence to connect a significant risk of developing IE from the bacteremia of invasive and dental procedures. The 2007 AHA and updates guidelines consider only cardiac conditions with the highest risk of adverse outcome from endocarditis for which prophylaxis should be recommended (Box

BOX 37.3

Cardiac conditions warranting endocarditis prophylaxis

Prophylaxis recommended

Prosthetic heart valves
Previous history of endocarditis
Certain congenital heart conditions, including
- unrepaired or incompletely repaired cyanotic congenital heart disease, including those with palliative shunts and conduits
- a completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
- any repaired congenital heart defect with residual defect at the site or adjacent to the site of a prosthetic patch or a prosthetic device

Valvular disease in cardiac transplant recipients

Prophylaxis no longer recommended

Mitral valve prolapse
Rheumatic heart disease
Bicuspid valve disease
Calcified aortic stenosis
Congenital heart conditions such as ventricular septal defect, atrial septal defect, and hypertrophic cardiomyopathy

BOX 37.4

Procedures warranting endocarditis prophylaxis

Prophylaxis recommended

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
Tonsillectomy and/or adenoidectomy
Invasive respiratory procedures to treat infection
Surgical procedures involving infected skin and soft tissues

Prophylaxis not recommended

Injection of local intraoral anesthetic through noninfected tissue
Taking dental radiograph
Placement of removable prosthodontic or orthodontic appliances
Adjustment of orthodontic appliances
Placement of orthodontic brackets
Shedding of deciduous teeth
Bleeding from trauma to the lips or oral mucosa
Endotracheal intubation
Bronchoscopy without biopsy
Tympanectomy tube insertion
Transesophageal echocardiogram
Gastrointestinal or genitourinary procedures
Vaginal delivery or vaginal hysterectomy
Cesarean section
Dilatation and curettage
Ear and body piercing
Tattooing

37.3). The procedures are limited to dental and invasive respiratory procedures and surgery of infected soft tissues (Box 37.4). The antibiotic regimens are listed in Box 37.5.

Since 2007, there has been a 64% fall in prescription rates for antibiotic prophylaxis for moderate-risk individuals and a 20% decrease in patients at high risk. Well before these changes, there was a gradual increase in the cases of IE; this was attributed to aging of the general population and to increased rates of invasive procedures and intravascular device placement. However, several recent studies have demonstrated a rise in IE that exceeds these historical changes. There has been a moderate increase in IE among those of moderate risk but a significant increase (177%) among patients at high risk. It is not yet clear what is causing this. However, these figures compel a re-examination of prophylactic recommendations, one that should be more focused on prophylaxis in the placement of intravascular devices.

Surgical indications in the management of infective endocarditis

In certain cases of IE, surgery is associated with improved patient outcomes. Some of these indications are strongly supported by evidence. Other indications are more relative and have conflicting evidence, but expert opinion often favors surgical intervention (Table 37.6). CHF resulting from acute aortic insufficiency remains the major indication for immediate valve replacement because of the unacceptably high mortality rate in medically treated patients. Nonresponse to antimicrobial therapy may mandate valve removal

BOX 37.5

American Heart Association recommended prophylactic regimens

Single dose 30–60 minutes before procedure
Oral
Amoxicillin 2 g
Unable to take oral medications
Ampicillin 2 g IV/IM or cefazolin/ceftriaxone[a] 1 g IV/IM
Allergic to penicillin
Clindamycin 600 mg or azithromycin/clarithromycin 500 mg or cephalexin 2 g
Allergic to penicillin and unable to take oral medications
Clindamycin 600 mg IV or cefazolin/ceftriaxone[a] 1 g IV/IM

[a] Use only if non-IgE-mediated allergic reaction.

TABLE 37.6 **INDICATIONS FOR SURGICAL INTERVENTION IN NATIVE AND PROSTHETIC VALVE INFECTIVE ENDOCARDITIS (IE)**

Surgery usually recommended	Surgery to be considered
Congestive heart failure from acute aortic insufficiency	Large (10 mm) anterior mitral leaflet vegetation
Infective endocarditis caused by organism that may respond poorly to antimicrobial therapy (e.g., fungal or *Brucella* spp.)	Increase in vegetation size despite adequate treatment (after 4 weeks of antibiotic)
Persistent bacteremia after 1 week of adequate antibiotic therapy	Periannular extension on infection or myocardial abscesses
More than one embolic event occurring within the first 2 weeks of antibiotic therapy	IE caused by resistant enterococci species when effective bactericidal therapy is not available
Presence of echocardiography finding consistent with local cardiac complications such as valve dehiscence, large perivalvular abscess, rupture, or perforation of a valve Heart block	Uncontrolled infection caused by highly antibiotic-resistant pathogens despite optimal therapy (enterococci or gram-negative bacilli)
Staphylococcus aureus prosthetic valve endocarditis complicated by perivalvular abscess or dehiscence (reduces mortality rates)	
PVE or left-sided IE caused by gram-negative bacteria such as *Serratia marcescens, Pseudomonas* spp.	

Abbreviations: PVE = prosthetic valve endocarditis.

if no alternative source for the continued bacteremia or fungemia is found. Fungal endocarditis on a prosthetic valve almost always requires valve replacement. With aggressive pre- and postoperative antibiotic therapy, valve replacement with a mechanical prosthesis during active IE is a safe procedure. The risk of relapse of endocarditis in a newly implanted prosthetic valve is minimal. There is no strong evidence supporting the superiority of early versus later surgical treatment in NVE patients with indications for surgical intervention.

Treatment duration after surgery depends on culture data from the operating room; if operating room cultures are sterile, the antibiotic duration does not change. If operating room cultures are still positive, antibiotic therapy is considered to start at the time of surgery and should continue to completion following the NVE guidelines for the particular organism and not those for PVE. Similarly, those individuals with NVE who receive a prosthetic valve are treated for NVE, not for PVE.

Local cardiac complications of IE may require surgical intervention. TEE may detect valvular dehiscence, rupture, fistula, perforation, perivalvular extension of abscess, a large abscess, or a large vegetation (10 mm) on an anterior mitral valve leaflet. Because large vegetations tend to embolize, valve replacement or vegetectomy may be indicated in a patient with suspected or documented recurrent central nervous system or large-vessel emboli. The incidence of stroke from embolic events in patients receiving appropriate antimicrobial therapy in a recent European study was 4.82/1,000 patient days in the first week of therapy and fell to 1.71/1,000 patient days in the second week.

Anticoagulation should never be considered in patients with embolic complications of IE because of the significant risk of intracerebral hemorrhage. Maintenance anticoagulation in a patient with a prosthetic valve should be continued regardless of the diagnosis of endocarditis because of the risk of mechanical thrombosis. It may be prudent to monitor these patients on 2 weeks of heparin therapy following current guideline recommendations.

Suggested reading

Bor DH, Woolhandler S, Nardin R, Brusch J, Himmelstein D. Infective endocarditis in the US, 1998–2009: A nationwide study. *PLos One*. 2013;8:e60033.

Brusch JL. Infective endocarditis. Medscape. January 3, 2019.

Hoen B, Duval X. Clinical practice. Infective endocarditis. *N Engl J Med*. 2013;368(15):1425–1433.

Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49(1):1–45.

Thornhill MH, Gibson BT, Cutler E, et al. Anti-prophylaxis in incidence of endocarditis before and after the 2007 AHA recommendations. *J Amer Coll Cardiol*. 2018;72:2443–2454.

Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: Guidelines from the American Heart Association: A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116:1736–1754.

38

Acute pericarditis

Richard A. Martinello and Michael Cappello

Introduction

The pericardium serves to protect the heart from physiologic changes in intracardiac pressure related to respiration and postural change, and it may also augment the mechanical function of the cardiac chambers. The pericardium is composed of a visceral layer that directly adheres to the epicardium and an outer parietal layer. These two layers are separated by 10 to 35 mL of serous fluid. *Pericarditis* refers to the inflammation of these tissues. It may be acute, recurrent, or chronic, and it can be due to a wide array of etiologies.

Epidemiology and etiologic agents

Both infectious and noninfectious processes have been identified as causes of pericarditis (inflammation of the pericardium). Most cases are caused by viruses, are self-limited, and the specific pathogen is often unidentified. Purulent pericarditis, due to bacterial or fungal pathogens, is less common and the incidence is much lower than during the pre-antibiotic era. In one recent series, pericarditis was diagnosed in 5% of adults presenting for emergency care due to chest pain that was not associated with myocardial infarction. While pericarditis can affect patients across the spectrum of age, an analysis of US Medicare recipients (patients ≥65 years) cared for and diagnosed with pericarditis found that, between 1999 and 2012, the rate of hospitalization for pericarditis remained stable at about 26 cases/100,000 person years, with a modest decrease in the 30-day and 1-year all-cause observed mortality over this time period.

Most episodes of pericarditis occur in the spring and summer, coincident with the peak prevalence of enteroviral infections. During the winter months, influenza virus is a frequent cause of pericarditis, whereas pericarditis due to bacterial or atypical pathogens occurs throughout the year. There are no clinical features that allow a differentiation between viral and idiopathic causes of acute pericarditis. Approximately 15% of episodes of viral and idiopathic pericarditis are associated with concomitant myocarditis.

In areas of the world where the incidence of infection with *M. tuberculosis* remains high, tuberculosis is responsible for >50% of cases of acute pericarditis. Tuberculosis should be considered in persons who have spent significant time in endemic countries, including international adoptees, immigrants, and refugees. Patients with HIV infection are more likely to experience nonpulmonary manifestations of tuberculosis, such as pericarditis, and have been shown to experience higher rates of mortality due to tuberculous pericarditis than their non-HIV counterparts.

Pericarditis may also develop following cardiothoracic surgery. This may be due to a bacterial surgical site infection or postpericardiotomy syndrome, a noninfectious inflammatory condition that generally develops days to 6 months following cardiac surgery. In immunocompromised hosts, the range of potential pathogens that can cause pericarditis is quite broad and includes viruses, bacteria, fungi/yeasts, and parasites (Box 38.1) Cases of pericarditis associated with COVID have been published, though the characteristics of the relationship between infection with SARS-CoV-2 and pericarditis remain unclear. Acute pericarditis can also be

BOX 38.1

Infectious causes of acute pericarditis

Viruses
- Coxsackievirus A
- Coxsackievirus Ba
- Echoviruses
- Middle East Respiratory Syndrome-Coronavirus
- Mumps virus
- Influenza viruses
- Cytomegalovirus
- Herpes simplex virus
- Hepatitis B virus
- Measles virus
- Adenovirus
- Human immune deficiency virus
- Varicella virus

Bacteria
- *Burkholderia pseudomallei*
- *Staphylococcus aureus*[a]
- *Streptococcus pneumoniae*[a]
- *Haemophilus influenzae*[a]
- *Neisseria meningitidis*[a]
- *Streptococcus pyogenes*
- α-Hemolytic streptococci
- *Klebsiella* spp.
- *Pseudomonas aeruginosa*
- *Escherichia coli*
- *Salmonella* spp.
- *Shewanella algae*

Anaerobes
- *Listeria monocytogenes*
- *Neisseria gonorrhoeae*
- *Coxiella burnetii*
- *Actinomyces* spp.
- *Nocardia* spp.
- *Mycoplasma pneumoniae*

Mycobacteria
- *Mycobacterium tuberculosis*
- Mycobacterium avium complex

Fungi
- *Histoplasma capsulatum*
- *Blastomyces dermatitidis*
- *Candida* spp.
- *Aspergillus* spp.
- *Cryptococcus neoformans*
- *Coccidioidomycosis*

Parasites
- *Toxoplasma gondii*
- *Entamoeba histolytica*
- *Toxocara canis*
- Schistosomes
- *Wuchereria bancrofti*

[a] Most common causes of acute bacterial or viral pericarditis in North America.

BOX 38.2

Major noninfectious causes of acute pericarditis

Collagen vascular diseases
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Scleroderma
- Rheumatic fever

Drugs
- Procainamide
- Hydralazine
- Monoclonal antibody therapeutics

Myocardial injury
- Acute myocardial infarction
- Chest trauma (penetrating or blunt)
- Postpericardiotomy syndrome

Sarcoidosis

Familial Mediterranean fever

Uremia

Neoplasia
- Primary
- Metastatic
- Irradiation

due to noninfectious causes (Box 38.2). Very rarely, pericarditis has been observed within weeks of vaccination, particularly after vaccination against smallpox, though whether other vaccinations may cause pericarditis is uncertain.

Pathogenesis

Microbial pathogens may gain entry into the pericardial space by direct extension from the chest (e.g., in the context of pneumonia or mediastinitis), through direct extension from the heart itself (e.g., endocarditis), through hematogenous or lymphatic spread (bacteremia or viremia), or via direct inoculation (e.g., surgery, trauma). The presence of an adjacent or otherwise concurrent infection as well as a history of recent surgery or trauma may provide significant clues to specific pathogens. For example, purulent pericarditis due to *N. meningitidis* has been diagnosed in patients with concurrent bacterial meningitis. In a review of 162 children with purulent pericarditis, all but 10 patients had at least one additional site of infection, suggesting that isolated cardiac disease occurs infrequently in those with purulent pericarditis. In cases where either *S. aureus* or *H. influenzae* type B was the responsible pathogen, pneumonia, osteomyelitis, and cellulitis were the most frequently identified additional sites of infection. Tuberculous pericarditis, however, usually occurs in the absence of identifiable pulmonary disease, thus suggesting that the pathogenesis involves the spread of mycobacteria from adjacent mediastinal lymph nodes into the pericardium.

The inflammatory response in the pericardial space leads to extravasation of additional pericardial fluid, polymorphonuclear white blood cells, and monocytes. During bacterial or fungal pericarditis, the inflammatory process may be sufficient to lead to loculation and fibrosis. Significant fibrosis may lead to constrictive pericarditis, which is manifest by signs and symptoms associated with compromised ventricular filling. The rapid accumulation of exudative fluid, as is often seen in purulent pericarditis, frequently leads to hemodynamic changes. Cardiac tamponade occurs when the pressure caused by an increased fluid volume within the pericardial space prevents adequate right atrial filling and leads to reduced stroke volume, low-output cardiac failure, and shock. If the accumulation of pericardial fluid occurs more slowly, as is common with viral pericarditis, large amounts may be present without hemodynamic effect.

Symptoms and clinical manifestations

Chest pain is the most common presenting symptom of acute pericarditis. Due to the relationship between the phrenic nerve and pericardium, pain resulting from inflammation of the pericardium may be retrosternal with radiation to the shoulder and neck or may localize between the scapulae. Often, the pain is worsened by swallowing or deep inspiration, or it is positional and worsened when the patient is supine but lessened by leaning forward while sitting. Dyspnea is also a common presenting symptom. If pericarditis has resulted from contiguous spread of bacteria or fungi from an adjoining structure, the signs and symptoms of the primary infectious process may predominate. Purulent pericarditis due to a bacterial pathogen tends to be more acute and severe in nature, whereas viral pericarditis is typically of lesser severity. Symptoms of tuberculous pericarditis tend to be insidious in presentation.

In infants, the presenting signs and symptoms of pericarditis may be nonspecific and include fever, tachycardia, and irritability. Older children may complain of chest and/or abdominal discomfort. A study by Carmichael et al. in 1951 showed that more than half of patients diagnosed with "nonspecific" pericarditis of presumed viral origin described a respiratory illness preceding the diagnosis of pericarditis by 2 to 3 weeks.

On physical exam, nearly all patients with pericarditis, regardless of cause, will have tachycardia. Those with bacterial pericarditis are also likely to have fever and tachypnea as well as possible evidence of at least one additional site of infection (e.g., pneumonia, surgical site infection, osteomyelitis, etc.). Perhaps the most characteristic physical finding in acute pericarditis is the presence of a friction rub on cardiac auscultation. The rub may be confused with a high-pitched murmur, particularly when it is only present in systole. Pericardial friction rubs may have as many as three components corresponding with atrial systole, ventricular systole, and rapid ventricular filling during early diastole. A rub may be best appreciated with the patient leaning forward or in the knee-chest position. Although more than one component of a pericardial rub may be present, all three components were noted in fewer than 50% of patients in one case series.

The presence of a pulsus paradoxus or jugular venous distention suggests the possibility of cardiac tamponade, which may require emergent intervention. This is most frequently seen in the presence of a large or rapidly accumulating pericardial effusion but can also result from constrictive disease due to long-standing pericarditis with fibrosis.

Diagnosis

An acutely enlarged cardiac silhouette on chest radiograph, particularly in the absence of increased pulmonary vascularity, suggests the presence of pericardial effusion. However, there may be no radiographic abnormalities detected in patients with small but rapidly accumulating effusions, as well as in those with constrictive disease.

Although the pericardium is not involved in the electrical activity of the heart, pericarditis is associated with classic electrocardiographic (EKG) changes, which are likely due to concomitant inflammatory changes in the epicardium and outer myocardium. Electrocardiographic changes may be present in 50% of patients with acute pericarditis, and the specific changes evolve over time. Elevation or depression of the ST and/or depression of the PR segments may occur early in the disease process (Figure 38.1). Over subsequent days, the ST segment returns to baseline. Late EKG changes in pericarditis may include flat or inverted T waves. These EKG changes can be differentiated from those due to myocardial infarction as it is uncommon for T-wave inversions to be detected until the ST segment changes resolve. Large pericardial effusions may result in reduced voltage or electrical alternans due to beat-to-beat variation in the position of the heart within the pericardial fluid.

Echocardiography is the diagnostic study of choice for detecting excess pericardial fluid and is recommended for all patients in whom pericarditis is suspected. In patients with post-sternotomy pericarditis, CT scan and cardiac MRI are both extremely useful for identifying mediastinal fluid collections and potential abscesses. Pericarditis occurs concurrently with myocarditis in approximately 20% to 30% of patients, and myocarditis can be noted by the presence of elevated troponins and/or myocardial edema on cardiac MRI.

Pericardiocentesis is the most specific means of determining the etiology of pericarditis, although the overall diagnostic yield may be low. Drainage of pericardial fluid should be performed when there is evidence for cardiac tamponade or a suspicion of tuberculous, neoplastic, or purulent pericarditis. The fluid should be transported quickly to the microbiology laboratory for Gram, acid-fast, and silver stains, as well as culture for bacteria (aerobic and anaerobic), fungi, mycobacteria, and viruses, as indicated. Pericardial fluid should also be analyzed for cell count and differential, glucose, total protein, and red blood cell count, and cytology may be considered. When tuberculous pericarditis is suspected, biopsy of the pericardium for histology and polymerase chain reaction (PCR) is useful, and an adenosine deaminase level should be measured in the pericardial fluid. The interferon-γ release assay has been shown to have both favorable sensitivity and specificity when studied in countries with modest to high rates of tuberculosis.

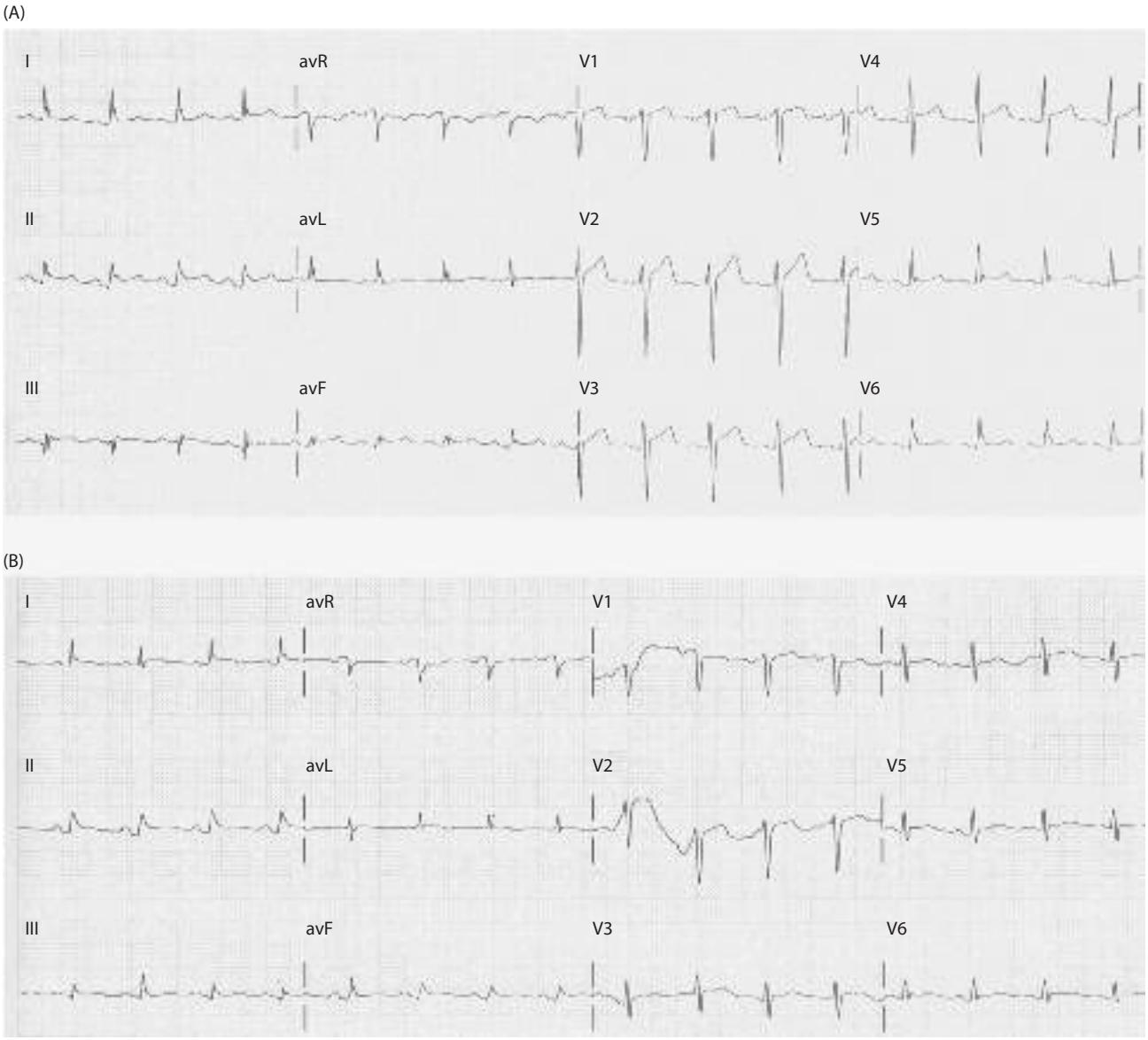

FIGURE 38.1 (A) Electrocardiogram (EKG) in acute pericarditis. ST segment elevation is noted with an upward concave appearance in all leads except I, aVR, and aVL. PR segment depression is noted in I, II, III, aVF, and the precordial leads. (B) EKG from the same patient as in A, but 3 days later. Note that PR segment depression persists in II, III, and aVF. Some ST elevation persists but has markedly diminished compared with the initial EKG

Courtesy Dr. Thuy Le.

For patients in whom a viral etiology is suspected, swabs from the nasopharynx, throat, and rectum may be obtained for PCR or culture as these sites are more likely to yield a positive result for enterovirus than the pericardial fluid itself. However, extensive testing to identify the etiology of viral pericarditis has not been found, in general, to be clinically useful. In the setting of pneumonia, sputum or tracheal aspirates can be cultured for bacteria, and diagnostic studies for respiratory viruses, including influenza A or B, should be obtained. Acute and convalescent antibody titers may be measured for the common enterovirus serotypes and other pathogens.

In patients with purulent pericarditis, blood cultures are frequently positive. These patients should be carefully evaluated for other infectious processes, including pneumonia, osteomyelitis, and meningitis. A positive bacterial culture from one of these alternative sites is strongly suggestive of the identity of the pericardial pathogen.

The diagnosis of tuberculous pericarditis can be particularly challenging. Although a study by Strang et al. found cultures of pericardial fluid to be positive in 75% of suspected cases, results may not be available for weeks. In this setting, pericardial biopsy may yield a more rapid diagnosis of *M. tuberculosis* infection, particularly if the characteristic granulomatous changes are present. Cigielski et al. have recently shown that a PCR-based assay was nearly as sensitive as culture (81% vs. 93%) for detecting *M. tuberculosis* in pericardial biopsy specimens. The obvious advantage to PCR is the speed with which results can be obtained, although false-positive results may occur more frequently than with culture.

Treatment

Urgent drainage of pericardial fluid should be considered in any patient with a possible diagnosis of purulent pericarditis or if hemodynamic compromise is identified. The outcome in these patients is generally poor without drainage even when appropriate antibiotics are administered. Likewise, purulent infections contiguous with the mediastinum should be drained. Intrapericardial fibrinolysis for persons with purulent pericarditis may prevent future complications of constrictive or persistent pericarditis.

If the Gram stain of pericardial fluid does not suggest an etiologic agent in the setting of purulent pericarditis, then empiric antibiotic coverage should be initiated while awaiting the results of cultures. The antibiotic(s) for empiric coverage should be chosen according to whether the patient has evidence for a contiguous site of infection, history of recent cardiothoracic surgery, trauma, or other relevant risk factors. In patients with community-acquired purulent pericarditis and no history of antecedent surgery or trauma, empiric treatment directed at *S. aureus* (oxacillin, nafcillin, or vancomycin) and common respiratory pathogens (ceftriaxone) would be appropriate.

If a viral etiology is suspected, nonsteroidal anti-inflammatory drugs (NSAIDs) are used as first-line therapy and have been found to relieve chest discomfort in 85% to 90% of patients. Typically, ibuprofen (1,600–3,200 mg/d in divided doses) is the drug of choice due to its low incidence of adverse events compared with other NSAIDs. Some experts favor the use of aspirin (650–975 mg q6–8h) in patients who have experienced a recent myocardial infarction because evidence from animal studies has led to concern that other NSAIDs may impair scar formation. Indomethacin should be avoided in persons with coronary artery disease as it has been shown to decrease coronary artery blood flow.

As the signs, symptoms, and pathological findings in pericarditis are often primarily due to the inflammatory response, pharmacological management is directed toward modifying inflammation in addition to addressing an infectious cause if one is present and treatable. Randomized trials have shown that colchicine (0.5–0.6 mg once daily if <70 kg, twice daily if >70 kg), in addition to an NSAID, effectively decreases the incidence of both the persistence of symptoms and the incidence of primary and secondary recurrent pericarditis. Colchicine is generally continued for 3 months. Markers of inflammation (i.e., erythrocyte sedimentation rate [ESR] and c-reactive protein [CRP]) may be followed to assess disease progression and help guide tapering of NSAIDS. It is recommended that NSAIDs be tapered once the patient's signs and symptoms have resolved for at least 24 hours and the inflammatory markers have normalized. Evidence supporting the use of systemic corticosteroids is limited and there is concern that their use, especially higher doses, may be associated with greater rates of relapse; use should only be considered in persons with persistent symptoms despite full doses of NSAIDs or in persons in whom NSAIDs are contraindicated (e.g., third trimester of pregnancy) or not tolerated despite acid suppressive therapy. For persons with recurrent pericarditis and those for whom NSAIDs and colchicine are unable to control symptoms, a progressive escalation of anti-inflammatory medications (i.e., corticosteroids, azathioprine, intravenous immunoglobulin, and anakinra-a recombinant IL-1 receptor antagonist given daily by subcutaneous injection) may be considered.

It is recommended that patients avoid strenuous activity during the initial weeks after diagnosis of acute pericarditis, but patients may then reintroduce activities after complete resolution of symptoms. Typically, competitive athletics should be avoided for 3 months.

Tuberculous pericarditis should be treated with four active antimicrobial agents until susceptibilities are known. The recommended duration of therapy for pericarditis caused by *M. tuberculosis* is 6 to 12 months, with the longer durations reserved for patients who improve more slowly. The use of corticosteroids as an adjunct does not appear to decrease mortality, although some investigators have concluded that there may be some benefit in reducing the occurrence of constrictive pericarditis. Likewise, it is not clear that there is a role for routine pericardial drainage or pericardiectomy in the treatment of tuberculous pericarditis.

Complications

Increased intrapericardial pressure due to an accumulating effusion may result in cardiac tamponade. Tamponade should be suspected if the patient's hemodynamic status is unstable, heart sounds are diminished, jugular venous pressure is raised, or if pulsus paradoxus is present. Echocardiography may note significant variation in blood flow across the mitral and tricuspid valves with respiration and collapse of the right-sided chambers during diastole. Drainage of the pericardial effusion is essential in the setting of purulent pericarditis or in the presence of tamponade. Patients with purulent pericarditis should be treated with a combination of both antimicrobial therapy and drainage. High mortality rates have been observed for patients with purulent pericarditis who have received only medical or surgical management in isolation.

A minority of patients may experience recurrent pericarditis involving reaccumulation of the pericardial effusion, fever, and chest pain. These episodes may relapse and remit for several years and are most commonly diagnosed in patients with prior viral pericarditis. Recurrent episodes are rarely complicated by either tamponade or constriction and are effectively treated with NSAIDs with or without colchicine or corticosteroids. Pericardiectomy, pericardial window placement, or other surgical procedures may be considered for those with the most recalcitrant signs and symptoms who fail aggressive medical management.

Constrictive pericarditis occurs due to the development of a thickened fibrous exudate within the pericardium, and the pericardium itself may calcify. The reduced compliance of the pericardial sac may impair diastolic filling and result in hemodynamic compromise. Constrictive pericarditis has most commonly been associated with antecedent tuberculous pericarditis, cardiac surgery, and radiation-induced pericarditis, though patients with a history of prior pericarditis of any etiology are at risk for developing constrictive disease. Constrictive pericarditis typically presents within 3 to 12 months of the initial episode, though the time interval may be days to years. Less severe cases may be managed medically by careful

monitoring of the patient's fluid status, but pericardiectomy remains the definitive therapy.

Suggested reading

Alabed S, Perez-Gaxiola G, Buris A. Colchicine for children with pericarditis: Systematic review of clinical studies. *Arch Dis Child*. 2016;101(10):953–956.

Fanne RA, Banai S, Chorin U, Rogowski O, Keren G, Roth A. Diagnostic yield of extensive infectious panel testing in acute pericarditis. *Cardiology*. 2011;119:134–139.

Galluzzo A, Imazio M. Advances in medical therapy for pericardial diseases. *Exp Rev Cardiovasc Ther*. 2018;16(9):635–643.

Imazio M. Efficacy and safety of colchicine for pericarditis prevention. Systematic review and meta-analysis. *Heart*. 2012;98:1078–1082.

Imazio M, Belli R, Brucato A, et al. Efficacy and safety of colchicine for the treatment of multiple recurrences of pericarditis (CORP–2): A multicentre, double-blind, placebo-controlled, randomised trial. *Lancet*. 2014;383:2232–2237.

Imazio M, Brucato A, Cemin R. A randomized trial of colchicine for acute pericarditis. *N Engl J Med*. 2013;369:1522–1528.

Imazio M, Gaita F. Acute and recurrent pericarditis. *Cardiol Clin*. 2017;35(4):505–513.

Lazaros G, Imazio M, Brucato A, et al. Anakinra: An emerging option for refractory idiopathic recurrent pericarditis: A systematic review of published evidence. *J Cardiovasc Med*. 2016;17:256–262.

Levy PY, Corey R, Berger P, et al. Etiologic diagnosis of 204 pericardial effusions. *Medicine (Baltimore)*. 2003;82:385–391.

LeWinter M. Acute pericarditis. *N Engl J Med*. 2014;371:2410–2416.

Mayosi BM, Wiysonge CS, Ntsekhe M, et al. Clinical characteristics and initial management of patients with tuberculous pericarditis in the HIV era: The Investigation of the Management of Pericarditis in Africa (IMPI Africa) registry. *BMC Infect Dis*. 2006;6:2.

Mody P, Behnood B, Wang B, et al. Trends in acute pericarditis hospitalizations and outcomes among the elderly in the USA, 1999–2012. *Eur Heart J*. 2018;4:98–105.

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Myocarditis

Lori Blauwet and Andrew Rosenbaum

Definition

Myocarditis is a rare, potentially deadly and often underdiagnosed cause of acute or chronic heart failure that primarily affects children and younger adults. The incidence is estimated at 22 per 100,000 people. Historically, the diagnosis of myocarditis was confirmed by histologic analysis of endomyocardial biopsy (EMB) specimens with findings of an inflammatory cellular infiltrate of the myocardium with or without myocyte necrosis and/or degeneration of adjacent myocytes. The type of inflammatory infiltrate, its distribution in cardiac tissue, and the degree of myocardial injury help construct the differential diagnosis.

Clinically, myocarditis is defined by the time course and severity of illness. Acute myocarditis is the presence of an acute cardiomyopathy with myocardial inflammation. The presentation is highly variable. Chronic myocarditis is subdivided into two entities. *Chronic active myocarditis* has variable symptomatology, is accompanied by impaired cardiac function, and is marked by relapses of symptomatology and histology. *Chronic persistent myocarditis* is described by persistent symptoms, evidence of ongoing myocardial immune infiltrate on biopsy, but without ventricular dysfunction.

Fulminant myocarditis is described as acute onset of severe heart failure/cardiogenic shock or life-threatening arrhythmias due to myocarditis. *Cardiac sarcoidosis* is an uncommon form of inflammatory myocarditis distinguished histologically by non-necrotizing interstitial granulomas. Idiopathic *giant cell myocarditis* (GCM) is another rare form of inflammatory myocarditis that is characterized histologically by multinucleated giant cells, myocyte necrosis, and a lymphocytic inflammatory infiltrate.

Etiology

Most cases of myocarditis are triggered by infection or exposure to a toxin, although some cases are thought to be due to primary immunologic abnormalities in the patient (Box 39.1A,B). Viral infection is the most common cause of myocarditis in North America and Europe, with adenoviruses and enteroviruses (especially coxsackievirus B3 [CVB3]) historically being the most common culprits. However, parvovirus B19, cytomegalovirus, Ebstein–Barr virus, herpes simplex virus 1 and 2, human herpesvirus 6 (HHV 6), and hepatitis C are commonly observed. With the development of new molecular techniques such as polymerase chain reaction (PCR) and in situ hybridization, data suggest that PVB19 and HHV 6 are the most common viruses detected. Whether geographical differences account for the varying distribution of viral species implicated in myocarditis or whether these differences are more likely due to temporal epidemiologic differences as well as differences in diagnostic procedures also remains unclear.

At least one cardiotropic viral genome has been identified in 75% of EMBs performed for myocarditis. Two or more viruses are not infrequently found during PCR examination of myocardial tissue, but it is unclear whether this represents concurrent, past viral infection, or innocent bystander. Some studies have suggested that PVB19 is not a pathological agent in adult myocarditis because persistent low-level titers

BOX 39.1

A. Infectious etiologies of myocarditis

Viral
- **Adenovirus**
- Arborvirus
- Chikungunya virus
- **Enterovirus**
  - Echovirus
  - Coxsackie A
  - **Coxsackie B**
  - Polio
- Flavivirus
  - Dengue
  - Yellow fever
- Hepatitis B virus
- **Hepatitis C virus**
- Herpes viruses
  - Cytomegalovirus
  - Epstein–Barr
  - Herpes simplex
  - **Human herpesvirus 6**
  - Varicella-zoster
- **Human immunodeficiency virus**
- Influenza A and B
- Lassa fever virus
- Measles virus
- Mumps
- **Parvovirus** (especially *Parvovirus B-19*)
- Rabies
- Respiratory syncytial virus
- Rubeola
- Rubella
- Vaccinia
- Variola (*smallpox*)

Bacterial
- Actinomyces
- Burkholderia pseudomallei (*melioidosis*)
- Brucella
- Campylobacter jejuni
- Chlamydia (especially *Chlamydia pneumonia* and *Chlamydia psittacosis*)
- Clostridium
- **Corynebacterium diphtheriae** (*diphtheria*)
- Francisella tularensis (*tularemia*)
- Haemophilus influenzae
- Gonococcus
- Legionella pneumophila (*Legionnaire's disease*)
- Listeria monocytogenes
- **Mycobacterium** (*tuberculosis*)
- Mycoplasma pneumoniae
- Neisseria meningitidis
- Salmonella
- Staphylococcus aureus
- **Streptococcus A** (*rheumatic fever*)
- **Streptococcus pneumoniae**
- Tetanus
- Vibrio cholera

Spirochetal
- **Borrelia burgdorferi** (*Lyme disease*)
- Borrelia recurrentis (*relapsing fever*)
- Leptospira
- Treponema pallidum (*syphilis*)

Rickettsial

Coxiella burnetii (*Q fever*)
- Rickettsia prowazekii (*typhus*)
- Rickettsia rickettsii (*Rocky Mountain spotted fever*)
- Rickettsia tsutsugamushi (*scrub typhus*)

Fungal
- Aspergillus
- Blastomyces
- Candida
- Coccidioides
- Cryptococcus
- Histoplasma
- Mucor species
- Nocardia
- Sporothrix schenckii
- Strongyloides stercoralis

Protozoal
- Balantidium
- Entamoeba histolytica (*amebiasis*)
- Leishmania
- Plasmodium falciparum (*malaria*)
- *Sarcocystis*
- **Toxoplasma gondii** (*toxoplasmosis*)
- Trichinella spiralis
- **Trypanosoma cruzi** (*Chagas disease*)
- Trypanosoma brucei (*African sleeping sickness*)

Helminthic
- Ascaris
- Echinococcus granulosus
- *Heterophyes*
- Paragonimus westermani
- Schistosoma
- Strongyloides stercoralis
- Taenia solium (*cysticercosis*)
- Toxocara canis (*visceral larva migrans*)
- Trichinella spiralis
- Wuchereria bancrofti (*filariasis*)

B. Noninfectious etiologies of myocarditis

Toxins

Drugs
- Aminophylline
- Amphetamines
- Anagrelide
- Catecholamines

- Chemotherapy agents
  - **Anthracyclines**
  - Cyclophosphamide
  - Cytarabine
  - 5-fluorouracil
  - **Immune checkpoint inhibitors**
  - Mitomycin
  - Monoclonal antibodies
  - Paclitaxel
  - **Tyrosine kinase inhibitors (including trastuzumab)**
- Chloramphenicol
- Chloroquine
- **Cocaine**
- Ephedrine
- Ethanol
- Interleukin-2
- Methysergide
- Minoxidil
- Phenytoin
- Zidovudine
- **Environmental**
- Arsenic
- Carbon monoxide
- Heavy metals (cobalt, copper, iron, lead)

Hypersensitivity reactions

- *Drugs*
- Allopurinol
- Antimicrobials
  - Amphotericin B
  - Azithromycin
  - Cephalosporins
  - Chloramphenicol
  - Dapsone
  - Isoniazid
  - Penicillins
  - Streptomycin
  - Stibogluconate
  - Sulfonamides
  - Tetracycline
- Dobutamine
- Gefitinib
- Loop diuretics
- Methyldopa
- Mexiletine
- Nonsteroidal anti-inflammatories
  - Indomethacin
  - Mesalamine
- Psychiatric medications
  - Benzodiazepines
  - Carbamazepine
  - Clozapine
  - Lithium
  - Phenobarbital
  - Tricyclic antidepressants
- Thiazide diuretics
- *Vaccines*
  - **Smallpox vaccination**
  - Tetanus toxoid
- *Venoms*
  - Insects (bee, wasp)
  - Spider (black widow)
  - Scorpion
  - Snake

Autoimmune diseases

- ANCA-associated vasculitis
- Behçet's disease
- Crohn's disease
- Dermatomyositis/polymyositis
- **Giant cell myocarditis**
- Inflammatory bowel disease
- Myasthenia gravis
- Rheumatoid arthritis
- Sjögren syndrome
- Still's disease
- **Systemic lupus erythematosus**
- Systemic sclerosis (scleroderma)
- Takayasu's arteritis
- Ulcerative colitis
- Wegener's granulomatosis

Systemic diseases

- **Celiac disease**
- Churg–Strauss syndrome
- Collagen-vascular diseases
- **Hypereosinophilic syndrome with eosinophilic endomyocardial disease**
- Kawasaki's disease
- **Sarcoidosis**

Other

- Heat stroke
- Hypothermia
- Transplanted heart rejection
- Radiation

of PVB19 are fairly common and may not be related to myocardial injury.

Myocarditis can also be triggered by bacterial and protozoal infections. The most common nonviral pathogens which that directly infect the heart or activate inflammatory mechanisms are *Corynebacterium diphtheriae* (diphtheria), *Streptococcus A* (rheumatic fever), *Borrelia burgdorferi* (Lyme disease), and *Trypanosoma cruzi* (Chagas disease). Chagas disease is the most common etiology of myocarditis in Latin America. Bacterial myocarditis, typically associated with a neutrophilic infiltrate, is rare.

Numerous medications and environmental exposures can have toxic effects on the myocardium. In particular, several chemotherapy drugs are known to be potentially cardiotoxic. Type I chemotherapy agents (e.g., the anthracyclines) cause permanent

damage to the myocardium, while type 2 agents such as tyrosine kinase inhibitors (including trastuzumab) cause acute myocardial damage which is usually reversible once the offending drug is discontinued. Myocarditis caused by the immune checkpoint inhibitors, agents used to promote T-cell response against cancers, is often fulminant. Drug-induced hypersensitivity reactions can induce hypersensitivity eosinophilic myocarditis. The most common drugs include allopurinol, antimicrobials, antipsychotics, antiepileptics, and anti-inflammatories. Myocardial damage due to hypersensitivity reaction is usually reversible once the causative agent is withdrawn. Eosinophilic-lymphocytic myocarditis has also been associated with smallpox, tetanus, meningococcal C, and hepatitis B vaccines.

Systemic diseases, particularly Churg–Strauss syndrome, hypereosinophilic syndrome, Loeffler's endocarditis, and malignancies including T-cell lymphoma and cancer of the lung and biliary tract, have also been associated with eosinophilic myocarditis. Acute necrotizing eosinophilic myocarditis is a rare but fulminant form of myocarditis with acute onset and high mortality.

Pathogenesis

The pathogenesis of myocarditis in humans is not completely understood. Much of our understanding of the pathophysiology of myocarditis has been derived from murine models of enteroviral infection, particularly Coxsackievirus B3, which suggests that viral myocarditis is characterized by three stages (Figure 39.1). Stage I involves viral entry into the cardiomyocyte via endothelial cell receptors. Group B coxsackieviruses and some adenoviruses use the coxsackievirus-adenovirus receptor (CAR) to transport their viral genomes into myocytes. In addition to CAR, coxsackieviruses use decay-accelerating factor (DAF) and adenoviruses use special integrins ($\alpha_{v\beta3}$ and $\alpha_{v\beta5}$) as co-receptors for viral entry. Differential binding to DAF increases viral virulence in coxsackievirus B infections. Viral infection does not occur in the absence of CAR expression on myocytes.

Stage I also involves acute myocardial injury due to a combination of direct viral injury to the myocytes and the innate immune response, which is initially triggered by interferon release and involves upregulation of multiple inflammatory mediators including cytokines, nitric oxide, toll-like receptors, and complement and exposure of intracellular antigens such as cardiac myosin. Viruses that evade the innate immune response replicate, producing proteins that lead to myocyte apoptosis and necrosis.

Stage II begins approximately 4 to 5 days post viral infection, when the acquired immune response arises. Lasting several weeks to several months, this subacute phase is characterized by an antigen-specific response mediated primarily by T lymphocytes. Virus-specific T-killer cells are targeted to infected cells and destroy these host cells through secretion of cytokines or perforins. B lymphocytes produce antibodies directed against viral antigens and autoantibodies directed against endogenous cardiac proteins that may augment myocardial damage.

In most patients with myocarditis, viral clearance and downregulation of the immune system occurs during stage III, resulting in complete myocardial recovery without sequelae. In some patients, however, the virus is not cleared and cardiac-specific inflammation persists, resulting in chronic myocardial damage which leads to myocardial remodeling and the development of dilated cardiomyopathy (DCM). CVB3 myocarditis is associated with high titers of autoantibodies targeted at heart-specific proteins, suggesting a role for autoimmunity in those who progress to chronic myocarditis. In animal models, exposure to concealed proteins, such as α-myosin heavy chain, results in development of autoimmunity. Progression to DCM may also involve an underlying genetic substrate.

Epidemiology

Due to varying clinical presentations and infrequent utilization of EMB, the diagnosis of myocarditis is often missed, making it difficult to estimate the true incidence of this disease. Autopsy studies have estimated the incidence of myocarditis to range from 0.12% to 12%, depending on the population studied. The Myocarditis Treatment Trial showed that biopsy-proven myocarditis occurred in 9.6% of adult patients with unexplained heart failure. An analysis of hospital dismissal ICD-9 codes estimated that between 0.5% and 4% of heart failure cases are due to myocarditis.

Myocarditis has a slightly greater prevalence in men compared to women. Most trials and registries have a female to male ratio of 1:1.5 to 1:1.7. This sex difference may be at least partially explained by sex hormones. Estrogenic hormones have been shown to protect against viremia and viral infectivity of cardiomyocytes while also decreasing the potentially harmful inflammatory response in female mice. Testosterone, on the other hand, has been shown to inhibit anti-inflammatory responses in male mice.

Clinical presentation

The clinical presentation of acute myocarditis in adults varies by clinical scenario. Typically, but not always, a viral prodrome including fever, myalgias, arthralgias, rash, and respiratory or gastrointestinal symptoms precedes the onset of acute myocarditis by several days to several weeks. Patients with myocarditis may present with chest pain, dyspnea, palpitations, fatigue, edema, syncope, and/or decreased exercise tolerance. The presence of pleuritic chest pain, particularly in the setting of pericardial effusion, may indicate myopericarditis. Cardiac arrhythmias are common.

Patients with fulminant myocarditis usually present with severe heart failure symptoms that rapidly lead to cardiogenic shock, whereas patients with cardiac sarcoidosis tend to present in a more indolent manner with chronic DCM and either high-grade atrioventricular block (AVB) or new ventricular arrhythmias. Patients with GCM tend to present with acute heart failure symptoms that inexorably progress to probable early death or transplant despite guideline-directed heart failure therapy.

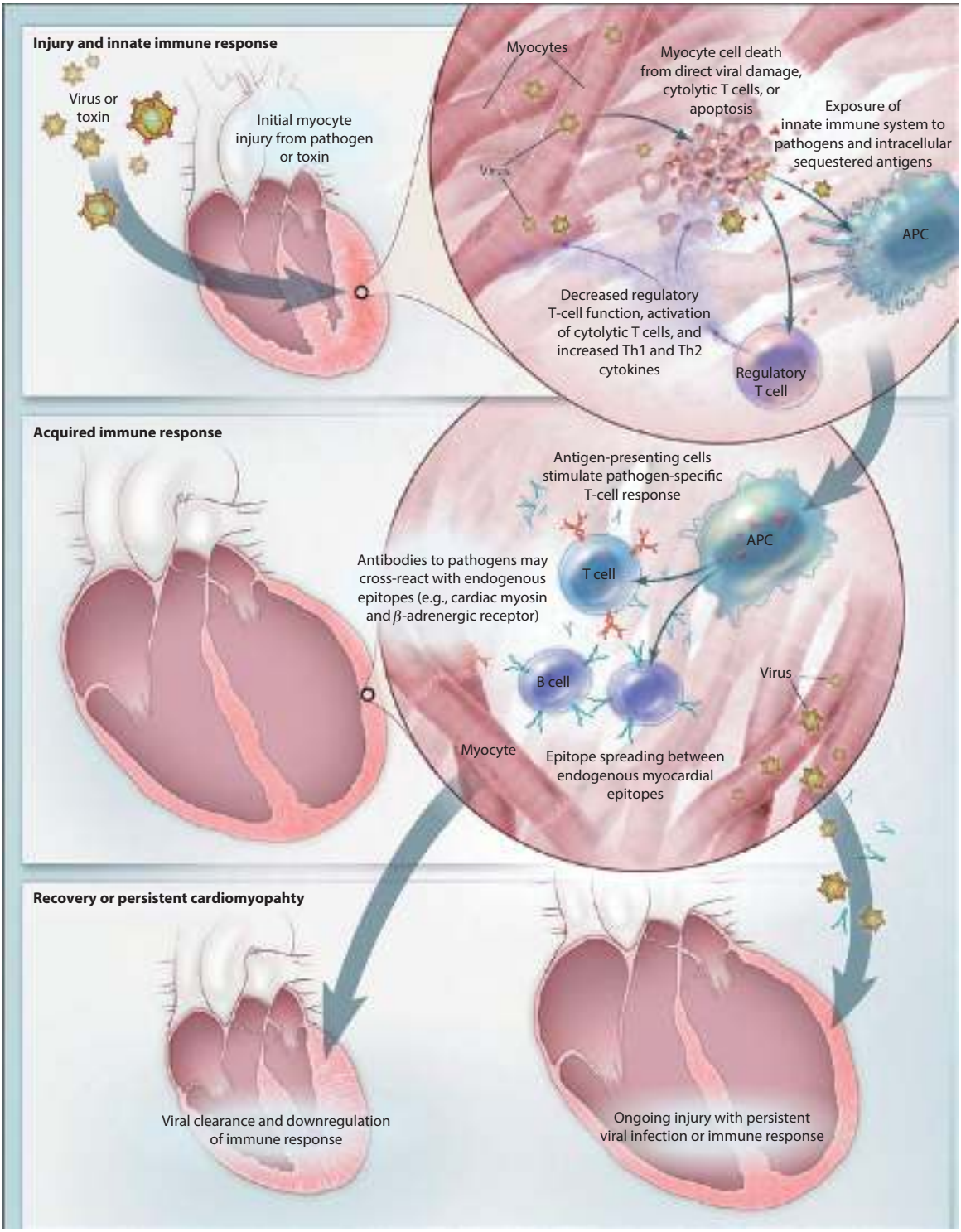

FIGURE 39.1 Pathogenesis of viral myocarditis. The current understanding of the pathogenesis of viral myocarditis is based on murine models. In these models, myocarditis progresses from acute injury to chronic dilated cardiomyopathy (DCM) in three distinct stages. During stage I, viral entry into cells results in direct myocardial injury, exposure of host antigens such as cardiac myosin, and activation of the innate immune system. The acquired immune response is the dominant feature in stage II, whereby activated T lymphocytes, antibodies, and autoantibodies induce significant myocardial inflammation. In most patients, stage III involves viral clearance, downregulation of the immune system, and complete myocardial recovery. In some patients, however, stage III is characterized by the persistence of viral genomes and cardiac-specific inflmmation in the myocardium, leading to chronic DCM.
APC, antigen presenting cell.

From LT Cooper, Jr. Myocarditis. *N Engl J Med*. 2009;8:1526–1538. Copyright Massachusetts Medical Society. Reprinted with permission.

Diagnosis

The first step in diagnosing myocarditis is to exclude more common causes of cardiac dysfunction such as atherosclerosis or valvular heart disease. There are no laboratory, electrocardiographic (EKG), or echocardiographic findings specific for myocarditis. When acute myocarditis is suspected, initial laboratory testing usually includes assessment of serum cardiac biomarkers. Troponin T, troponin I, and/or CK-MB may be elevated. Serum markers of inflammation including C-reactive protein, erythrocyte sedimentation rate, and leukocyte count are frequently elevated, but these are nonspecific. Serologic testing of suspected viral agents is not recommended as the viruses that cause myocarditis are common and positive serology does not necessarily establish causality. Evaluation for the presence of HIV, Lyme disease, or Chagas disease should be dictated by individual risk. Testing for noninfectious causes of heart failure including autoimmune disease, infiltrative myocardial diseases such as amyloidosis and hemochromatosis, and thyroid dysfunction may be warranted.

Most myocarditis patients have nonspecific changes on their initial EKG, including sinus tachycardia, ST-segment, or T-wave abnormalities that may mimic acute myocardial infarction or acute pericarditis, AVB, and partial or complete bundle branch block. Nonsustained ventricular or supraventricular arrhythmias are fairly common. The presence of Q waves or a QRS duration of >120 ms is associated with increased risk of cardiac death or heart transplantation. Chest x-ray may show cardiomegaly, pulmonary venous congestion, interstitial infiltrates, and/or pleural effusions.

The most common echocardiographic findings in patients with acute myocarditis are a dilated left ventricle with reduced left ventricular ejection fraction (LVEF). New regional wall abnormalities may be present, either in a coronary or noncoronary distribution. Decreased right ventricular function is less common than decreased left ventricular function but is a strong predictor of poor prognosis.

Cardiac MRI has become a routine noninvasive test that may be highly sensitive and specific for diagnosing acute myocarditis, particularly when both T1 and T2 weighted images are obtained. Both the typical T1 and T2 weighted changes observed in acute myocarditis decrease with time, so it is important to obtain cardiac MRI testing as soon as possible after symptom onset as sensitivity wanes as the disease moves to a chronic phase. Cardiac MRI has also been shown to be helpful in guiding EMB and provides prognostic information. Coronary angiography may be indicated if the patient's history and clinical presentation is suspicious for ischemic heart disease.

Histological or immunohistological evidence of an inflammatory infiltrate with or without myocyte necrosis on myocardial biopsy specimens remains the gold standard for the diagnosis of myocarditis. The Dallas criteria, proposed in 1986, define *active myocarditis* as the presence of both inflammatory cells and adjacent myocyte necrosis, and *borderline myocarditis* as the presence of inflammatory cells without associated myocardial injury. The Dallas criteria have been criticized due to interreader variability in interpretation, low sensitivity due to sampling error, discrepancy with other markers of viral infection, and immune activation in the myocardium and lack of prognostic value. Immunohistochemical stains that detect cellular surface antigens such as anti-CD3, anti-CD4, and anti-CD28 (T lymphocytes), anti-CD8 (macrophages), and Class I and II anti-human leukocyte antigens may have greater sensitivity than the Dallas criteria and may have prognostic value. The Marburg criteria, proposed in 1997, state that a clear-cut infiltrate of ≥14 leukocytes/mm^2 (quantitated by immunohistochemistry), including up to 4 monocytes/mm^2 and CD3 positive T lymphocytes at >7 cells/mm^2, and myocyte necrosis or degeneration must be present to diagnose acute myocarditis. Chronic myocarditis is defined as an infiltrate of ≥14 leukocytes/mm^2 without myocyte necrosis or degeneration. Fibrosis may or may not be present in either acute or chronic myocarditis.

Outside of a few tertiary medical centers, EMB is not routinely performed in adult patients with suspected myocarditis due to perceived risk and the cost of the procedure. EMB is strongly indicated in adult patients with either of the following two clinical scenarios: (1) new unexplained heart failure symptoms of <2 weeks' duration coupled with a normal or dilated left ventricle and hemodynamic compromise, or (2) new unexplained heart failure symptoms of 2 weeks to 3 months duration with a dilated left ventricle and ventricular arrhythmias, high-grade AVB, or failure to respond to guideline-directed heart failure therapy within 1 to 2 weeks. These clinical scenarios suggest the diagnosis of either necrotizing eosinophilic myocarditis (scenario 1) or GCM (scenarios 1 or 2), both of which have a poor prognosis that may be modified with immunosuppressive treatment. EMB may be considered in adults who present with other clinical scenarios, including patients with (1) DCM of any duration with suspected allergic reaction and peripheral eosinophilia, (2) unexplained heart failure of any duration associated with anthracycline therapy, or (3) unexplained heart failure associated with restrictive cardiomyopathy. However, European guidelines have recently broadened criteria for consideration of EMB to any patients with clinically suspected acute myocarditis. EMB is considered reasonable in the setting of unexplained cardiomyopathy in children as biopsy results may help to identify those who will likely respond to medical treatment and thus decrease the need for cardiac transplantation. EMB is usually obtained transvenously from the right ventricle and carries a less than 1:1,000 risk of major complications when performed by experienced operators.

A three-tiered classification for diagnosing acute myocarditis has recently been proposed (Table 39.1). A patient may be classified with *subclinical acute myocarditis* if (1) they are asymptomatic, (2) other causes of acute cardiomyopathy are excluded, and (3) they have had a recent trigger for myocarditis such as a viral illness plus one or more of the following: (a) an otherwise unexplained troponin elevation, (b) EKG changes suggestive of acute myocardial injury, or (c) echocardiographic or cardiac MRI evidence of cardiac dysfunction. Patients who meet the criteria for subclinical acute myocarditis and also present with symptoms consistent with acute myocarditis can be classified as having *probable acute myocarditis*. If histology or immunohistology results are consistent with myocarditis, then the patient has *definite myocarditis*, even if asymptomatic.

TABLE 39.1 **MYOCARDITIS DIAGNOSTIC CLASSIFICATION**

Classification	Patient presentation	Criteria	Histologic classification	Biomarker, ECG, and/or imaging findings consistent with myocarditis	Treatment
Possible subclinical acute myocarditis	Asymptomatic	1 or more of the following required: 1. Troponin elevation 2. ECG findings suggestive of acute cardiac injury 3. Echocardiographic or cardiac MRI findings consistent with abnormal cardiac function	Absent	Present	Unknown
Probable acute myocarditis	Symptomatic	1 or more of the following required: 1. Troponin elevation 2. ECG findings suggestive of acute cardiac injury 3. Echocardiographic or cardiac MRI findings consistent with abnormal cardiac function	Absent	Present	Per clinical syndrome
Definite myocarditis	Symptomatic or asymptomatic	Histologic or immunohistologic evidence of myocarditis	Present	Present or absent	Per clinical syndrome

Treatment

Guideline-directed medical therapy

There are no guidelines to direct therapy for patients with subclinical acute myocarditis. If the LVEF is <40%, then it would be reasonable to consider either an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) and a β- blocker, with regularly scheduled clinical follow-up in accordance with heart failure treatment guidelines.

Therapy for adult patients who present with heart failure symptoms and are diagnosed with probable or definite myocarditis consists of guideline-directed heart failure therapy including sodium and fluid restriction as well as treatment with diuretics and an ACE-I or an ARB. β-blocker therapy should be added once acute heart failure symptoms have resolved. The potential benefit of calcium channel blocker therapy in patients with viral myocarditis patients has not been established. Digoxin should be used with caution in patients with viral myocarditis as administration of high-dose digoxin to mice with viral-induced myocarditis increased mortality. Nonsteroidal anti-inflammatory medications should be avoided as use of these medications in mouse models of viral myocarditis results in augmented inflammation and increased mortality. Strenuous exercise should be avoided for 6 months after acute infection as mouse models have shown this type of activity to be deleterious. Patients who present with severe heart failure symptoms may require intravenous (IV) vasodilators or inotropes, while patients in cardiogenic shock may require mechanical circulatory support with intra-aortic balloon pumps, extracorporeal membrane oxygenation, or left ventricular/biventricular assist devices. Cardiac transplantation is reserved for patients who do not respond to guideline-directed heart failure therapy and mechanical circulatory support.

Antiviral therapy

As myocarditis is most often caused by viral infection, it would seem reasonable that elimination of viral translation, transcription, and proliferation with the use of antiviral medications that target viral attachment to host-cell receptors, virus entry, or virus uncoating such as Pleconaril or soluble CAR-Fc, would be effective in early stages of the disease, but, unfortunately, most patients present several weeks after viral infection. These agents are therefore likely providing little benefit to patients with acute viral myocarditis. Anecdotal evidence has suggested a role for nucleoside analogues, such as ganciclovir, in the treatment of HHV-6 related myocarditis, but clinical trials are lacking. Similarly, a small study called the PreTopic study evaluated telbivudine, another nucleoside analog, in treatment of parvovirus and found an improvement in symptoms and reduction in viral load.

Immunosuppressive therapy

Treatment of acute viral myocarditis with immunosuppressive drugs has not shown to be beneficial in adults. Results from the Myocarditis Treatment Trial showed that myocarditis patients

treated with prednisone plus either azathioprine or cyclosporine had similar changes in LVEF and transplant-free survival compared to patients treated with placebo. Immunosuppression in patients with GCM, cardiac sarcoidosis, necrotizing eosinophilic myocarditis, and myocarditis associated with connective tissue disorders, however, is warranted because immunosuppression has been shown to improve outcomes in patients with these disorders. Several small case control studies have shown that immunosuppressive treatment may be effective in children with acute myocarditis, but randomized controlled trials in this regard are lacking.

The Tailored Immunosuppression in Inflammatory Cardiomyopathy (TIMIC) trial randomized 85 adult patients with chronic myocarditis without persistent viral genomes to either prednisone and azathioprine or placebo. Patients in the immunosuppression group experienced significant improvement in LVEF and quality of life, while none of the patients in the placebo group had sustained improvement in either of these outcomes, indicating that immunosuppression may be efficacious in patients with chronic myocarditis/DCM.

Immunomodulatory therapy

Small studies using IV immunoglobulin (IVIG) in adult myocarditis patients have shown mixed results. The IMAC trial randomized 62 patients with recent onset cardiomyopathy and LVEF of <40% to either treatment with IVIG or placebo. Patients in the IVIG and placebo groups had identical survival and improvement in LVEF at 1 year. In contrast, a small retrospective study assessing the efficacy of high-dose IVIG (2 g/kg) in children with presumed acute myocarditis demonstrated a trend for improved survival in the IVIG compared to historical controls. High-dose IVIG has been utilized in one small series for CMV myocarditis and was associated with greater clearance of the virus.

Interferon-α and interferon-β therapy in mice with viral-induced myocarditis reduces myocyte injury, decreases inflammatory cell infiltrates, and results in elimination of cardiac viral load. A small case series of patients with chronic DCM and persistent enteroviral or adenoviral genomes in their myocardium showed that treatment with interferon-β eliminated viral genomes and improved LVEF compared to placebo. The subsequent Betaferon in patients with Chronic viral Cardiomyopathy (BICC) trial randomized 143 patients to treatment with interferon-β-1b or placebo. The interferon-β-1b group had significantly reduced cardiac enteroviral load, increased LVEF, and decreased left ventricular volumes compared to the placebo group. Whether these results can be extrapolated to treatment of other viruses (e.g., PVB19 or HHV 6) remains unclear.

The European Study of Epidemiology and Treatment of Cardiac Inflammatory Disease (ESETCID) is an ongoing randomized, double-blind, placebo-control trial evaluating a pathogen-guided treatment approach involving high-dose IVIG for CMV myocarditis, α-interferon for enterovirus, and immunosuppression for virus-negative myocarditis.

Natural history and prognosis

Natural history and prognosis in acute myocarditis varies by clinical scenario. Patients with acute lymphocytic (viral) myocarditis who present with mild symptoms and normal or near normal LVEF usually spontaneously improve without consequences, although approximately 15% of these patients may develop recurrent myocarditis. In contrast, the Myocarditis Treatment Trial revealed that symptomatic adult patients who presented with an LVEF <45% have a 1-year mortality of 20% and a 2-year mortality of 56%. The Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) trial enrolled 62 patients with recent-onset heart failure due to myocarditis or idiopathic DCM and a baseline LVEF of <40%, randomizing them to conventional heart failure therapy plus/minus IVIG. Overall, LVEF improved from a mean of 25% at baseline to a mean of 41% at 6 months and 42% at 12 months, regardless of treatment arm. Transplant-free survival was 92% at 1 year and 88% at 2 years. The IMAC-2 trial enrolled 373 patients with recent-onset nonischemic DCM and showed that recovery differed between sexes. Mean LVEF in men increased from 23% at baseline to 39% at 6 months, while mean LVEF in women with non-peripartum cardiomyopathy increased from 24% at baseline to 42% at 6 months. Women with peripartum cardiomyopathy had the greatest myocardial recovery, with mean LVEF increasing from 24% at baseline to 45% at 6 months. There were no deaths at 4 years.

Future directions

Although EMB remains the gold standard for the diagnosis of myocarditis, it is an invasive test with associated risks of major complications. Molecular diagnostics may help provide improved characterization of inflammation and organisms if present, including translational activity to determine if the organism is pathogenic. The development of a sensitive and specific noninvasive test that can provide both diagnostic and prognostic information is sorely needed. Effective therapy specifically targeted for viral myocarditis is lacking. Use of selected antiviral and antimicrobial therapies may be beneficial, but adequately powered randomized controlled trials are needed to determine their efficacy. Other potential therapies that remain to be assessed include cell-based therapies targeted toward T cells in order to modulate the immune response to viral infection. Prevention of myocarditis is yet another area that warrants further research. Vaccinations against many viruses, including measles, mumps, and polio, have made myocarditis secondary to these diseases quite rare, which raises the possibility that vaccination development and usage against cardiotropic viruses such as enterovirus, adenovirus, PVB19, HHV-6, and HIV may decrease the incidence of myocarditis in the future.

Suggested reading

Cooper LT, Mather PJ, Alexis JD, et al. Myocardial recovery in peripartum cardiomyopathy: prospective comparison with recent onset cardiomyopathy in men and nonperipartum women. *J Card Failure*. 2012;18:28–33.

Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol*. 2009;53:1475–1487.

Frustaci A, Russo MA, Chiment C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J*. 2009;30:1995–2002.

Kuhl U, Lassner D, Von Schlippenbach J, Poller W Schultheiss HP. Interferon-Beta improves survival in enterovirus-associated cardiomyopathy. *J Am Coll Cardiol*. 2012;60:1295–1296.

Kuhl U, Pauschinger M, Seeberg B, Lassner D, Noutsias M, Poller W, Schultheiss HP. Viral persistence in the myocardium is associated with progressive cardiac dysfunction. *Circulation*. 2005;112:1965–1970.

Mahfoud F, Gartner B, Kindermann M, et al. Virus serology in patients with suspected myocarditis: utility or futility? *Eur Heart J*. 2011;32:897–903.

Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, Moon TE. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. *N Engl J Med*. 1995;333:269–275.

McNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation*. 2001;103:2254–2259.

Sagar S, Liu PP, Cooper LT, Jr. Myocarditis. *Lancet*. 2012;379:738–747.

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Mediastinitis

Ravi Karra and Keith S. Kaye

The mediastinum is the space in the thorax between the lungs; it houses the heart, great vessels, esophagus, trachea, thymus, and lymph nodes. The connective tissues of the mediastinum are continuous with the long fascial planes of the head and neck, one reason why mediastinitis was primarily a complication of pharyngeal infections until the advent of thoracic surgery. By virtue of its deep position within the thorax, the mediastinum is a relatively protected organ space. There are four major portals of entry into the mediastinum: (1) direct inoculation of the mediastinum following sternotomy (i.e., postoperative mediastinitis [POM]); (2) spread along the long fascial planes of the neck (i.e., descending mediastinitis); (3) rupture of mediastinal structures, such as the esophagus; and (4) contiguous spread of infection from adjacent thoracic structures.

Postoperative mediastinitis

Postoperative mediastinitis (POM) is classified as an organ/ space infection by Centers for Disease Control and Prevention (CDC) criteria and is a dreaded complication of median sternotomy. POM classically presents as a febrile illness with sternal wound dehiscence and purulent drainage, usually 2 to 4 weeks after sternotomy. Occasionally POM presents as a more chronic, indolent infection months to years after sternotomy. Sometimes, only superficial signs of infection are present, making POM difficult to diagnose. Frequently, a high index of clinical suspicion is required to differentiate POM from a more superficial sternal wound infection.

Pathogenesis

Infection most often occurs as the result of direct inoculation of host bacteria into the mediastinum during surgery. Bacteria that colonize the skin and oral mucosa, such as coagulase-negative *Staphylococcus* (CoNS) and *Staphylococcus aureus* are the most common causes of POM. Gram-negative bacilli, a less common cause of POM, are believed to spread to the mediastinum from the abdomen. Infrequently, pathogens such as *S. aureus* might be introduced into the mediastinum by a member of the surgical team or by contaminated operative instruments. Whether bacterial contamination develops into full-blown infection is a combination of three major factors: (1) inoculum of bacterial contamination, (2) the degree of local tissue and vascular damage, and (3) host immunity. Larger inoculum and greater perioperative tissue damage both increase the risk for infection. Decreased host immunity increases susceptibility to the development of POM, contributing to an elevated risk for mediastinitis after cardiac transplantation.

Epidemiology and outcomes

Despite advances in surgical techniques and the use of preoperative prophylactic antibiotics, rates of POM in the modern era remain around 1.0%. The high number of median sternotomies performed annually makes POM a frequently encountered problem.

Risk factors for the development of POM comprise three categories: (1) host-related factors, (2) hospital-related factors, and (3) technical or operative factors. Host-related factors include diabetes, obesity, advanced age, prior sternotomy, chronic obstructive pulmonary disease, and New York Heart Association (NYHA) class III or IV heart failure. Hospital factors include prolonged postoperative mechanical ventilation and prolonged postoperative stay in an intensive care unit. Operative factors include mobilization of an internal mammary artery, increased duration of surgery, and surgical complexity. Complex surgeries are simultaneous coronary artery bypass grafting and valve repair, "repeat" or "redo" median sternotomy, and surgical re-exploration following initial sternotomy.

POM is associated with significant attributable morbidity and mortality. Estimates of postoperative mortality range from 11.8% to 14% in patients with POM compared to 2.7% to 5.5% in uninfected operative controls. Some series report mortality rates as high as 40%. Risk factors for mortality in the immediate postoperative period are related to the patient (advanced age and postoperative bacteremia), the hospitalization (e.g., mechanical circulatory support and prolonged postoperative mechanical ventilation), technical factors (prolonged operative duration, surgical re-exploration, blood transfusion), and the specific pathogen. POM due to methicillin-resistant *S. aureus* (MRSA) is associated with particularly adverse clinical outcomes. Patients with POM are not only at increased risk for mortality during the immediate postoperative period but also carry a two- to four-fold increased risk for death for up to 10 years following cardiothoracic surgery. Risk factors for long-term mortality in patients with POM include age >65 years, serum creatinine >2.0 mg/dL prior to surgery, infection with MRSA, delay of sternal closure more than 3 days following therapeutic debridement for POM, and failure to treat POM with effective antimicrobial agents within 7 days of therapeutic sternal debridement.

Descending necrotizing mediastinitis

Mediastinitis arising from the migration of pathogens from head or neck infection, as opposed to direct inoculation of the mediastinum, is classified as descending necrotizing mediastinitis. Pharyngeal infections cause nearly 50% of all descending necrotizing mediastinitis. However, virtually any infection of the head and neck can spread into the mediastinum. If infections of the head and neck are treated with appropriate antimicrobial agents, descending necrotizing mediastinitis can be prevented. In the modern age of antibiotics, descending mediastinitis is becoming increasingly rare.

Pathogenesis

Spread to the mediastinum can occur via each of the three spaces of the head and neck: the pretracheal space (suppurative thyroid and tracheal infections), the perivascular space (oropharyngeal infections), and the retrovisceral space (oropharyngeal infections). Negative intrathoracic pressure during inspiration acts to draw infection into the mediastinum from these spaces. The retropharyngeal space houses the "danger" space, so named because it extends from the base of the skull all the way to the diaphragm. Spread within the retropharyngeal space is involved in the pathogenesis of approximately 70% of cases of descending mediastinitis. Infections of the perivascular space can also be complicated by thrombophlebitis of the jugular vein (Lemierre's disease) and direct extension of infection into the carotid artery. (See Chapter 10, Deep neck infections.)

Epidemiology and outcomes

The microbiology of descending necrotizing mediastinitis reflects the bacteria that usually colonize or infect the head and neck. Often, descending necrotizing mediastinitis is a polymicrobial infection involving anaerobes. Common anaerobes include *Fusobacterium*, *Prevotella*, *Vellionella*, *Peptostreptococcus*, and other oral anaerobes. *Streptococcus* spp. are common pathogens. *Actinomyces* can also cause descending mediastinitis.

Patients with descending necrotizing mediastinitis often present with fevers, signs of an underlying head and neck infection, and sometimes sepsis. However, in immunocompromised patients, obvious clinical signs and symptoms may not be readily apparent. Signs of associated neck infection can provide clues to the presence of descending mediastinitis and include trismus, pain of the oropharynx, pain on movement of the neck, dysphagia, hoarseness, stridor, and occasionally erythema of the overlying skin. Overall, the diagnosis of descending necrotizing mediastinitis requires a high degree of clinical suspicion. Early recognition and treatment is important, as this syndrome can be rapidly fatal, with an estimated mortality rate of 15% in spite of therapy.

Mediastinitis originating from mediastinal structures

Mediastinitis can also occur as a result of direct spillage of bacteria from mediastinal structures. Perforation of any of the organs or vessels housed in the mediastinum, most commonly the esophagus, can lead to mediastinitis. Perforation of the esophagus can occur after heavy emesis (as in Boerhaave's syndrome); following ingestion of sharp objects; or following procedures involving the esophagus such as endoscopy, myotomy, or esophageal stenting. Mediastinitis can develop following tracheal perforation, which sometimes occurs as a complication of endotracheal intubation and bronchoscopy. Rare cases of mediastinitis have been reported as a consequence of spread of infection from the aorta following surgical repair or central venous line placement.

In mediastinitis originating from mediastinal structures, particularly Boerhaave's syndrome, patients often present with chest pain and fever. If mediastinitis is suspected, special attention in the history should be focused on recent procedures involving the trachea or esophagus or episodes of heavy retching.

Mediastinitis from contiguous thoracic infections

If untreated, pulmonary infections due to bacteria, fungi, and *Mycobacteria* can cause secondary mediastinitis by contiguous spread. Mediastinitis caused by bacterial pathogens usually presents as an acute infection. Mediastinitis due to tuberculosis or histoplasmosis tends to have a subacute or chronic course compared to bacterial infection. These infections can lead to granulomatous mediastinitis or immune-related deposition of collagen within the mediastinum and resultant fibrosing mediastinitis.

Evaluation of suspected mediastinitis

It is important to obtain a history of predisposing events, such as median sternotomy, head and neck illness, or endoscopy or bronchoscopy.

Patients with mediastinitis classically present with chest pain and fever. The chest pain is sometimes pleuritic in nature. On exam, patients with mediastinitis usually display signs of severe systemic illness such as hypotension and sepsis. In some instances, patients may not present with overwhelming systemic signs and symptoms of infection. Often, a high degree of clinical suspicion is needed to differentiate POM from superficial infection.

Mediastinitis may present differently depending on the type of infection present in a given case. For example, patients with POM classically present within 3 weeks of surgery with erythema or frank purulent drainage at the sternal incision site. If the sternum is firmly depressed on either side of the incision, a sternal "click" is sometimes elicited, representing sternal instability from damage of underlying tissue planes. Unfortunately, acute signs and symptoms of POM might not be present and sometimes patients present with only mild signs of infection, such as small amounts of drainage or erythema from a median sternotomy site. In contrast, patients with descending necrotizing mediastinitis often have signs of head and neck infection, making evaluation of the head and neck a critical component of the physical exam. Sometimes, in cases of dental abscess, fluctuant masses are present at the base of the teeth. Other signs include tonsillar exudates, pharyngeal inflammation, or cervical lymphadenopathy. Neck tenderness may represent tracking of infection from the head or neck to the mediastinum. "Hamman's crunch," present in some cases of mediastinitis, refers to crunching sounds on cardiac auscultation with each heartbeat and is indicative of air in the mediastinum. Patients with mediastinitis secondary to spread of infection from adjacent organs often have signs or symptoms associated with infection of the adjacent organ space (e.g., findings of pulmonary consolidation in cases of pneumonia).

When considering mediastinitis, diagnostic evaluation includes complete blood count, white blood cell differential, blood cultures, C-reactive protein, and imaging. Chest x-ray may show a widened mediastinum (most commonly seen in cases of descending necrotizing mediastinitis). Rarely, chest x-ray might demonstrate pneumomediastinum. Chest computed tomography (CT) and magnetic resonance imaging (MRI) are the most useful radiographic tests. CT and MRI commonly demonstrate fluid in the mediastinum and pneumomediastinum. While remaining sensitive for POM, chest CT or MRI are less specific, as postoperative inflammation can be difficult to differentiate from infection or abscess.

Prevention and treatment of suspected mediastinitis

Postoperative mediastinitis

In patients undergoing sternotomy, preoperative antibiotic prophylaxis is recommended. First- or second-generation cephalosporins can be administered within 60 minutes prior to surgery. In patients or institutions with high rates of MRSA or in patients with a penicillin allergy, vancomycin can be considered as part of the prophylactic regimen in combination with agents active against gram-negative bacilli. Organized programs to preoperatively decontaminate the nasopharynx and the nares of patients with chlorhexidine prior to surgery have been shown to reduce the incidence of postoperative infection, including deep sternal infections. More recently, implementation of a program consisting of preoperative chlorhexidine baths and mupirocin treatment of the nares for patients with *S. aureus* colonization was shown to reduce rates of deep surgical site infections, including mediastinitis. Other approaches such as use of implantable antibiotic sponges at the time of surgery or vaccination against *S. aureus* have proven to be less effective.

Optimal treatment of POM involves a combination of definitive surgical debridement and appropriate antimicrobial therapy. In POM, the most common pathogens are gram-positive cocci (*Staphylococcus* spp. and *Streptococcus* spp, ~70% of cases) and gram-negative bacilli (~12% of cases). Therefore, initial antimicrobial therapy typically includes two agents: one with activity against aerobic gram-positive cocci and one with activity against aerobic gram-negative bacilli. Gram-positive coverage usually includes a β-lactam (such as nafcillin or cefazolin) or glycopeptides (such as vancomycin). At institutions where MRSA is a notable POM pathogen, vancomycin should be used for empiric gram-positive therapy. Empiric coverage for gram-negative pathogens usually involves treatment with a fluoroquinolone, aminoglycoside, or extended-spectrum cephalosporin. *Pseudomonas* is a rare pathogen in mediastinitis and, therefore, antipseudomonal drugs are not typically required for empiric therapy. Antimicrobial therapy should be tailored based on culture results from the sternum and/ or mediastinum; and blood. Results from sternal culture specimens, ideally obtained in the operating room, are usually available within 3 to 5 days after they are submitted.

Immediate surgical debridement, including removal of sternal wires, is needed to confirm the diagnosis of mediastinitis (by demonstrating the presence of pus in the mediastinum), to obtain tissue for microbiologic culture, and to remove purulent material and devitalized or grossly infected tissue. Sternectomy, including

removal of the avascular costal cartilage, usually is necessary due to concurrent sternal osteomyelitis. After initial debridement and sternectomy, various therapeutic operative approaches can be implemented. Historically, the sternum was left open and packed until granulation tissue visibly developed. However, this approach was associated with considerable morbidity and mortality, often due to superinfection of the open mediastinum. Utilization of negative pressure wound therapy (NPWT, Wound Vacs) for mediastinitis may improve outcomes. Several series demonstrate shorter hospital stays, faster time to complete sternal closure, and even decreased mortality with NPWT compared to an open sternum. The preferred approach for sternal closure following sternectomy is to use a muscle flap, usually derived from the pectoralis or omentum, with the use of fenestrated drains in the mediastinum. Closure of the sternum with a muscle flap typically occurs either immediately after sternectomy and debridement or soon afterward. Delayed closure is associated with adverse outcome. Occasionally, the sternum is closed primarily without use of a muscle flap.

Descending necrotizing mediastinitis, mediastinitis originating from mediastinal structures, and mediastinitis from contiguous thoracic infections

In descending necrotizing mediastinitis, empiric antimicrobial therapy should provide activity against gram-positive cocci, anaerobes, and gram-negative rods. When the infection is restricted to the upper mediastinum, transcervical drainage is recommended. However, when infection includes the lower mediastinum, thoracotomy and open drainage is often necessary.

Mediastinitis following rupture of a mediastinal viscus requires open surgical drainage and repair of the perforated viscus. In the case of Boerhaave's syndrome, antibiotics with activity against aerobic gram-negative bacilli and anaerobes should be used. For example, an extended-generation cephalosporin in combination with metronidazole or clindamycin would be a reasonable empiric regimen. Other single-drug regimens might include a β-lactam/β-lactamase inhibitor combination such as piperacillin–tazobactam; or a carbapenem. Surgical intervention is guided by the degree of infection and the perforation. Large collections of infection require drainage, and large esophageal tears require local esophagectomy and repair.

Mediastinitis secondary to spread of a contiguous thoracic infection should be empirically treated with broad-spectrum antibiotics with activity against pulmonary pathogens such as *Streptococcus pneumoniae*, *S. aureus*, and gram-negative bacilli. In cases of suspected aspiration pneumonia, anaerobes should also be covered. An appropriate empiric regimen might include a third-generation cephalosporin or aztreonam in combination with vancomycin and either clindamycin or metronidazole. Definitive therapy requires debridement of the mediastinum and drainage of infected thoracic collections, usually via chest tube. Antibiotic regimens should be tailored based on intraoperative culture results.

Fibrosing mediastinitis due to either mycobacterial infection or fungal infection is a therapeutic challenge. Empiric therapy for *Mycobacterium tuberculosis* includes the standard four-drug regimen (e.g., isoniazid, rifampin, pyrazinamide, and ethambutol). For the treatment of fungal infections, itraconazole, sometimes in combination with amphotericin for histoplasmosis, is used. However, the utility and effectiveness of antimicrobial therapy in the treatment of fibrosing mediastinitis due to these pathogens remains unclear. Surgical debridement is primarily used to relieve vascular and airway obstruction.

Suggested reading

Bode LG, Kluytmans JA, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med*. 2010;362:9–17.

Rebmann T, Kohut K. Preventing mediastinitis surgical site infections: executive summary of the Association for Professionals in Infection Control and Epidemiology's elimination guide. *Am J Infect Control*. 2011;39:529–531.

Ridder GJ, Maier W, Kinzer S, *et al*. Descending necrotizing mediastinitis: contemporary trends in etiology, diagnosis, management, and outcome. *Ann Surg*. 2010;251:528–534.

Risnes I, Abdelnoor M, Almdahl SM, Svennevig JL. Mediastinitis after coronary artery bypass grafting risk factors and long-term survival. *Ann Thorac Surg*. 2010;89:1502–1509.

Segers P, Speekenbrink RG, Ubbink DT, van Ogtrop ML, de Mol BA. Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: a randomized controlled trial. *JAMA*. 2006;296:2460–2466.

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Vascular infection

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Diagnosis and treatment of vascular infections are complex and depend on a variety of factors, including the location of the infected tissue, the microbiology of the infection, and patient-specific factors such as anatomy and immune status. Purulent or suppurative thrombophlebitis is inflammation of a peripheral or central venous wall because of the presence of microorganisms. Endarteritis (or infective arteritis) and mycotic aneurysms are infections of the arterial walls; arterial aneurysms or pseudoaneurysms are usually present because endarteritis may be difficult to diagnose unless an aneurysm is present. The term *mycotic aneurysm* is a misnomer that refers to any arterial aneurysm of infectious cause, fungal or bacterial, and may also include secondary infections of preexisting aneurysms or pseudoaneurysms. Vascular graft infections present an even wider spectrum of disease that depends on the type and location of the graft. Management of infections located on vascular prostheses is further complicated by the fact that prosthesis excision can jeopardize a patient's life and organ function, and alternative grafting techniques, including ex situ bypass, autologous reconstruction, and a variety of other graft materials, must be considered. Finally, endovascular repair of aneurysms has resulted in a variety of infectious complications of endovascular stents, stent-grafts, and other intra-arterial devices.

Purulent phlebitis of peripheral and central veins

Pathogenesis and diagnosis

Septic thrombophlebitis is characterized by inflammation with suppuration of the vein wall. The various anatomic sites of this serious condition determine the clinical significance and manifestations. Superficial suppurative thrombophlebitis is most often a complication of indwelling intravenous (IV) catheters or IV substance use. Suppurative thrombophlebitis due to IV catheters occurs more commonly with plastic than with steel cannulas. Irritation of the vein wall and subsequent development of purulent thrombophlebitis occurs more often with polyethylene catheters than with Teflon or Silastic catheters and is higher in lower extremity cannulation. Central vein thrombosis is a relatively common complication of central venous catheterization, occurring in as many as one-third of patients in some autopsy and clinical series. Peripherally inserted central venous catheters are also associated with increased risk of symptomatic thrombosis. Suppurative thrombophlebitis of the thoracic central veins results from the bacterial or fungal contamination (sepsis) of these, often asymptomatic, thrombi. The second major type of septic thrombophlebitis occurs by invasion from adjacent primary nonvascular infections and includes Lemierre's syndrome (internal jugular vein septic thrombophlebitis caused by anaerobic gram-negative organisms) as well as other entities discussed elsewhere. Lemierre's syndrome, although rare, usually follows an oropharyngeal infection and occurs most often in previously healthy patients aged 16 to 25 years.

Diagnosis of peripheral suppurative thrombophlebitis may be difficult if local findings of inflammation are absent, as often occurs in lower extremity cannulization. Local findings, including swelling, erythema, induration, and/or a palpable cord, are much more common in suppurative thrombophlebitis of the upper

extremities. Bacteremia is present in as many as 90% of patients with peripheral suppurative thrombophlebitis, and gross pus within the vein may be apparent in half of the patients. Suppurative thrombophlebitis of the thoracic central veins should be considered in any septic patient with a central venous catheter when bacteremia (or fungemia) fails to resolve after removal of the catheter and institution of appropriate antimicrobial therapy. Diagnosis can be established by venography with the demonstration of thrombi in a patient with bacteremia or fungemia. CT with contrast is also likely to be diagnostic; presence of gas in the venular lumen is typical of this condition. MRI may be even more sensitive for diagnosis. Fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful, particularly in neutropenic patients suspected to have infection. In Lemierre's syndrome, the course is described by the triad of pharyngitis, a tender/swollen neck, and noncavitating pulmonary infiltrates. Septic pulmonary emboli occurred in 97% of cases in two series. Oropharyngeal findings alone, however, are not diagnostic, and a tender and/ or swollen neck occurs in only about 50% of patients. CT with contrast, ultrasound, or MRI can document this syndrome.

Therapy

Treatment of superficial suppurative thrombophlebitis traditionally has consisted of surgical excision plus parenteral antimicrobials. Currently available literature, most of which is derived primarily from burn center studies, strongly recommends vein excision, indicating that patients treated with antibiotics alone had much higher mortality rates than patients who underwent surgical exploration. Other studies suggest that local incision and drainage of the involved site plus appropriate antimicrobial therapy may be sufficient in many nonburn cases. Patients who fail less radical surgery should then be referred for extensive surgical excision with total removal of all involved veins and drainage of contiguous abscesses.

In recently published reviews, Enterobacteriaceae caused more than half of all cases of suppurative thrombophlebitis, followed by *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida* spp. Initial empiric treatment might include vancomycin and either an aminoglycoside or a third- or fourth-generation cephalosporin with antipseudomonal activity to cover the Enterobacteriaceae, *Pseudomonas*, and *S. aureus* (both methicillin-resistant and methicillin-sensitive) until a culture of the infected material can be performed. Blood cultures should always be drawn before antibiotics are initiated and will very frequently yield the invading pathogen. Empiric antibiotic choices should be tailored for known resistance patterns within hospitals and in geographic areas and may be adjusted based on Gram stain results. For example, a Gram stain of venular material showing gram-negative rods should result in discontinuation of vancomycin. Therapy with an appropriate antibiotic(s) should be continued once culture results are available. Treatment of superficial suppurative thrombophlebitis caused by *Candida albicans* is controversial because most of these infections can be cured by vein excision alone. Nonetheless, fluconazole, 400 to 800 mg/d, may be used, and amphotericin B or fluconazole is mandatory in the immunosuppressed patient or if metastatic complications occur.

Treatment of central suppurative thrombophlebitis consists of catheter removal and parenteral antibiotics. The addition of full-dose anticoagulation is more controversial, although one review concluded that the administration of heparin in these settings may be beneficial. Empiric antibiotic treatment is the same as for peripheral suppurative thrombophlebitis, with the potential addition of an antipseudomonal penicillin. The antibiotics appropriate for the organisms identified from cultured material should be continued for at least 2 weeks after catheter removal. A minimum of 4 weeks of antimicrobial treatment is recommended after catheter removal when *S. aureus* is involved. Amphotericin B to a total dosage of at least 22 mg/kg ± 5-fluorocytosine is recommended for suppurative thrombophlebitis of the great central veins caused by *Candida* spp.; for the intrinsically resistant species, including *C. glabrata* and *C. krusei*, echinocandins may be an acceptable alternative. Lemierre's syndrome should be treated with a prolonged course of either clindamycin or metronidazole. Surgical treatment is usually not necessary.

Arterial infections (mycotic aneurysms and arteritis)

Pathogenesis and diagnosis

Mechanisms of arterial infection include (1) embolomycotic aneurysm secondary to septic microemboli (most commonly in the setting of infective endocarditis), (2) extension from a contiguous infected focus, (3) hematogenous seeding during bacteremia originating from a distant site, and (4) trauma to the vessel wall with direct contamination, with the latter mechanism occasionally associated with iatrogenic manipulation of the artery (e.g., cannulation). Normal arterial intima is quite resistant to infection, but congenital or acquired malformation or disease (e.g., atherosclerosis) lowers resistance to infection, and hematogenous seeding of a previously damaged arteriosclerotic vessel currently constitutes the most common mechanism of infection (Figure 41.1). Mycotic aneurysms complicate infective endocarditis in approximately 5% to 10% of cases, with about half of these aneurysms involving the brain. Brain MRI with angiography may be more sensitive than CT scans for neurologic manifestations of infective endocarditis, including cerebral mycotic aneurysms.

Staphylococcus spp. and *Salmonella* spp. are the two most commonly cultured organisms in mycotic aneurysms, with staphylococci most commonly infecting preexisting aneurysms and *Salmonella* most common in causing aortitis of the non-aneurysmal aorta. When aneurysms are associated with endocarditis, gram-positive organisms account for at least 80% of pathogens.

Clinical manifestations depend to a large extent on the site of the aneurysm (Table 41.1), although mycotic aneurysms are often clinically unsuspected. Most infected aortic aneurysms occur in elderly atherosclerotic men rather than women (4:1 ratio), but symptoms are nonspecific and may overlap with those of uninfected aneurysms. Fever and continuing bacteremia despite seemingly appropriate

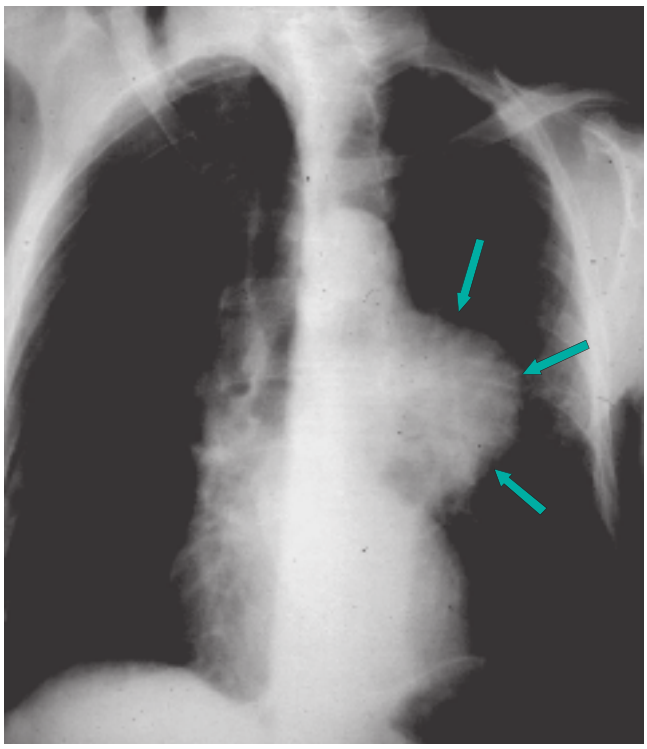

FIGURE 41.1 Infected atherosclerotic aneurysm of descending thoracic aorta (*arrows*): blood cultures grew *Salmonella*.
Courtesy of David Schlossberg, MD.

antimicrobial therapy are suggestive of an infected intravascular site. CT scan is considered the optimal initial imaging technique, with multiple newer imaging modalities including MRI, FDG-PET, and single-photon emission computed tomography (SPECT) emerging as increasingly feasible and helpful, although costly, adjunctive imaging techniques.

A variety of intra-arterial prosthetic devices are now being used in cardiovascular medicine, including arterial closure devices, prosthetic carotid patches, coronary artery stents, and endovascular stents and stent-grafts. Infections of these devices remain either uncommon or extremely rare, but infectious complications associated with the placement of these devices are often devastating. *S. aureus* has been implicated in as many as three-quarters of these cases and has been the primary pathogen, even in late-onset infections. Blood cultures should be obtained from all patients who have a history of endovascular stent placement and local or systemic signs of infection.

Therapy

Despite improved prognosis for infected aneurysms of the thoracoabdominal vessels associated with earlier diagnosis and treatment, the case fatality rate for aortic aneurysms infected with gram-negative organisms is extraordinary and may be as high as 75%. Currently accepted management is IV antibiotic therapy, excision and debridement of the artery or aneurysm, and extra-anatomic vascular reconstruction along an uncontaminated path where possible. As a general principle, antibiotic therapy alone is insufficient without surgical resection of the infected tissue. Despite this axiom, surgical management of asymptomatic intracranial mycotic aneurysms does depend on their size and location because small lesions may resolve with antibiotic therapy alone. A reasonable approach would be to monitor by MRI every 2 to 3 weeks for 2 months, although this approach may carry a higher risk of rupture and bleeding. Surgery is indicated if the infected vessel is accessible or the lesions increase in size and should be considered if the lesions fail to decrease in size.

Basic principles of grafting in this situation include the use of autogenous rather than synthetic grafts and insertion only in clean, noninfected tissue planes. Use of cryopreserved allografts allows in situ reconstruction, and these grafts are increasingly used, particularly for cases involving the thoracic or suprarenal aorta. Direct (in situ) reconstruction with synthetic or autologous grafts has become increasingly common, and short- and mid-term outcomes of this approach appear to be acceptable. At surgery the aneurysm must be sectioned, Gram-stained, and cultured; appropriate antibiotic therapy must be individualized and based on culture and sensitivity results. Bactericidal antibiotics should be continued for 6 to 12 weeks postoperatively, and some authors recommend indefinite antibiotics with in situ graft placement.

Endovascular aneurysm repair (EVAR) or endoluminal stenting for mycotic aneurysms is an additional alternative that reduces hospital stay and frequency of surgical complications but that raises significant concern because of the potential for persistent infection. In many cases, these endovascular stents are short-term solutions (i.e., "bridge" repairs) until definitive surgical repair can be performed, and chronic oral antimicrobial therapy is required. Nonetheless, endovascular grafts may now be used preferentially in patients with limited life expectancy and multiple comorbidities for whom conventional surgical methods carry extremely high risk. As technology has continued to advance, a shift toward EVAR has occurred. More recent data indicate better short-term survival in comparison with open repair and a similar incidence of serious infectious complications. Gram-positive organisms are the most common cause of infections (primarily staphylococci), and infected endografts are increasingly being diagnosed with FDG-PET and CT scan. A lifelong follow-up strategy for patients treated with EVAR is vital given the potentially devastating consequences of infection, including higher mortality rates with recurrent or new infection.

Vascular graft infections

Pathogenesis and diagnosis

Reported incidence of vascular graft infections ranges from 0.8% to 6% and varies with the site of graft placement and the graft material selected for insertion. For example, procedures requiring an inguinal incision have an incidence of infection that is two to three times higher than procedures not requiring an inguinal incision; use of a vascular prosthesis results in significantly higher infection rates than autologous reconstruction. Surgical site infections, longer procedure times, and mycotic aneurysms also are independent determinants of graft infections. Most contamination likely occurs

TABLE 41.1 **DIAGNOSIS AND MANAGEMENT OF MYCOTIC ANEURYSMS**

Site	Clinical presentation	Imaging	Microbiology	Management
General				
All infected aneurysms	Fever common (70–94%) Malaise, weight loss Pain (100%) Rapidly expanding mass Leukocytosis (65–85%) Positive blood cultures (50–75%)	*Findings:* Aneurysm with lack of intimal calcification Perianeurysmal fluid/gas collection *Studies:* CT angiography, MRI Ultrasonography (if accessible) Radionuclide-tagged WBC scans	*Staphylococcus* 50–60% (at least 66% *S. aureus*) *Salmonella* 30–40% *Streptococcus* *Escherichia coli* IVDU: *S. aureus*, *Pseudomonas* spp. *Enterococcus* spp., *Streptococcus* *Viridans*	*Surgical:* Wide debridement, irrigation with antibiotic solution of involved tissues, complete resection of aneurysm if possible *Antibiotic:* Empiric treatment with IV antibiotics for 6–12 wk after surgery based on culture results of resected tissue Follow-up blood cultures Consider chronic suppressive oral antibiotic therapy when extra-anatomic bypass is not performed (i.e., for in situ repairs)
Specifics				
Aorta Infrarenal abdominal aorta[a] Ascending aorta and arch (secondary to endocarditis)	Abdominal or back pain (65–90%) Palpable abdominal lesions (about 50–65%) Vertebral osteomyelitis (lumbar/thoracic)	Frontal, lateral abdominal x-ray studies Abdominal ultrasound	*Salmonella* spp. have predilection for suprarenal aorta *Staphylococcus* predominates in infrarenal aorta	Extra-anatomic arterial reconstruction (axillofemoral or aortofemoral) If risk too high, in situ reconstruction with cryopreserved allograft
Visceral artery Superior mesenteric,[a] splenic, hepatic, celiac, renal	Colicky abdominal pain Jaundice (hepatic artery) Hemoptysis or hemothorax (celiac artery)	Ultrasound may exclude other causes (e.g., pancreatic masses)	*Bacteroides fragilis* reported from supraceliac aorta and celiac artery	Complete excision may be hazardous; careful drainage and longer term antibiotic therapy may be necessary
Iliac	Thigh pain, quadriceps wasting, depressed knee jerk Arterial insufficiency of extremity			Excision and arterial ligation; reconstruction usually can wait until infection has resolved
Arm Radial artery[a] Humeral artery Axillary artery	Pain over site of lesion About 90% palpable May appear as cellulitis, abscess; distal embolic lesions; skin changes common		Gram-positive including *Staphylococcus* and *Streptococcus*	Proximal ligation of the vessel, resection of the aneurysm, and appropriate drainage should be followed by antibiotic therapy.
Leg Femoral artery[a]	Pain over site of lesion About 90% palpable Pulsatile mass, decreased peripheral pulses Possible local suppuration, distal embolic lesions; petechiae, purpura		*S. aureus* incidence as high as 65%	Excision and arterial ligation; reconstruction usually can wait until infection has resolved Autogenous grafting may allow reconstruction through the bed of the resected aneurysm if anastomoses performed in clean tissue planes
Intracranial Peripheral middle cerebral artery[a]	Usually clinically silent May appear as severe unremitting headache Usually secondary to endocarditis	Multislice CT angiography (CTA) or magnetic resonance angiography (MRA) equivalent MRI in endocarditis	*S. aureus 2° endocarditis* *Viridians group streptococci* *Enterococcus* spp. *Pseudomonas* spp. *Candida albicans*	Clipping or embolization may decrease mortality, but nonoperative management may be acceptable when lesions are small or inaccessible

[a] Most common site or manifestation.
Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; WBC = white blood cell; IV = intravenous; IVDU = intravenous drug user.

at the time of implantation, although hematogenous seeding and retrograde infection from superficial wound infection, as well as bacteria harbored in atherosclerotic plaques may account for some late graft infections. Prophylactic systemic antibiotics at time of graft placement have been associated with a decrease in vascular graft infections. Prophylactic antibiotics should be considered mandatory with placement of vascular grafts.

Staphylococci remain the most prevalent pathogens, with *S. epidermidis* infections often presenting months to years after the operation and *S. aureus* most commonly causing early infections (Table 41.2). More than 70% of infections involving vascular grafts of the groin and lower extremities develop within 1 to 2 months of surgery, whereas 70% of intra-abdominal graft infections do not manifest until months or years after surgery. An aortoenteric fistula can be the presenting sign in 25% to 30% of aortic graft infections, while systemic symptoms, including fever, leukocytosis, elevated inflammatory markers, and bacteremia, are much more variable.

Appropriate imaging of the infected area is vital to diagnosis because the extent of local infections may not be recognized if imaging techniques are inadequate. Angiography often is unhelpful in the diagnosis of vascular graft infections, but it is useful for identifying aortoenteric fistulas as well as for guiding the surgical procedure. An anatomic imaging study should be performed. Ultrasound can be used for extracavitary vascular graft infections and superficial grafts, including dialysis shunts; a CT with contrast or an MRI with contrast and fat saturation should be performed for deeper grafts.

TABLE 41.2 **DIAGNOSIS AND MANAGEMENT OF VASCULAR GRAFT INFECTIONS**

Site	Clinical presentation	Microbiology	Imaging	Management
General				
Any infected vascular graft	*Early (≤4 mo):* Immediate postoperative infections rare; usually associated with wound sepsis Fever, leukocytosis, bacteremia Anastomotic bleeding (most common with gram-negative organisms) Wound healing complication *Late:* Systemic signs few or absent; WBC count often normal Tenderness, erythema of skin over prosthesis Anastomotic false aneurysm Graft-enteric erosion, fistula	Coagulase- negative staphylococci *Staphylococcus aureus* *Pseudomonas* *Streptococcus* *Escherichia coli*	*Findings:* Perigraft fluid, gas collection; abnormal appearance of perigraft soft tissues; abscess; pseudoaneurysm formation *Studies: Anatomic imaging study:* 1. CT with contrast, or 2. MRI with contrast and fat saturation; or, for superficial grafts: 3. Ultrasonography *Radioisotope studies that may be useful:* 1. WBC-labeled indium scan, or 2. Tc99-HMPAO-labeled WBC, if available 3. FDG-PET/CT	*Surgical:* Wide debridement, irrigation with antibiotic solution of involved tissues (commonly used but efficacy data not available), graft excision when possible with ex situ bypass reconstruction Consider thorough debridement with myocutaneous flap for patients with a patent graft, intact anastomoses, absence of hemorrhage, and sterile blood cultures *Antibiotic:* Empiric treatment with IV antibiotics for 4–6 wk after surgery based on culture results of resected tissue Follow-up blood cultures Consider 3–6 mon of follow-up oral therapy. Consider chronic suppressive oral antibiotic therapy if infected graft not removed
Specific				
Aortoiliac	Higher incidence in months 8–15 First symptoms, fever, slightly increased WBC count Later, abdominal, back pain, false aneurysm formation Finally, hemorrhage Aortoenteric fistula (30% of aortic graft infections)	*E. coli S. aureus* *Streptococcus* Coagulase- negative staphylococci	MRI more sensitive than CT for aortal graft infection	Place axillofemoral or bifemoral graft, then remove entire aortic graft Close arteriotomy sites with monofilament sutures, irrigate with antibiotic solution (no efficacy data)

TABLE 41.2 CONTINUED

Site	Clinical presentation	Microbiology	Imaging	Management
Aortofemoral	*False aneurysm in groin site* *Wound infection or abscess* *In inguinal incision* *Pulsatile mass at groin site*	*S. aureus* *S. epidermidis* *Proteus spp.* *E. coli Streptococcus* *Other gram-negative bacilli*	Ultrasonography can be useful in femoral area	May be possible to remove only infected part of graft (one limb), although continued infection likely without removal of entire graft Extra-anatomic bypass when possible
Axillofemoral	Same as for aortofemoral	Same as for aortofemoral	Same as for aortofemoral	Remove entire graft Intra-abdominal graft may suffice for revascularization; high amputation and death rates
Femoropopliteal	Higher incidence in first 3 mo Small sinus tract, abscess, cellulitis in inguinal incision	*S. aureus* *Streptococcus* *S. epidermidis* Other gram- negative bacilli		Remove entire graft Nonviable limbs must be revascularized or amputated; delay amputation as long as possible to allow maximum development of collaterals

Abbreviations: WBC = white blood cell; MRI = magnetic resonance imaging; CT = computed tomography; IV = intravenous.

If doubt about infection still exists, radioisotope imaging can be performed using either indium-111–labeled leukocytes or, if available, technetium-99 hexamethylpropylene-amine oxime (HMP AO)-labeled leukocytes. Other nuclear medicine techniques, including FDG-PET imaging and SPECT/CT, are being investigated for diagnosis of suspected vascular graft infections and appear promising. These studies, although sensitive, are limited by low specificity, particularly in the early postoperative setting (i.e., in the period up to 12 weeks following surgery). Imaging findings that suggest the presence of graft infection include the presence of fluid around the graft ≥3 months postimplantation, air (perigraft gas volume on serial CT images), the definition of abnormal tissue planes, extensive soft-tissue swelling, anastomotic aneurysms, and the identification of pseudoaneurysms, especially when more than one is apparent.

Therapy

Conventional gold standard treatment after vascular graft infection is defined as intensive antibiotic therapy and graft excision with extra-anatomic bypass revascularization if distal ischemia is present. Revascularization should be delayed, if possible, to establish potential collateral circulation and to decrease bacterial levels (i.e., a two-stage procedure). Vascular graft material does appear to affect outcome, with autogenous (often the femoral vein) and cryopreserved allografts having the best overall success rates.

Although antibiotic treatment and local wound care are unsuccessful when used alone, a subset of patients may be managed without removal of the entire graft or with in situ grafting. Criteria for complete graft preservation include the following (at a minimum): a patent graft, intact and uninvolved anastomoses, absence of hemorrhage, and sterile blood cultures. Partial graft excision may be attempted with intact anastomoses but occluded grafts, whereas bacteremia, systemic sepsis, or involvement of anastomoses mandate complete graft removal. Diabetic patients and those receiving long-term systemic steroid therapy should be considered at highest risk for continued infection without graft removal and extra-anatomic bypass. Likelihood of successful graft preservation appears to be highest with early, low-grade infections (e.g., early coagulase-negative staphylococcal infection) and lowest with gram-negative infections and *S. aureus*. Muscle flap coverage after aggressive perigraft debridement should be considered a vital component during attempts to salvage grafts. The optimal therapy of infected vascular grafts remains removal of the entire graft and revascularization where necessary through uninfected tissue planes.

If a new graft must be placed in the infected field (in situ grafting), use of autogenous artery or vein grafts may decrease susceptibility to infection. In the absence of available autologous vessels, cryopreserved arterial allografts may be used or prosthetic conduits (including rifampin-bonded or silver-coated synthetic grafts) if necessary. Parenteral antibiotics should be administered for 4 to 6 weeks after the infected graft is removed, and some authorities have recommended administering oral antibiotics for an additional 1 to 3 months. Because of the risk of reinfection regardless of the treatment chosen, surveillance ultrasound examination should be performed every 6 to 12 months for life.

Suggested reading

Anagnostopoulos A, Ledergerber B, Kuster SP, et al. Inadequate perioperative prophylaxis and postsurgical complications after graft implantation are important risk factors for subsequent vascular graft infections: Prospective results from the Vascular Graft Infection Cohort Study. *Clin Infect Dis*. 2019; in press. https://doi.org/10.1093/cid/ciy956

Argyriou C, Georgiadis GS, Lazarides MK, Georgakarakos E, Antoniou GA. Endograft infection after endovascular abdominal aortic aneurysm repair: a systematic review and meta-analysis. *J Endovasc Ther*. 2017;24:688–697.

Langenberg JCM, Kluytmans JAJW, de Groot HWG, et al. Surgical site and graft infections in endovascular and open abdominal aortic aneurysm surgery. *Surg Infect (Larchmt)*. 2018;19:424–429.

Sorelius K, Wanhainen A, Wahlgren CM, et al. Nationwide study on treatment of mycotic thoracic aortic aneurysms. *Eur J Vasc Endovasc Surg*. 2019; in press. doi:10.1016/j.ejvs.2018.08.052.

Wilson WR, Bower TC, Creager MA, et al. Vascular graft infections, mycotic aneurysms, and endovascular infections: A scientific statement from the American Heart Association. *Circulation* 2016;134:e412–e460.

42

Infections of cardiovascular implantable devices

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Cardiovascular implantable electronic devices (CIED) include permanent pacemakers (PPM), implantable cardioverter-defibrillators (ICD), and cardiac resynchronization therapy (CRT) devices. The reported risk of CIED infection ranges from 1% to 10% and depends on the complexity of the device and host comorbid conditions. Once infected, complete device removal and systemic antibiotic therapy are necessary to achieve cure.

Earlier versions of CIEDs required surgical placement of epicardial leads, which was facilitated by sternotomy, and generators were mostly placed in the abdominal area. However, in contemporary practice, most device leads are placed percutaneously via the subclavian vein and the device generator resides in a subcutaneous pocket in the pectoral area. Use of epicardial leads is now reserved for special situations where transvenous lead placement is not possible or deemed high risk due to active or recent bloodstream infection.

Risk factors for CIED infection

Purported risk factors for CIED infection include procedure, device, and host-related elements. Several comorbid conditions including diabetes mellitus, renal failure, chronic anticoagulation, long-term corticosteroid therapy, and malignancy have been associated with increased risk of CIED infection. Procedure-related risk factors include generator or lead exchange or revision, lack of antibiotic prophylaxis at the time of implantation, prolonged surgery, and postoperative hematoma at the generator pocket. Device-related risks comprise the presence of multiple leads (>2), abandoned leads, epicardial leads, other hardware (central venous catheters, prosthetic vascular grafts, etc.), and complexity of device (CRT > ICD > PPM).

Microbiology of CIED infections

Staphylococcal species (coagulase-negative staphylococci and *Staphylococcus aureus*) are the predominant organisms responsible for CIED infection. Device infections that present early (within 4 weeks of implantation) are generally related to device or wound contamination at the time of surgery. *S. aureus* is the most common microorganism encountered in this situation. However, pocket infection with coagulase-negative staphylococci can present weeks or months after device implantation. In contrast, the majority of late-onset CIED lead infections are caused by hematogenous seeding of device leads from remote sources of bloodstream infection. In published series, up to 40% of the patients who present with *S. aureus* bacteremia have underlying CIED lead infection, even when the generator pocket has no obvious inflammatory signs. Therefore, transesophageal echocardiography (TEE) is recommended in patients with CIEDs and positive blood cultures with *S. aureus*. In contrast, hematogenous seeding of CIED leads with gram-negative bacteria is an exceedingly rare complication, and routine use of TEE is not recommended in these cases. Moreover, gram-negative bacteria are also an uncommon cause of CIED pocket infections but may be seen in patients with multiple comorbid conditions and those with long-term central venous catheters (e.g., hemodialysis

populations). Mycobacterial or fungal CIED infections are exceedingly rare and the subject of case reports.

Clinical presentation and diagnosis

CIED infections primarily manifest in two distinct ways: local infection, limited to the generator pocket, or systemic infection involving CIED leads, heart valves, or both. Pocket infection is the most common manifestation of device infection, and these patients typically present with inflammatory changes at the pocket site that may include localized pain, erythema, drainage, or cellulitis around the pocket site. Occasionally, erosion of the device generator or leads through the skin is the sole manifestation of chronic smoldering infection. Systemic findings may or may not accompany local infections.

Systemic symptoms and signs such as fever, chills, rigors, malaise, or diaphoresis are hallmarks of CIED lead infection or endocarditis. Blood cultures are typically positive in these cases but could be negative, especially if drawn after administration of antibiotics. Patients with CIED lead infection or endocarditis could present with evidence of septic emboli to the lungs or other organs, especially if left-sided heart valves are also involved.

Diagnosis of CIED pocket infection is relatively straightforward based on inflammatory changes at the generator pocket site. However, blood cultures should be obtained in all cases prior to initiating antibiotic therapy even if systemic symptoms are not overt. In cases where blood cultures are reported positive, echocardiography should be performed to look for evidence of CIED lead or valvular vegetations. TEE is preferred because it has a sensitivity of about 95% for the detection of lead or valve vegetation compared with a sensitivity of <50% with transthoracic echocardiography (TTE). Occasionally, additional testing such as 18-FDG position emission tomography (PET) combined with CT (PET-CT), MRI, or Indium -111 leukocyte scanning may be necessary to evaluate CIED infection and associated complications such as deep abscesses or metastatic foci of infection in the spine, brain, or other organs.

A particularly challenging aspect of diagnosing CIED infection is the cases where blood cultures are positive for staphylococci (especially *S. aureus*) but there are no inflammatory changes at the generator pocket and TEE shows no clear evidence of vegetations on CIED leads or heart valves. Whether these devices should be left in place or taken out is a complex decision, and PET-CT may be helpful in guiding decision-making. Based on published series, the following factors increase the likelihood that the CIED is seeded with *S. aureus*: (1) no other identifiable source of infection, (2) persistently positive blood cultures for 72 hours or longer, (3) community-onset *S. aureus* bacteremia (SAB), and (4) SAB within 3 months of device implantation. If any of these factors is present, we favor removal of the CIED. In the absence of any of these features, it may be reasonable to treat for 2 to 4 weeks depending on the presumed source of SAB and closely follow-up for any evidence of relapse of infection. If the patient has relapse of SAB, the CIED should then be removed.

Management

For patients who present with systemic manifestations of infection, it is reasonable to start empiric antibiotic therapy once blood cultures have been obtained. However, for cases where infection is limited to the generator pocket without any systemic signs and the device extraction is planned within 24 to 48 hours of presentation, it is prudent to wait until pocket and device cultures are submitted at the time of explantation and then start empiric therapy. Empiric coverage should include antimicrobials with activity against *S. aureus* and coagulase-negative staphylococci. Until sensitivities are known, vancomycin is a reasonable choice as it is active against methicillin-resistant staphylococci. If vancomycin cannot be clinically tolerated, daptomycin or linezolid are reasonable second-line agents. Once culture data are available, antimicrobial therapy should be tailored accordingly.

In cases where infection appears to be limited to cellulitis or superficial surgical site infection (infected incision or stitch abscess), a 7- to 10-day trial of antibiotic therapy may be reasonable before extraction is considered. However, complete removal of all hardware (CIED generator and all leads) is generally required for eradicating infection involving generator pockets or device leads. In our institutional experience and that of others, conservative management of the device (antimicrobial therapy alone without device removal) is almost always associated with treatment failure and is the single most important predictor of relapse of infection. Based on these data, the most recent guidelines from the American Heart Association (AHA) recommend complete removal of the device for CIED infection (Class 1A recommendation). Duration of antimicrobial therapy for various CIED infection syndromes is summarized in Figure 42.1.

In contemporary practice, most device leads are removed percutaneously using a transvenous approach. For CIED leads that were implanted relatively recently (weeks or months), removal by applying countertraction may be adequate. However, this procedure can be very difficult and can result in avulsion of the tricuspid valve, arteriovenous fistulas, or retention of the lead tip, especially if leads have been in place for a longer period of time (months to years). In these cases, use of a laser sheath is more appropriate. In this approach, a laser sheath is slid over the length of the electrode and used to excise the implanted lead, allowing the entire lead to be withdrawn with little trauma. However, expertise in lead removal via laser sheath is usually limited to high-volume referral centers.

Percutaneous lead extraction also appears safe in patients with lead vegetations. However, some experts recommend surgical removal of leads via cardiotomy in patients who have lead vegetations >5 cm due to concern for clinically significant pulmonary emboli. Failure of the transvenous approach or the need to remove epicardial patches are other indications for open surgical procedures.

For patients who present with bloodstream infection, blood cultures should be repeated after device removal. Once blood cultures obtained after device removal are reported negative and the infected pocket has been adequately debrided, it is reasonable

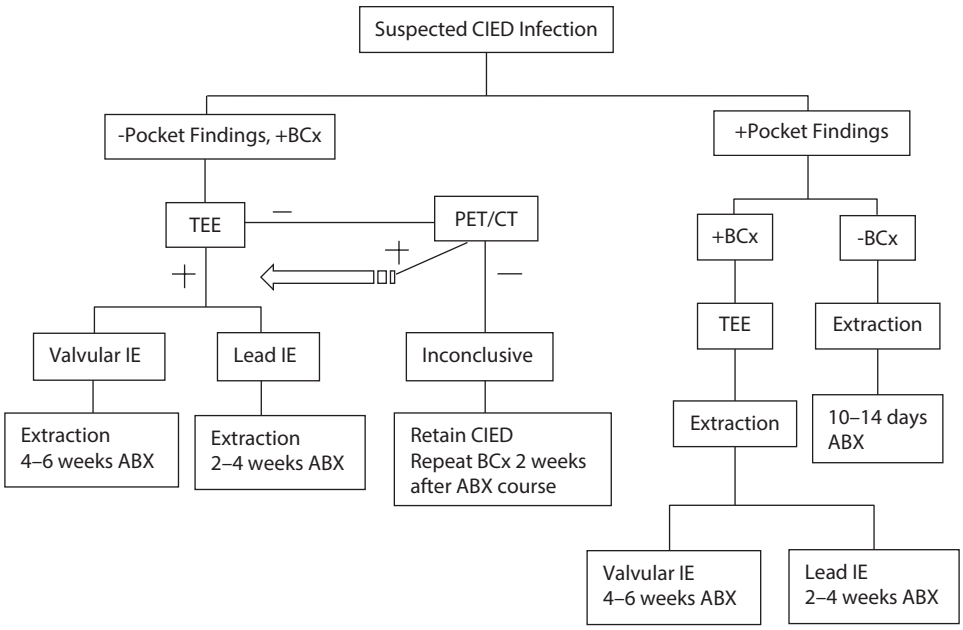

FIGURE 42.1 **CIED** - Cardiovascular implantable electronic device, **BCx** - Blood culture, **TEE** - Transesophageal echocardiogram, **ABX** - Antibiotics, **PET/CT** - Positron emission tomography/computed tomography, **IE**-Infective endocarditis

to implant a new device. However, a longer interval (up to 2 weeks or more) is usually recommended in the setting of CIED infection complicated by right-sided valvular endocarditis.

Limited data suggest that same-day reimplantation may be reasonable in patients who present with CIED infection limited to the generator pocket and in whom physical examination, laboratory parameters, and blood cultures do not show any evidence of systemic involvement.

The new CIED system (when required) should be implanted at a distant site. However, it is worth noting that a significant proportion of patients (up to 30% in some studies) do not require ongoing device therapy. Therefore, it is critical that the need for ongoing CIED therapy be assessed prior to implantation of a new device (preferably even before removal of the infected device).

Prevention

Preventing CIED infections is fundamental due to the morbidity and mortality associated with device infections. Because most early-onset infections result from pocket or device contamination at the time of surgery, meticulous attention to aseptic techniques during surgery is essential. Efficacy of antistaphylococcal antimicrobial prophylaxis before CIED implantation has been demonstrated in randomized clinical trials. In general, cefazolin 1 g is administered intravenously within an hour prior to starting the device implantation procedure. However, for patients who are allergic to cephalosporins, vancomycin is a reasonable alternative. For patients with known colonization with methicillin-resistant staphylococci, vancomycin should be administered in addition to cefazolin. This is because vancomycin is inferior to β-lactam antibiotics in preventing infection due to methicillin-susceptible staphylococci. Some implanters continue antibiotic prophylaxis for 24 to 48 hours or longer. However, there are no good data to support the added benefit of this practice.

Optimal management of host comorbidities (diabetes, renal failure, heart failure, etc.) is also important to minimize the risk of CIED infection. Another issue is optimal management of anticoagulation therapy to minimize the risk of pocket hematoma in patients who are on long-term oral anticoagulants for prosthetic heart valves or secondary prevention of venous thromboembolism. Earlier practice was to hold the oral anticoagulation therapy and "bridge" the perioperative period with unfractionated heparin. However, more recent clinical trials have demonstrated that continuation of oral anticoagulation is associated with a lower incidence of pocket hematomas compared with "bridge" therapy with heparin.

Guidelines from the AHA issued in 2010 do not recommend antimicrobial prophylaxis for patients with CIEDs undergoing dental or other procedures associated with transient bacteremias.

VAD infection

Ventricular assist devices (VADs) are increasingly being used in patients with end-stage heart failure as both a bridge to

transplantation and as myocardial surrogate (destination) therapy. VADs are undergoing rapid evolution, and most recent devices use continuous flow pump mechanisms, which improve the device function and lower the risk of infection. However, infection remains a major complication of VAD therapy, with reported risk varying from 25% to 60%.

Purported risk factors for VAD infection include length and complexity of the implantation procedure, hemorrhage at the surgical site, malnutrition, diabetes, obesity, and presence of central venous catheters. Moreover, friction-related trauma at the driveline exit site may result in cutaneous migration of microbes along the driveline and is a well-established risk factor for late-onset driveline infection. Use of an abdominal binder can minimize movement at the exit site and reduce the risk of driveline infection.

VAD infections can present as local driveline or pocket infections that result in pain, erythema, swelling, or purulence at the exit site. More severe infections can involve pump or cannula infection, bloodstream infection, or endocarditis (Figure 42.2). The majority of VAD pocket or pump infections, with or without bacteremia, occur within 30 days of device implantation, though late infections have been reported.

The most common pathogens responsible for VAD infection include *S. aureus*, *Staphylococcus epidermidis*, *Enterococcus* spp., *Pseudomonas aeruginosa*, and *Candida* spp. VAD infections due to gram-negative pathogens are mostly of nosocomial origin and are difficult to eradicate or suppress due to multidrug resistance of the organisms.

Driveline exit site infections are usually managed with wound debridement and a short course (typically 2 weeks) of antimicrobial therapy. If local VAD infection is complicated by bloodstream infection, then treatment is prolonged to 4 weeks or longer. However, management of VAD pump or cannula infection presents a major challenge. Unlike other prosthetic devices where removal of the infected hardware is the cornerstone of management, VADs cannot be easily removed or replaced because these patients cannot survive without a device. Therefore, a 4- to 6-week course of intravenous antimicrobial therapy followed by chronic suppression, targeted at the causative pathogen and guided by antimicrobial susceptibility testing, is typically prescribed. Occasionally, VAD may be replaced due to uncontrolled infection despite appropriate antimicrobial therapy. However, suppressive antibiotic therapy should be continued as the new device is placed in an actively infected pocket.

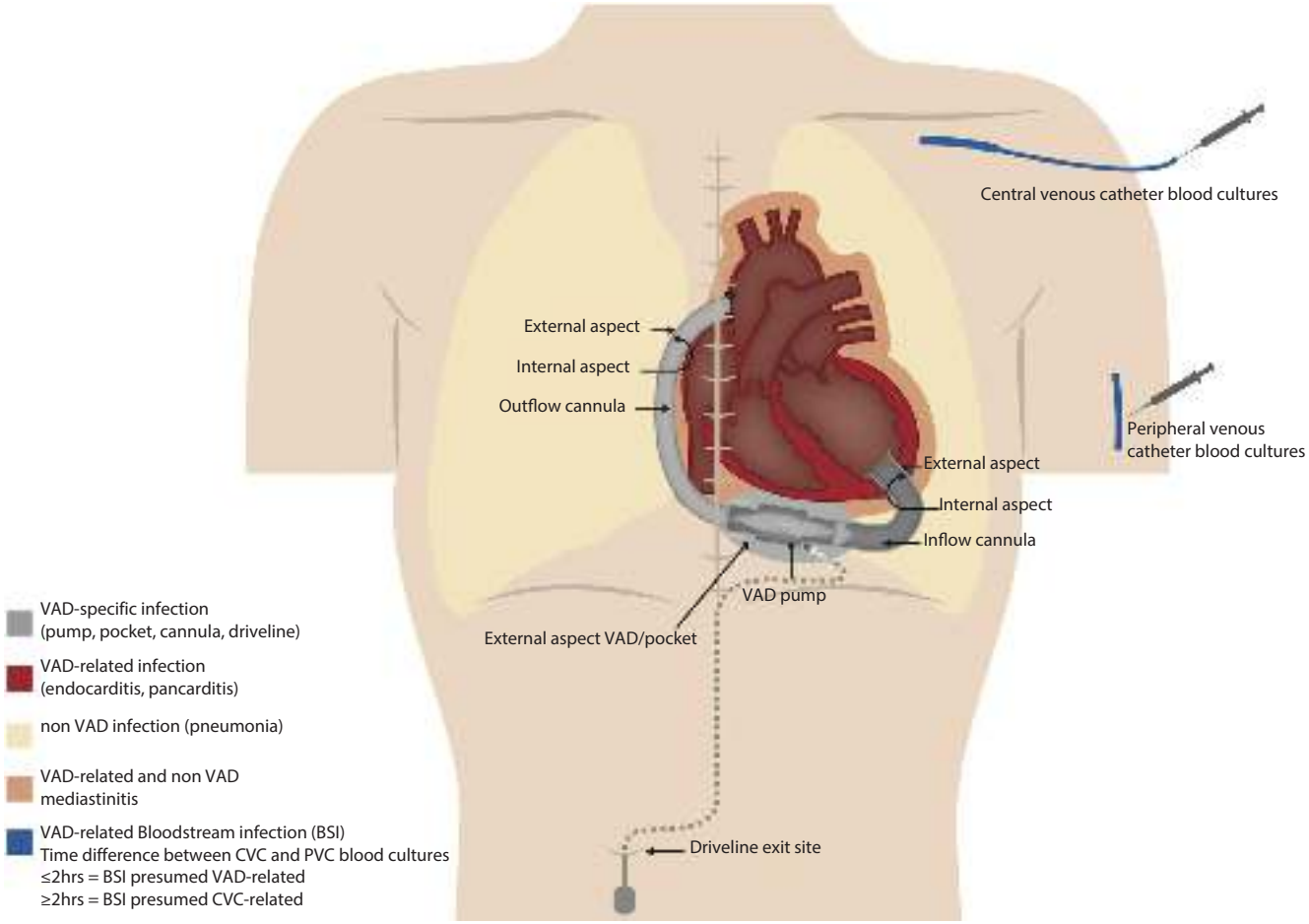

FIGURE 42.2 Ventricular assist device, VAD-specific, VAD-related, and non-VAD infection
From Hamman MM, et al. *J Heart Lung Transplant*. 2011;30(4):375–384, with permission.

Suggested reading

Athan E, Chu VH, Tattevin P, et al. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA*. 2012;307(16):1727–1735.

Baddour LM, Eppstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management: A scientific statement from the American Heart Association. *Circulation*. 2010;121(3):458–477.

DeSimone DC, Sohail MR. Approach to diagnosis of cardiovascular implantable-electronic-device infection. Kraft CS, ed. *J Clin Microbiol*. 2018;56(7): e01683–17.

Gordon RJ, Weinberg AD, Pagani FD, et al. Prospective, multicenter study of ventricular assist device infections. *Circulation*. 2013;127(6):691–702.

Kusne S, Staley L, Arabia F. Prevention and infection management in mechanical circulatory support device recipients. Snydman DR, ed. *Cin Infect Dis*. 2017;64(2):222–228. doi:10.1093/cid/ciw698.

Kusumoto FM, Schoenfeld MH, Wilkoff BL, et al. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. *Heart Rhythm*. 2017;14(12):e503–e551.

Nagpal A, Baddour LM, Sohail MR. Microbiology and pathogenesis of cardiovascular implantable electronic device infections. *Circulation Arrhythm Electrophysiol*. 2012;5(2):433–441.

Nienaber J, Wilhelm MP, Sohail MR. Current concepts in the diagnosis and management of left ventricular assist device infections. *Expert Rev Anti Infect Ther*. 2013;11(2):201–210.

Sohail MR, Eby EL, Ryan MP, et al. Incidence, treatment intensity, and incremental annual expenditures for patients experiencing a cardiac implantable electronic device infection: Evidence from a large US payer database 1-year post implantation. *Circulation Arrhythm Electrophysiol*. 2016;9(8):e003929.

Sohail MR, Uzlan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. *J Am Coll Cardiol*. 2007;49(18):1851–1859.

Section 7

Clinical syndromes: Gastrointestinal tract, liver, and abdomen

43

Acute viral hepatitis

Kalyan Ram Bhamidimarri and Paul Martin

Acute viral hepatitis is a systemic infection with predominant hepatic involvement and remains a significant cause of morbidity and mortality in the United States despite the availability of effective vaccines against two major infections (hepatitis A and B) that cause acute viral hepatitis. There are five major hepatotropic viruses (A, B, C, D, and E) and several non-hepatotropic viruses that cause acute hepatitis characterized by acute hepatic inflammation and necrosis. Acute viral hepatitis typically runs its course in 6 months or less, in contrast to chronic hepatitis, which persists for longer. However, with modern serologic, molecular diagnostic testing and efficacious therapeutic options the time course is less important in distinguishing acute from chronic viral hepatitis. The clinical illness produced by these viruses can range from asymptomatic or clinically inapparent to a fulminant and fatal acute infection. A major distinction between hepatitis A and hepatitis B, C, D, and E is that the former causes acute hepatitis only, in contrast to the latter four which cause acute and chronic hepatitis. Nonhepatotropic viral infections, such as herpes simplex virus (HSV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), and parvovirus B19, can present with prominent hepatic dysfunction, although they are usually multisystem disorders. Hepatitis G, human herpesviruses, adenovirus, coronavirus, and TT virus (TTV) have also been implicated in causing hepatic dysfunction, but their clinical significance remains dubious.

Hepatitis A virus

The hepatitis A virus (HAV) is an RNA virus identified in 1973; it is transmitted predominantly via the fecal–oral route and is a common cause of acute viral hepatitis worldwide. Community outbreaks due to contaminated water or food were common prior to 1995, but person-to-person transmission is now frequently responsible since 2016. Inhabitants in low-socioeconomic areas, homeless individuals, international travelers, intravenous (IV) drug users, and men who have sex with men (MSM) are at particular risk of HAV infection. The epidemiology of HAV in the United States has changed drastically over the past few decades with a significant reduction in incidence rates prior to 2011, and it had plateaued until 2016. However, >8,000 outbreaks were reported in 12 US states as of October 2018. The incidence of HAV, once predominantly higher (up to 20% reported in 1980s) among persons with IV drug use (PWIDs) and the homeless, has surged in the past 3 years. Unsafe sanitary conditions, poor hygiene in congregated living facilities (sheltered or unsheltered), contaminated paraphernalia among PWIDs, and high-risk sexual behavior accounted for most of the cases transmitted from person to person. California, Kentucky, Michigan, and Utah were four states that reported large sustained within-state transmission but eight other states including Florida also had a public health advisory due to increased incidence of HAV. The infection was reported across all demographic groups, but men aged 30 to 49 years (median age 37 years) accounted for 68% of the cases. In underdeveloped countries, HAV infection typically occurs in childhood and is subclinical (age ≤6 years, 70% are asymptomatic), with most of the population infected before adulthood acquiring life-long immunity. HAV infection occurring in older children and adults is more likely to be symptomatic, with increased morbidity and even mortality (Figure 43.1).

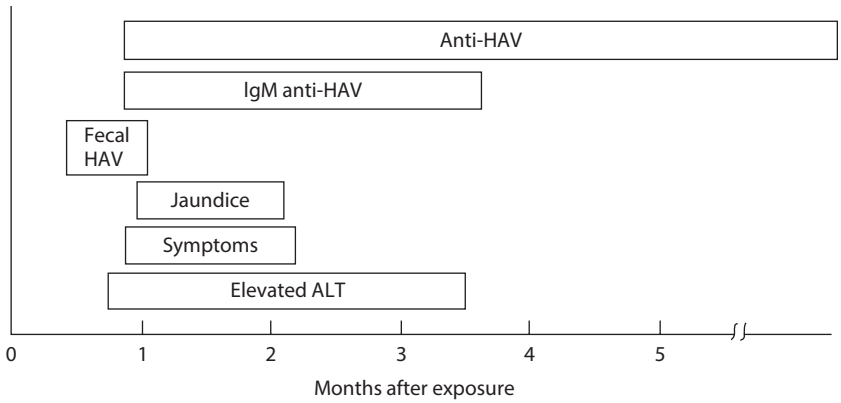

FIGURE 43.1 Course of acute hepatitis A.

ALT, alanine aminotransferase; anti-HAV, antibody to hepatitis A virus; HAV, hepatitis A virus.
Adapted from Martin P, Friedman LS, Dienstag JL. Diagnostic approach to viral hepatitis. In Thomas HC, Zuckerman AJ, eds. *Viral hepatitis*. Edinburgh: Churchill Livingstone; 1993: 393–409.

The average incubation period of HAV infection is 28 days (range 15–50 days), with peak fecal viral shedding and infectivity occurring 3 weeks before and 1 week after the onset of clinical symptoms, which may include anorexia, fever, malaise, fatigue, nausea, vomiting, diarrhea, and right upper quadrant discomfort. In acute HAV infection, these symptoms tend to occur 1 to 2 weeks before the onset of jaundice. Replication of HAV occurs exclusively within the cytoplasm of the hepatocyte, where the virus causes a noncytopathic infection. Hepatocellular damage is due to the host's immune response as the infected hepatocytes are cleared and is clinically observed by marked reduction of HAV RNA. Acute liver failure is rare and occurs in about 0.5% of infected individuals, more frequently in adults than in children. Recent acute HAV outbreaks have been associated with increased rates of hospitalizations (72% vs. 42% prior to 2016), of which 3% had confirmed or probable hepatitis B virus (HBV), and 22% had confirmed or probable hepatitis C virus (HCV) and concomitant alcoholic liver disease. The recent case fatality rate of acute HAV was also higher at 3% compared to previously reported 0.3% to 1.8% and could have been prevented by HAV vaccination. Prompt referral of patients who develop acute liver failure cases to a transplant center is indicated. It is well known that patients with chronic liver disease are at increased risk of hepatic decompensation and death from acute HAV, which has led to the recommendation that HAV-naïve patients with chronic liver disease should be vaccinated against HAV. Based on the recent reports, the Advisory Committee for Immunization Practices (ACIP) unanimously voted for HAV vaccination in another identified risk group: the homeless population. Most infected individuals recover uneventfully although the illness can occasionally be bimodal or relapsing. Chronic infection with HAV does not occur, but a protracted cholestatic phase may be present with persistent jaundice and pruritus before the eventual recovery.

Extrahepatic manifestations of HAV include acute pancreatitis, acalculous cholecystitis, autoimmune hemolytic anemia, aplastic anemia, reactive arthritis, effusions, mononeuritis multiplex, and Guillain–Barré syndrome. HAV-related acute kidney injury has been reported in cases from Asia, possibly mediated by immune complexes or interstitial nephritis.

Routine diagnosis of acute HAV infection is made by detection of immunoglobulin M (IgM) anti-HAV antibody in serum (Table 43.1), which becomes detectable 5 to 10 days before the onset of symptoms and persists for 3 to 12 months after infection. IgG anti-HAV antibody develops early in infection and persists indefinitely. The presence of IgG anti-HAV in the absence of IgM anti-HAV reflects immunity either from prior infection or from vaccination. Testing for HAV polymerase chain reaction (PCR) and genotypes is not routinely recommended or available. However, HAV PCR, genotyping, and viral sequencing are of epidemiological value. Three HAV genotypes 1a, 1b, and 3a are common in the North and South Americas and a significant epidemiologic shift is noteworthy. A CDC report by the US Centers for Disease Control and Prevention (CDC) that genotype 1a, which was the predominant strain prior to 2017, has been replaced with genotype 1b, which now accounts for 96% of cases in recent outbreaks.

Therapy

Acute HAV infection is self-limited without chronic sequelae. About 85% of acute HAV cases have clinical and biochemical recovery within 3 months, and nearly all have complete recovery by 6 months from the time of initial infection. Treatment is largely supportive and includes adequate nutrition and hydration, avoidance of hepatotoxic medications, steroids, and abstinence from alcohol (Table 43.2). Because acute HAV is more likely to lead to hepatocellular failure in adults, especially in those with underlying chronic liver disease, these patients require close follow-up until symptoms resolve.

Universal precautions to prevent transmission among close contacts, good personal hygiene, and immunization are recommended. Passive prophylaxis with intramuscular polyclonal immunoglobulin before and after exposure is safe and efficacious. Pre-exposure prophylaxis with immunoglobulin should be reserved for nonimmune patients at risk for HAV who are allergic to

TABLE 43.1 **DIAGNOSTIC TESTING FOR VIRAL HEPATITIS**

Type	Diagnostic tests	Comments
Hepatitis	IgM anti-HAV	Acute infection
A virus (HAV)	IgG anti-HAV	Resolved infection, immunity
Hepatitis	HbsAg	Indicates infection
B virus (HBV)	IgM anti-HBc	Acute infection
	HBeAg, HBV DNA	Indicates replication
	Anti-HBs	Indicates immunity
	IgG anti-HBc	Current or prior infection
Hepatitis	Anti-HCV	Indicates infection
C virus (HCV)	HCV RNA	Indicates infection/viremia
Hepatitis D virus (HDV)	IgM anti-HDV	IgM anti-HBc positive Indicates coinfection
	Anti-HDV	IgG anti-HBc positive Indicates superinfection
		Indicates infection
	HDV RNA and HDV antigen	Research tools at present
Hepatitis	IgM anti-HEV	Acute infection
E virus (HEV)	IgG anti-HEV	Resolved infection
EBV	EBV IgM and PCR	Indicates infection
CMV	CMV IgM and PCR	Indicates infection

Abbreviations: CMV= cytomegalovirus, EBV= Epstein–Barr virus.

HAV vaccine. Postexposure prophylaxis with immune globulin is recommended for the following high-risk groups in whom protective antibody titers should be generated quickly: (1) close household and sexual contacts of an index patient with documented acute HAV, (2) staff and patients of institutions for the developmentally disabled with outbreaks of HAV, (3) children and staff of daycare centers with an index case of HAV, (4) those exposed to protracted community outbreaks, and (5) travelers and military personnel who plan to visit

TABLE 43.2 **THERAPY OF ACUTE VIRAL HEPATITIS**

Type	Major focus	Comments
Hepatitis A	Symptomatic therapy	Recognition of ALF and promptly refer to transplant center
Hepatitis B	Symptomatic therapy. Oral agents for acute severe HBV	Observe for ALF
Hepatitis C	Pegylated interferon +/− ribavirin	Treatment efficacious in acute HCV
Hepatitis D	Consider anti-HBV agents in severe cases	Clinically more severe than HBV alone
	Prevention: HBV vaccine	
Hepatitis E	Ribavirin monotherapy is effective	FHF common in pregnant women.
		Transmission can be enteric or zoonotic. Can become chronic in immunocompromised
EBV	Symptomatic therapy	Risk factor for PTLD
CMV	Immunocompetent: monitor	
	Immunocompromised: ganciclovir, foscarnet, or cidofovir	

Abbreviations: CMV = cytomegalovirus, EBV = Epstein–Barr virus, FHF = fulminant hepatic failure, PTLD = posttransplantation lymphoproliferative disease.

countries endemic for HAV. The recommended dose of immune globulin for passive immunity is currently five times higher than in previous years as immunoglobulin titers are now low in the donor pool. Active immunization with an inactivated HAV vaccine has been available in the United States since 1995. The vaccine is highly immunogenic and most immune-competent individuals (>95%) develop protective antibodies within 4 weeks of receiving the first dose and almost 100% protection after the second vaccine dose. HAV vaccine is superior to passive immunization even for postexposure prophylaxis. It is also important to note that although the two-dose HAV vaccine series given 6 months apart is recommended, a single dose of HAV vaccine has durable efficacy for up to 11 years or even life-long in several reports. Single-dose HAV vaccine is not only expected to confer personal protection but also would contribute to herd immunity for a reasonable duration and is expected to reduce the large-scale person-to-person outbreaks. Therefore, completion of the two-dose vaccine series should not be a deterrent for initiation of vaccination, especially in the homeless. Various public health departments have increased their effort in educational campaigns to augment public awareness and ensure vaccination of those at high-risk as necessary.

Hepatitis B virus

HBV is the most common cause of chronic viral hepatitis worldwide and is also a major cause of acute viral hepatitis, especially in developing nations. There are an estimated 257 million people chronically infected with HBV worldwide. In the Far East and sub-Saharan Africa, up to 20% of the population has serologic evidence of current or prior HBV infection. In the United States, although HBV infection is less frequent, the prevalence of chronic HBV is much higher in certain immigrant communities, including Asian Americans. After acute HBV infection, the risk of chronic infection varies inversely with age. Thus, children younger than 5 have a high risk of chronicity after acute HBV infection (>90%), whereas an immunocompetent adult has a ≤10% likelihood.

HBV is a DNA virus transmitted predominantly by a parenteral route or through intimate contact with an infected subject. In Asia and other hyperendemic areas, vertical transmission is an important transmission route, whereas sexual and percutaneous transmission predominates in the Western world. The incubation period is 45 to 160 days. The typical course of a patient with acute HBV infection is illustrated in Figure 43.2. Typically, elevated alanine aminotransferase (ALT) levels and clinical symptoms appear earlier than jaundice. However, not all patients with acute HBV infection develop jaundice. About 70% of patients with acute HBV infection develop subclinical or anicteric hepatitis, and only 14% to 30% develop icteric hepatitis. Paradoxically, the patient with anicteric and clinically less severe acute HBV infection is more likely to become chronically infected than the individual with more symptomatic acute infection because a brisk immune response causes more hepatic dysfunction but also a greater likelihood of ultimate clearance of HBV infection. The symptomatic patient should be reassured that full recovery is likely but should be warned to report back if symptoms such as deepening jaundice, severe nausea, or somnolence develop because these symptoms may herald acute hepatic failure. Approximately 1% to 4% of acute HBV can present with acute liver failure (ALF), of which approximately 20% to 80% can result in death or liver transplantation. A recent study from China that evaluated 293 hospitalized patients with acute HBV reported that total bilirubin of five times the upper limit of normal, low prothromin time activity (PTA <20%), and grade III–IV hepatic encephalopathy were independent predictors of ALF and

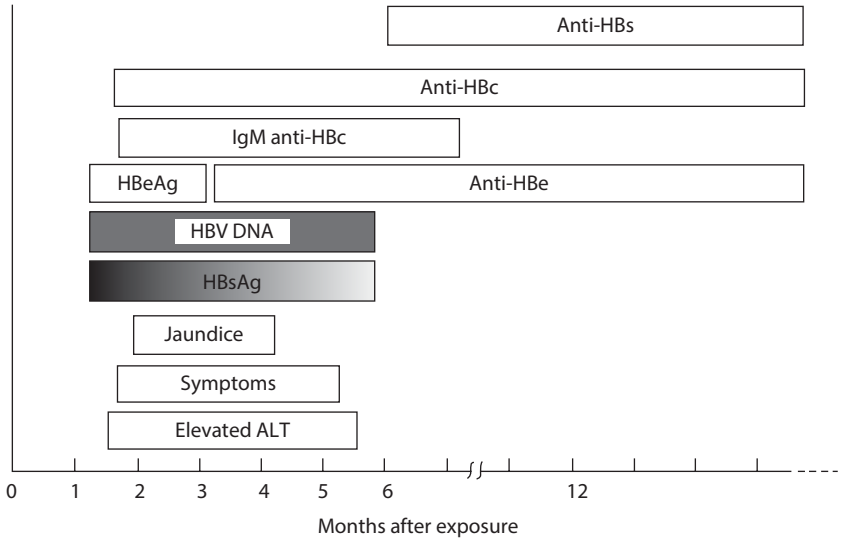

FIGURE 43.2 Typical course of acute hepatitis B.

ALT, alanine aminotransferase; Anti-HBc, antibody to hepatitis B core antigen; Anti-HBe, antibody to hepatitis B e antigen; Anti-HBs, antibody to hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus DNA.
Adapted from Martin P, Friedman LS, Dienstag JL. Diagnostic approach to viral hepatitis. In Thomas HC, Zuckerman AJ, eds. *Viral hepatitis*. Edinburgh: Churchill Livingstone; 1993: 393–409.

prognosticated the risk of death or liver transplantation. Like acute HAV, acute HBV infection may be more severe in patients with underlying chronic liver disease.

The diagnosis of acute HBV hepatitis is made by detection of hepatitis B surface antigen (HBsAg) and IgM anti-hepatitis B core antibody (anti-HBc IgM) in the serum (Box 43.1). Resolution of HBV infection is characterized by loss of HBsAg. Development of the corresponding neutralizing antibody to HBsAg, anti-HBs, indicates resolution of infection. IgM anti-HBc declines and becomes undetectable whereas IgG ("total") anti-hepatitis B core antibody (anti-HBc IgG) persists after resolution of infection. Detection of IgG anti-HBc distinguishes immunity acquired from prior infection from vaccination in a patient with detectable anti-HBs.

The rate of progression of acute to chronic HBV is typically quoted to be around 5% to 10%. Some studies have proposed a specific HBV genotype as a determinant of likelihood of chronicity, but this remains to be confirmed. A recent study from Northern Ireland reported that subjects >50 years had a higher rate of progression from acute to chronic infection when compared to those <50 years (36.36% vs. 16.28%, p = 0.0068). It appears from the study that older individuals had lower rates of clearance of acute HBV than younger peers. Individuals who are immunocompromised or have another chronic condition such as renal failure are more likely to develop chronic infection. Children <5 years and the elderly also have a greater likelihood of becoming chronically infected. The absence of a brisk immune response during acute HBV infection, implied by a relative absence of symptoms, with modest aminotransferase elevation in an anicteric patient, indicates that infection is more likely to become chronic. Chronic HBV infection is suggested by HBsAg positivity for >6 months with the absence of IgM anti-HBc. However, in severe reactivation of chronic HBV infection (spontaneous or iatrogenic due to administration of corticosteroids or chemotherapy to an infected patient), IgM anti-HBc may reappear in serum although usually in low titers. The presence of HBeAg and HBV DNA in the serum suggests ongoing active viral (wild-type) replication or a "high replicative state" in patients with chronic infection. The absence of these markers of active replication in a chronically infected patient with no clinical evidence of liver disease is referred to as the *nonreplicative* or *inactive carrier state*.

BOX 43.1

Initial serologic workup of suspected acute hepatitis

IgM anti-HAV
HBsAg (if positive, then IgM anti-HBc, HBV DNA, HBeAg)
Anti-HCV antibody (if positive, then HCV RNA)
Consider testing for HEV, HSV, CMV, and EBV if A, B, and C tests are negative. Testing for other viruses is at clinician's discretion.

Therapy

Interferon-α, pegylated interferon-α 2a, lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir are currently approved therapies in the United States for the treatment of chronic HBV infection. Interferon, entecavir, and tenofovir are the currently recommended first-line agents in the treatment of chronic HBV infection. Interferon's side effects have limited its use, with the introduction of well-tolerated oral agents. Given the high rate of spontaneous resolution of acute HBV in otherwise healthy adults, antiviral therapy is generally not recommended. Treatment with oral agents should be initiated in acute severe cases of HBV or in those who are immunosuppressed. Early referral to a transplant center is highly recommended for patients with severe liver injury suggested by hepatic encephalopathy, worsening coagulopathy, or ascites. Posttransplant outcomes for HBV are now excellent for HBV. There has been a very low rate of recurrence of viral infection posttransplant with current immune-prophylaxis regimens using an oral antiviral agent with high-dose hepatitis B immunoglobulin (HBIG). However, indefinite HBIG therapy is both cumbersome and expensive. Accordingly, transplant programs are evaluating the use of alternative schedules of HBIG administration and combinations of antiviral agents to prevent allograft reinfection. Therapy for chronic HBV infection is discussed in Chapter 44, "Chronic viral hepatitis."

The highly effective recombinant HBV vaccine is recommended for newborns, infants, adolescents, healthcare workers, hemodialysis patients, household contacts and sexual partners of HBV-infected individuals, international travelers to endemic areas, injection drug users, MSM or heterosexuals with multiple sexual partners, patients with chronic liver disease, and those who are potential organ transplant recipients. Postexposure prophylaxis should consist of a combination of HBV vaccination and passive protection with HBIG.

Hepatitis C virus

The HCV is a single-stranded RNA virus. It is estimated that about 170 million people in the world are chronically infected with HCV. Acute HCV is typically subclinical, with <25% of patients developing jaundice, and thus acute illness usually escapes medical attention. If symptomatic, acute HCV is less likely to lead to chronicity. HCV infection is usually transmitted parenterally. In the past, this was often by contaminated blood products. Now, most HCV infection is contracted by sharing contaminated needles among IV drug abusers or by other percutaneous or high-risk practices such as tattooing or possibly intranasal cocaine use, although the latter is controversial. Sexual and maternal–neonatal transmission can occur, but these are generally less efficient routes of transmission although maternal HIV coinfection appears to increase the risk of perinatal transmission. Sexual transmission of HCV is also recognized in MSM, especially those coinfected with HIV. There is a rising incidence of acute HCV in HIV-infected MSM. There is a high clustering of sexually transmitted infections (STI) as well in this cohort, which reflects high-risk practices. Acute HCV infection

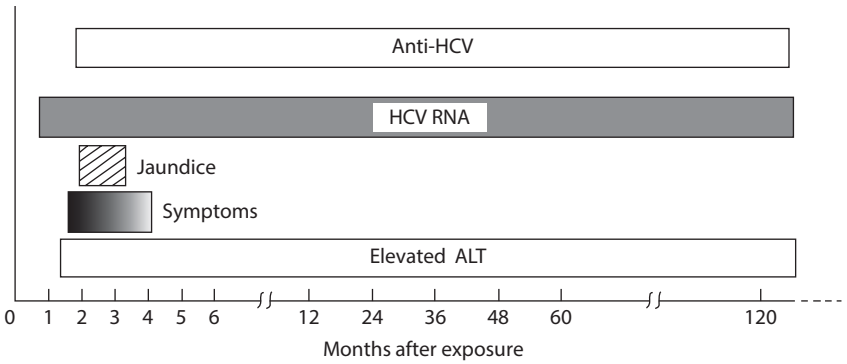

FIGURE 43.3 Typical course of acute hepatitis C progressing to chronic hepatitis C.

anti-HCV, antibody to the hepatitis C virus; HCV, hepatitis C virus.
Adapted from Martin P, Friedman LS, Dienstag JL. Diagnostic approach to viral hepatitis. In Thomas HC, Zuckerman AJ, eds. *Viral hepatitis*. Edinburgh: Churchill Livingstone, 1993: 393–409.

results in a high rate of chronicity, up to 85% in some series. Figure 43.3 illustrates the course of a patient with acute HCV infection progressing to chronicity. The incubation period is 14 to 180 days, after which elevation of ALT levels occurs and symptoms may appear, although, as noted, the acute illness is frequently subclinical. Fulminant hepatic failure due to acute HCV infection is very rare but may be more common in patients with underlying chronic HBV infection.

Routine diagnosis is made by detection of antibodies in serum to HCV (anti-HCV) by enzyme-linked immunosorbent assay (ELISA) testing. The recombinant immunoblot assay (RIBA) test was formerly used to enhance specificity as a supplemental test in ELISA-positive individuals. However, it has generally been supplanted by PCR testing to confirm viremia. Fluctuating ALT levels are characteristic of chronic HCV infection. Perhaps a fifth of chronically infected patients have ALT levels regarded as within the normal range, although this reflects a lack of sensitivity of aminotransferases in detecting lesser degrees of necro-inflammatory activity in the liver rather than an absence of liver injury. PCR techniques vary in their sensitivity in detecting HCV RNA. The more sensitive transcription-mediated amplification (TMA) technique can detect even minute quantities of HCV RNA (0.9–5.2 copies/mL).

Therapy

Acute HCV infection is most typically recognized in a healthcare worker after a needle-stick injury or, rarely, in someone who develops a hepatitis flare. A small subset of patients, especially those with a favorable IL28B genotype (C/C), can have spontaneous clearance of the virus. Therefore, acute hepatitis C patients should be closely monitored and those with persistent viremia beyond 12 weeks should be offered treatment. Delaying antiviral therapy for 2 to 4 months after acute HCV infection does not compromise efficacy. This short delay allows spontaneous resolution of HCV without embarking on unnecessary treatment that is expensive. Direct-acting antivirals (DAAs) have revolutionized HCV therapy. Treatment of HCV during the acute phase is highly effective, and sustained virologic response can be anticipated in up to 95% of treated patients. A recent study from the Netherlands where acute HCV is frequent, reported a 70% reduction of acute HCV cases due to widespread use of DAAs. Modeling and cost effectiveness studies also support the treatment of acute HCV as a preventive measure to curtail the person-to-person transmission among high-risk groups. Therapy of chronic HCV infection is discussed in more detail in Chapter 44, "Chronic viral hepatitis." The World Health Organization (WHO) declares an ambitious target of HCV eradication via micro-elimination by 2030.

An HCV vaccine is not yet available because of the virus' heterogeneity and the lack of seroprotective capability of HCV antibodies. There is no benefit from γ-globulin administration following a needle-stick exposure to HCV. Universal precautions are mandatory because the risk of HCV transmission to healthcare workers is substantial, averaging about 3% particularly with hollow-bore needles. Routine screening by blood banks for HCV has reduced the risk of transmission by transfusion to a negligible level.

Hepatitis D virus

The hepatitis delta virus (HDV) is an incomplete RNA virus that depends on HBsAg to complete its replicative cycle. It is estimated that 5% of chronic HBV patients worldwide are coinfected with HDV. HDV is transmitted parenterally in developed countries, whereas in other areas of high endemicity (Mediterranean basin), transmission is through intimate contact. Immigration from highly endemic areas is implicated in the recent increase in prevalence in Western Europe. HDV has been called by several names: "black vomiting fever," Bangui fever in Africa, Santa Marta hepatitis in Colombia, and Labrea hepatitis in Brazil. HDV may be transmitted simultaneously with HBV (coinfection) or acquired in chronic HBV carriers (superinfection). Most cases of coinfection are self-limited, but patients are more likely to develop fulminant hepatitis than with HBV monoinfection. If HDV is acquired by

superinfection, infection tends to become chronic, with higher rates of progression to cirrhosis than with HBV alone. HBV viral load is typically suppressed by active HDV infection.

The diagnosis of HDV coinfection is made if serum IgM anti-HDV, HBsAg, and IgM anti-HBc are simultaneously present in serum. HDV superinfection is denoted by IgM anti-HDV, HBsAg, and IgG anti-HBc with absent IgM anti-HBc. During the acute infection, HDV serologies are often insensitive, and repeat testing may be required in cases with high clinical suspicion (see Table 43.1). HDAg (direct immunofluorescence) or HDV RNA (reverse transcriptase assay) testing in the serum or on liver tissue can be performed, but these techniques are not widely available for clinical use.

Therapy

There is no specific treatment for acute HDV infection as most patients have spontaneous resolution after the flare. Among hepatotropic viruses, HDV is the only infection without satisfactory oral treatment options. Interferon is the only effective therapy against HDV but is contraindicated during an acute flare due to risk of acute hepatic failure. Antiviral agents against hepatitis B are generally not useful because HBV is usually suppressed, but they can be tried in patients who are at risk of fulminant liver failure. Liver transplantation is the only option for patients with acute liver failure from HDV coinfection. Control of HBV with antiviral agents plus or minus HBIG prevents HDV recurrence in the graft. Vaccination against HBV prevents HDV infection. Newer agents against HDV are currently being investigated.

Hepatitis E virus

The hepatitis E virus (HEV) is an RNA virus first identified in 1980 as an enterically transmitted hepatitis virus similar to HAV. Currently, there are four genotypes identified. Genotypes 1 and 2 are predominant in developing countries with enteric transmission, whereas genotypes 3 and 4 are predominant in developed countries and have zoonotic transmission (consumption of contaminated uncooked meat, especially pork). The incubation period is 15 to 60 days, with high infection rates in adults between the ages of 15 and 40. Antibodies against HEV have been found in up to 20% of the general population in developed countries and may account for 3% of cases of putative drug-induced liver injury presenting with acute liver failure.

HEV infection is usually acute and self-limited, but chronic HEV progressing to cirrhosis has been increasingly recognized especially in genotype 3 and immunocompromised subjects. A unique feature of this disease in developing nations is that fulminant hepatic failure occurs more frequently in pregnant women during the third trimester and carries a high mortality rate (15–25%). HEV is diagnosed by IgM and IgG anti-HEV antibodies and HEV RNA. HEV RNA, although diagnostic of active infection, could be a fleeting presence during an acute phase of HEV infection and may be undetectable in up to 40% of infected individuals.

Therapy

Acute HEV infection is self-limited and treatment is mainly supportive. Pregnant women should not travel to areas endemic for HEV. Acute severe hepatitis can be treated with ribavirin monotherapy (dose 600–1,000 mg/d) for 3 to 6 months, which can result in rapid clinical improvement. Ribavirin is teratogenic, however, and thus contraindicated in pregnancy. Interferon is contraindicated in severe hepatitis as it can exacerbate the ALT flare, leading to fulminant hepatic failure. Chronic HEV in immunosuppressed transplant recipients can be treated with lowering of immunosuppression, ribavirin monotherapy or pegylated interferon monotherapy, or a combination of these. HEV vaccines are currently in the developmental phases, with promising preliminary results.

Herpes simplex virus

HSV is a capsulated double-stranded DNA virus. Infection can rarely lead to acute liver failure (1–2% of all acute liver failure cases). Acute severe hepatitis is associated with high mortality rates of 75% to 90% and is commonly seen in immunocompromised patients, pregnant women (late trimester), neonates, and, rarely, in immunocompetent individuals.

Clinical features of HSV can vary from mild asymptomatic anicteric hepatitis to fulminant hepatic failure or severe HSV sepsis (pneumonitis, esophagitis, encephalitis) resulting in multiorgan failure. Newborns presenting with systemic infection, herpes neonatorum, have high rates of brain injury and a 25% mortality rate. Mucocutaneous lesions are found only in 50%, with their absence often resulting in diagnostic delay. Most cases of acute HSV hepatitis reflect acute infection rather than viral reactivation. Fever, flu-like symptoms, and leukopenia are typical. Serologies are usually nondiagnostic, and thus diagnosis rests on detection of viremia by HSV PCR and/or liver biopsy. Presence of viral Cowdry type A nuclear inclusion bodies, positive HSV immunohistochemical stains, HSV PCR, and electron microscopy if liver biopsy is performed aid in confirming the diagnosis.

Early treatment with high-dose acyclovir (10 mg/kg IV TID) is highly effective. Delay in treatment can result in lowered efficacy, and thus empiric treatment is recommended in cases with typical features of HSV hepatitis. Foscarnet can be used if there is concern about acyclovir resistance. Patients with fulminant liver failure should be carefully evaluated for liver transplantation although the 1 year posttransplant survival rate is around 43%, usually due to disseminated and uncontrolled HSV infection. Indefinite antiviral therapy is indicated to prevent recurrence following spontaneous resolution or transplant.

Epstein–Barr virus

EBV is the causative agent for infectious mononucleosis, with asymptomatic liver enzyme and lactate dehydrogenase elevations up

to three times the upper limits of normal occurring in 80% to 90% of cases. Clinical manifestations include fever, pharyngitis, lymphadenopathy, abdominal pain, hepatosplenomegaly, and, rarely, jaundice. The serum aminotransferases typically rise over 1 to 2 weeks, and, in most patients, the disease is self-limited with resolution of symptoms and normalization of enzymes over the subsequent 4 to 6 weeks. Severe hepatitis and fulminant hepatic failure are rare but have been reported.

Leukocytosis (predominance of lymphocytes and monocytes) and mild thrombocytopenia is common. EBV IgM antibodies peak early and can persist for months, after which EBV IgG develops. Although the Monospot is sensitive in detecting heterophile antibodies, it is not specific for EBV infection. EBV DNA quantification can be accomplished through PCR assays on blood or plasma. Liver biopsy is not usually indicated although in situ hybridization or PCR of the biopsy sample may be used to confirm the diagnosis. Treatment is largely supportive as no specific treatment exists. Acyclovir has been used without effect on symptoms or outcome. EBV may rarely cause chronic infection in immunocompetent patients. EBV infection is an important factor in the development of posttransplantation lymphoproliferative disease (PTLD) in transplant recipients.

Cytomegalovirus

CMV infection frequently involves the liver, most commonly with asymptomatic elevation of serum transaminases. It can be a result of a primary infection or reactivation of latent infection in an immunocompromised host. In immunocompetent children and adults, primary CMV infection is usually subclinical but may cause an illness that can mimic mononucleosis. The clinical course is typically mild and self-limited, but CMV has been implicated in hepatic granulomata, cholestatic hepatitis (mimicking primary sclerosing cholangitis), and even rare cases of fatal hepatic necrosis. CMV can be severe and even life-threatening in patients with impaired cellular immunity, due to disseminated infection.

Antibody testing is of low utility in immunocompromised patients and therefore CMV PCR is the most reliable and specific diagnostic test. Liver biopsy may be indicated and confirmatory in an immunocompromised patient or a transplant recipient when the characteristic multinucleated giant cells and owl-eye inclusions can be identified. No definite therapy is required in immunocompetent patients with mild CMV infection. In immunocompromised patients, effective therapies include ganciclovir or, alternatively, foscarnet or cidofovir if ganciclovir fails. Therapy should be continued until patients become aviremic and preferably maintained during the intense immunosuppressive period.

Parvovirus B19

Human parvovirus B19 is a small nonenveloped single-stranded DNA virus which is a rare (probably underdiagnosed) cause of acute hepatitis and liver failure in immunocompetent individuals. It is a common infection of childhood called *erythema infectiosum* or *fifth disease,* with up to 50% of adolescents developing parvovirus antibodies by age 15. The virus is transmitted via respiratory droplets, blood products, and solid organ transplantation. Adults can present with acute upper respiratory viral syndrome, arthropathy, and varying severity of bone marrow suppression and liver injury. Rare hematologic manifestations include pure red cell aplasia, pancytopenia, and hematopoietic failure, which are thought to be due to viral interaction with P-antigen. Although most case reports describe a lesser degree of elevation of transaminases (<2,000), levels of ALT >9,000 have also been reported. The pathogenic mechanisms involved in liver injury are unclear but may be due to caspase-mediated apoptosis from direct viral invasion. Diagnostic workup includes serum parvovirus B19 IgM, IgG, DNA, and liver biopsy. Bone marrow biopsy can show characteristic red cell aplasia and giant pro-normoblasts. There is no standard treatment, but there are several case reports describing the use of supportive treatments, including IV immunoglobulin (IVIG), tacrolimus, cyclosporine, mycophenolate mofetil, azathioprine, steroids, and plasmapheresis, with varying outcomes. Patients with fulminant hepatic failure require liver transplantation although there are limited data on the outcomes and hematopoietic recovery posttransplant. Recurrence of pure red cell aplasia after transplantation is approximately 10%, and prolonged courses of IVIG appear to be beneficial.

Miscellaneous viruses

Nonhepatotropic viruses such as hepatitis G (HGV), Zika, Ebola/Marburg, TTV, human herpesvirus (HHV-6, HHV-8), varicella zoster virus (VZV), adenovirus, and coronavirus can all cause acute hepatic inflammation resulting in mild to modest increase in transaminases. HGV, also known as GBV-C, is a single-stranded RNA virus which is mainly transmitted parenterally and has some genomic similarity to HCV. HGV is lymphotropic but not hepatotropic, and thus some authors debate its inclusion as a hepatitis virus. HGV coinfection in HIV-positive patients is associated with favorable outcomes, including lower levels of HIV viremia, higher CD4 count, better response to antiretroviral therapy, lower transmission rates, and 2.5-fold reduction in mortality compared to those who are not coinfected with HGV. TTV is a single-stranded DNA virus first isolated in 1997 as a cause of posttransfusion hepatitis, but current data suggest that TTV does not play a significant role in the genesis of acute or chronic liver disease. HHV-6 is associated with hepatic artery thrombosis, encephalitis, and sepsis, and HHV-8 is associated with development of Kaposi's sarcoma, especially in immunocompromised transplant recipients. Outbreaks of Ebola and Marburg viruses have been reported in individuals who traveled to West Africa. Icteric-hemorrhagic fevers with acute hepatitis have been reported with Dengue, Hanta, and yellow fever viruses, which typically present with multiorgan dysfunction and failure. Zika and Chikungunya viruses have not been associated with severe hepatitis to date. Similar to HGV and TTV, other

viruses such as Sanban, Yonban, and SEN viruses do not cause clinical hepatitis, and their role in human pathogenesis is controversial.

Suggested reading

Bhamidimarri KR, Park J, Dieterich D. Management of hepatitis B virus coinfection: HIV, hepatitis C virus, hepatitis D virus. *Curr Hepatitis Rep*. 2011;10(4):262–268.

Bhattarai N, Stapleton JT. GB virus C: The good boy virus? *Trends Microbiol*. 2012;20(3):124–130.

Deterding K, Grüner N, Buggish P, et al. Delayed versus immediate treatment for patients with acute hepatitis C: A randomised controlled non-inferiority trial. *Lancet Infect Dis*. 2013;13(6):497–506.

Doshani M, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Hepatitis A Vaccine for persons experiencing homelessness. *MMWR Morb Mortal Wkly Rep*. 2019;68(6):153–156.

Foster M, et al. Hepatitis A virus outbreaks associated with drug use and homelessness: California, Kentucky, Michigan, and Utah, 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(43):1208–1210.

Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. *Nat Rev Gastroenterol Hepatol*. 2013;10(9):553–562.

Jeong SH, Lee HS. Hepatitis A: Clinical manifestations and management. *Intervirology*. 2010;53(1):15–19.

Jindal A, Kumar M, Sarin SK. Management of acute hepatitis B and reactivation of hepatitis B. *Liver Int*. 2013;33(Suppl 1):164–175.

Jung YM, Park SJ, Kim JS, et al. Atypical manifestations of hepatitis A infection: A prospective, multicenter study in Korea. *J Med Virol*. 2010;82(8):1318–1326.

Koh C, et al. Pathogenesis of and new therapies for hepatitis D. *Gastroenterology*. 2019;156(2): 461–476 e461.

McKeating C, et al. Progression from acute to chronic hepatitis B is more common in older adults. *Ulster Med J*. 2018;87(3):177–180.

Norvell JP, Blei AT, Jovanovic BD, Levitsky J. Herpes simplex virus hepatitis: An analysis of the published literature and institutional cases. *Liver Transpl*. 2007;13(10):1428–1434.

Popping S, et al. Early treatment of acute hepatitis C infection is cost-effective in HIV-infected men-who-have-sex-with-men. *PLoS One*. 2019;14(1):e0210179.

Smedile A, Rizzetto M. HDV: Thirty years later. *Dig Liver Dis*. 2011;43(Suppl 1):S15–S18.

Todesco E, et al. High clustering of acute HCV infections and high rate of associated STIs among Parisian HIV-positive male patients. *Int J Antimicrob Agents*. 2019.

Xiong QF, et al. Early predictors of acute hepatitis B progression to liver failure. *PLoS One*. 2018;13(7):e0201049.

Young NS, Brown KE. Parvovirus B19. *N Engl J Med*. 2004;350(6):586–597.

44

Chronic viral hepatitis

Michelle E. Freshman and Lawrence S. Friedman

Chronic hepatitis is defined as necroinflammation of the liver of more than 3 to 6 months' duration, demonstrated by persistently elevated serum aminotransferase levels and associated with characteristic histologic findings. The causes of chronic hepatitis include hepatitis B, C, and D viruses (HBV, HCV, and HDV) as well as noninfectious disorders, including nonalcoholic steatohepatitis, autoimmune hepatitis, hepatitis following alcohol or medication exposure (e.g., isoniazid or nitrofurantoin), Wilson disease, α_1-antitrypsin deficiency, and, rarely, celiac disease. Hepatitis A virus does not cause chronic hepatitis, but hepatitis E virus may rarely lead to chronic hepatitis in immunosuppressed persons or transplant recipients. Chronic hepatitis is characterized on the basis of etiology; grade of portal, periportal, and lobular inflammation (minimal, mild, moderate, or severe); and stage of fibrosis (none, mild, moderate, severe, cirrhosis).

In the absence of advanced cirrhosis, patients are often asymptomatic or have mild, nonspecific symptoms. Infection caused by HBV may be associated with arthritis-dermatitis and, rarely, polyarteritis nodosa, glomerulonephritis, or mixed cryoglobulinemia. HCV is a more common pathogenetic factor in mixed cryoglobulinemia as well as membranoproliferative glomerulonephritis and may be related to lichen planus, autoimmune thyroiditis, lymphocytic sialadenitis, idiopathic pulmonary fibrosis, sporadic porphyria cutanea tarda, and monoclonal gammopathies. HCV infection confers a 20% to 30% increased risk of non-Hodgkin B-cell lymphoma and may induce insulin resistance (which in turn increases the risk of hepatic fibrosis); moreover, the risk of type 2 diabetes mellitus and cardiovascular disease is increased in persons with chronic hepatitis C. Hepatic steatosis is a particular feature of infection with HCV genotype 3 and may also occur in patients infected with other HCV genotypes who have risk factors for fatty liver. On the other hand, chronic HCV infection is associated with a decrease in serum cholesterol and low-density lipoprotein levels.

Chronic hepatitis B

Chronic hepatitis B affects 248 million people worldwide (Figure 44.1). Two billion persons overall have been infected; endemic areas include Southeast Asia (excluding Japan), China, and sub-Saharan Africa. In the United States, up to 2.2 million (predominantly males) have HBV infection. Chronic hepatitis B may be identified as a continuation of acute hepatitis B or by repeated detection of hepatitis B surface antigen (HBsAg) in serum, often in a person with elevated serum aminotransferase levels (Table 44.1).

Five phases of chronic HBV infection are recognized (Figure 44.2 and Table 44.2), historically designated as the immune tolerant phase, immune active (or immune clearance) phase, inactive HBsAg carrier state, reactivated chronic hepatitis B phase, and HBsAg-negative phase. Revised nomenclature for the five stages are hepatitis B e antigen (HBeAg)-positive chronic HBV infection, HBeAg-positive chronic hepatitis B, HBeAg-negative chronic HBV infection, HBeAg-negative chronic hepatitis B, and the HBsAg-negative phase (functional cure).

In *HBeAg-positive chronic HBV infection*, HBeAg and HBV DNA are present in serum and indicative of active viral replication, and serum aminotransferase levels are normal, with little necroinflammation in the

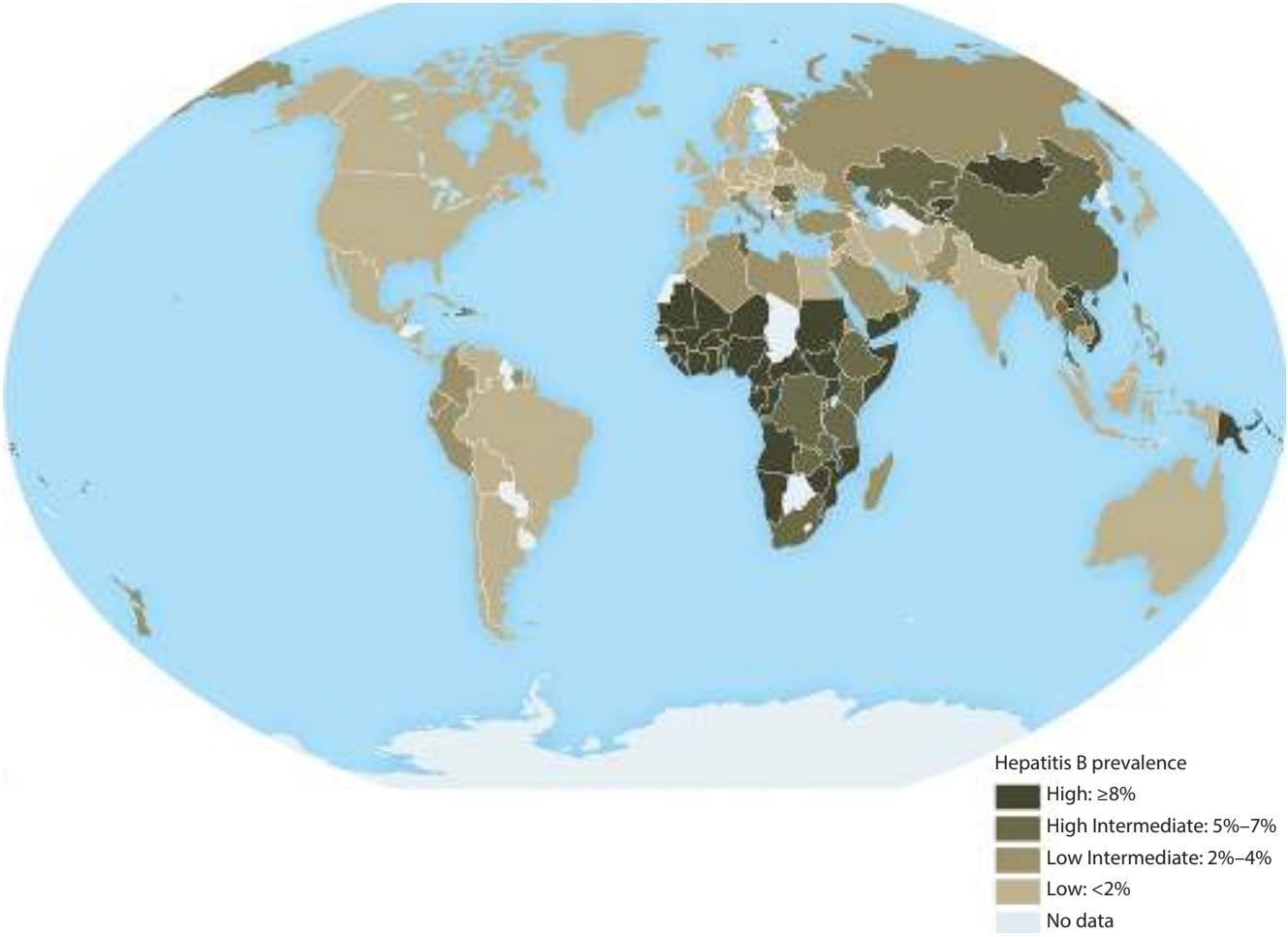

FIGURE 44.1 World map showing the prevalence of the chronic hepatitis B virus infection in low- (very light brown, <2%), low intermediate- (light green, 2–4%), low intermediate- (darker green, 5–7%), and high- (darkest green, ≥8%) prevalence areas.
Adapted from Centers for Disease Control website. https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/hepatitis-b

liver. This phase is common in infants and young children whose immature immune system fails to mount an immune response to HBV.

Persons with HBeAg-positive chronic HBV infection and those who acquire HBV infection later in life may enter an immune active phase, or *HBeAg-positive chronic hepatitis B*, in which aminotransferase levels are elevated and necroinflammation is present in the liver, with a risk of progression to cirrhosis (at a rate of 2–5.5% per year) and of hepatocellular carcinoma (at a rate of >2% per year in those with cirrhosis); low-level immunoglobulin M antibody to hepatitis B core antigen (immunoglobulin M (IgM) anti-HBc) is present in serum but below the detection assay of the standard serologic assay in about 70%. Seroconversion with the loss of HBeAg and the appearance of anti-HBe occurs at the end of this phase. For those persons who seroconvert after age 40, the risk of cirrhosis and hepatocellular carcinoma is greater than in those who seroconverted at a younger age.

Persons with *HBeAg-negative chronic HBV infection* have experienced biochemical improvement following immune clearance. This improvement coincides with disappearance of HBeAg and reduced HBV DNA levels ($<10^5$ copies/mL, or <20,000 international units [IU]/mL) in serum, appearance of antibody to hepatitis B e antigen (anti-HBe), and integration of the HBV genome into the host genome in infected hepatocytes. In the research setting, detection in serum of a hepatitis B core-related antigen correlates with intrahepatic covalently closed circular DNA, a marker of transcriptional activity. Patients in this phase are at a low risk for cirrhosis (if it has not already developed) and hepatocellular carcinoma, and those with persistently normal serum aminotransferase levels infrequently have histologically significant liver disease, especially if the serum HBsAg level (not generally measured in practice) is low.

HBeAg-negative chronic hepatitis B ("reactivation") may result from infection by a pre-core mutant of HBV or spontaneous mutation of the pre-core or core promoter region of the HBV genome during the course of chronic hepatitis caused by wild-type HBV. HBeAg-negative chronic hepatitis B accounts for <10% of cases of chronic hepatitis B in the United States, up to 50% in southeast Asia, and up to 90% in Mediterranean countries, reflecting in part differences in the frequencies of HBV genotypes. In reactivated chronic hepatitis B, there is a rise in serum HBV DNA levels and possible progression to cirrhosis (at a rate of 8–10% per year),

TABLE 44.1 **INTERPRETATION OF SEROLOGIC TESTS FOR HEPATITIS B VIRUS (HBV) INFECTION**

	Susceptible	Immune due to vaccination	Immune due to natural infection	Acute infection	Chronic infection	Various interpretations[a]
HBsAg	–	–	–	+	+	–
Anti–HBc	–	–	+	+	+	+
IgM anti–HBc	–	–	–	+	–[b]	–
HBeAg	–	–	–	+	±	–
Anti–HBe	–	–	±	–	±	±
Anti–HBs	–	+	+ ≥10 mIU/mL[c]	–	–	–

[a] (1) Recovering from acute HBV infection, (2) chronically infected with an undetectable level of HBsAg in serum, (3) susceptible with a false-positive anti-HBc result, (4) distantly immune and the test is not sensitive enough to detect a very low viral levels of anti-HBs in serum.
[b] IgM anti-HBc may be positive (in low titers) in some persons with chronic hepatitis B.
[c] Threshold level of anti-HBs antibody concentration considered adequate for immunization protection.
Anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; IgM anti-HBc, IgM antibody to hepatitis B core antigen; mIU/mL, milli-international units per milliliter.
Adapted from http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/hepb.pdf, accessed 1/28/19.

particularly when additional mutations in the core gene of HBV are present. Risk factors for reactivation include male sex and HBV genotype C as well as immunosuppression. Treatment of HCV infection with direct-acting antiviral agents (see later discussion) has been reported to lead to instances of HBV reactivation. For persons who have serum HBsAg concentrations of 1,000 IU/mL or more, the risk of cirrhosis and hepatocellular carcinoma is increased.

In persons with either HBeAg-positive or HBeAg-negative chronic hepatitis B, the risk of cirrhosis and of hepatocellular carcinoma correlates with the serum HBV DNA level. Other risk factors include advanced age, male sex, alcohol use, cigarette smoking, HBV genotype C, and coinfection with HCV or HDV. HIV coinfection is also associated with an increased frequency of cirrhosis when the CD4 count is low.

Occasional infected persons reach the *HBsAg-negative phase*, or functional cure, in which anti-HBe remains the only serologic marker of HBV infection, serum ALT levels are normal, and HBV DNA is undetectable in serum but remains present in the liver. HBsAg seroclearance (0.7–2.3%) is associated with a negligible risk of cirrhosis in noncirrhotic patients and a substantially decreased risk of hepatocellular carcinoma, including in persons with cirrhosis.

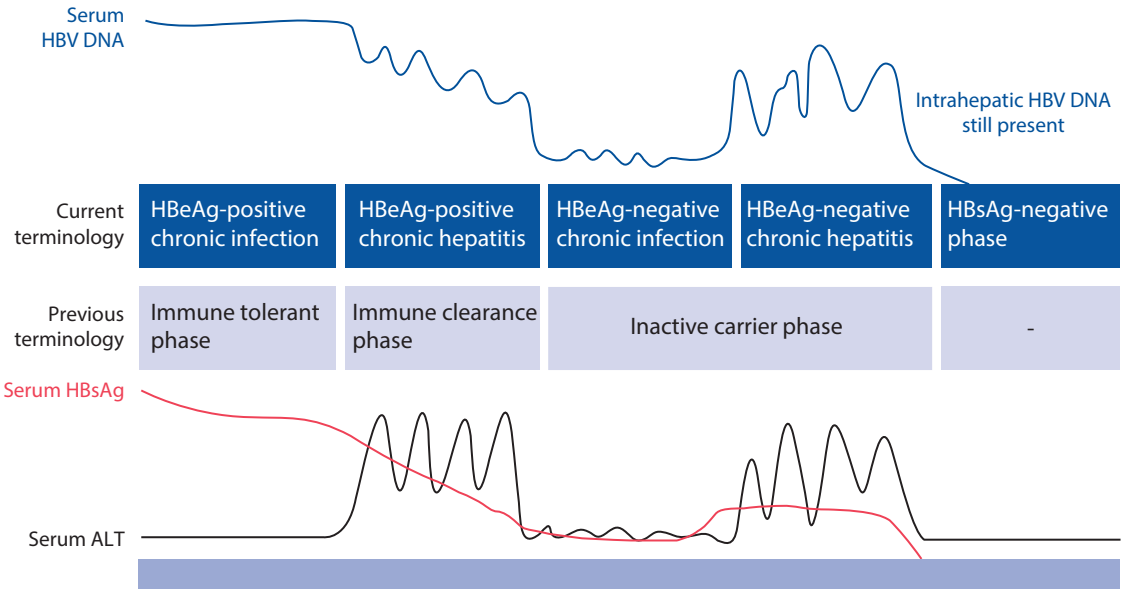

FIGURE 44.2 Phases of course of hepatitis B infection.
Adapted from Seto WK, et al. Chronic hepatitis B virus infection. *Lancet*. 2018 Nov 24;392(10161):2313–2324.

TABLE 44.2 **FIVE PHASES OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND ASSOCIATED BIOCHEMICAL, SEROLOGIC, AND HISTOLOGIC FINDINGS**

Phase (New terminology)	Phase (Old terminology)	ALT	HbeAg	Anti–HBe	HBV DNA (IU/mL)	Liver histology	Natural history
HBeAg-positive chronic HBV infection	Immune tolerant	Normal	+	–	≥20,000	Minimal inflammation	Low risk of progression to advanced liver disease
HBeAg-positive chronic hepatitis B	Immune active (Immune clearance)	Elevated (fluctuating)	+	+/–	≥20,000 (fluctuating)	Variable inflammation +/– fibrosis	Associated with hepatitis flares
HBeAg-negative chronic HBV infection	Inactive HBsAg carrier state	Normal	–	+	<2,000	Minimal inflammation and liver damage	Low risk of advanced liver disease HBsAg loss in 1% per year; 10–20% have reactivation of HBV replication after many years
HBeAg-positive chronic hepatitis B	Reactivated chronic hepatitis B	Elevated	–	+	2,000–20,000 (may be higher)	Inflammation and often significant fibrosis	High risk of progression to advanced liver disease
HBsAg-negative phase	HBsAg-negative	Normal	–	+/–	Undetectable	Minimal inflammation if prolonged viral suppression	Low risk of advanced liver disease if prolonged viral suppression

Abbreviations: ALT = serum alanine aminotransferase level, anti-HBe = antibody to hepatitis B e antigen, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, IU = international units.

Treatment

Patients with active viral replication (HBeAg, HBV DNA [$\geq 10^5$ copies/mL, or ≥20,000 IU/mL], and elevated aminotransferase levels in serum) may be treated with a nucleoside or nucleotide analog or with pegylated interferon, although interferon is rarely used now (Figure 44.3). Nucleoside and nucleotide analogs are preferred because they are better tolerated and can be taken orally. For patients who are negative for HBeAg, the threshold for treatment is a serum HBV DNA level of 10^4 copies/mL, or 2000 IU/mL (Figure 44.3). If the threshold HBV DNA level for treatment is met but the serum ALT level is normal, treatment may still be considered in patients older than 35 to 40 years if liver biopsy or a noninvasive assessment of liver fibrosis demonstrates a fibrosis stage of 2 of 4 (moderate) or higher. For those who do not meet standard criteria but are positive for HBeAg, are older than 30 years of age, have a family history of hepatocellular carcinoma, or have extrahepatic manifestations, the European Association for the Study of the Liver advocates treatment. Therapy is aimed at reducing and maintaining the serum HBV DNA level at the lowest possible levels, normalization of the serum ALT level, and histologic improvement. An additional goal in HBeAg-positive patients is seroconversion to anti-HBe, and some responders eventually clear HBsAg (see Figure 44.2 and Box 44.1). Although nucleoside and nucleotide analogs generally have been discontinued 6 to 12 months after HBeAg-to-anti-HBe seroconversion, some patients (especially Asian patients) serorevert to HBeAg after discontinuation, have a rise in HBV DNA levels and recurrence of hepatitis activity, and require long-term therapy, which also is required when seroconversion does not occur and in patients with cirrhosis (at least until HBsAg clears and possibly indefinitely).

BOX 44.1

Goals of therapy for chronic hepatitis B virus (HBV) infection

Sustained suppression of HBV replication
HBV DNA undetectable in serum
HBeAg to anti-HBe seroconversion
HBsAg to anti-HBs seroconversion

Remission of liver disease
Normalization of serum ALT levels
Improvement in liver histology

Improvement in clinical outcome
Prevention of liver failure and hepatocellular carcinoma
Improved survival

Abbreviations: ALT = serum alanine aminotransferase level, anti-HBe = antibody to hepatitis B e antigen, anti-HBs = antibody to hepatitis B surface antigen, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen.

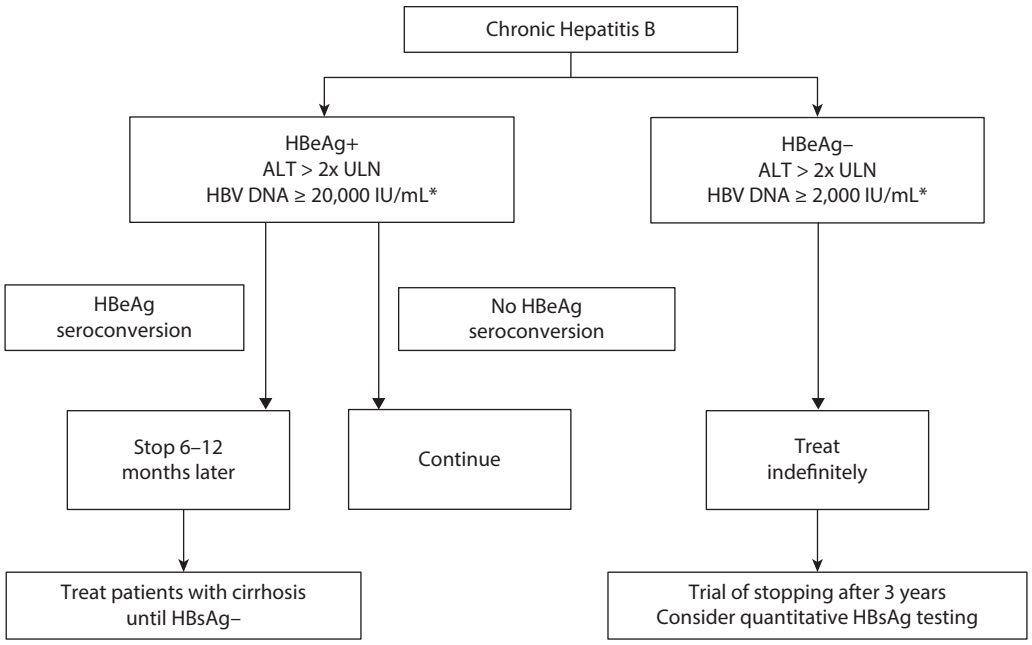

FIGURE 44.3 Indications for treatment and treatment endpoints in HBeAg-positive and HBeAg-negative persons. The following patients not fulfilling treatment indications can be considered for treatment: HBeAg-positive and >30 years of age, family history of hepatocellular carcinoma, and extrahepatic manifestations. Fibrosis stage can be assessed by noninvasive methods or liver biopsy.

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ULN, upper limit of normal.

Patients with HBeAg-negative chronic hepatitis B also generally require long-term therapy because relapse is frequent when therapy is stopped; a low serum HBsAg level identifies patients at low risk for relapse and in whom HBsAg is more likely to clear if therapy is stopped after 3 years than if therapy is continued indefinitely.

The available nucleoside and nucleotide analogs—entecavir, tenofovir, lamivudine, adefovir, and telbivudine—differ in efficacy and rates of resistance (Table 44.3); however, in HBeAg-positive patients, they all achieve an HBeAg-to-anti-HBe seroconversion rate of about 20% at 1 year, with higher rates after more prolonged therapy (Box 44.2). The preferred first-line oral agents are entecavir and tenofovir. Entecavir is rarely associated with resistance unless a patient is already resistant to lamivudine. The daily dose is 0.5 mg orally for patients not resistant to lamivudine and 1 mg for patients who previously became resistant to lamivudine. Suppression of HBV DNA in serum occurs in nearly all treated patients (>95%), and histologic improvement is observed in 70% of patients after at least 5 years of treatment. Entecavir has been reported infrequently to cause lactic acidosis when used in patients with decompensated cirrhosis.

Tenofovir disoproxil fumarate, 300 mg/d orally, is equally effective and is used as a first-line agent or when resistance to a nucleoside analog has developed. Like entecavir, tenofovir has a low rate of resistance when used as initial therapy. Long-term use may lead to an elevated serum creatinine level and reduced serum phosphate level (Fanconi-like syndrome) that is reversible with discontinuation of the drug. Tenofovir alafenamide, 25 mg/d orally, is an alternative formulation of tenofovir that was approved by the US Food and Drug Administration (FDA) in 2016 and may be associated with a lower rate of renal and bone toxicity than tenofovir disoproxil fumarate.

The first available nucleoside analog was lamivudine, 100 mg/d orally, which is no longer considered first-line therapy in the United States but may be used in countries in which cost is a deciding factor. By the end of 1 year of therapy with lamivudine, however, 15% to 30% of responders experience a relapse (and occasionally frank decompensation) as a result of a mutation in the polymerase gene (the YMDD motif) of HBV DNA that confers resistance to lamivudine. The rate of resistance reaches 70% by 5 years of therapy. Adefovir dipivoxil has activity against wild-type and lamivudine-resistant HBV but is the least potent of the oral antiviral agents for HBV and is rarely if ever used now. The standard dose is 10 mg orally once a day for at least 1 year. As with lamivudine, only a small number of patients achieve sustained suppression of HBV replication with adefovir, and long-term suppressive therapy is often required. Resistance to adefovir occurs in up to 29% of patients treated for 5 years. Patients with underlying kidney dysfunction are at risk for nephrotoxicity from adefovir. Telbivudine, given in a daily dose of 600 mg orally, is more potent than either lamivudine or adefovir but, like them, is associated with resistance, particularly in patients who are resistant to lamivudine. Elevated serum creatine kinase levels are common in patients treated with telbivudine (see Table 44.3).

Nucleoside and nucleotide analogs are well tolerated even in patients with decompensated cirrhosis (for whom the treatment threshold may be an HBV DNA level of $<10^4$ copies/mL and therapy should be continued indefinitely) and may be effective in

TABLE 44.3 **DRUGS USED TO TREAT CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THEIR ADVANTAGES AND DISADVANTAGES**

Agent/Dose	**Entecavir** (nucleoside analog) 0.5 mg/d (1.0 mg/d in lamuvidine-resistant patients)	**Tenofovir disoproxil** (nucleotide analog) 300 mg/d	**Tenofovir alafenamide** (nucleotide analog) 25 mg/d	**Adefovir dipivoxil** (nucleotide analog) 10 mg/d	**Lamivudine** (nucleoside analog) 100 mg/d	**Telbivudine** (nucleoside analog) 600 mg/d	**Peginterferon alfa-2a** 180 μg SC weekly for 48 weeks
Advantages	Oral Negligible side effects More potent than other oral agents; little resistance (requires ≥3 mutations to confer resistance)	Oral Negligible side effects More potent than other oral agents; no in vivo resistance seen after 8 years of use	Oral Negligible side effects; more potent than other oral agents; low chance of resistance; approved for ESRD +/- dialysis; pregnancy risk unknown	Oral Negligible side effects Effective against lamivudine-resistant mutants	Oral Negligible side effects Has been used in pregnancy and prior to chemotherapy	Oral Negligible side effects Effective against lamivudine-resistant mutants	Finite duration Durable response No resistant mutants HBsAg-to-anti-HBs seroconversion, common in responders
Disadvantages	Indefinite duration of therapy in incomplete responders Risk of lactic acidosis in patients with decompensated cirrhosis; hepatomegaly 10% cross-resistance with lamivudine; 94% undetectable at 5 years; for nucleoside-naïve patients, 1.2% resistance at 5 years	Indefinite duration of therapy in incomplete responders Renal toxicity in higher doses; caution in underlying kidney dysfunction; risk of Franconi syndrome Risk of lactic acidosis, hepatomegaly, gastrointestinal distress, rash, itching, osteopenia Negligible resistance as initial therapy (1 treatment naïve case, 2018)	Indefinite duration of therapy in incomplete responders Renal toxicity much less likely than TD; caution in new onset kidney dysfunction; risk of Franconi syndrome Risk of lactic acidosis, hepatomegaly, gastrointestinal distress, rash, itching; reduced BMD, much less so than TD (long-term data unavailable) Presumed negligible resistance as initial therapy	Indefinite duration of therapy in incomplete responders Risk of lactic acidosis, hepatomegaly Renal toxicity in higher doses; hypophosphatemia (Franconi-like syndrome); pancreatitis Risk of lower bone mineral density, SJS, TEN Resistant mutants (29% at 5 years); relatively weak agent when used alone; used as add-on to lamivudine or telbivudine	Indefinite duration of therapy in incomplete responders Nausea, headaches; malaise and fatigue Risk of lactic acidosis, pancreatitis High rate of resistant mutants (>70% by 5 years); considered for hepatic decompensation or HCC	Indefinite duration of therapy in incomplete responders Risk of elevated CK level Some cross-resistance with lamivudine (up to 25% in HBeAg-positive and 11% in HBeAg- negative patients at 2 years)	Injection Side effects (see Table 44.6) Up to 60% sustainability of response over 4 years of therapy in patients with HBeAg-negative chronic hepatitis B; not appropriate for decompensated cirrhosis; 20-50% clearance of HDV

Abbreviations: Anti-HBs = antibody to hepatitis B surface antigen, BMD = bone mineral density, CK = creatine kinase, ESRD = end-stage renal disease, HBeAg = hepatitis B e antigen HBsAg = hepatitis B surface antigen, HCC = hepatocellular carcinoma, SC = subcutaneously, SJS = Stevens-Johnson syndrome, TD = tenofovir disoproxil, TEN = toxic epidermal necrolysis.

BOX 44.2

Features of therapy with nucleoside and nucleotide analogs for chronic hepatitis virus (HBV) infection

HBeAg to anti-HBe seroconversion in 12–21% at 1 year
HBeAg to anti-HBe seroconversion increases over time
Serum ALT level predicts HBeAg loss
HBeAg-negative patients are more likely than HBeAg-positive patients to become HBV DNA-negative, but response is much less durable, typically requires ongoing therapy
Liver histology improves
Degree of viral suppression varies among drugs
Rate of serum HBsAg loss is low (<1%) after 1 year
Resistance profiles vary

Abbreviations: ALT = serum alanine aminotransferase level, anti-HBe = antibody to hepatitis B e antigen, anti-HBs = antibody to hepatitis B surface antigen hepatitis B virus, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen.

patients with rapidly progressive hepatitis B ("fibrosing cholestatic hepatitis") following organ transplantation. Combined use of a nucleoside and nucleotide analog or of peginterferon and a nucleoside or nucleotide analog has not been shown convincingly to have a substantial advantage over the use of one drug alone.

Nucleoside analogs are also recommended for inactive HBV carriers (and those positive only for anti-HBc) prior to the initiation of immunosuppressive therapy (including rituximab or an anti-tumor necrosis factor antibody) or cancer chemotherapy to prevent reactivation. In patients infected with both HBV and HIV, antiretroviral therapy, including two drugs active against both viruses (e.g., tenofovir plus lamivudine or emtricitabine), has been recommended when treatment of HIV infection is indicated. Tenofovir, telbivudine, and lamivudine have been shown to be safe in pregnant women. Antiviral therapy has been recommended, beginning in the third trimester, when the mother's serum HBV DNA level is ≥200,000 IU/mL to reduce levels at the time of delivery. Prophylactic tenofovir disoproxil fumarate has been shown to be cost-effective if the rate of compliance with hepatitis B vaccination in a population is at least 98%.

Peginterferon alfa-2a is still an alternative to the oral agents in selected cases. A dose of 180 μg subcutaneously once weekly for 48 weeks leads to sustained normalization of aminotransferase levels, disappearance of HBeAg and HBV DNA from serum, and appearance of anti-HBe in up to 40% of treated patients and results in improved survival. A response is most likely in patients with a low baseline HBV DNA level and high aminotransferase levels and is more likely in those who are infected with HBV genotype A than with other genotypes (especially genotype D) and who have certain favorable polymorphisms of the interferon lambda (*IFNL3*), also known as the interleukin 28B (*IL28B*) gene. Moreover, many complete responders eventually clear HBsAg and develop antibody to hepatitis B surface antigen (anti-HBs) in serum and are thus cured. Relapses are uncommon in complete responders who seroconvert from HBeAg to anti-HBe. Peginterferon may be considered in order to avoid long-term therapy with an oral agent, as in young women who may want to become pregnant in the future. Patients with HBeAg-negative chronic hepatitis B have a response rate of 60% after 48 weeks of therapy with peginterferon, but the response may not be durable once peginterferon is stopped. A rapid decline in serum HBsAg titers predicts a sustained response and ultimate clearance of HBsAg. The response to peginterferon is poor in patients with HIV coinfection. Interferon is associated with a variety of side effects and is contraindicated in persons with decompensated cirrhosis.

New treatments with novel modes of action and the potential to increase the chance of a functional cure are under study. These include HBV entry inhibitors, agents that target covalently closed circular DNA, inhibitors of gene expression, and compounds that target nucleocapsid assembly.

Chronic hepatitis D

HDV (the delta agent) is a defective RNA agent that only infects (either concurrently or sequentially) persons also infected with HBV. Acute hepatitis D infection superimposed on chronic HBV infection may result in severe chronic hepatitis, which may progress rapidly to cirrhosis and may be fatal. HBsAg is required only for assembly but not replication of HDV.

Among HBV carriers, the estimated rate of HDV coinfection worldwide is as high as 13%. Unlike HBV, perinatal exposure is not a significant route of HDV transmission. The prevalence of HDV infection is reported to be highest in the Mediterranean region, the Middle East, central and northern Asia, west and central Africa, Taiwan, and the Amazon basin, particularly in the western Amazon region of South America, where the frequency of coinfection is 32%. Highly endemic regions include Cameroon, the Central African Republic, and Gabon. Patterns of immigration and intravenous (IV) drug use appear to be contributing to increasing rates of HDV in the Mediterranean region, whereas improved hepatitis B vaccination rates and the use of barrier protection against sexual transmission have been mitigating factors. In survey data among HBsAg-positive persons who inject drugs in Baltimore and San Francisco, HDV infection rates have been as high as 50% and 36%, respectively.

Chronic HDV infection is diagnosed by the detection of IgM and IgG anti-HDV in serum. IgM anti-HDV is often detectable in high titers in patients with chronic HDV infection, and levels tend to parallel the activity of liver disease; therefore, it is frequently regarded as a marker of serious liver damage. A decline in IgM anti-HDV levels may indicate either a decline in disease activity or resolution of HDV infection. In patients in whom HDV infection resolves, IgG anti-HDV may remain detectable in serum, but levels are low. IgG anti-HDV is not a protective antibody. The presence of HDV RNA in serum distinguishes chronic hepatitis D from recovery. In the late phase of chronic HDV infection, declining serum HDV RNA levels may be accompanied by an increase in serum HBV DNA levels (Table 44.4).

The majority of patients with chronic HDV infection demonstrate an initial active hepatitis that progresses rapidly to cirrhosis, after which the hepatitis becomes inactive and runs a more indolent course. Patients with long-standing chronic hepatitis D and B often have inactive cirrhosis and are at risk for decompensation and hepatocellular

TABLE 44.4 **SEROLOGIC MARKERS IN HEPATITIS D VIRUS (HDV) INFECTION**

Serologic marker	Acute HBV-HDV coinfection	Acute HDV superinfection	Chronic HDV infection
HbsAg	Positive	Positive	Positive
IgM anti-HBc	Positive	Negative	Negative
HDAg	Positive (early and transient)	Positive (early and transient)	Negative
Total anti-HDV	Weakly positive (transient low titers)	Positive (with rising titers)	Positive (with high sustained titers)
IgM anti-HDV	Weakly positive (transient low titers; may be the only marker of infection)	Positive (with rising titers)	Positive (with high sustained titers)
HDV RNA	Positive (early and transient)	Positive (early and persistent)	Positive (usually persistent)

Abbreviations: Anti-HDV = antibody to HDV, HBsAg = hepatitis B surface antigen, HDAg = hepatitis D antigen.
From Ghany MG. Hepatitis D. In: Feldman M, Friedman LS, Brandt LJ, eds., Wilcox CM, Chung RT, Rubin DR, assoc. eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management*, 11th ed. Philadelphia: Elsevier 2021;1283-91.

carcinoma. Of the eight known HDV genotypes, some are associated with a more severe outcomes (e.g., HDV genotypes 1, 3, and 4), whereas for others (e.g., HDV genotypes 5–8) natural history data are lacking. HDV genotype 3, which has been associated with outbreaks of severe acute hepatitis and an increased rate of acute liver failure and death, may be more responsive to peginterferon therapy than other genotypes (see later discussion). Durable suppression of HDV RNA has been shown to be associated with a reduced risk of liver-related complications (hepatic decompensation, hepatocellular carcinoma, liver transplantation, and liver-related death; see later discussion).

Treatment

In persons with chronic hepatitis D, peginterferon alfa-2b, 1.5 μg/kg/wk for 48 weeks, may lead to normalization of serum aminotransferase levels, histologic improvement, and elimination of HDV RNA from serum in 20% to 50% of patients, but subsequent relapse may occur and tolerance is poor. Nucleoside and nucleotide analogs are generally not effective in treating chronic hepatitis D; prenylation inhibitors (e.g., lonafarnib) and HBV-HDV–specific receptor blockers (e.g., bulevirtide) are under study, as are a variety of targeted immune system inhibitors.

Chronic hepatitis C

Chronic hepatitis C develops in up to 85% of patients with acute hepatitis C. It is clinically indistinguishable from chronic hepatitis due to other causes and may be the most common type. Worldwide, 71 million people (about 1% of the population), are infected with HCV, with 1.8% of the US population infected, although most are unaware they have it. In 2005, the peak prevalence (about 2.7%) in the United States was in persons 55 to 64 years of age. As a result, it is recommended that all persons born between 1945 and 1965 be tested for anti-HCV. Coincident with the aging of the population with untreated hepatitis C, disease-related mortality has accelerated since 2003; however, this trend is likely to slow by 2030 due to effective treatment options (see later discussion). In the United States, Australia, and other developed countries, peak prevalence is in persons 40 to 49 years of age, and analysis of risk factors suggests that most HCV transmission occurred between the mid-1980s and the mid-1990s, through injection drug use. The frequency of HCV infection in persons who inject drugs (PWID) ranges from 57% to 90%, and the majority of PWID become anti-HCV positive within 6 months of initiating injection drug use with shared needles.

In approximately 40% of cases with chronic HCV infection, serum aminotransferase levels are persistently normal. The diagnosis is confirmed by detection of anti-HCV by enzyme immunoassay (EIA). In rare cases of suspected chronic hepatitis C but a negative EIA, the diagnosis is made by detection of HCV RNA through polymerase chain reaction (PCR) testing.

Progression to cirrhosis occurs in 20% of affected persons after 20 years, with an increased risk in men, those who drink >50 g of alcohol daily, and those who acquire HCV infection after 40 years of age. The rate of progression of hepatic fibrosis accelerates after age 50, and cirrhosis has been predicted to develop in most patients with chronic hepatitis C by about 65 years of age, irrespective of the age at infection. Blacks have a higher rate of chronic HCV infection, but lower rates of fibrosis progression and response to therapy, than whites. Immunosuppressed persons—including patients with hypogammaglobulinemia or HIV infection with a low CD4 count or those receiving immunosuppressants—appear to progress more rapidly to cirrhosis than immunocompetent persons with chronic hepatitis C. Tobacco and cannabis smoking and hepatic steatosis also appear to promote progression of fibrosis, but coffee consumption appears to slow progression. Persons with chronic hepatitis C and persistently normal serum aminotransferase levels usually have mild chronic hepatitis with slow or absent progression to cirrhosis; however, cirrhosis is present in 10% of these patients. Serum fibrosis testing (e.g., FibroSure) or elastography (by ultrasound or magnetic resonance to measure liver stiffness) may be used to suggest the absence of fibrosis or presence of cirrhosis. Overall, chronic hepatitis C is responsible for approximately 25% of cases of hepatocellular carcinoma worldwide.

Treatment

The introduction of direct-acting and host-targeting antiviral agents has rapidly expanded the therapeutic armamentarium against HCV (Table 44.5 and Table 44.6). Standard therapy for HCV

TABLE 44.5 **RECOMMENDED FDA-APPROVED ORAL DIRECT-ACTING ANTIVIRAL AGENTS FOR HCV INFECTION (IN ALPHABETICAL ORDER WITHIN CLASS).**[a]

NS 3/4A Protease Inhibitors			
Glecaprevir	[a–f]	300 mg orally once daily	Used with pibrentasvir +/− ribavirin
Grazoprevir	[a, d]	100 mg orally once daily	Used with elbasvir[d]
Paritaprevir	[a, d]	150 mg orally once daily	Used with ombitasvir and dasabuvir; ritonavir (100 mg) boosted[c]; for genotype 1b with cirrhosis and genotype 1a, used with ribavirin. Used in combination with omitasvir, ritonavir boosting, and ribavirin for genotype 4.[f]
Simeprevir	[a, d]	150 mg orally once daily	Used with sofosbuvir
Voxilaprevir	[a–f]	100 mg orally once daily	Used with sofosbuvir and velpatasvir[g]
NS5A Inhibitors			
Daclatasvir[h]	[a–f]	60 mg orally once daily	Used with sofosbuvir (genotypes 1–6, +/− ribavirin depending on presence of cirrhosis) or with asunaprevir (not available in US)
Elbasvir	[a–f]	50 mg orally once daily	Used with grazoprevir
Ledipasvir	[a, d–f]	90 mg orally once daily	Used with sofosbuvir
Ombitasvir	[a, d]	25 mg orally once daily	Used with paritaprevir (ritonavir boosted) +/− dasabuvir and +/− ribavirin as per paritaprevir above
Pibrentasvir	[a–f]	120 mg orally once daily	Used with glecaprevir +/− ribavirin
Velpatasvir	[a–f]	100 mg orally once daily	Used with sofosbuvir.[j] May be used with sofosbuvir and voxilaprevir.
NS5B Nucleos(t)ide Polymerase Inhibitor			
Sofosbuvir	[a–f]	400 g orally once daily	Used alone (genotypes 2 and 3) or with simeprevir (genotypes 1,3, 4) or with velpatasvir (all genotypes) or with velpatasvir and voxilaprevir (all genotypes).
NS5B Non-Nucleos(t)ide Polymerase Inhibitor			
Dasabuvir	[a, d]	250 mg orally twice daily	Used with paritaprevir (ritonavir boosted) and ombitasvir +/− ribavirin as per paritaprevir above

[a] Regimen approved by the FDA as of early 2019.
[b] The preferred regimen and duration of treatment may vary depending on HCV genotype, presence or absence of cirrhosis or chronic kidney disease, or nonresponse to prior therapy for HCV infection. In selected cases, testing for resistance-associated substitutions may be considered.
[c] Marketed as Mavyret (AbbVie).
[d] Marketed as Zepatier (Merck).
[e] Marketed as Viekira Pak and Viekira XR (AbbVie).
[f] Marketed as Technivie (AbbVie).
[g] Marketed as Vosevi (Gilead Sciences).
[h] Approved by the FDA for use with sofosbuvir in HCV genotypes 1 and 3 infection.
[i] Marketed as Harvoni (Gilead Sciences).
[j] Marketed as Epclusa (Gilead Sciences).

infection from the late 1990s to the early 2010s was a combination of peginterferon plus ribavirin, and ribavirin continues to be used occasionally in some all-oral regimens. Sustained virologic response rates (negative HCV RNA in serum at 24 weeks after completion of therapy) for peginterferon plus ribavirin were 45% in patients with HCV genotype 1 infection and 70% to 80% in those with genotype 2 or 3 infection. Response of genotype 1 infection to peginterferon plus ribavirin was associated most strongly with the CC genotype of the *IFNL3* gene, with sustained response rates as high as 80%, compared with 40% for the CT genotype and 30% for the TT genotype. Higher rates of response were achieved in persons infected with HCV genotype 1 when a first-generation direct-acting antiviral agent—boceprevir or telaprevir (agents no longer available in the United States), nonstructural (NS) 3/4A serine protease inhibitors—was added to peginterferon plus ribavirin. Sustained response rates were as high as 75% for HCV genotype 1 with a standard three-drug regimen. With the addition of the protease inhibitor, the treatment duration for HCV genotype 1 infection

TABLE 44.6 **PREFERRED FDA-APPROVED ORAL DIRECT-ACTING ANTIVIRAL TREATMENT REGIMENS FOR INITIAL AND RETREATMENT OF HEPATITIS C VIRUS INFECTION**[1]

Regimen	Indication	Duration of Treatment in Noncirrhotic Treatment-Naïve Patients (weeks)
Glecaprevir and pibrentasvir	Genotypes 1–6 and DAA-experienced genotype 1	8
Sofosbuvir and velpatasvir	Genotypes 1–6, and DAA-experienced genotypes 1b and 2	12
Sofosbuvir, velpatasvir, and voxilaprevir	DAA-experienced genotypes 1–6	–

[1]Based on the American Association for the Study of Liver Diseases/Infectious Diseases Society of America Guidance. In late 2020, two preferred regimens were recommended: glecaprevir and pibrentasvir for 8 weeks (genotypes 1–6) and sofosbuvir and velpatasvir for 12 weeks (genotypes 1, 2, 4, 5, 6), with sofosbuvir, velpatasvir, and voxilaprevir as a rescue regimen for rare nonresponders to first-line therapy. See HCV Guidance: Recommendation for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org, accessed December 18, 2020.

could be shortened to 24 weeks, depending on the rapidity of clearance of HCV RNA from serum—so-called *response-guided therapy*. Treatment with peginterferon-based therapy was associated with frequent, often distressing, side effects, and discontinuation rates were as high as 15% to 30%.

After the introduction of all-oral regimens, the criterion for a sustained virologic response was shortened from 24 weeks to 12 weeks following the completion of treatment. The definition of clearance of HCV RNA requires use of a sensitive real-time reverse transcriptase-PCR assay to monitor HCV RNA during treatment (the lower limit of quantification should be ≤25 IU/mL, and the limit of detection should be 10–15 IU/mL).

Several types of direct-acting antiviral agents have been developed (see Table 44.5). HCV protease inhibitors ("–previrs") generally have high antiviral potency but differ with respect to the development of resistance (although resistance-associated substitutions in the HCV genome tend not to persist after therapy, after these agents are stopped). Examples include glecaprevir and voxilaprevir. Some of the compounds show better response rates in HCV genotype 1b than in genotype 1a infection. Simeprevir is less effective in patients with genotype 1a and a nonstructural protein Q80K mutation than in those without the mutation. Drugs in this class are contraindicated in persons with decompensated cirrhosis.

NS5A inhibitors ("–asvirs"), such as ledipasvir and velpatasvir, are characterized by high antiviral potency at picomolar doses. The cross-genotype efficacy of these agents varies.

HCV polymerase inhibitors ("–buvirs") are categorized as nucleoside or nucleotide analog and non-nucleoside polymerase inhibitors. Nucleos(t)ide analogs are active against all HCV genotypes and have a high barrier to resistance. Sofosbuvir has been the sole available agent in this category. Non-nucleos(t)ide polymerase inhibitors, such as dasabuvir, are the weakest class of compounds against HCV because of a low barrier to resistance. Drugs in this class are generally more active against HCV genotype 1b than HCV genotype 1a. They have been developed to be used only in combination with the other direct-acting antiviral agents, mainly protease inhibitors and NS5A inhibitors.

In late 2019, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommended two preferred combination regimens: glecaprevir plus pibrentasvir for 8 weeks for genotypes 1–6 and sofosbuvir plus velpatasvir for 12 weeks for genotypes 1, 2, 4, 5, or 6 (see Table 44.6). The combination of glecaprevir and pibrentasvir is approved for 8 weeks in treatment-naïve, noncirrhotic or compensated cirrhotic and treatment-experienced noncirrhotic patients, including those coinfected with HIV, and for 12 weeks in treatment-experienced, compensated cirrhotic patients. Sofosbuvir and velpatasvir should also be administered for 12 weeks in treatment-experienced compensated cirrhotic patients. Additional modifications may be required in patients with genotype-3 treatment-experienced compensated or decompensated cirrhosis. The combination of glecaprevir and pibrentasvir is also a pangenotypic option for patients with chronic kidney disease, including those receiving dialysis. The combination of sofosbuvir, velpatasvir, and voxilaprevir is recommended as "rescue" therapy in patients with nonresponse or relapse following treatment with an NS5A-containing regimen. Other "rescue" regimens are under study, including grazoprevir, ruzasvir (an NS5A inhibitor), and uprifosbuvir (an NS5B polymerase nucleotide inhibitor), with or without ribavirin, for patients who have not responded to NS5A-containing therapy. Where available, testing for resistance-associated substitutions may be helpful in some cases before re-treatment. Use of any regimen containing a protease inhibitor is contraindicated in patients with decompensated cirrhosis.

Overall treatment rates are still less than 20% and lowest among Hispanics and persons with Medicaid or indigent care insurance. The cost of direct-acting antiviral agents has been high (although declining), and lack of insurance coverage has often been a barrier

to their use. Additional factors to consider in the selection of a regimen are the presence of cirrhosis or kidney dysfunction, prior treatment, potential drug interactions (of which there are many) (see Table 44.7), and the likelihood that a patient may require liver transplantation in the future. Certain cytochrome P450/P-glycoprotein inducing agents, such as carbamazepine, phenytoin, and phenobarbital, contraindicate the use of all HCV direct-acting antiviral regimens. HCV genotype 1 is now easy to cure with oral direct-acting agents, with expected sustained virologic response rates well above 90%, and virtually all HCV genotype 2 infection is curable with all-oral regimens. HCV genotype 3 infection, particularly in association with cirrhosis, has been the most challenging to treat, but the newest regimens achieve a high rate of cure. Interferon is now rarely required, and the need for ribavirin has decreased also. Other agents that have been studied include NS3/4A protease inhibitors (eg, danoprevir); polymerase inhibitors (eg, mericitabine); virus entry, assembly, and secretion inhibitors; microRNA-122 antisense oligonucleotides (eg, miravirsen); cyclophilin A inhibitors (eg, alisporivir); interferon lambda-3; and therapeutic vaccines.

Patients with HCV-HIV coinfection have been shown to respond well to treatment of HCV infection. Moreover, in persons coinfected with HCV and HIV, long-term liver disease–related mortality increases as HIV infection–related mortality is reduced by antiretroviral therapy. Occasional instances of reactivation of HBV infection, as well as herpesvirus, have occurred with direct-acting antiviral agents for HCV infection, and all candidates should be prescreened for HBV infection, with the initiation of antiviral prophylactic therapy in those who are positive for HBsAg when treatment of HCV infection is begun. Antiviral therapy of HCV is beneficial in the treatment of HCV-associated cryoglobulinemia; an acute flare of cryoglobulinemia may first require treatment with rituximab, cyclophosphamide plus methylprednisone, or plasma exchange. Antiviral therapy can be used in patients who have undergone liver transplantation, thereby expanding the donor pool to include HCV-positive persons. There are insufficient safety data regarding the use of direct antiviral agents in pregnancy; therefore, they are not recommended during pregnancy.

Prognosis

The sequelae of chronic hepatitis secondary to hepatitis B include cirrhosis, liver failure, and hepatocellular carcinoma. The 5-year mortality rate is 0% to 2% in those without cirrhosis, 14% to 20% in those with compensated cirrhosis, and 70% to 86% following decompensation. The risk of cirrhosis and hepatocellular carcinoma correlates with serum HBV DNA levels, and a focus of therapy is to suppress HBV DNA levels <300 copies/mL (60 IU/mL). In patients with cirrhosis, even low levels of HBV DNA in serum increase the risk of hepatocellular carcinoma compared with undetectable levels. HBV genotype C is associated with a higher risk of cirrhosis and hepatocellular carcinoma than other genotypes. Antiviral treatment improves the prognosis in responders, prevents (or leads to regression of) cirrhosis, and decreases the frequency of liver-related complications (although the risk of hepatocellular carcinoma does not become as low as that of inactive HBV carriers, and hepatocellular carcinoma may even occur after clearance of HBsAg). A risk score (PAGE-B) based on a patient's age, sex, and platelet count has been reported to predict the 5-year risk of hepatocellular carcinoma in white patients taking entecavir or tenofovir. Emerging therapies are likely to provide a functional cure, achieved through HBsAg seroclearance, through a combination of drug therapies used to isolate the viral components in the covalently closed circular DNA that remain in hepatocytes indefinitely without foreseeable eradication by available antiviral agents.

Chronic hepatitis C is an indolent, often subclinical disease that may lead to cirrhosis and hepatocellular carcinoma after decades. The overall mortality rate in patients with transfusion-associated hepatitis C may be no different from that of an age-matched control population. Nevertheless, mortality or transplantation rates clearly rise to 5% per year once cirrhosis develops. A risk score combining age, sex, platelet count, and AST-to-ALT ratio is useful for estimating survival. There is some evidence that HCV genotype 1b is associated with a higher risk of hepatocellular carcinoma than other genotypes. Antiviral therapy has a beneficial effect on mortality and quality of life, is cost-effective, appears to retard and even reverse fibrosis, and reduces (but does not eliminate) the risk of decompensated cirrhosis and hepatocellular carcinoma in responders with advanced fibrosis. Even patients who achieve a sustained virologic response remain at an increased risk for mortality compared with the general population. An increased risk of death from extrahepatic cancers has been described in this group, as well as in patients who achieve suppression of HBV infection. Although mortality from cirrhosis and hepatocellular carcinoma due to hepatitis C is still substantial, the need for liver transplantation for chronic hepatitis C has declined, and survival after transplantation has improved. The risk of mortality from drug addiction is higher than that for liver disease in patients with chronic hepatitis C. HCV infection appears to be associated with increased cardiovascular mortality, especially in persons with diabetes mellitus and hypertension. Statin use has been reported to be associated with improved virologic response to antiviral therapy and decreased progression of liver fibrosis and frequency of hepatocellular carcinoma.

Prevention

Chronic hepatitis B and D

Strict isolation of patients with chronic hepatitis B is not necessary. Thorough hand-washing by medical staff who may contact contaminated utensils, bedding, or clothing is essential. Medical staff should handle disposable needles carefully and not recap them. Screening of donated blood for HBsAg, anti-HBc, and anti-HCV has reduced the risk of transfusion-associated hepatitis markedly. All pregnant women should undergo testing for HBsAg. HBV-infected persons should practice safe sex. Immunoprophylaxis of the neonate reduces the risk of perinatal transmission of HBV infection; as noted earlier, when the mother's serum HBV DNA level is ≥200,000 IU/mL (or the mother's serum HBsAg level is >4–4.5 log10 IU/mL), antiviral treatment of the mother should also be initiated in the third trimester and is particularly important if

TABLE 44.7 **DRUG INTERACTIONS BETWEEN DIRECT-ACTING ANTIVIRALS AND SELECTED MEDICATIONS**

Concomitant Medication(s)	DCV	LDV	PrOD	SMV	SOF	EBV/GRZ	VEL	GLE/PIB
Acid-reducing agents (proton pump inhibitors, histamine blockers and acid neutralizers)[a]		x	x				x [b]	
Afulozin/tamsulozin			x [c]					
Amiodarone	x [c]	x [c]	x [c]	x [c]	x [c]		x [c]	
Angiotensin-receptor blockers			x [b]					
Anticonvulsants[a]	x [c]	x [c]	x [c]	x [c]	x [c]	x [c]	x [c]	x [c]
Antipsychotic (pimozide)			x [c]					
Antiretrovirals[a]	See HIV prescribing[b]	See HIV prescribing	See HIV prescribing[b,c]	See HIV prescribing[c]	See HIV prescribing[c]	See HIV prescribing[c]	See HIV prescribing [c]	See HIV prescribing[b,c]
Azole antifungals[a]	x [b]		x [b,c]	x [c]				
Buprenorphine/naloxone	x [b]		x [b]	x		X		X
Calcineurin inhibitors (e.g., cyclosporine, tacrolimus)[a]			x [b,c]	x [b,c]		x [b]		x [c]
Calcium channel blockers[a]			x [b]	x [c]				
Colchicine			x [c]					
Dabigatran etexilate mesylate	x [b,c] (if renal impairment)							x [b]
Digoxin	x	x		x			x [b]	x [b]
Ergot derivatives			x [c]					
Ethinyl estradiol-containing products			x [c]					x [c]
Gemfibrozil			x [c]					
Glucocorticoids[a]	x [b]		x (inhaled, intranasal) [c]	x [c]				
St. John's Wort	x [c]	x [b]	x [c]	x [c]	x [c]	x [b]	x [c]	x [c]
HMG-CoA reductase inhibitors (statins)[a]	x	x	x [c]	x [b]		X	x [a]	x [b,c]
Macrolide antimicrobials[a]	x [b]			x [c]				
Metformin			x [b]					
Other antiarrhythmics[a]			x [b,c]	x [b,c]				
Phosphodiesterase inhibitors[a]			x [c]	x [b]				
Rifamycin antimicrobials[a]	x [c]	X [b]	x [c]	x [c]	x [c]	x [c]	x [c]	x [c]
Sedatives[a]			x [c]	x [b]				

[a] Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.
[b] Requires DAA dose modification or selected medication adjustment or monitoring for adverse events.
[c] Contraindicated, or not recommended. In rare cases, coadministration with stringent monitoring may be warranted.
DCV, daclatasvir; EBV/GRZ, elbasvir/grazoprevir; GLE/PIB, glecaprevir/pibrentasvir; LDV, ledipasvir; PrOD, paritaprevir, ritonavir, ombitasvir, dasabuvir; SMV, simeprevir; SOF, sofosbuvir; VEL, velpatasvir.
Also see the Full Prescribing Information for each DAA listed.

the initial vaccine injection of the neonate may be delayed. HBV-infected healthcare workers are not precluded from practicing medicine or dentistry if they follow Centers for Disease Control and Prevention (CDC) guidelines.

Hepatitis B immune globulin (HBIG) may be protective—or may attenuate the severity of illness—if given within 7 days after exposure (adult dose is 0.06 mL/kg body weight) followed by initiation of the HBV vaccine series. This approach is recommended for unvaccinated persons exposed to HBsAg-contaminated material via mucous membranes or through breaks in the skin and for individuals who have had sexual contact with a person with HBV infection (irrespective of the presence or absence of HBeAg in the source). HBIG is also indicated for newborn infants of HBsAg-positive mothers, with initiation of the vaccine series at the same time, both within 12 hours of birth (administered at different injection sites).

The CDC recommends HBV vaccination of all infants and children in the United States and all adults who are at risk for hepatitis B (including persons >60 with diabetes mellitus) or who request vaccination; the vaccine appears to be underutilized in adults for whom vaccination is recommended. More than 90% of recipients of the vaccine mount protective anti-HBs levels; immunocompromised persons, including patients receiving dialysis (especially those with diabetes mellitus), respond poorly. Reduced response to the vaccine may have a genetic basis in some cases and has also been associated with age >40 years and celiac disease. The standard regimen for adults is 10 to 20 μg (depending on the formulation) repeated again at 1 and 6 months, but alternative schedules have been approved, including accelerated schedules of 0, 1, 2, and 12 months and of 0, 7, and 21 days plus 12 months. For greatest reliability of absorption, the deltoid muscle is the preferred site of inoculation. Vaccine formulations free of the mercury-containing preservative thimerosal are given to infants under 6 months of age. A newer vaccine, Heplisav-B, which uses a novel immune system–stimulating ingredient, was approved by the FDA for adults in 2017. Immunization requires only two injections, and Heplisav-B appears to be more effective than previous HBV vaccines. When documentation of seroconversion is considered desirable, postimmunization anti-HBs titers may be checked. Protection appears to be excellent even if the titer wanes—persisting for at least 20 years—and booster reimmunization is not routinely recommended but is advised for immunocompromised persons in whom anti-HBs titers fall below 10 mIU/mL. For vaccine nonresponders, three additional vaccine doses may elicit seroprotective anti-HBs levels in 30% to 50% of persons. Doubling of the standard dose may also be effective. Universal vaccination of neonates in countries endemic for HBV has reduced the incidence of hepatocellular carcinoma, although resource allocation remains a challenge. Incomplete immunization is the most important predictor of liver disease among vaccinees. The World Health Organization's Global Strategy for Viral Hepatitis includes the elimination of hepatitis B as a global health threat by 2030. Vaccination against HBV necessarily protects against HDV infection.

Chronic hepatitis C

Testing donated blood for HCV helped reduce the risk of transfusion-associated hepatitis C from 10% in 1990 to about 1 case per 2 million units in 2011. The US Preventive Services Task Force has recommended that asymptomatic adults age 18 to 79 be screened for HCV infection. The CDC subsequently recommended screening of all persons over age 18 at least once in a lifetime and in all pregnant women (in both cases except in settings where the prevalence of HCV infection is less than 0.1%, which is unusual). Screening of all pregnant women for HCV infection has been recommended by professional societies. HCV-infected persons should practice safe sex, but there is little evidence that HCV is easily spread by sexual contact or perinatally, and no specific preventive measures are recommended for persons in a monogamous relationship or for pregnant women. Because a majority of cases of HCV infection are acquired by IV drug use, public health officials have recommended avoidance of shared needles and access to needle exchange programs for PWID. As yet, there is no vaccine for HCV. Vaccination again HAV (after prescreening for prior immunity) and HBV is recommended for patients with chronic hepatitis C, just as vaccination against HAV is recommended for patients with chronic hepatitis B.

Suggested reading

Hepatitis B virus

Hassanein TI (editor). Hepatitis B virus update. *Clin Liver Dis*. 2019 Aug;23(3):383–572. [Full issue]

Lim JK, et al. Prevalence of chronic hepatitis B virus infection in the United States. *Am J Gastroenterol*. 2020 Sep;115(9):1429–38. PMID: 32483003.

Seto WK, et al. Chronic hepatitis B virus infection. *Lancet*. 2018 Nov 24;392(10161):2313–24. PMID: 30496122.

Schillie S, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2018 Jan 12;67(1):1–31. PMID: 29939980.

US Preventive Services Task Force; Owens DK, et al. Screening for hepatitis B virus infection in pregnant women: US Preventive Services Task Force reaffirmation recommendation statement. *JAMA*. 2019 Jul 23;322(4):349–54. PMID: 31334800.

Hepatitis C virus

AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2018 Update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. *Clin Infect Dis*. 2018 Oct 30;67(10):1477–92. PMID: 30215672.

Chen H-Y, et al. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. *Gut*. 2019;68:512–21. PMID: 30228220.

Chou R, et al. Screening for hepatitis C virus infection in adolescents and adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2020;323(10):976–91. PMID: 32119034.

European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series. *J Hepatol*. 2020 Nov;73(5):1170–218. PMID: 32956768.

Havens PL, et al. Updated CDC recommendations for universal hepatitis C virus screening among adults and pregnant women: implications

for clinical practice. *JAMA*. 2020 Jun 9;323(22):2258–9. PMID: 32271870.

Hofmeister MG, et al. Estimating prevalence of hepatitis C virus infection in the United States, 2013–2016. *Hepatology*. 2019 Mar;69(3):1020–31. PMID: 30398671.

Price JC, et al. Updated hepatitis C virus screening recommendation-a step forward. *JAMA Intern Med*. 2020 May 1;180(5):637–9. PMID: 32119030.

Rabaan AA, et al. Overview of hepatitis C infection, molecular biology, and new treatment. *J Infect Public Health*. 2020 May;13(5):773–83. PMID: 31870632.

Schillie S, et al. CDC recommendations for hepatitis C screening among adults - United States, 2020. *MMWR Recomm Rep*. 2020 Apr 10;69(2):1–17. PMID: 32271723.

Spearman CW, et al. Hepatitis C. *Lancet*. 2019 Oct 19;394(10207):1451–66. PMID: 31631857.

Stockdale AJ, et al. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. *J Hepatol*. 2020 Sep;73(3):523–32. PMID: 32335166.

US Preventive Services Task Force, et al. Screening for hepatitis C virus infection in adolescents and adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2020;323(10):970–5. PMID: 32119076.

Hepatitis D virus

Palom A, et al. Long-term clinical outcomes in patients with chronic hepatitis delta: the role of persistent viraemia. *Aliment Pharmacol Ther*. 2020 Jan;51(1):158–66. PMID: 31721254.

Yurdaydin C, et al; Hepatitis Delta International Network (HDIN). Treating chronic hepatitis delta: the need for surrogate markers of treatment efficacy. *J Hepatol*. 2019 May;70(5):1008–15. PMID: 30982526.

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Biliary infection

Cholecystitis, cholangitis

Raghav Chandra and Robert V. Rege

This chapter discusses the pathogenesis, diagnosis, and treatment of infections of the gallbladder and bile ducts. Bacterial disorders of the biliary tract range from simple colonization of bile with bacteria to serious, life-threatening problems requiring prompt diagnosis and treatment.

Acute cholecystitis

Acute cholecystitis is a common disorder that manifests as acute inflammation of the gallbladder. In 98% of patients, the pathogenesis of the disease involves obstruction of the cystic duct by an impacted gallstone at the gallbladder neck with resulting inflammation, Cystic ductal obstruction results in nonvisualization of the gallbladder on technetium radionucleotide cholescintigraphy (HIDA) scan. In 2% to 5% of cases, gallstones are not present, a condition termed acute *acalculous cholecystitis*. While acute acalculous cholecystitis is most often encountered in debilitated or critically ill patients who have not been fed by mouth for extended periods of time, it can occur in otherwise healthy patients as well, including children. It is believed that biliary stasis in the gallbladder lumen leads to gallbladder wall inflammation in both calculous and acalculous cholecystitis. Secondary superinfection of static bile with gram-negative and anaerobic bacteria further promotes gallbladder wall inflammation and ultimately compromise (Figure 45.1). If unchecked, the process progresses to complicated cholecystitis with gangrene or perforation of the gallbladder, which can result in rupture, fistulae, sepsis, and death. For this reason, early diagnosis and effective management of acute cholecystitis is imperative.

Bacteriology

Interestingly, bacteria are not isolated from bile in the great majority of patients undergoing operation early in the course of the disease. In a study of 509 patients who underwent cholecystectomy or cholecystostomy tube placement for acute cholecystitis, bile cultures were positive in only 34% of patients (Hadi et al., 2016). Bacteria in bile increase as the duration from the onset of symptoms increases, and the majority of patients demonstrate bacteriobilia by 3 days. The relative proportion of organisms varies in studies, but in general, the most common organisms isolated include the gram-negative bacteria including *Escherichia coli, Klebsiella, Proteus*, and *Pseudomonas*; anaerobes such as *Bacteroides* and gram-positives, particularly *Enterococcus* (Table 45.1). Polymicrobial infection is common. Anaerobic bacteria are reportedly isolated in >10% of cases, but may be more common as culturing these organisms using standard techniques is difficult. *Candida* spp. are uncommon in normal patients but are frequently encountered in immunosuppressed patients and those with underlying maligiancies.

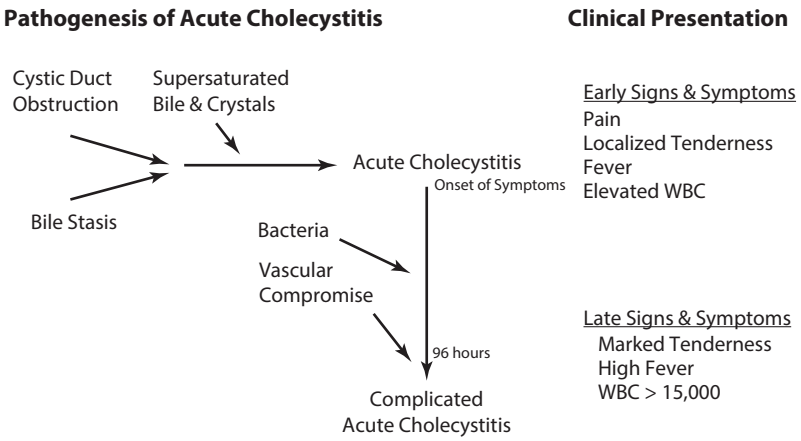

FIGURE 45.1 The pathogenesis of acute cholecystitis is illustrated on the left side of the figure, whereas differences in clinical presentation between acute cholecystitis and complicated acute cholecystitis are shown on the right. Note that bacteria do not play a primary role but result in progression of the disease to its complicated form.

Acalculous cholecystitis

While the majority of cases of acute cholecystitis are caused by secondary infection of the gallbladder after biliary obstruction from a gallstone, there are several other etiologies of cholecystitis as well. Critical illness, major abdominal surgery, malnutrition, severe burns, and immunosuppression are known risk factors for a highly aggressive infection of the gallbladder termed *acute acalculous cholecystitis*. As the name suggests, acalculous cholecystitis does not occur in the presence of gallstones. The pathophysiology of acalculous cholecystitis is multifactorial and includes systemic inflammation, biliary stasis, ischemia, and infection. Histologically, acalculous cholecystitis is characterized by gallbladder wall edema, bile infiltration into the gallbladder wall, and microvascular occlusion (Huffman & Schenker, 2010). Immunosuppressed patients, in particular, are at significantly increased risk of serious systemic infections, including cholecystitis. In these high-risk patients including those on post-transplant immunosuppression or those with acquired immunodeficiency syndrome (AIDS), acalculous cholecystitis has been associated with opportunistic infections including cytomegalovirus (CMV), *Cryptosporidium*, or *Mycobacterium avium complex* (Cacciarelli et al., 1998; Drage et al., 2009).

Diagnosis

Acute cholecystitis must be distinguished from biliary colic, and clues need to be sought to determine if complicated cholecystitis is imminent or already present. While both patients with acute cholecystitis and biliary colic experience right upper quadrant abdominal pain, the pain associated with acute cholecystitis is persistent, lasts more than 3 to 4 hours, and is associated with abdominal tenderness. Tenderness is well-localized in the right upper quadrant of the abdomen directly over the gallbladder and increases when the patient inspires as the gallbladder strikes the examiner's hand (Murphy's sign). The maneuver can be duplicated with the ultrasound probe (sonographic Murphy's sign). Diffuse right upper quadrant tenderness is suggestive of a liver problem, and severe tenderness or peritonitis is indicative of complicated cholecystitis or another upper abdominal cause of pain.

Systemic signs of inflammation, including low-grade fever and moderately elevated white blood cell (WBC) count, are usually present. The presence of dark urine, acholic stool, or jaundice raises the concern of common bile duct stones (choledocholithiasis). Conversely, if these findings are accompanied by painless jaundice, malignant ductal obstruction should be suspected. Back pain and epigastric tenderness should also heighten the clinician's suspicion of choledocholithiasis or biliary pancreatitis.

TABLE 45.1 **COMMON BACTERIA IN BILE**

Gram-negative	Gram-positive	Anaerobes	Fungi
Escherichia coli	*Enterococcus*	*Bacteroides* spp.	*Candida* spp.
Klebsiella spp.	*Streptococcal* spp.	*Clostridium* spp.	
Proteus spp.			
Pseudomonas spp.			
Enterobacter spp.			

Approximately 65% of patients are colonized with a single species of bacteria; 35% are polymicrobial. Gram-negative bacteria are cultured from nearly 75% of patients.

Physical examination can, however, be misleading. Some patients exhibit few signs and symptoms of acute cholecystitis, which may delay the diagnosis and underestimate the severity of the disease. Such patients are more likely to be elderly, male, and have a history of cardiac disease. Furthermore, while leukocytosis is common, WBC counts >15,000 suggest severe disease (gangrene or perforation of the gallbladder). A high index of suspicion for complicated cholecystitis must be maintained for such patients, as they may present with minimal symptoms prior to decompensation. Laboratory testing should include CBC with differential, liver function tests, serum amylase, and serum lipase. The latter three tests may suggest choledocholithiasis or biliary pancreatitis when abnormal. Ultrasound of the abdomen reliably demonstrates gallstones in the majority of patients. A typical clinical presentation, coupled with a "positive" ultrasound for stones suffices for the diagnosis. More specific findings of acute cholecystitis including gallbladder wall thickening and pericholecystic fluid are less frequent and suggest more severe disease. A HIDA scan may be helpful in patients without gallstones or atypical presentation. Nonvisualization of the gallbladder is specific for acute cholecystitis (the gallbladder is visualized in only about 2% of patients with acute cholecystitis); demonstration of the gallbladder argues strongly against acute cholecystitis.

Treatment

All patients should be evaluated and prepared for operation, which may be required at any time if the disease progresses. Intravenous (IV) fluid resuscitation and antibiotics should be started, and patients should be placed on bowel rest. Antibiotics must cover the spectrum of bacteria just outlined, and complicated cholecystitis and immunosuppressed patients may require broader coverage (Box 45.1). Antibiotic coverage must include gram-negative rods, gram-positive organisms, and anaerobes. The Tokyo 2018 guidelines recommend piperacillin/tazobactam for most cases of acute cholecystitis and cholangitis for both community-acquired and healthcare-associated disease. For severe community-acquired or healthcare-associated disease, addition of vancomycin to cover *Enterococcus* is also recommended. Vancomycin-resistant *Enterococcus* (VRE), particularly in the hospital setting, may require initiation of daptomycin or linezolid. If there is concern for extended-spectrum β-lactamase–producing organisms, imipenems are advised (Gomi et al., 2018).

BOX 45.1

Summary of antibiotic regimens for acute cholecystitis and acute cholangitis

Acute cholecystitis
Cefoxitin 1–2 g IV q6–8h
Ampicillin-sulbactam (Unasyn) 3 g IV q6h
Acute cholangitis
Single agents
Ciprofloxacin 400–800 mg IV q12h
or
Piperacillin-Tazobactam (Zosyn) 3.375 g IV q6h
or
Imipenem 500 mg IV q6h
Multidrug therapy
Ampicillin 2 g IV q6h + gentamicin 5–7 mg/kg IV q24h
or
Ceftazidime 1–2 g IV q8–12h + Ampicillin 2 g IV q6h + Metronidazole 500 mg IV q6h

Some physicians recommend medical treatment with a delay of 6 weeks to definitive operation. Their rationale is that elective operation is safer than an emergent procedure and that conversion to open rates will be lower than after the acute attack resolves. Although most patients have some response to medical therapy, it is not clinically safer than surgery, nor does it reduce the rate of conversion. It may play a role in a few selected patients with severe, potentially reversible comorbidities which preclude an operative approach. If such patients fail medical therapy, they can be salvaged with percutaneous drainage of the gallbladder through placement of a cholecystostomy tube. Cholecystectomy may be performed electively later, but it is arguable whether all patients require cholecystectomy after nonoperative therapy.

Early laparoscopic cholecystectomy is the definitive treatment for most patients with acute cholecystitis. It is safe in the hands of experienced biliary surgeons, avoids the progression of the disease (which can be observed in as many as 30% of medically treated patients), and has conversion rates similar to elective cholecystectomy (<5%). As the duration of symptoms surpasses 96 hours, conversion rates rise because complicated cholecystitis develops. Although laparoscopic cholecystectomy can still be performed in the majority of these patients as well, the operation is more difficult and morbid. If laparoscopic surgery is attempted late in the disease, surgeons should convert to open operation liberally if marked inflammation or fibrosis is encountered.

It is my preference to admit a patient with acute cholecystitis to the hospital and perform operation within 72 hours from onset of symptoms. The patient is treated with medical therapy (IV antibiotics and fluids) until operation. Patients with early disease often spend <24 hours in the hospital. Those with severe or late disease require urgent or emergent intervention and continued medical therapy postoperatively. Patients who are poor operative risks are the exception; medical therapy and/or percutaneous cholecystostomy tube drainage is a consideration.

After laparoscopic cholecystectomy, patients with mild to moderate disease should discontinue antibiotic therapy. For patients with severe disease, antibiotic therapy should be continued for up to 7 days (Gomi et al., 2018).

Acute cholangitis

Acute cholangitis refers to inflammation and infection of the intra- and extrahepatic biliary tree. Bacterial infection is the most common etiology, but cholangitis can result from parasitic infections, autoimmune diseases, and chemical irritants. *Toxic cholangitis* manifests when bacteria in bile gain access to hepatic sinusoids and are rapidly disseminated, resulting in sepsis, multisystem organ failure, and death.

Pathogenesis

The pathogenesis of acute cholangitis involves a combination of factors including ductal obstruction, injury to the biliary epithelium, and the presence of bacteria in bile. Most patients harboring bacteria in bile do not have an infection, and, in fact, asymptomatic colonization of bile with bacteria increases with advancing age. Bacteriobilia is a risk for acute cholangitis once biliary obstruction develops or if the epithelium is injured, as might occur during an invasive biliary procedure. This is the rationale for prophylactic antibiotic coverage during biliary tract invasive procedures.

Most cases of cholangitis in the United States are secondary to partial or complete biliary obstruction, usually by gallstones which have migrated from the gallbladder into the common bile duct and have caused an obstruction. Normal biliary intraductal pressure is between 7 and 12 mm H_2O. Increased intraductal pressure behind the impacted gallstone disrupts epithelia and intracellular junctions between epithelial cells in the proximal biliary tree. When intraductal pressures increase beyond 25 mm H_2O, the resulting weakening of the lumen wall results in translocation of bacteria systemically into the venous system, termed *cholangiovenous reflux* (Kimura et al., 2007; Ahmed, 2018).

Non-gallstone etiologies of acute cholangitis include benign strictures, stenosis, iatrogenic injury, external compression from gallstones at the neck of the gallbladder (Mirizzi's syndrome), pancreatic cancer, gallbladder cancer, or duodenal lesions (cancer, duodenal or Lemmel's diverticulum). Cholangitis can also occur with malignant biliary obstruction caused by a primary bile duct cancer (cholangiocarcinoma). Patients with malignant obstruction usually present with painless jaundice and sterile bile, though bacteriobilia can be found in 20% of cases. Patients with colonized bile are at higher risk for cholangitis after procedures in the biliary tract. Expectedly, the incidence of iatrogenic cholangitis is rising as the volume of endoscopic and radiological bile duct procedures performed continues to increase. Prophylactic antibiotics and adequate drainage are therefore recommended to minimize the risk of bacterial cololnization of sterile bile during such invasive diagnostic tests.

Microbiology

Causative organisms of acute cholangitis are similar to those isolated from acute cholecystitis, and the most commonly identified pathogens include *E. coli, Klebsiella*, and *Enterococcus*. However, infections from these pathogens are significantly more severe, and blood cultures more often positive, when patients have cholangitis compared to those who have bacteriobilia. Some studies show differences in the incidence of causative organisms between benign and malignant causes of ductal obstruction. Indeed, multiple studies show that patients with malignant obstruction have a higher incidence of bile colonized with *Candida* spp. (Table 45.1). Other infectious etiologies associated with cholangitis include parasitic infections (*Clonorchis sinensis, Ascaris lumbricoides*, and *Opisthorchis* spp.) and AIDS cholangiopathy, often secondary to the similar organisms that can cause opportunistic cholecystitis (*Cryptosporidium*, CMV) (Kimura et al., 2007; Yusuf & Baron, 2004; Ahmed, 2018).

Diagnosis

The classic description of patients with acute cholangitis—Charcot's triad—consists of abdominal pain, fever, and jaundice. Unfortunately, only 50% of patients present with all three signs and symptoms which may delay diagnosis. Fever and chills, present in 90% of patients, are the most consistent signs of acute cholangitis and are often high and spiking in nature. Reynolds' pentad—Charcot's triad as well as hypotension and altered sensorium—is indicative of toxic cholangitis. All five features are present in the minority of patients with toxic cholangitis, so acute and toxic cholangitis must be considered in patients who have any of these signs or symptoms.

Physical examination most often reveals right upper quadrant abdominal tenderness and jaundice. However, as many as 20% of patients with acute cholangitis have a serum bilirubin level of <2.0 mg/dL, the absence of jaundice does not exclude acute cholangitis. Physical findings are typically accompanied by leukocytosis, fever, and/or abnormal liver function tests. Septic patients may have a deceptively low white cell count as well as signs of hemodynamic instability. Ultrasound should be performed urgently to distinguish between "medical" and "surgical" jaundice; dilated bile ducts are indicative of obstruction and surgical jaundice. Endoscopic retrograde cholangiography (ERC; see "Treatment") is diagnostic but can also be therapeutic. Percutaneous transhepatic cholangiography is helpful when ERC is unsuccessful.

Treatment

Acute cholangitis requires aggressively addressing both infection and biliary obstruction. The majority of nonseptic patients respond quickly to fluid resuscitation and appropriate antibiotics. Subsequent measures need to be taken promptly to address the underlying problems causing acute cholangitis. Because toxic cholangitis is a life-threatening problem, these patients should be placed in the intensive care unit for careful hemodynamic monitoring. IV hydration should correct the hypovolemia associated with biliary obstruction, and urine output should be followed closely. Restoration of normal intravascular volumes before undergoing invasive diagnostic and therapeutic procedures is essential to ameliorate the risk of renal failure. Patients in septic shock often exhibit coagulopathy that must be corrected with vitamin K, fresh frozen plasma (FFP), and platelets.

Broad-spectrum antibiotic therapy is essential and should be instituted immediately before any diagnostic and therapeutic interventions are undertaken. Choice of an antibiotic should take into account the profile of organisms commonly cultured at the hospital, especially for hospitalized individuals undergoing invasive procedures. Coverage should be later tailored to match the sensitivities of organisms isolated from bile or blood cultures. The long-standing regimen of ampicillin and an aminoglycoside continues to provide excellent gram-negative and gram-positive coverage for the major culprits, including *Enterococcus* spp., but aminoglycoside-induced nephrotoxicity greatly limits long-term use of this agent. First- and second-generation cephalosporins, while adequate for prophylaxis for elective biliary surgery, lack the

breadth of gram-negative coverage required to treat patients with established infections. Third- and fourth-generation cephalosporins provide gram-negative coverage but do not treat *Staphylococcus* and *Enterococcus* spp. nor anaerobic bacteria effectively. Historically, triple therapy with ceftazidime, ampicillin, and metronidazole provided adequate coverage, but the trend has shifted to single-drug therapy with piperacillin/tazobactam or ampicillin/sulbactam, which is as efficacious as triple-drug therapy or ampicillin plus an aminoglycoside. Fluoroquinolones or carbapenems are good alternatives if first-choice antibiotics are ineffective. Furthermore, ciprofloxacin can be used long-term orally to suppress recurrent attacks of cholangitis. The duration of therapy for antibiotics for acute cholangitis is typically 4 to 7 days, pending adequate drainage of the biliary tree (Gomi et al., 2018).

After adequate resuscitation and antibiotic administration, the primary therapeutic objective is to relieve the obstruction of the biliary tree. This is currently accomplished using either endoscopic retrograde cholangiopancreatography (ERCP)-mediated drainage or percutaneous transhepatic cholangiography (PTC). ERCP is the first choice as it is less risky than PTC in critically ill patients. ERCP is also the gold standard for diagnosing the etiology of acute cholangitis. Effective decompression of the biliary tree can be accomplished by removal of obstructing gallstones with or without stenting of the duct. Cancers of the biliary tree can be visualized and biopsied. PTC is reserved for failure of ERCP or for patients with obstructing cholangiocarcinoma of the proximal bile duct. Adequate drainage should result in prompt improvement.

Decisions about timing of intervention depend on the severity of disease. Factors associated with the need for emergent treatment include older age, high bilirubin levels, prolonged prothrombin time, dilated common bile ducts, and the presence of liver abscesses. Literature suggests that ERCP performed within 24 hours of initial diagnosis is associated with reduced rate of recurrent cholangitis and length of stay (Alizadeh et al., 2017). Salek et al. developed scoring systems to determine mortality risk after cholangitis and identified 18 variables associated with mortality and 15 variables associated with need for early ERCP. They noted that the presence of liver abscess, total bilirubin serum levels, and prothrombin time were predictive of mortality, and alanine aminotransferase level and WBC predicted the need for urgent ERCP with good sensitivity and specificity (Salek, Livote, Sideridis, & Bank, 2009).

If appropriate, definitive procedures should be performed to treat the cause of biliary obstruction because recurrent cholangitis is common. Cholecystectomy should be performed during the index admission if choledocholithiasis was the inciting event. Curable malignancies should be resected. Benign strictures require balloon dilatation or choledochointestinal bypass, whereas unresectable tumors are either bypassed or palliated with internal drainage or external stents.

Timing of operation for patients who present with a transient episode of biliary pancreatitis (low to moderate risk of choledocholithiasis) is somewhat controversial; most stones pass from the common duct spontaneously without complication and the incidence of retained common bile duct stones is highest early after an attack and decreases with time. However, patients in whom choledocholiths do not pass are at high risk for recurrent pancreatitis, obstructive jaundice, and acute cholangitis. The timing of treatment then depends on a balance between the risk of intervention for and further complications from retained common duct stones. Low-risk patients with mild pancreatitis may be taken to the operating room for laparoscopic cholecystectomy with intraoperative cholangiography if the surgeon is prepared to perform laparoscopic common bile duct exploration. The standard of care in this country is to intervene during or shortly after the index admission.

However, patients who present with severe, complicated gallstone pancreatitis may be poor candidates for surgery. Most surgeons allow them to recover from their episode of pancreatitis before definitive intervention. The probability of developing cholangitis is low. Patients with unrelenting pancreatitis, persistently elevated liver enzymes, or jaundice are at high risk for common bile duct stones and should be evaluated for ERCP. Cholecystectomy is performed later to avoid recurrent complications of stones if the patient is an acceptable operative risk.

References

Ahmed M. Acute cholangitis: An update. *World J Gastrointest Pathophysiol*. 2018;9:1–7.

Alizadeh M, et al. Cholangitis: Diagnosis, treatment and prognosis. *J Clin Transl Hepatol*. 2017;5:404–413.

Cacciarell AG, et al. Acute cholecystitis in AIDS patients: correlation of Tc-99m hepatobiliary scintigraphy with histopathologic laboratory findings and CD4 counts. *Clin Nucl Med*. 1998;23:226–228.

Drage M, et al. Acute cytomegalovirus cholecystitis following renal transplantation. *Am J Transplant*. 2009;9(5):1249–1252.

Gomi H, et al. Tokyo Guidelines 2018: Antimicrobial therapy for acute cholangitis and cholecystitis. *J Hepato-Biliary-Pancreat Sci*. 2018;25:3–16.

Hadi YB, et al. Bacterobilia in acute cholecystitis: Bile cultures' isolates, antibiotic sensitivities and antibiotic usage. A study on a Pakistani population. *J Pakistani Med Assn*. 2016;66(Suppl 3):S50–S52.

Huffman J, Schenker S. Acute acalculous cholecystitis: A review. *Clin Gastroenterol Hepatol*. 2010;8:15–22.

Kimura Y, et al. Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg*. 2007;14:15–26.

Salek J, Livote E, Sideridis K, Bank S. Analysis of risk factors predictive of early mortality and urgent ERCP in acute cholangitis. *J Clin Gastroenterol*. 2009;43:171.

Yusuf TE, Baron TH. AIDS cholangiopathy. *Curr Treat Opt Gastroenterol*. 2004;7:111–117.

46

Pyogenic liver abscess

Patricia Wong and H. Franklin Herlong

First described by Hippocrates around 400 BC, pyogenic liver abscess is an uncommon hepatic infection, but is associated with significant morbidity and healthcare costs. With the advent of imaging techniques that allow for prompt diagnosis, potent antibiotics, and effective drainage procedures, the mortality from pyogenic liver abscess has declined dramatically over the past several decades.

Epidemiology

The epidemiology of liver abscesses has changed significantly over the years. There is increasing recognition that geography plays a significant role in the demographics, etiologic factors, and clinical presentation of pyogenic liver abscesses. In the first large published series of cases of pyogenic liver abscess in the United States in 1938, there was an incidence of 8 cases per 100 000 admissions and a mortality rate of 72%. More recent US-based population studies estimate the annual incidence to be 3.6 per 100 000 population, with a higher incidence among men than women (incidence risk ratio 1.85). Significantly higher incidence rates have been reported in Taiwan at 17.6 per 100 000 population. Reported risk factors include diabetes, underlying hepatobiliary disease, and liver transplantation. In-hospital mortality ranges from 2% to 12% in developed countries and has been reported at 5.6% in the United States. Risk factors for mortality include older age; comorbidities such as cirrhosis, chronic renal failure, and malignancy; the presence of anaerobic infection; and open surgical drainage. The significant decline in associated mortality reflects changes in the underlying source of bacterial seeding and advances in diagnostic and treatment options.

Etiology

Pyogenic liver abscesses result from seeding of the liver from biliary tract disorders (choledocholithiasis, malignant obstruction, strictures, biliary procedures), portal vein pyemia (appendicitis, diverticulitis, colon cancer, inflammatory bowel disease), direct extension (peritonitis, subphrenic abscess), hematogenous spread (pneumonia, endocarditis), or hepatic trauma (infected necrosis, bile leak, or hematoma). Rarely, abscesses develop after arterial embolization or radiofrequency ablation of hepatic tumors. Biliary tract disorders have emerged as the most common causative condition, accounting for 40% to 60% of liver abscess cases. Cholangitis from obstructing cholangiocarcinomas is more common than infections resulting from calculus obstruction.

Liver abscesses from intra-abdominal infective processes have decreased dramatically because of improvements in the diagnosis and treatment of these primary infections. No identifiable source of infection, or "cryptogenic abscess," is found in up to 25% of cases. Most liver abscesses are solitary and occur in the right lobe of the liver, likely due to its greater blood supply compared to the left and caudate lobes.

Clinical presentation

Most patients with pyogenic liver abscesses appear acutely ill with fever and right upper quadrant pain. However, in elderly, debilitated patients, clinical signs may be minimal, potentially delaying diagnosis. Many patients have tender hepatomegaly, occasionally with focal tenderness over the intercostal spaces of the right upper quadrant. However, absence of right upper quadrant findings does not exclude the diagnosis and in patients with liver transplants, denervation may prevent the pain of hepatic enlargement. Nonspecific systemic symptoms such as fatigue, malaise, nausea, and weight loss are common. Jaundice is unusual unless the abscess compresses the biliary tact. An associated pleural effusion may obliterate breath sounds at the right bases. Laboratory abnormalities frequently include leukocytosis and elevated C-reactive protein levels. A modest elevation of alkaline phosphatase is seen in up to 90% of cases. Serum aminotransferases and bilirubin are elevated in about one-half of cases. Blood cultures are positive in less than 50% of cases. No single test or combination of tests can accurately predict the outcome, size, or number of abscesses or complications.

Cultures from liver abscesses usually yield polymicrobial flora. Mixed enteric facultative and anaerobic species are the most common pathogens. A single organism indicates hematogenous spread. Enteric aerobic gram-negative bacilli, such as *Escherichia coli*, and enterococcus suggest a biliary source. Mixed enteric flora containing anaerobes such as *Bacteroides fragilis* originate from portal bacteremias. Monomicrobial *Klebsiella pneumoniae* infection is the most common cause of pyogenic liver abscesses in Taiwan and accounts for a large proportion of cases throughout Asia. These patients have a unique clinical presentation with classic symptoms but no identifiable coexisting intra-abdominal pathology and metastatic complications, such as endophthalmitis. Most patients also have diabetes mellitus. *Yersinia enterocolitica* is an unusual pathogen associated with patients with diabetes or underlying liver disease, particularly hemochromatosis.

Gram-positive organisms such as *Staphylococcus aureus* and *Streptococcus milleri* often originate from infections outside of the abdominal cavity. *S. aureus* is a common cause of liver abscess in children and trauma patients and has been associated with transarterial embolization for hepatocellular carcinoma. Species of *Candida* cause abscesses in immunosuppressed patients, particularly those receiving chemotherapy. The abscess may not be apparent until the neutrophil count rebounds (Table 46.1).

TABLE 46.1 **CLINICAL FINDINGS IN PYOGENIC LIVER ABSCESS**

Signs and symptoms	Incidence (%)
Fever	75
Chills	60
Abdominal pain	60
Weight loss	30
Hepatomegaly	50
Right upper quadrant tenderness	40
Jaundice	25
Laboratory values	
Leukocytosis	70
Elevated bilirubin	40
Elevated alkaline phosphatase	50
Elevated aminotransferases	60

Diagnosis

The diagnosis of pyogenic liver abscess is made through radiographic imaging and aspiration and culture of abscess material. Ultrasonography is the preferred initial test for diagnosing liver abscesses, with a sensitivity of 75% to 95%. Examination of the liver shows a round, focal defect with irregular walls and variable echogenicity. Abscesses may be septated or multiloculated and contain internal echoes caused by debris. Small abscesses, <2 cm in diameter, may not be detected. Contrast-enhanced computed tomography (CT) has a sensitivity of 95% and can detect abscesses as small as 0.5 cm. It can also identify associated intra-abdominal pathology. CT typically shows a fluid collection with surrounding edema or stranding. It is important to distinguish liver abscesses from tumors and cysts. Magnetic resonance imaging and tagged white blood cell scans are less effective at detecting and distinguishing abscesses from other liver lesions.

Treatment

The mainstay of treatment of pyogenic liver abscess is systemic antimicrobial therapy in combination with drainage. When pyogenic liver abscess is suspected, blood cultures should be obtained immediately, followed by initiation of broad-spectrum parenteral antibiotics before blood culture results are available, based on the most probable source of infections (Table 46.2). Initial antibiotic

TABLE 46.2 **EMPIRIC ANTIBIOTIC THERAPY FOR PYOGENIC LIVER ABSCESS**

Potential source	Suggested regimen
Biliary	PipTz 4.5 g q8h IV or
	AMSB 3.0 g q6h IV or
	ERTA 1.0 g IV qd or
	MER 1.0 g q8h IV or
	CIP 400 mg IV BID + metro 1.0 g IV then 0.5 g q6h
Intra-abdominal	IMP 500 mg IV q6h or
	MER 1 g IV q8h or
	AMP 2 g IV q6h + metronidazole 500 mg IV q6h +
	CIP 400 mg IV q12h

Abbreviations: AMP = ampicillin; AMSB = ampicillin–sulbactam (Unasyn); CIP = ciprofloxacin; ERTA = ertapenem; IMP = imipenem cilastatin (Primaxin); MER = meropenem; metro = metronidazole; PipTz = piperacillin–tazobactam.

therapy should be tailored to information obtained from the Gram stain and cultures of aspirated abscess contents and blood cultures. Anaerobic coverage should be continued if multiple organisms are recovered, regardless of whether anaerobes are isolated, since they are difficult to culture. Most abscesses require at least 4 to 6 weeks of total antibiotic therapy with 2 to 4 weeks of parental therapy.

Successful treatment of pyogenic liver abscesses with antibiotics alone is rare, and some form of drainage procedure is almost always required. Exceptions include abscesses less than 3 cm in diameter or multiple small abscesses that are not amenable to surgical or catheter drainage.

Drainage techniques include percutaneous approaches (closed aspiration or with catheter placement), surgical drainage, or drainage by endoscopic retrograde cholangiopancreatography (ERCP). Closed aspiration is a reasonable approach for single abscesses <5 cm. It is the simplest, quickest, and least costly approach with low risk of procedural complications. However, reaccumulation often requires repeat aspiration, catheter placement, or surgical intervention. Placement of a catheter into the abscess cavity under ultrasound guidance is an effective and widely used method of drainage at many centers. This technique is preferred over needle aspiration for single abscesses >5 cm, and is often used if closed aspiration is unsuccessful.

Open surgical drainage has decreased in popularity, with the trend towards percutaneous techniques. However, surgical treatment should be considered for single abscesses >5 cm, multiple or loculated abscesses, inadequate response to percutaneous drainage, viscous contents obstructing the drainage catheter, or concurrent intra-abdominal surgical pathology. Surgical intervention allows for exploration of the abdomen and liver for multiple abscesses. A laparoscopic approach to surgical drainage may also be considered.

Endoscopic abscess drainage has emerged more recently as a treatment option for patients with abscesses that communicate with the biliary tree. This is performed through ERCP with sphincterotomy, dilation, insertion of a nasobiliary catheter, or stenting. Successful endoscopic management of liver abscess complicated by biliary fistula has also been described.

Prognosis

Current mortality rates associated with liver abscesses range from 2% to 12% in developed countries. Few patients die from complications of the abscess itself, such as sepsis or peritonitis. The most important factor in determining survival is the lethality of the primary disease process.

Suggested reading

Aydin C, Piskin T, Sumer F, Barut B, Kayaalp C. Laparoscopic drainage of pyogenic liver abscess. *JSLS*. 2010;14:418–420.

Chen SC, Huang CC, Tsai SJ, et al. Severity of disease as main predictor for mortality in patients with pyogenic liver abscess. *Am J Surg*. 2009;198:164–172.

Derosier LC, Canon CM, Vickers SM. Liver abscess. In: Yeo CJ, ed. *Shackelford's Surgery of the Alimentary Tract*, 6th edn, vol. II Philadelphia, PA: Saunders Elsevier; 2007:1640–1658.

Heneghan HM, Healy NA, Martin ST, et al. Modern management of pyogenic hepatic abscess: a case series and review of the literature. *BMC Res Notes*. 2011;4:80.

Kaplan GG, Gregson DB, Laupland, KB. Population-based study of the epidemiology of and the risk factors for pyogenic liver abscess. *Clin Gastroenterol Hepatol*. 2004;2:1032–1038.

Lederman ER, Crum HF. Pyogenic liver abscess with a focus on *Klebsiella pneumoniae* as a primary pathogen: an emerging disease with unique clinical characteristics. *Am J Gastroenterol*. 2005;100:322–331.

Malik AA, Bari SU, Rouf KA, Wani A. Pyogenic liver abscess: changing patterns in approach. *World J Gastrointest Surg*. 2010;2(12):295–401.

Meddings L, Myers RP, Hubbard J, et al. Population-based study of pyogenic liver abscesses in the United States: incidence, mortality, and temporal trends. *Am J Gastroenterol*. 2010;105:117–124.

Pang TC, Fung T, Samra J, Hugh TJ, Smith RC. Pyogenic liver abscess: an audit of 10 years' experience. *World J Gastroenterol*. 2011;17 (12):1622–1630.

Reid-Lombardo KM, Khan S, Sclabas G. Hepatic cysts and liver abscess. *Surg Clin North Am*. 2010;90:679–697.

Serste T, Bourgeois N, Eynden FV, et al. Endoscopic drainage of pyogenic liver abscesses with suspected biliary origin. *Am J Gastroenterol*. 2007;102:1209–1215.

47

Infectious complications in acute pancreatitis

Jodie A. Barkin and Jamie S. Barkin

Introduction

Patients with acute pancreatitis (AP) have two types of diseases, as shown in detail in Figure 47.1. Type 1 is edematous or mild, non-necrotic pancreatitis, which is usually not associated with persistent or multiorgan system failure (MOSF) that lasts >48 hours. Type 2 is necrotizing pancreatitis which is often associated with persistent organ system failure (>48 hours) and is prone to development of pancreatic infection.[1]

The overall mortality of acute pancreatitis is approximately 5% due to organ system failure secondary to systemic inflammatory response syndrome (SIRS) and infection. The sites of infection are pancreatic and peri-pancreatic, lung with pneumonia and circulating bacteremia.[2] Xue et al. reported that AP patients with infectious complications had a significantly higher severity index, incidence of complications, and mortality than did noninfected patients.

Necrotizing pancreatitis is associated with organ system failure (OSF) and higher morbidity and mortality versus edematous pancreatitis. The fluid collections resulting from edematous and necrotizing AP differ, with the defining criteria being the presence or absence of an enclosing wall and the contents—whether it is only liquid or mixed with solid necrotic debris (necrotizing).[3] Walled-off necrosis contents are a mixture of solid and liquid (edematous) necrosis whereas pseudocysts resulting from edematous pancreatitis are comprised predominantly of liquid contents. The natural history of walled-off necrosis (WON) versus pancreatic pseudocyst is different. WON has a much higher chance of becoming infected (ranging from 20% to 40%) than does pancreatic pseudocyst. WON may become symptomatic early on after AP onset, often requiring intervention, or it may remain asymptomatic. The natural course of asymptomatic WON was reported by Rana et al.[4] They found that 30% of patients developed complications or symptoms that occurred prior to 6 months following an AP episode, and these included pain, infection, rupture into the GI tract, and bleeding.

Petrov et al. reported in a meta-analysis on whether organ failure (OF) or infected pancreatic necrosis (IPN) is the main determinant of severity in acute pancreatitis.[5] They found that the absolute influence of IPN is comparable to development of, with a mortality of approximately 30%. The relative risk of mortality doubles when both OF and IPN are present. These studies emphasize the important role of infection in the outcome of patients with AP.

The usual classification of patients with AP is that early complications and mortality are associated with SIRS and that late complications (after 1–2 weeks) are related to infection. Lytras et al. reported that persistent early OF was significantly associated with the development of infected necrosis and worse outcomes.[6] This illustrates that complications are an interrelated spectrum, that infection may occur early, and that OSF may predispose to infection via increased bacterial translocation from gastrointestinal hypoperfusion.

When does pancreatic necrosis become infected, and where does the bacteria originate?

IPN in AP patients was found to occur by routine use of CT-guided fine needle aspiration (FNA) within 14 days of hospital admission. Besselink et al., in a prospective study, similarly found that infected necrosis

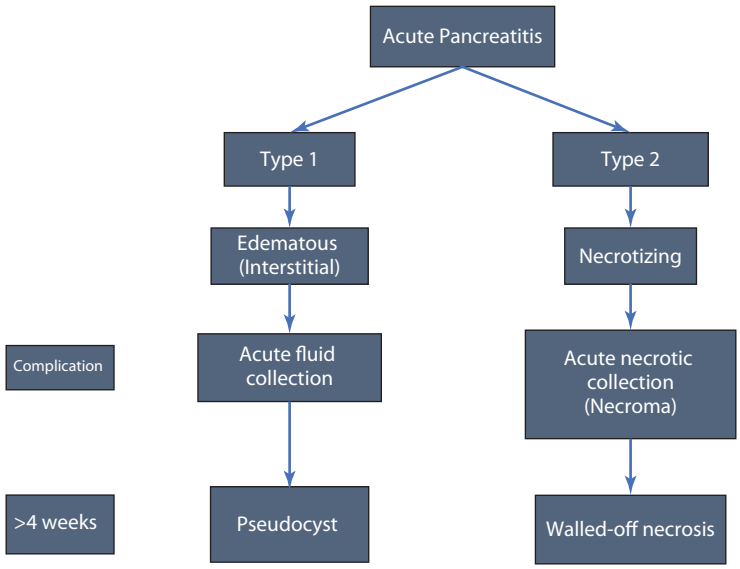

FIGURE 47.1 Types of acute pancreatitis

occurred as early as 1 week after onset of AP and peaked at week 4.[7] They also reported the importance of bacteremia, as it was found to be an independent predictor of death and was associated with an increased risk of pancreatic parenchymal necrosis becoming infected and a higher mortality rate associated with infected necrosis. Bacteremia and pneumonia are earlier events than infected necrosis. Bacteremia in patients AP originates from extra-pancreatic sources (i.e., pneumonia), as well as from the bowel. Fritz et al. showed in an animal study that bacterial translocation from the colon is less frequent than bacterial translocation from the small bowel, which is likely the main source of enteral bacteria in IPN.[8]

Extra-pancreatic infections occurred in 25% of patients with AP.[9] Urinary tract infection was the most common. Risk factors for the development of extra-pancreatic infection were use of total parenteral nutrition (TPN), severe AP disease, and presence of persistent SIRS. TPN was related to IPN because it results in intestinal barrier dysfunction, which favors bacterial translocation. AP itself affects the gut barrier function, especially in patients with organ dysfunction, which results in increased intestinal permeability.[10] Possible mechanisms include hypovolemia and SIRS. Liu et al. found that intestinal mucosal function is injured in the early phase of AP, more so in patients with organ dysfunction.[10] This allows translocation of bacteria and inflammatory and toxic products from the intestinal wall and the bowel to enter the systemic circulation.[11]

The diagnosis of infection in pancreatitis has been based on culture from pancreatic necrosis.[12] Busquets et al. expanded this concept of pancreatic infection status; they found that infection can be present by itself in intra-abdominal free fluid and peri-pancreatic fat and/or bile, or associated with pancreatic necrosis. They reported high mortality in patients with sterile pancreatitis with infected ascites who had undergone early surgical intervention. Applying the present approach of delaying surgical intervention, we should perform a diagnostic paracentesis in patients with AP and ascites to allow early diagnosis of infection.

Radiologic diagnosis of pancreatic infections

CT and MRI of the pancreas cannot accurately detect infected pancreatic collections. The only finding that is suggestive of infection is the presence of gas bubbles in the collection. However, gas bubbles within a pancreatic collection can be the result of infection or secondary to rupture of the pancreatic collection into the GI tract. Islim et al. found air bubbles in only 40% of infected pancreatic collections.[13] However, when gas bubbles are present in the appropriate clinical setting, they should be considered as evidence of pancreatic infection.

Volume replacement

AP patients can be viewed similarly to the burn patient. Their major therapeutic regimen is adequate fluid resuscitation because they have hemoconcentration. AP, especially severe AP (SAP), results in vascular leak syndrome with hypovolemia and hypotension. This frequently causes acute tubular necrosis, renal failure, intestinal ischemia, and decreased pancreatic microcirculation resulting in necrosis.[11] The majority of fluid resuscitation should be given primarily in the first 24 hours to decrease the risk of SIRS and OF. The present regime for patients with SAP is infusion of Ringer's lactate given as a 1-liter bolus, followed by 250 to 300 cc/hr for 24 hours, depending on patient comorbidities; then reassess volume status and fluid needs. During this initial period, we follow frequent measurements of urine output, respiratory and cardiac rates, blood pressure, and changes in hematocrit/blood urea nitrogen (BUN). The goal in the early phase (up to 1 week) of AP is to prevent and treat OF as outlined in Box 47.1.

Prophylactic antibiotics

The basis for prophylactic antibiotics use was to prevent infection in patients with necrotizing AP. Mortality is higher in patients with

BOX 47.1

Prevention of necrosis and recognition of infection in acute pancreatitis

Prevention of necrosis
- Volume for appropriate fluid resuscitation
- No role for prophylactic antibiotics
- Enteral nutrition early in the course

Recognition of infection (bacterial/fungal)
- Unexplained fever, leukocytosis
- Organ system failure
- Hypotension
- Increasing abdominal pain
- CT with air in pancreatic fluid collection

Petrov MS, Kukosh MV, Emelyanov NY. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. *Dig Surg*. 2006;23(5–6):336–44; Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med*. 2001;29(12):2264–70.

necrotic versus edematous or interstitial AP (up to 20% vs. 5%).[14] Once infection complicates necrosis, mortality increases to 30% to 40%. Therefore, prophylactic antibiotics would appear to be a reasonable therapeutic approach. However, this treatment has been shown *not* to be effective in a Cochrane Database systematic review of antibiotic therapy for prophylaxis against infection of pancreatic necrosis in AP by Villatoro et al. They found no benefit of antibiotics to prevent pancreatic necrosis infection or decrease mortality.[15]

Subgroup analysis of patients who received imipenem showed a significant decrease in pancreatic infection but no significant reduction in mortality. Antibiotics should only be administered early in AP patients who have suspected biliary sepsis as well as extra-pancreatic infection (i.e., urinary tract infection and/or positive blood cultures). In addition, antibiotic treatment should be used for suspected or diagnosed pancreatic or peripancreatic infections in the later phase (1–2 weeks) after onset of disease. The role of antibiotics in this phase is to allow the organization of the necrosis as well as delay surgery, usually until 4 weeks, as this is associated with decreased mortality versus early intervention. In addition, delay and use of antibiotics may allow for application of less invasive drainage procedures. In addition, as Adler and Runzi reported, antibiotic therapy alone can effectively treat a subgroup of patients with infected necrosis.[16,17]

An initial report by Runzi et al. of nonsurgical treatment of severe AP with IPN showed 16 patients who were treated with nonsurgical therapy alone had a 12% mortality rate.[17] This placed a wedge in the concept that all patients with IPN needed immediate open pancreatic surgical drainage. The currently accepted management is that IPN can generally be managed nonsurgically with antibiotics in the initial stage and that antibiotics alone can also be definitive therapy. The second concept is that surgery can be delayed, which allows the operative intervention to be performed electively and with less invasive intervention.

Recognition of infection

Recognition of infection in patients with necrotizing pancreatitis is based primarily on clinical suspicion and imaging (Box 47.1). Infection usually occurs during the so-called second phase of disease, 1 to 2 weeks after onset of necrotizing pancreatitis, when the patient's immune system is likely suppressed, thus increasing susceptibility to infection.[18] Clinically, the patient may have persistent or new-onset sepsis without another source (i.e., pneumonia, urinary tract infection). Bacteremia is a poor prognosis factor, and patients may have clinical deterioration with OSF despite maximum support. Contrast-enhanced CT may reveal gas bubbles within the pancreatic or peri-pancreatic necrosis, and while this is highly suggestive of infected necrosis, it can be the result of a fistula between the pancreatic collection and the bowel. Laboratory findings may include leukocytosis, acidosis, and positive blood culture. Previously, Barkin et al. described CT-guided percutaneous FNA for diagnosing pancreatic infection.[19] Presently, percutaneous pancreatic aspiration by FNA is not routinely utilized because of a high rate of false-negative aspirations. The role of FNA in the diagnosis of IPN was reported by van Baal et al.[20] who found that IPN can generally be diagnosed based on clinical or imaging signs of infection. FNA may be useful in patients with unclear clinical signs and/or no imaging signs of IPN. We also utilize FNA in patients who are clinically not responding to empiric antibiotic therapy as this may be due to bacterial antibiotic resistance and/or fungal infection. The impact of antibiotic-resistant bacterial and/or fungal infections on outcome of AP was reported by Moka et al.[21] They found fungal infection in 102/556 patients, of which 28/102 had fungal infection without bacterial infection. Culture-proven IPN collection was present in 161/556 (29%). Drug resistance to tigecycline was 21% in their series. Drug resistance and rate of fungal infection increased in patients with ICU stay and increased length of hospital admission. Our approach to patients with suspected pancreatic infection is empiric antibiotics and delay of intervention. This conservative approach for IPN was summarized by Mouli et al.[22] who reported that conservative management of IPN, with intravenous (IV) antibiotics and nutritional support with or without catheter drainage, was successful for 64% of patients (with a mortality of 12%) and that only 26% of patients required necrosectomy or additional surgery for complications. Thus, the currently adopted modified conservative approach is drugs, delay, and then drain/debride.

Role of enteral nutrition to prevent infection

Enteral nutrition (EN) when compared to parenteral nutrition (PN), in patients with AP reduces mortality, multiorgan failure (MOF), infections, and operative intervention. In addition, it reduces local septic complications as well as other local complications. Subgroup analysis of EN versus TPN in patients with SAP showed a relative risk of death in the EN group of 0.18 and a relative risk for MOF of 0.46.[23]

EN likely improves intestinal barrier function and prevents bacterial translocation (see the earlier section "When does pancreatic necrosis become infected?"). EN can be administered either via nasogastric or nasojejunal feedings. In patients with SAP who are

unable to tolerate oral liquids, EN should begin early in their course, within 48 hours of admission, as it significantly reduces MOF, pancreatic infection, and mortality. Petrov, in a systemic review on timing of artificial nutrition in AP, found that EN begun within 48 hours of admission versus TPN resulted in significant reduction in risk of MOF, pancreatic infectious complications, and mortality. These benefits were not found if EN was begun after 48 hours of admission.[24]

Approach and treatment of pancreatic infection

Mowbray et al. reported the microbial spectrum seen in IPN that revealed a high frequency of polymicrobial infection with predominance of enterococci, staphylococci, and *Escheria coli* bacteria.[25] In his own population, he found that pathogens causing IPN were predominantly gastrointestinal flora (i.e., *Enterococcus faecalis* and *faecium* and *E. coli*). Almost half of their patients grew multiple organisms. The median time to drainage was 29 days. Carbapenem antibiotics provided good antimicrobial coverage against these enteric microorganisms (see Box 47.2).

Sahr et al. reported culture results at a median of 45 days (mean 87 days) from the onset of AP. In their nontransfer group of patients, there was an almost equal distribution of single microorganism and polymicrobial cultures.[26] Predominant microorganisms were *Staphylococcus* spp. and *Streptococcus* spp. In the transfer group, of whom 80% were previously treated with antibiotics, infected WON was found in 70% of patients previously treated with antibiotics versus only 20% in patients without previous antibiotics. The most common microorganisms included *Candida* spp., *Enterococcus* spp., and coagulase-negative staphylococci.

The emergence of multidrug resistant (MDR) microorganisms is a major concern in treating critically ill patients, such as those with SAP. Lee et al. found MDR organisms in 63% of their 46 patients.[27] The most frequent MDR bacteria was methicillin-resistant *Staphylococcus aureus*. Transferred patients, as in other studies, had a higher incidence of MDR infections than did primary admitted patients, in a ratio of 2:1. Mortality was not significantly different in the patients with MDR infections versus those without. Conversely, Jain et al.[28] reported that IPN due to infection with MDR organisms was an independent predictor of mortality, whereas IPN by itself was not a predictor. This is explained likely by the improved present-day management of IPN with IV antibiotics, drainage, and minimally invasive necrosectomy. In this transferred group, almost half of patients had received prophylactic antibiotics.

Fungi, especially *Candida* spp., are the most frequently isolated fungi in patients with IPN.[29] *Torulopsis glabrata* is the second most common species in IPN. Primary fungal infections, which occur in the absence of intervention, may be more likely to occur in patients receiving TPN and in elderly patients. Fungal infections are being increasingly recognized in patients with a complicated course of AP, especially in those who received antibiotics.[30] Kochhar et al. reported primary fungal infections in up to 17% of patients with IPN and in up to 32% during their disease course (secondary fungal infection).[31] Reuken et al. found fungal pancreatic infections (FPI) in 46% of aspirates. These were predominantly caused by *Candida* spp. Increased risks for FPI were having previously received antibiotic therapy and for a longer duration (9 vs. 2 days).[30] This population had a lower long-term, 1-year survival (78% vs. 95%) than those with only bacterial infection. Other studies have questioned whether antibiotic therapy predisposes to fungal infection or whether FPI is simply an indicator of increased disease severity and comorbidities. Gram-positive bacteria are more common in patients with primary candida infection, whereas gram-negative bacteria are more common in secondary infections. Mortality is higher in secondary fungal infections.[31]

The clinical presentation of fungal infection mimics bacterial infection except for a more indolent course compared to bacterial infection.29 While there are no clinical features of fungal infection in patients with AP, it has been reported to occur 22 to 33 days from admission. Diagnosis can be via culture or polymerase chain reaction assay. Treatment with fluconazole or amphotericin B is appropriate for *Candida* spp., whereas amphotericin B is appropriate for *T. glabrata*. There is controversy over whether antifungal therapy changes the outcome. Werge et al. found no significant difference in mortality (21% vs. 13%) or OF between the group treated with antifungals after the first fungal finding compared with the group not treated or treated inadequately.[32] Similar to IPN from bacteria, minimally invasive debridement should be evaluated in the presence of ongoing infection and/or deterioration of clinical parameters.

BOX 47.2

Initial approach to acute pancreatitis patients with suspected infection during the course of acute pancreatitis by clinical features and/or imaging

- Culture blood or other fluid collection—ascites, pleural
- Begin carbapenem drugs if negative culture—meropenem or imipenem
- Failure to respond to antibiotics—evaluate for fine-needle aspiration with drainage

Treatment of infected pancreatic necrosis

Debridement or necrosectomy is a foundation of therapy for organized IPN, as shown in Table 47.1 and Box 47.3. This treatment is presently based on an organ-preserving approach, combined with maximization of removal of retroperitoneal debris and exudates. Our approach has evolved from open surgery to minimally invasive surgery. The surgical odyssey for patients with SAP has evolved from simple drainage to resection of necrosis, to debridement, and now to sequestration.[33] Bradley emphasizes that delayed complications may still require surgical intervention, including gastroduodenal or common bile duct obstruction by necrotic collections, fistulization of the necrotic collections into adjacent bowel, disconnected pancreatic duct syndrome secondary to pancreatic ductal necrosis, and intraperitoneal hemorrhage.[34] Presently, intervention is primarily

TABLE 47.1 **TREATMENT OF PANCREATIC INFECTION (4 D'S)**

Drugs	Empiric antibiotics, enteral nutrition
Delay	Watch and wait for 4 weeks to allow for localization of infection in a stable patient
Drain	Drainage initial modality can be done prior to 4 weeks
Debride	Minimal invasive approach by endoscopic transluminal, percutaneous catheter drainage, video-assisted retroperitoneal dissection

Modified from Besselink MGH. *Dig Liver Dis.* 2011; 43:421–422

applied sparingly to patients with IPN because the majority of patients with necrotizing pancreatitis have sterile necrosis, which can be successfully treated conservatively.[18] The conservative approach, known as the "step-up-approach" to patients with IPN, is advocated by Besselink.[35] It is based on allowing the inflammatory process to become localized (the so-called "delay"). Use of antibiotics is associated with decreased mortality, and the role of antibiotics is to prevent systemic sepsis ("drugs"). The approach then moves to minimally invasive procedures (percutaneous or endoscopic) to drain the infection ("drain"), and, last, to debridement ("debride"), again using minimally invasive methods (i.e., video-assisted retroperitoneal dissection [VARD] or endoscopic or percutaneous catheters).[33] This step-up-approach was found, when compared to open necrosectomy, to reduce mortality (12% vs. 40%) and cost. The step-up approach applies minimally invasive techniques (MITs), that are associated with less physiologic stress when compared with open surgical procedures and therefore less morbidity and mortality.[36] The MITs include percutaneous catheter drainage, endoscopic transluminal drainage and debridement, and retroperitoneal surgical necrosectomy. Initially, minimally invasive drainage was by percutaneous drainage alone. Minimally invasive percutaneous drainage is used to control sepsis in patients with IPN. All minimally invasive procedures including endoscopic therapy can be the final therapy needed or a bridge to definitive therapy and can be successfully applied, prior to 4 weeks, with no increase in complications.[37] The goal is removal of infected material and to allow reabsorption of remaining material. Thus, surgical intervention has changed from early open surgical necrosectomy with possibly an open incision to facilitate second debridement (multiple) to delayed operation for debridement of a localized infected area.[37]

BOX 47.3

When to consider drainage/debridement

- Walled-off pancreatic or peripancreatic infection optimal >4 weeks
- Patients with severe clinical deterioration resulting in ongoing organ failure
- Minimally invasive drainage/debridement can be utilized prior to 4 weeks without increased mortality

Guo Q, Hu WP. *Ann Surg*. 2017;265:e64–e65.

This delay in postponing surgical necrosectomy until 30 days after initial hospitalization is associated with decreased mortality. The drawback to this "delayed approach" may be an increase in fungal infections and infection with antibiotic-resistant organisms.

A follow-up study on the original patient groups that were randomized to a surgical step-up approach or open necrosectomy by Hollemans et al. reported that a significantly lower proportion of patients in the step-up group died or had major complications, including decreased incisional hernias, pancreatic exocrine insufficiency, and endocrine insufficiency. No differences were found in patients requiring additional drainage procedures or pancreatic surgery or in recurrent AP. Thus, the step-up approach is superior to open necrosectomy.[38] Van Baal et al. performed a systematic review of percutaneous catheter drainage (PCD) used in patients with suspected infected pancreatitis or sterile, symptomatic collections.[39] They found in this primarily retrospective study cohort that 71% were infected. Overall, 56% of all patients undergoing PCD did not require additional surgical necrosectomy. Complications were mostly internal and external fistulas. Mortality rate in infected patients was 15%. PCD of sterile pancreatic collections can introduce infection more so than percutaneous aspiration. In addition, the authors noted that PCD is a labor-intensive and time-consuming therapy (i.e., daily lavage of the catheter by the patient and frequent need for catheter replacement by the interventional radiologist).

Liang Ji et al. evaluated the risk factors for need of surgical necrosectomy after PCD of IPN.[40] They found on CT that the mean density of the necrotic fluid collection was an independent risk factor, emphasizing that PCD does not debride necrotic debris effectively, thus favoring the initial use of endoscopic drainage and debridement for IPN. Hollemans et al. also found that increasing amounts of pancreatic necrosis and heterogeneous collections were negative predictors for successful catheter drainage in infected necrotizing pancreatitis.[41] Hollemans et al. and the previous study by Liang Ji et al. also reported that MOF was also a negative feature. Thus, the catheter sizes used for percutaneous drainage allows for drainage primarily of fluids but limits the effective debridement of necrotic material, which is an especially important limitation in patients with MOF.[40]

PCD is an especially useful drainage procedure in patients who (1) cannot tolerate the anesthesia needed for endoscopic procedures, (2) when collections are too distant (>2 cm) from the stomach for endoscopic drainage, and (3) there is no window to allow for endoscopic drainage and debridement. Percutaneous drainage is usually CT-guided, and multiple catheters may be needed. Follow-up procedures using CT imaging are needed to upsize the catheter to facilitate drainage of debris. In addition, ongoing drainage from the

pancreatic duct may require endoscopic stent placement.[42] PCD can be combined with video-assisted endoscopic debridement and/or endoscopic drainage and debridement.

Surgical laparoscopic necrosectomy

Surgical laparoscopic necrosectomy (SLN) can be applied by itself, at the later stage of disease, and/or combined with other needed surgical procedures (i.e., cholecystectomy in patients with biliary AP). Its advantages over MIP include the more likely complete removal of necrotic infected material in a single session.[43] Its disadvantages include the need for general anesthesia and pneumoperitoneum, and it is overall more invasive, thus favoring MIP.

Video-assisted retroperitoneal debridement allows debridement via direct or guided (via PCD tract) placement of a scope into a retroperitoneal collection. It avoids pneumoperitoneum and entry into peritoneum as needed for open surgery, but it requires multiple procedures. It should be regarded as a possible next step for drainage of collections that previously had undergone PCD. Its complications include bleeding and colon perforation.[43] Open necrosectomy is being utilized less frequently for IPN but has a role in patients with complications (i.e., perforation). Noninvasive modalities each have advantages, and their combined use can improve patient outcomes.

Endoscopic transluminal drainage and debridement has become the initial step-up procedure for drainage of IPN. Endoscopic step-up was compared to an open surgical step by Bakker et al.[44] Eighty percent of their study population previously had catheter drainage, accounting for their high surgical complication rate. Endoscopic transgastric necrosectomy significantly reduced postprocedural interleukin (IL-6) levels compared with surgical necrosectomy. In addition, endoscopic transgastric necrosectomy did not cause new-onset MOF, which is a major cause of morbidity and mortality in AP (0% vs. 50% surgical), and it reduced the number of pancreatic fistulas.[44] Endoscopic drainage is becoming the primary step-up drainage/debridement procedure. The follow-up article by van Brunschot et al. from the same group randomly compared endoscopic necrosectomy to percutaneous catheter drainage followed, if needed, by VARD. Endoscopic necrosectomy prevailed because the rate of pancreatic fistulas and length of hospitalization were lower in the endoscopic group. The major complications and mortality did not differ. Thus, the endoscopic approach offers an incisionless approach over PCD (followed, if necessary, by VARD) to a very difficult problem.[45] Bang et al. compared outcomes of minimally invasive surgery, laparoscopy, or VARD with or without PCD to endoscopic approaches for patients with confirmed or suspected IPN in a randomized trial.[46] Overall, there was no difference in mortality (8.8 vs. 6.3 surgery). However, no patients developed enteral or pancreatic cutaneous fistula in the endoscopic group versus 28.1% in the surgical group, and the surgical group had significantly more complications compared to the endoscopy group. The endoscopy group had better quality of life scores and lower mean total costs. Nutritional support was provided to both groups.

Khan et al. conducted a systematic review and meta-analysis to compare the safety of endoscopic drainage (ED) with minimally invasive surgery for managing IPN.[47] They reported that the rate of mortality for ED was 8.5% versus 14.2% for minimally invasive surgery. The pooled odds ratio was 0.59 in favor of ED. Development of new MOSF rates after intervention was 12% for ED and 54% for MIS. ED was associated with significantly lower rates of pancreatic fistula formation and shorter length of hospital stay. Thus, ED is the preferred invasive management strategy over minimally invasive surgery.

Conclusion

Pancreatic infection is associated with increased mortality and morbidity compared with sterile pancreatic necrosis. Overall, these patients are best managed by "a city" that comprises a multidisciplinary team of specialists, including dedicated pancreatologists, infectious disease specialists, interventional endoscopists, radiologists, nutritionists, and surgeons. This team approach will result in improved survival with decreased morbidity. Our approach is the "4 D's":

1. Drugs—antibiotics and enteral nutrition
2. Delay intervention until the acute process is localized
3. Drain by a minimally invasive procedure/s
4. Debride—may be combined with drainage, as in endoscopic necrosectomy, to improve the outcome of patients with pancreatic infections. Surgery may be needed in select patients with complications.

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References

1. Besselink MG, van Santvoort MA, Boermeester VB, et al. Timing and impact of infections in acute pancreatitis. *Br J Surg*. 2009;96:267–273.
2. Xue P, Deng L-H, Zhang Z-D, Yang X-N, et al. Infectious complications in patients with severe acute pancreatitis. *Dig Dis Sci*. 2009;54:2748–2753.
3. Banks PA, Bollen TL, Dervenis, et al. Classification of acute pancreatitis. *Gut*. 2013;62:102–111.
4. Rana SS, Sharma RK, Gupta P, Gupta R. Natural course of asymptomatic walled-off pancreatic necrosis. *Dig Liver Dis*. 2018. https://doi.org/10.1016/j.dld.2018.10.010
5. Petrov MS, Shanbhag S, Chakraborty M, et al. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology*. 2010;139:813–820.
6. Lytras D, Manes K, Triantopoulou C, et al. Persistent early organ failure: Defining the high-risk group of patients with severe acute pancreatitis. *Pancreas*. 2008;36:249–254.

7. Besselink MG, van Santvoort HC, Boermeester MA, et al. Timing and impact of infections in acute pancreatitis. *Brit J Surg*. 2009;96:267–273.
8. Fritz S, Hackert T, Hartwig W, et al. Bacterial translocation and infected pancreatic necrosis in acute necrotizing pancreatitis derives from small bowel rather than from colon. *Am J Surg*. 2010;200:111–117.
9. Pando E, Alberti P, Hidalgo J, et al. The role of extra-pancreatic infections in the prediction of severity and local complications in acute pancreatitis. *Pancreatology*. 2018;18:486–493.
10. Liu H, Li w, Wang X, et al. Early gut mucosal dysfunction in patients with acute pancreatitis. *Pancreas*. 2008;36:192–196.
11. Capurso G, Zerboni G, Signoretti M, et al. Role of the gut barrier in acute pancreatitis. *J Clin Gastroenterol*. 2012;46:S46–S51.
12. Busquets J, Fabregat J, Pelaez N, et al. Factors influencing mortality in patients undergoing surgery for acute pancreatitis. *Pancreas*. 2013;42:285–292.
13. Islim F, Salik AE, Bayramoglu S, et al. Non-invasive detection of infection in acute pancreatic and acute necrotic collections with diffusion-weighted magnetic resonance imaging: Preliminary findings. *Abdom Imaging*. 2014;39:472–481.
14. Zavyalov T, Khotsyna Y, Tenner S. The role of antibiotics in the management of patients with acute necrotizing pancreatitis. *Curr Infect Dis Rep*. 2010;12:13–18.
15. Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database of Syst Rev*. 2010 May 12;2010(5):CD002941. doi:10.1002/14651858.CD002941.pub3
16. Adler DG, Chari ST, Dahl TJ, et al. Conservative management of infected necrosis complicating severe acute pancreatitis. *Am J Gastroenterol*. 2003;98:98–102.
17. Runzi M, Niebel W, Goebell H, Gerken G, Layer P. Severe acute pancreatitis: Nonsurgical treatment of infected necroses. *Pancreas*. 2005;30:195–199.
18. van Brunschot S, Bakker OJ, Besselink MG, et al. Treatment of necrotizing pancreatitis. *Clin Gastroenterol Hepatol*. 2012;10:1190–1201.
19. Barkin JS, Smith FR, Pereiras R, et al. Therapeutic percutaneous aspiration of pancreatic pseudocysts. *Dig Dis Sci*. 1981;26(7):585–587.
20. van Baal MC, Bollen TL, Bakker OJ, et al. The role of routine fine-needle aspiration in the diagnosis of infected necrotizing pancreatitis. *Surgery*. 2014;155:442–448.
21. Moka P, Goswami P, Kapil A, et al. Impact of antibiotic-resistant bacterial and fungal infections in outcome of acute pancreatitis. *Pancreas*. 2018;47:489–494.
22. Mouli VP, Sreenivas V, Garg PK. Efficacy of conservative treatment without necrosectomy for infected pancreatic necrosis: A systemic review and meta-analysis. *Gastroenterol*. 2013;144:333–340.
23. Al-Omran M, Albalawi ZH, Tashkandi MF, Al-Ansary LA. Enteral vs. parenteral nutrition for acute pancreatitis. *Cochrane Database Syst Revs*. 2010:CD002837.
24. Petrov MS, Pylychuk RD, Uchugina AF. A systematic review on timing of artificial nutrition in acute pancreatitis. *Br J Nutrition*. 2009;101:787–793.
25. Mowbray NG, Ben-Ismaeil B, Hammoda M, Shingler G. The microbiology of infected pancreatic necrosis. *Hepatobil Pancreat Dis Intl*. 2018;17:456–460.
26. Sahar N, Kozarek R, Kanji ZS, et al. The microbiology of infected pancreatic necrosis in the era of minimally invasive therapy. *Eur J Clin Microbiol Infect Dis*. 2018;37:1353–1359.
27. Lee H-S, Lee SK, Park DH, et al. Emergence of multidrug resistant infection in patients with severe acute pancreatitis. *Pancreatology*. 2014;14:450–453.
28. Jain S, Mahapatra SJ, Gupta S, et al. Infected pancreatic necrosis due to multidrug-resistant organisms and persistent organ failure predict mortality in acute pancreatitis. *Clin Transl Gastroenterol*. 2018;9:190.
29. Trikudanathan G, Navaneethan U, Vege SS. Intra-abdominal fungal infections complicating acute pancreatitis: A review. *Am J Gastroenterol*. 2011;106:1188–1192.
30. Reuken PA, Albig H, Rödel J, et al. Fungal infections in patients with infected pancreatic necrosis and pseudocysts: Risk factors and outcome. *Pancreas*. 2018;47:92–98.
31. Kochhar R, Noor MT, Wig J. Fungal infections in severe acute pancreatitis. *J Gastroenterol Hepatol*. 2011;26:952–959.
32. Werge M, Roug S, Novovic S. Fungal infections in patients with walled-off pancreatic necrosis. *Pancreas*. 2016;10:1447–1451.
33. Bradley EL (III), Dexter ND. Management of severe acute pancreatitis. *Ann Surg*. 2010;251:6–17.
34. Bradley EL (III). Justifying intervention in walled-off necrosis (WON) *Ann Surg*. 2018. doi:1097/SLA.
35. Besselink MGH. The step-up-approach to infected necrotizing pancreatitis: Delay, drain debride. *Dig Liver Dis*. 2011;43:421–422.
36. Bradley EL (III), Howard TJ, van Sonnenberg E, Fotoohi M. Intervention in necrotizing pancreatitis: An evidence-based review of surgical and percutaneous alternatives. *J Gastrointest Surg*. 2008;12:634–639.
37. Trikudanathan G, Tawfik P, Amateau SK, et al. Early (<4 weeks) standard (≥4 weeks) endoscopically centered step-up interventions for necrotizing pancreatitis. *Am J Gastroenterol*. 2018;10:1550–1558.
38. Hollemans RA, Bakker OJ, Boermeester MA, et al. Superiority of step-up approach vs. open necrosectomy in long-term follow-up of patients with necrotizing pancreatitis. *Gastroenterology*. 2018. https://doi.org/10.1053/j.gastro.2018.10.045
39. van Baal MC, van Santvoort HC, Bollen TL, et. al. Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. *Brit J Surg*. 2011;98:18–27.
40. Liang Ji, Wang G, Li L, et al. Risk factors for the need of surgical necrosectomy after percutaneous catheter drainage in the management of infection secondary to necrotizing pancreatitis. *Pancreas*. 2018;47:436–443.
41. Hollemans RA, Bollen TL, van Brunschot S, et al. Predicting success of catheter drainage in infected pancreatic necrosis. *Ann Surg*. 2016;263:787–792.
42. Shyu JY, Sainami NI, Sahni VA, et al. Necrotizing pancreatitis: Diagnosis, imaging and intervention. *RadioGraphics*. 2014;34:1218–1239.
43. Lim E, Sundaraanmoorthy RS, Tan D, et al. Step-up approach and video-assisted retroperitoneal debridement in infected necrotizing pancreatitis: A case complicated by retroperitoneal bleeding and colonic fistula. *Ann Med Surg*. 2015;4:225–229.
44. Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs. surgical necrosectomy for infected necrotizing pancreatitis. A randomized trial. *JAMA*. 2012;307:1053–1061.
45. van Brunschot S, van Grinsven J, van Santvoort H, et al. Endoscopic or surgical step-up approach for infected necrotizing pancreatitis: A multicenter randomized trial. *Lancet*. 2018;391:51–58.
46. Bang JY, Amoletti JP, Holt BA, et al. An endoscopic transluminal approach compared to minimally invasive surgery reduces complications and costs for patients with necrotizing pancreatitis. *Gastroenterology*. 2018. https://doi.org/10.1053/j.gastro.2018.11.031.
47. Khan MA, Kahaleh M, Khan Z, et al. Time for a changing of guard. From minimally invasive surgery (MIS) to endoscopic drainage (ED) for managing pancreatic walled-off necrosis. *J Clin Gastroenterol*. 2018.doi 10:1097/MCG.

48

Esophageal infections

Uni Wong and Jean-Pierre Raufman

Esophageal infections are commonly encountered in clinical practice and contribute significant morbidity, particularly in those with pathologic or iatrogenic impaired cellular immunity. Patients with AIDS encompass a large proportion of those with infectious esophagitis. However, with the increased use of highly active antiretroviral therapy (HAART) to treat HIV/AIDS, the risk of opportunistic esophageal infections has decreased in this patient population. Others who are particularly susceptible to opportunistic esophageal infections include those receiving chemotherapy, radiation, or immunotherapy for cancer, and those receiving immunosuppressants following solid organ or bone marrow transplantation.

Candida albicans is the most common pathogen underlying infectious esophagitis, but a variety of fungal, viral, and bacterial organisms are capable of triggering infection (see Box 48.1). Regardless of the causative organism, infection results in mucosal inflammation with hallmark symptom of odynophagia (painful swallowing). Erosions, ulcerations, and fistulae may occur. Prompt recognition with identification of the pathogen and initiation of therapy is of paramount importance because esophageal infections generally respond quickly to appropriate therapy.

Fungal infections of the esophagus

Candida species

C. albicans is the fungal organism most frequently implicated in infectious esophagitis. Other *Candida* spp. (*tropicalis, parapsilosis, krusei,* and *glabrata*) rarely cause disease in the absence of severe immunosuppression. *Candida* organisms are normal components of the oral flora; colonization of the esophagus is not unusual. In fact, a population-based study revealed colonization with *Candida* organisms in up to 20% of healthy adults. Rates of colonization are even higher—up to 80%—in those receiving critical care in an intensive care unit.

Progression to infectious esophagitis requires invasion of the epithelium, usually in the setting of defective cellular immunity. HIV infection, particularly when associated with CD4 counts of $<200/mm^3$ has long been an established risk factor for *Candida* esophagitis, an AIDS-defining illness. Other risk factors include hematological malignancies, diabetes mellitus, adrenal insufficiency, alcoholism, advanced age, radiation therapy (especially for head and neck cancers), systemic chemotherapy, systemic and topical oronasopharyngeal steroids, antibiotics, and suppressants of gastric acid secretion (e.g., proton pump inhibitors). Prolonged stasis of esophageal contents, for example in the setting of achalasia or scleroderma, may also predispose to epithelial invasion by microorganisms. Surprisingly, biologicals and immunomodulatory drugs used to treat inflammatory bowel diseases and rheumatoid arthritis do not appear to increase the risk of esophageal candidiasis.

BOX 48.1

Organisms associated with infectious esophagitis

Fungi

Candida spp. (especially *C. albicans*)
Aspergillus spp.
Histoplasma capsulatum
Blastomyces dermatitidis

Viruses

Herpes simplex virus type 1
Cytomegalovirus
Varicella-zoster virus
Human immunodeficiency virus
Human papilloma virus

Bacteria

Mycobacterium tuberculosis and *M. avium*
Actinomyces israelii
Staphylococcus aureus
Streptococcus viridans
Lactobacillus acidophilus
Treponema pallidum
Idiopathic ulcerative esophagitis in AIDS

Parasite

Trypanosoma cruzi

Clinical presentations

The symptoms of *Candida* esophagitis vary depending on severity of disease and the degree of host immunocompetency. Mild disease in immunocompetent hosts may cause minimal to no symptoms. When symptomatic, odynophagia is the most common complaint. In severe cases, patients may describe dysphagia (difficulty swallowing) and experience sitophobia (fear of eating). With severe inflammation and edema, some patients may even have difficulty tolerating oral secretions or experience chest pain even in the absence of swallowing. Particularly in profoundly granulocytopenic patients, disseminated candidiasis can result in fever, sepsis, and the development of fungal abscesses in the liver, spleen and kidneys.

Esophageal candidiasis is often associated with oropharyngeal thrush, but approximately 25% of the time *Candida* esophagitis occurs in the absence of thrush. In general, thrush has positive and negative predictive values for the presence of *Candida* esophagitis, in the range of 90% and 82%, respectively. A high index of suspicion remains necessary as the absence of thrush does not preclude the diagnosis of *Candida* esophagitis.

Notably, immunocompromised patients are at high risk for esophageal coinfection. The probability of viral coinfection in the setting of *Candida* esophagitis is reported as high as 50%. Cytomegalovirus (CMV) and herpes simplex virus (HSV) infections can be seen in HIV-infected patients with CD4 counts of <200/mm^3. Therefore, if odynophagia or dysphagia does not improve within 3 to 5 days on empiric therapy for *Candida* esophagitis, esophagoscopy is warranted to evaluate for existing coinfection.

Severe complications from *Candida* esophagitis are rare but can contribute substantially to the morbidity and mortality of the underlying disease. Low-grade upper gastrointestinal bleeding can occur with friability and ulcerations in the esophagus but generally does not require blood transfusion. Other complications include mucosal scarring and stricture, mucosal sloughing with replacement by pseudomembranes, and luminal obstruction from fungus balls. The most concerning complication associated with severe *Candida* esophagitis is the formation of fistulae from the esophagus to the trachea, bronchi, or mediastinum.

Diagnosis

Candida esophagitis should be suspected in any at-risk patients complaining of odynophagia or dysphagia. In the appropriate clinical setting, empiric therapy is recommended, and symptoms are expected to improve within 3 to 5 days in uncomplicated cases. However, due to the high frequency of coinfection, further evaluation with esophagoscopy is recommended for those not responding to treatment within 3 to 5 days.

Esophagoscopy with direct brushing and biopsy of abnormal mucosa remains the most accurate method to diagnose fungal esophagitis (Figure 48.1). Endoscopic findings of *Candida* esophagitis range from scattered white or pale yellow plaques (Figure 48.2A) to dense pseudomembranes consisting of fungi, sloughed mucosal cells, and fibrin overlying severely damaged mucosa. The latter findings are usually accompanied by severe symptoms. However, the endoscopic appearance alone is insufficient to diagnose *Candida* esophagitis. Brushings from the involved mucosa can be obtained with a sheathed cytology brush, spread onto slides, and stained with the periodic acid-Schiff (PAS), silver, or Gram methods. Mycelial forms and masses of budding yeast are consistent with *Candida* infection (Figure 48.2B). Fungal cultures are generally not needed unless an unusual pathogen (e.g., a resistant *Candida* species, such as *C. glabrata*) is suspected.

Due to nonspecific findings and high rates of coinfection, radiologic studies are generally not utilized to diagnose esophageal infections. Radiologic studies are useful, however, when esophagoscopy with biopsies is contraindicated due to severe thrombocytopenia or coagulopathy, or when a complication such as perforation, stricture, or fistula (severe dysphagia or coughing during meals) is suspected. Abnormal barium esophagrams may reveal a "shaggy" esophagus, plaques, pseudomembranes, cobblestoning, nodules, strictures, fistulae, or mucosal bridges.

Treatment

When *Candida* esophagitis is suspected in at-risk patients with complaints of odynophagia or dysphagia, empiric therapy should be initiated as soon as possible; endoscopic confirmation is

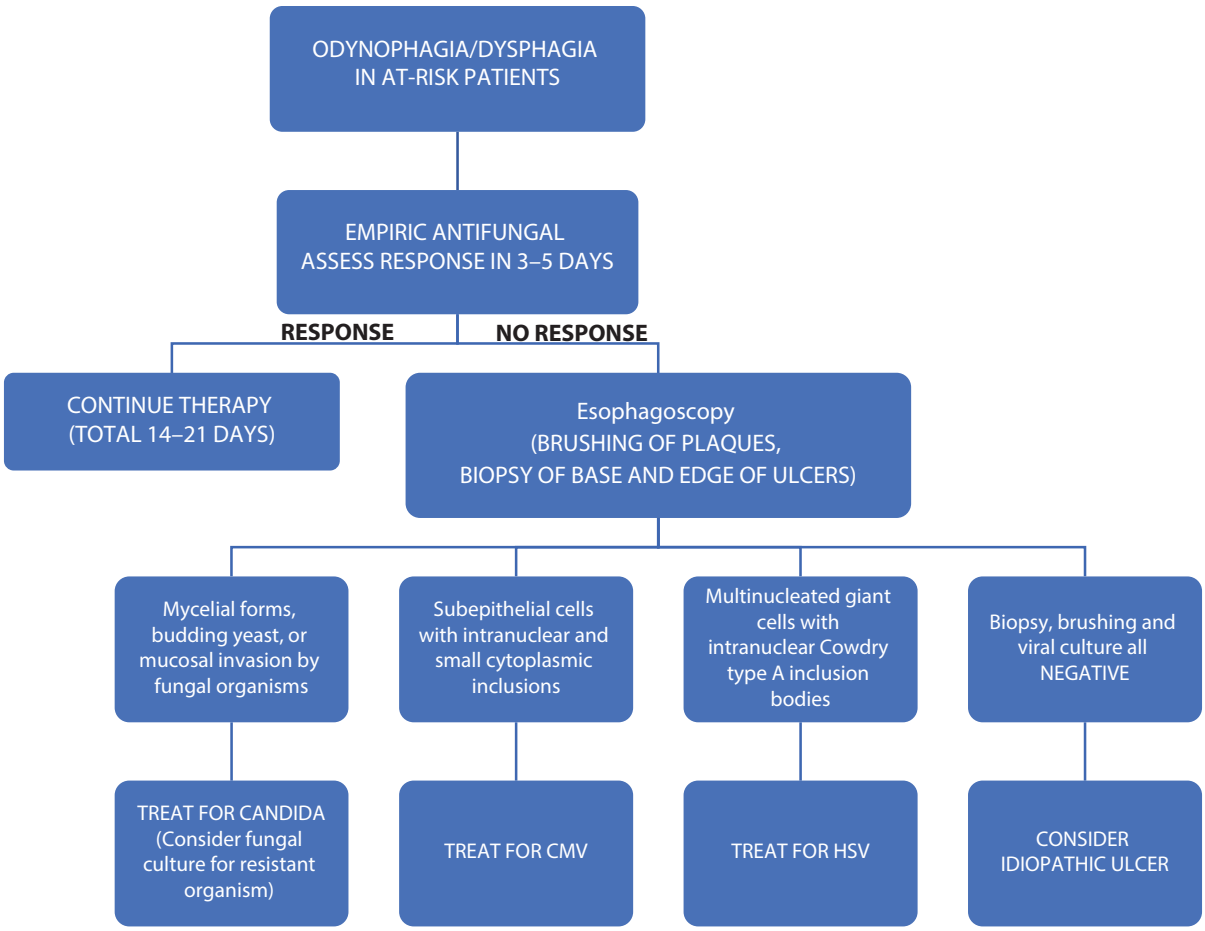

FIGURE 48.1 Suggested diagnostic approach to common esophageal infections.
CMV, cytomegalovirus; HSV, herpes simplex virus type 1.

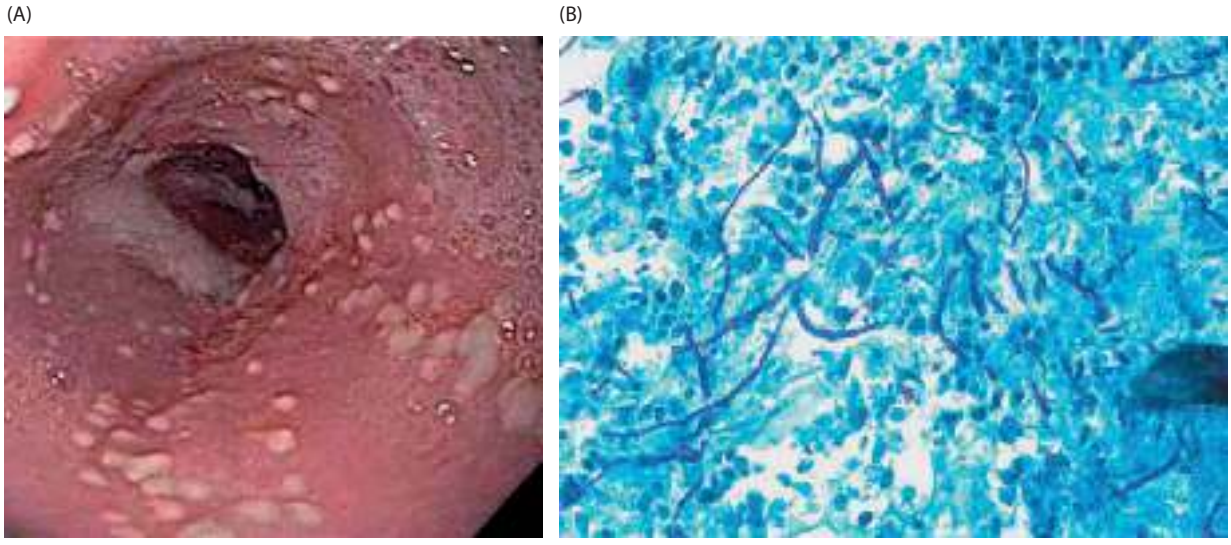

FIGURE 48.2 Endoscopic image of *Candida* esophagitis with multiple raised white plaques. (B) Biopsy revealing budding yeast cells, hyphae, pseudohyphae, and mucosal invasion by the organisms (periodic acid-Schiff 60×).
Courtesy of Harris Yfantis, MD, VA Medical Center, Baltimore, Maryland.

not required. Esophageal candidiasis always requires systemic rather than topical therapy. Treatment options include azoles, echinocandins, and amphotericin B. Azoles work by altering the fungal cell membrane permeability by inhibiting ergosterol synthesis. Echinocandins inhibit the synthesis of β(1,3)-D-glucan, an essential component of *Candida* cell walls. Amphotericin B binds irreversibly to fungal membrane sterols, thereby altering membrane permeability. If there is no response to empiric therapy within 3 to 5 days, esophagoscopy with biopsy and brushing is warranted to evaluate for coinfection.

According to the 2016 Update by the Infectious Diseases Society of America on the Clinical Practice Guideline for Management of Candidiasis, oral fluconazole remains the preferred first-line agent to treat esophageal candidiasis. Treatment with oral fluconazole (200–400 mg [3–6 mg/kg] daily) is recommended for 14 to 21 days. This is generally a safe, cost-effective approach. Toxicity is infrequent and the cost is low. Alternative therapies for those who cannot tolerate oral therapy include intravenous (IV) fluconazole (400 mg [6 mg/kg]) daily or an echinocandin such as micafungin (150 mg/d), caspofungin (70 mg loading dose followed by 50 mg/d), or anidulafungin (200 mg/d) for 14 to 21 days. Amphotericin B deoxycholate (0.3–0.7 mg/kg/d for 21 days) is a less favorable alternative due to the risk of renal toxicity. Once the patient can tolerate oral intake, switching to oral fluconazole (200–400 mg/d) is recommended.

For fluconazole-refractory infections, recommended therapies include itraconazole, voriconazole, micafungin, caspofungin, anidulafungin, and Amphotericin B deoxycholate. In randomized trials, itraconazole oral solution (200 mg/d) appears to be as effective as fluconazole but its use is limited by nausea. Absorption of the capsule form of itraconazole is unreliable compared to the solution. It is important to note that itraconazole inhibits the cytochrome p450 enzymes, thereby increasing the potential for drug interactions. In a large, randomized, double-blind, multicenter trial, voriconazole (200 mg [3 mg/kg] BID) was as effective as fluconazole; therefore, this is another alternative for fluconazole-refractory infection. Echinocandins (micafungin, caspofungin, anidulafungin) and Amphotericin B deoxycholate dosing for refractory *Candida* infection is the same as described earlier.

Patients with recurrent *Candida* esophagitis and those expected to remain on chemotherapy and/or corticosteroids should continue prophylactic fluconazole (100–200 mg three times per week). For HIV-infected persons, antiretroviral therapy (ART) is essential to minimize the risk of recurrent *Candida* infection. In addition, secondary prophylaxis should be considered in this population susceptible to frequent and severe infections until they achieve immune reconstitution on HAART. Fluconazole is generally well tolerated—the most common adverse reactions include headache, abdominal pain, nausea, vomiting, and diarrhea.

Another setting requiring special consideration is pregnancy. Imidazoles are teratogenic, and therefore fluconazole should not be used during the first trimester. Amphotericin B deoxycholate is the drug of choice to treat esophageal candidiasis during pregnancy. Echinocandins are not recommended due to lack of safety data in pregnant women.

Other fungal infections of the esophagus

Esophageal aspergillosis, histoplasmosis, and blastomycosis acquired from the environment rather than from endogenous flora are much less common than infection with *Candida* species. Blastomycosis and histoplasmosis generally invade the esophagus from paraesophageal lymph nodes. Esophageal blastomycosis and histoplasmosis are characterized by focal lesions and abscesses, whereas esophageal aspergillosis is characterized by large deep ulcers. Patients may complain of severe odynophagia if there is muscle layer involvement. Complications of esophageal stricture and tracheaesophageal fistulae are reported.

Viral infections of the esophagus

Herpes simplex virus type 1

HSV-1 is the most common herpesvirus infection of the esophagus, followed by CMV and varicella-zoster virus (VZV). HSV type 2 (HSV-2) infection of the esophagus is rare. HSV-1 esophagitis occurs most commonly in those on immunosuppressive therapy following solid organ and bone marrow transplantation, although infections in immunocompetent hosts are reported. Compared to posttransplant patients, HSV-1 infection occurs much less frequently in HIV-infected individuals (3–5%).

Most cases of HSV esophagitis result from reactivation of the virus in the root ganglia of nerves supplying the affected areas, such as the laryngeal, superficial cervical, and vagus nerves. Primary HSV esophagitis can occur through direct extension from oropharyngeal HSV infection when this double-stranded DNA virus invades the squamous epithelium of the esophagus.

As in fungal esophagitis, the presenting symptoms of HSV esophagitis are usually odynophagia and dysphagia. In some cases, symptom onset can be very abrupt. Other symptoms include chest pain, fever, nausea, and vomiting. Herpes labialis (i.e., cold sores) or oropharyngeal ulcers may precede or occur concurrently with esophageal infection. Approximately 25% of HSV esophagitis is accompanied by HSV or *Candida* infection in the oropharyngeal or genital area.

Immunocompetent hosts usually recover from HSV esophagitis within 1 to 2 weeks, although early use of antiviral therapy can hasten recovery. HSV esophagitis in immunocompromised hosts, on the other hand, can lead to esophageal hemorrhage, perforation with tracheoesophageal fistulas, food impaction, or dissemination to the liver, lungs, and central nervous system.

HSV esophagitis is usually diagnosed by endoscopy when at-risk patients fail to achieve symptomatic improvement after 3 to 5 days of empiric antifungal therapy (see Figure 48.1). In early-stage disease, vesicular herpetic lesions (round vesicles measuring 1–3 mm) may be observed in the mid to distal esophagus. More commonly, by the time endoscopy is performed, vesicles have sloughed to reveal discrete, punched-out, circumferential ulcers (usually <2 cm) with

raised edges (Figure 48.3A). On double-contrast barium studies of the esophagus, HSV esophagitis usually has a distinct appearance of volcano-like ulcers without plaques, whereas ulcerations in *Candida* esophagitis are usually seen with plaques. As disease progresses, however, the discrete HSV ulcers seen at early stages can coalesce into large lesions and can even progress to near-total denudation of the esophageal epithelium. Diffuse herpetic esophagitis can therefore lead to cobblestoning or a "shaggy" mucosa similar to the appearance of *Candida* esophagitis.

Establishing the diagnosis of HSV requires viral culture, histological or cytological examination of the endoscopic brushings, and biopsies obtained from the ulcer edges. HSV preferentially infects squamous epithelial cells, so viral cytopathic changes are most common at ulcer edges. Findings on histological examination of HSV-infected epithelial cells include multinucleated giant cells, ballooning degeneration, ground-glass nuclei and eosinophilic inclusions (Cowdry type A inclusion bodies), and margination of chromatin (Figure 48.3B). Immunohistochemical stains using monoclonal antibodies to HSV glycoproteins may also help establish the diagnosis. Viral culture is more sensitive than histological examination of the brushings and biopsy specimens and can be helpful if a resistant organism is suspected. Qualitative and quantitative polymerase chain reaction (PCR) testing has been used to detect HSV DNA from biopsy samples, although this has limited specificity and positive predictive value.

For immunocompromised patients able to take oral medications, the recommended therapy for HSV esophagitis is acyclovir (400 mg orally five times a day, renally adjusted if needed, for 14 to 21 days). Famciclovir (500 mg TID) and valacyclovir (1 g TID for the same duration) have similar efficacy as acyclovir but are more expensive. IV acyclovir (5 mg/kg q8h for 7–14 days) is recommended for those who cannot tolerate oral medications. Due to manufacturing shortages of IV acyclovir, oral acyclovir should be used to complete treatment when feasible. After 1 to 2 weeks, immunocompetent individuals usually have spontaneous resolution of HSV infection. Anecdotal reports suggest a short course of oral acyclovir (400 mg TID for 7–10 days) can accelerate recovery. Prophylaxis with oral acyclovir (or similar agent such as valacyclovir or famciclovir) should be considered in those remaining at risk for recurrent infection (e.g., undergoing treatment for organ rejection).

Resistant strains of HSV have emerged that typically exhibit cross-resistance to valacyclovir and famciclovir. With these infections, IV foscarnet (40 mg/kg TID) is recommended. Pritelivir, an investigational helicase-primase inhibitor, is currently being evaluated to treat acyclovir-resistant mucocutaneous HSV infection. Viscous lidocaine, often used for pain relief, has modest efficacy and the potential for systemic absorption and toxicity.

Cytomegalovirus

Unlike HSV esophagitis, CMV esophagitis occurs primarily in immunocompromised hosts; rare cases are reported in immunocompetent hosts. In healthy individuals with latent infection, CMV viral DNA can be detected in many tissues, including circulating leukocytes. Latent infection is responsible for the high transmission rate of the virus from CMV-seropositive donors to CMV-seronegative recipients after blood transfusion or organ transplantation. Most cases of CMV esophagitis occur in those with advanced immunosuppression, including AIDS with CD4 counts of <50 cells/mm^3 and CMV viremia. The onset of symptoms is typically more gradual with CMV compared to HSV or *Candida* esophagitis. In addition, odynophagia may be accompanied by fever, nausea, and substernal burning pain.

Endoscopy with biopsy is essential to diagnose esophageal CMV infection (see Figure 48.1). Findings can vary from superficial erosions to large, shallow, well-circumscribed ulcers, most commonly located in mid to distal esophagus. Biopsies should be targeted at the ulcer bases, where CMV-infected subepithelial fibroblasts

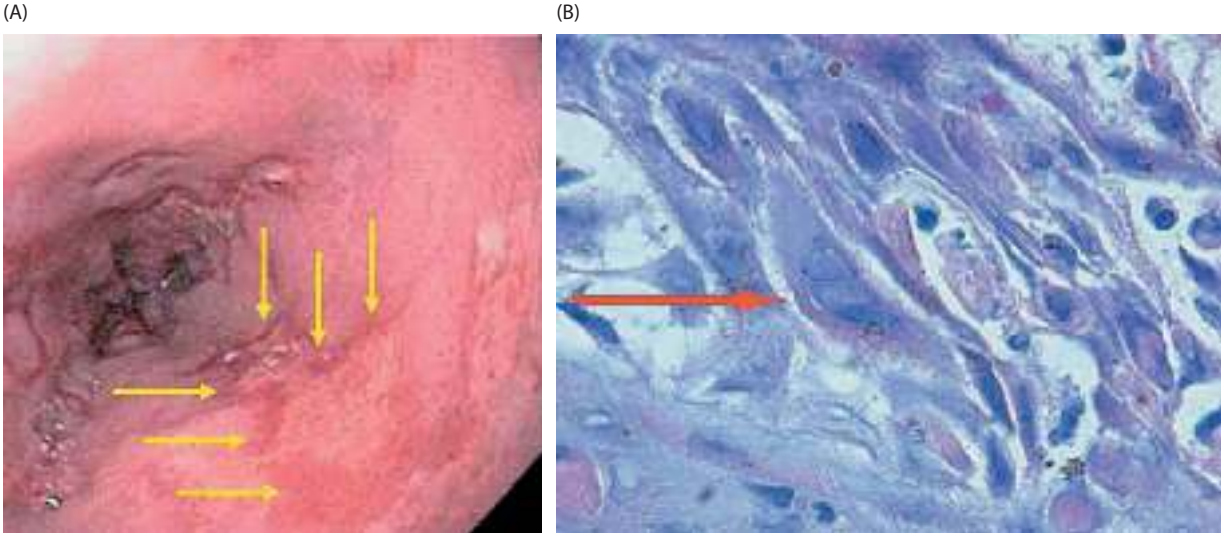

FIGURE 48.3 Endoscopic image revealing a large sharply demarcated ulcer with raised edges in mid esophagus. Ulcer borders are defined by arrows. (B) Biopsy from the ulcer margin demonstrating a multinucleated giant cell (hematoxylin and eosin stain, 100×).
Courtesy of Harris Yfantis, MD, VA Medical Center, Baltimore, Maryland.

and endothelial cells are most likely present. Superficial brushings for cytologic examination have low diagnostic yield. Histological features of CMV infection include the presence of large cells in the subepithelial layer with eosinophilic intranuclear inclusions, a "halo" around the nucleus, and basophilic intracytoplasmic inclusions (Figure 48.4A). Immunohistochemical staining and in situ hybridization can confirm CMV infection (Figure 48.4B), but viral cultures of tissue obtained from ulcer bases are most sensitive and least costly.

Detecting CMV DNA in blood or tissue and/or a positive CMV antibody does not confirm active CMV infection. In a study of patients with advanced AIDS and CMV viremia detected by PCR, fewer than half developed CMV disease after 1 year despite not receiving anti-CMV therapy. While CMV antibody positivity is not helpful in confirming disease, CMV seronegativity suggests an alternate etiology since infection often results from reactivation of latent virus.

Notably, CMV retinitis often occurs concurrently with extraocular CMV infection. Therefore, any patient diagnosed with CMV gastrointestinal disease should have formal ophthalmological screening for retinitis. An initial negative ophthalmologic exam should be repeated for any new visual symptom or followed by serial exams every 6 months until the patient's absolute CD4 cell count is restored to >50 cells/mm^3 with the use of ART.

If the index of suspicion for CMV esophagitis is high (CD4 cell count <50 cells/mm^3 and characteristic endoscopic finding) in someone with severe symptoms, empiric antiviral therapy should be considered. Both ganciclovir and foscarnet are effective treatment options for CMV esophagitis. Due to the risk of renal toxicity with foscarnet, ganciclovir (5 mg/kg IV q12h for at least 3 weeks) is the preferred option. However, foscarnet (90 mg/kg q12h for at least 3 weeks) is preferred for those with refractory leukopenia or thrombocytopenia, and/or when there is concern for ganciclovir resistance. The combination of ganciclovir and foscarnet has been used in resistant disease. Those who respond slowly may need up to 6 weeks of treatment. Maintenance therapy with valganciclovir (900 mg/d) is suggested in patients with recurrent infection until CD4 cell counts of >100 cells/mm^3 are sustained for at least 6 months on ART.

Restoration of a healthy immune system is key to prevent recurrent CMV infection. Most AIDS patients with CMV esophagitis are not on ART. For patients who are ART-naïve, ART should be initiated as long as CMV retinitis has been excluded. ART can induce immune reconstitution inflammatory syndrome (IRIS) in the eyes of patients with CMV retinitis, resulting in blindness. Therefore, in ART-naïve patients with CMV retinitis, anti-CMV therapy should precede ART by at least 2 weeks.

Varicella-zoster virus

VZV esophagitis is rarely symptomatic, and the incidence rate is uncertain. In immunocompromised individuals, VZV esophagitis can be severe but considerably minor compared to disseminated infections including varicella encephalitis, pneumonitis, and fulminant hepatitis. The clinical presentation and endoscopic finding of VZV are similar to those of HSV esophagitis. Dermatologic VZV lesions often occur concurrently with esophagitis, aiding diagnosis. VZV esophagitis may be treated with acyclovir and famciclovir. Foscarnet can be considered in acyclovir-resistant VZV infection.

Idiopathic esophageal ulcers in AIDS

HIV infection is occasionally associated with esophageal ulcers that lack an identifiable pathogen. These lesions, known as *HIV-associated* or *idiopathic esophageal ulcers*, appear as multiple, small aphthoid ulcers during seroconversion in early HIV infection that eventually become giant deep ulcers extending up to several centimeters (Figure 48.5). The latter are associated with severe, incapacitating odynophagia. The clinical, radiologic, and endoscopic appearance of these HIV-associated esophageal ulcers mimic those of CMV esophagitis but without the histological features of CMV infection. Initiation of HAART therapy is essential in healing these ulcers. Systemic and intralesional corticosteroids have been reported to provide symptomatic and endoscopic improvement.

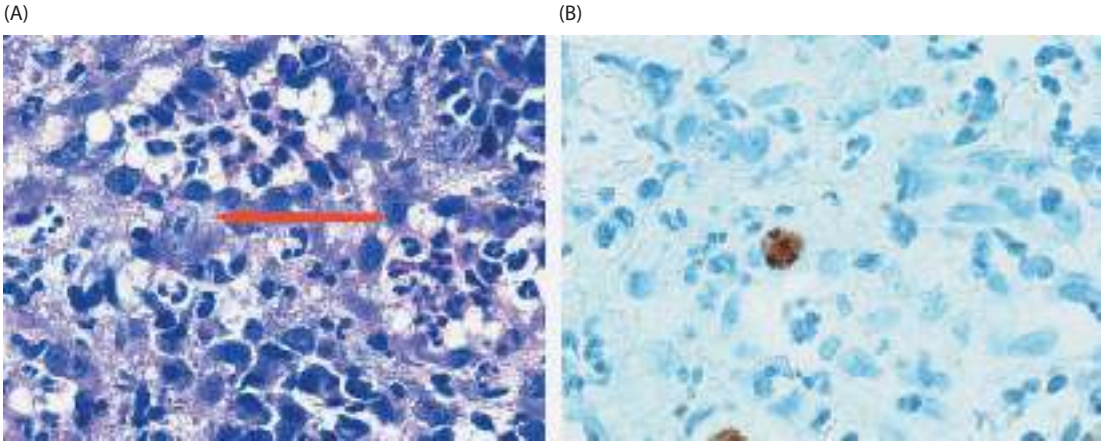

FIGURE 48.4 (A) Biopsy specimen from base of the an esophageal ulcer revealing a perinuclear "halo" suggestive of herpes simplex virus infection (hematoxylin and eosin stain, 100×). (B) Biopsy specimen revealing subepithelial cytomegalovirus by immunohistochemical staining (100×). Courtesy of Harris Yfantis, MD, VA Medical Center, Baltimore, Maryland.

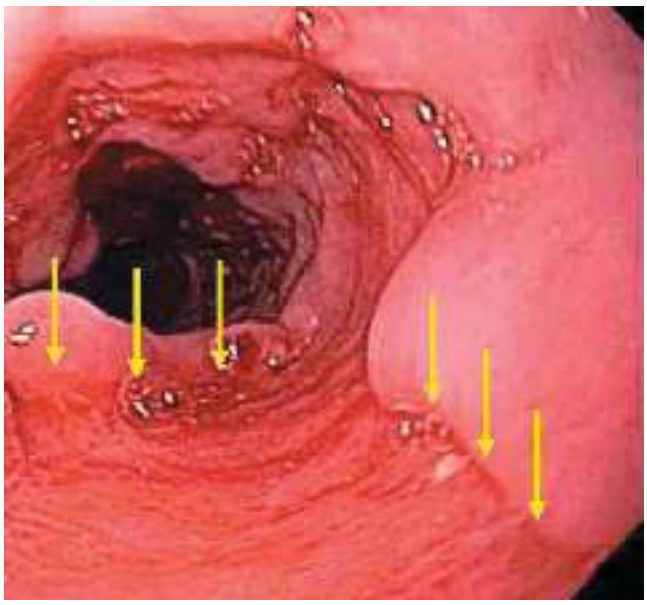

FIGURE 48.5 Endoscopic photograph of a large idiopathic esophageal ulcer crater in a patient with AIDS and odynophagia. Ulcer borders are defined by arrows.

Human papillomavirus

Human papillomavirus is a small DNA virus that infects squamous epithelia after sexual transmission. Warts and condylomata in the esophagus from HPV infection are usually asymptomatic and do not require treatment unless large lesions cause mechanical obstruction. Endoscopic findings include erythematous macules, nodules, plaques, or exophytic lesions found most commonly in the mid to distal esophagus. Diagnosis is based on histological findings of koilocytosis (atypical haloed nucleus), giant cells, or positive immunostaining.

Bacterial, mycobacterial, treponemal, and parasitic infections

Invasive bacterial infections of the esophagus account for a small proportion (11–16%) of infectious esophagitis in immunocompromised hosts. Use of gastric acid–suppressing medication, such as proton pump inhibitors, may increase risk of bacterial esophagitis. Similar to fungal or viral esophagitis, odynophagia and dysphagia are the most common presenting symptoms. Endoscopic findings are nonspecific, including mucosal friability, plaques, pseudomembranes, and ulcerations. Bacterial organisms can be detected on diagnostic biopsies. Standard therapy consists of a broad-spectrum β-lactam antibiotic combined with an aminoglycoside.

Mycobacterium tuberculosis and *avium* infections of the esophagus are rare. Esophageal involvement with tuberculosis often results from direct extension of the infection from mediastinal structures, with few cases of primary esophageal tuberculosis. Clinical presentations include odynophagia, dysphagia, weight loss, cough, chest pain, and fever. Endoscopic findings include shallow ulcers, malignant-appearing ulcerating lesions, and extrinsic compression of the esophagus from regional adenopathy. Biopsies often do not show caseating granulomas (sensitivity 25–60%) as the density of the tuberculous granulomas in the infected organ may be low. In suspected cases, deep tissue sampling of the submucosal layer is required to establish the diagnosis. Tissue biopsies and brushings should be sent for histology, routine culture, mycobacterial culture, acid-fast staining, and PCR. Mycobacteria infection of the esophagus is treated with standard multidrug therapy, guided in part by the sensitivity pattern in the community. Endoscopic stenting and surgery are sometimes needed to treat complications including fistulas and strictures.

Esophageal syphilis is extremely rare; dysphagia may occur many years after the initial infection. Classically, tertiary syphilis may be associated with gummas, diffuse ulcerations, fistulas to trachea, and stricture of the upper third of the esophagus. Diagnosis is suspected when syphilitic periarteritis is present on biopsy specimens, but immunostaining for *Treponema pallidum* should be performed for definitive diagnosis. Endoscopic and surgical interventions are warranted for strictures and fistulas, and penicillin is the antibiotic of choice for those without complications.

Trypanosoma cruzi, a protozoan endemic in parts of South and Central America, can lead to progressive destruction of nerve ganglion cells: *Chagas disease*. The esophagus and lower esophageal sphincter manifestations of Chagas disease include achalasia and megaesophagus. As a result, dysphagia is the most common presenting symptom. When compared to idiopathic achalasia, Chagas-related achalasia is associated with reduced pressure at the lower esophageal sphincter as a result of impaired excitatory and inhibitory innervation. Vasodilators including nitric oxide may improve emptying of the megaesophagus and lessen dysphagia, but their use is limited by side effects. Gastroesophageal junction myectomy and esophagectomy have been performed for refractory disease.

Suggested reading

Ahuja NK, Clarke JO. Evaluation and management of infectious esophagitis in immunocompromised and immunocompetent individuals. *Curr Treat Options Gastroenterol*. 2016 Mar;14(1):28–38.

Donatelli G, Vergeau BM, Tuszynski T, et al. Giant, deep, well-circumscribed esophageal ulcers. *Dis Esophagus*. 2016 Aug;29(6):684–685.

Eggimann P, Pittet D. Candida colonization index and subsequent infection in critically ill surgical patients: 20 years later. *Intensive Care Med*. 2014;40(10):1429–1448.

Hoversten P, Kamboj AK, Katzka DA. Infections of the esophagus: An update on risk factors, diagnosis, and management. *Dis Esophagus*. 2018 Dec 1;31(12).

Katzka DA. Esophageal disorders caused by medication, trauma and infection: Esophageal infections in the immunocompetent host. In Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's gastrointestinal and liver disease: Pathophysiology/diagnosis/management*, 10th ed. Philadelphia, PA: Saunders; 2016.

Kim KY, Jang JY, Kim JW, et al. Acid suppression therapy as a risk factor for *Candida* esophagitis. *Dig Dis Sci*. 2013;58(5):1282–1286.

Meredith M, Howley MS, Carter TC, et al. Fluconazole use and birth defects in the National Birth Defects Prevention Study. *Am J Obstet Gynecol*. 2016;657:e1–657.e9.

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases of America. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

Pappas PG, Kaufman CA, Andes D, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Disease Society of America. *Clin Infect Dis*. 2016;62;e1–e50.

Pinho J, Martins D, Cancela E, et al. A rare presentation of cytomegalovirus infection in an immunocompetent patient. *Gastrointest Endosc*. 2018 Jul;88(1):185–186.

Wilcox CM. Overview of infectious esophagitis. *Gastroenterol Hepatol (N Y)* 2013;9:517–519.

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Gastroenteritis

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Gastroenteritis

Gastroenteritis, broadly defined, refers to any inflammatory process of the stomach or intestinal mucosal surface. However, the term usually refers to acute infectious diarrhea, a diarrheal syndrome of less than 2 weeks' duration, which may be accompanied by fever, nausea, vomiting, abdominal pain, dehydration, and weight loss. This chapter provides an overview of the infectious enteritides. Other chapters consider food poisoning, travelers' diarrhea, antibiotic-associated diarrhea, sexually transmitted enteric infections, and *Helicobacter pylori* disease.

Gastroenteritis in high-income countries (HICs), similar to upper respiratory infections, is common and an inconvenience, but it usually does not require a physician visit, laboratory evaluation, or antibiotic treatment. In a US surveillance network with a population-based telephone survey of 12 075 adults (1998–1999), about 0.72 episodes per person-year were documented. In the 2009 US National Ambulatory Medical Care Survey, diarrhea was the second leading gastrointestinal (GI) symptom prompting an outpatient clinic visit, an estimated 4.2 million in total. The Centers for Disease Control and Prevention (CDC) estimates that known foodborne pathogens account for an estimated 14 million illnesses, 60 000 hospitalizations, and 1800 deaths. In the United States in children, it is estimated that acute diarrhea causes 300 to 400 deaths annually. Globally, gastroenteritis is the second principal cause of mortality, after cardiovascular disease. It is the leading worldwide cause of childhood death and of years of productive life lost, with approximately 12 600 deaths per day. Annual per-person attack rates range from 5 to 20 in the low- and middle-income countries (LMICs).

Pathophysiology

The GI tract is remarkably efficient at fluid reabsorption. Normally, of the 1 to 2 L of fluid ingested orally and the 7 L that enter the upper tract from saliva, gastric, pancreatic, and biliary sources, less than 200 mL of fluid are excreted daily in the feces. Thus, small increases in secretory rate or decreases in the absorptive rate can easily overwhelm the intestinal absorptive capacity. Diarrhea is generally defined as increased frequency (more than three bowel movements) or increased volume (>200 mL/day).

Intestinal infection with bacteria, viruses, and parasites that produce gastroenteritis usually follows fecal–oral transmission. Multiple host defenses are in place to protect the human GI tract (Table 49.1). The principal defenses include gastric acidity and the physical barrier of the mucosa. A gastric pH less than 4.0 will kill more than 99% of ingested organisms, although rota-virus and protozoal cysts can survive. Patients with achlorhydria or hypochlorhydria from chronic atrophic gastritis, gastric surgery, human immunodeficiency

TABLE 49.1 **HOST DEFENCES**

Host defense factor	Example disease state
Barrier	
Gastric acid	Achlorhydria (PPI, HIV, gastric surgery)
Mucosal integrity	Mucositis (chemotherapy)
Intestinal motility	
Peristalsis	Blind loop, antimotility drugs, hypomotility states (diabetes, scleroderma)
Commensal microflora	Antibiotics, age extremes
Sanitation	Contaminated water
Intestinal immunity	
Phagocytic	Neutropenia
Cellular	HIV
Humoral	IgA deficiency

Abbreviations: PPI = proton pump inhibitor; HIV = human immunodeficiency virus; IgA = immunoglobulin A.

TABLE 49.2 **VIRULENCE FACTORS**

Virulence factors	Examples
Inoculum size	*Shigella, Entamoeba, Giardia*
Adherence	Cholera, EPEC
Invasion	*Shigella, Salmonella typhi, Yersinia*, EIEC
Toxins	
Enterotoxin	Cholera, *Salmonella*, ETEC
Cytotoxin	*Shigella, Clostridium difficile*, EHEC
Neurotoxin	*Clostridium botulinum, Staphylococcus aureus, Bacillus cereus*

Abbreviations: EPEC = enteropathogenic *Escherichia coli*; EIEC = enteroinvasive *E. coli*; ETEC = enterotoxigenic *E. coli*; EHEC = enterohemorrhagic *E. coli*.

virus (HIV) infection, or proton pump inhibitor (PPI) use are at increased risk of developing infectious diarrhea. Disruption of the mucosal barrier, as with mucositis associated with chemotherapy or irradiation, may predispose patients to gram-negative bacteremia. Increased peristalsis in gastroenteritis propels organisms along the GI tract, analogous to the cough reflex with clearing of the lungs. The intestinal flora forms an important element of the host defense, both in terms of quantity and composition. The small intestine and colon contain approximately 10^4 and 10^{11} organisms per mL, respectively. More than 99% of the colonic bacteria are anaerobes. Their production of fatty acids with an acidic pH and their competition for mucosal attachment sites prevent colonization by invading organisms. At the extremes of age, in children and the elderly, and after recent antibiotic use, the flora is altered and the risk for gastroenteritis may be increased in some individuals. Impairment of intestinal immunity is also a risk factor for intestinal infections.

Virulence factors play a complementary role in acute infectious diarrhea. Whether an individual ingests an inoculum sufficient to establish clinical gastroenteritis is directly related to the organisms, community sanitation, and personal hygiene. Most organisms require an inoculum of 10^5 to 10^8 to establish infection. Exceptions include *Shigella* and protozoa such as *Giardia, Cryptosporidium*, and *Entamoeba*, which may cause diarrhea when only 10 to 100 organisms are ingested. Certain bacteria may produce toxins, which lead to a variety of clinical syndromes, and include enterotoxin (watery diarrhea), cytotoxin (dysentery), and neurotoxin. Botulinum toxin is the classic example of a preformed neurotoxin, but interestingly, both *Staphylococcus aureus* and *Bacillus cereus* also produce neurotoxins, which act on the central nervous system to produce emesis. Adherence and invasion factors facilitate colonization and contribute to virulence. Various forms of *Escherichia coli* express the gamut of virulence factors (Table 49.2).

Clinical syndromes

The acute infectious diarrheas can be divided into noninflammatory, inflammatory, and invasive (Table 49.3). Overall in the United States, the most common bacterial or protozoal pathogens in the acute setting are *Campylobacter*, *Salmonella*, *Shigella*, *E. coli* O157:H7, and more recently, *Clostridium difficile*. While the majority of noninflammatory episodes are viral, the more severe cases are often bacterial. The bacteria causing a noninflammatory diarrhea, such as *Vibrio cholerae* and enterotoxigenic *E. coli* (ETEC), typically secrete an enterotoxin, which affects the small intestine, producing a large volume of watery diarrhea without fecal leukocytes. Most forms of viral gastroenteritis fall into this group. The four most common enteric viral infections are norovirus, rotavirus, adenovirus, and astrovirus. The three most common parasites responsible for noninflammatory diarrhea are *Cryptosporidium*, *Giardia*, and *Cyclospora*.

The inflammatory diarrheas typically affect the colon, causing frequent small-volume stools, often with fecal white cells and either occult or gross blood. Fever, tenesmus, and bloody diarrhea are characteristic of dysentery. A pathogen is identified in about one-fifth of cases of bloody diarrhea, most commonly, enterohemorrhagic (EHEC) *E. coli* O157:H7, *Shigella*, *Campylobacter*, and *Salmonella*. Certain bacteria that cause inflammatory diarrhea produce cytotoxins. The invasive diarrheas may be considered a subset of the inflammatory diarrheas with invasion of the intestinal mucosa, and a propensity to cause bacteremia and distant disease. *Salmonella typhi* is the prototype. Typhoid bacteria are taken up and proliferate within the Peyer's patches of the distal ileum, then disseminate and multiply in the reticuloendothelial system to produce systemic disease. *E. coli* O157:H7 in human and animal studies has been shown to affect both the small and large intestines often with hemorrhage noted throughout. Both the *Shigella* and the EHEC pathogens have been associated with sequelae such as hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).

Patients with neutropenia, particularly with an absolute neutrophil count <500/mm^3 and secondary to immunodeficiency or cytotoxic medications (e.g., bone marrow transplantation) can develop

TABLE 49.3 **CLINICAL SYNDROMES**

	Noninflammatory	Inflammatory	Invasive
Syndrome	Watery diarrhea, emesis	Dysentery	Enteric fever
Site	Small intestine	Colon	Ileum, colon
Stool			
Volu me	Large	Small	Small
Fecal WBC s	Absent	Present	Present
Common organisms			
Bacteri a	*Vibrio cholerae*	*Shigella* spp.	*Salmonella typhi*
	ETEC	*Salmonella* spp. *Campylobacter jejuni*	*Yersinia* spp. *Brucella*
Viruse s	Rotavirus	—	—
	Norovirus[a]		
	Adenovirus		
	Astrovirus		
Parasit es	*Giardia Cryptosporidium*	*Entamoeba*	*Entamoeba*

Abbreviations: WBC = white blood cell; ETEC = enterotoxigenic *E. coli*; EIEC, enteroinvasive *E. coli*.
[a] Formerly known as the Norwalk agent or calicivirus.

neutropenic enterocolitis or typhlitis (from *typhlon*, the Greek term for cecum). In these patients, cytotoxic mucosal injury and neutropenia affect host defenses and mucosal integrity to allow invasion and produce fever, abdominal pain (often right lower quadrant), watery or bloody diarrhea, and thickening of the bowel wall on computed tomography (CT) imaging.

Certain populations of patients with gastroenteritis merit surveillance because of the organisms involved, the potential for severe disease, and the possible need for intervention (Table 49.4). Foodborne disease should be considered in outbreaks of acute GI symptoms affecting two or more persons. The most common causes include *Salmonella* species, *Campylobacter*, *Shigella* species, EHEC (Shiga toxin), *B. cereus*, and the parasites *Cryptosporidium* and *Cyclospora* (see Chapter 50, Food poisoning). The microbial pathogens responsible for travelers' diarrhea are dependent upon the region visited, with some of the most common being enteroaggregative *E. coli* (EAEC), ETEC, *Salmonella*, *Campylobacter*, and *Shigella* (see Chapter 121, Travelers' diarrhea). Patients with advanced acquired immunodeficiency syndrome (AIDS), particularly with CD4 counts <50/μL, are predisposed to a number of unique infections (microsporidia, *Cyclospora*, *Cystoisospora*—formerly known as isosporiasis, cytomegalovirus) which may be chronic, and more severe manifestations of otherwise common infections *(Salmonella, Campylobacter, Cryptosporidium)*. Acute infectious proctitis, which is often sexually transmitted, leads to tenesmus, hematochezia, and rectal pain. Syphilis, gonorrhea, and chlamydia are additional organisms to consider. The incidence of sexually transmitted proctitis is decreasing in the AIDS era with safer sex practices. Other important subpopulations include patients with antibiotic-associated diarrhea, especially those from hospitals or chronic care facilities (see Chapter 51, Antibiotic-associated diarrhea). *Helicobacter pylori* is the most common chronic bacterial infection in the world, and is associated with chronic gastritis, peptic ulcer, gastric adenocarcinoma, and gastric MALToma (Chapter 138, *Helicobacter pylori* infection).

Gastroenteritis is a major cause of global mortality and morbidity among infants and children. In HICs, acute diarrheal illnesses account for an estimated 7% of pediatric ambulatory visits and hospitalizations. Peak attack rates involve young schoolchildren and their younger siblings. Most cases are caused by viral agents: rotaviruses (10% to 50%), *Norovirus* (Norwalk agent, 10% to 30%), and the enteric adenoviruses (2% to 5%). Bacterial agents cause less than 15% of disease but may cause severe disease in patients with *Campylobacter* species, *E. coli* species, *Salmonella* species, or *Yersinia* species. EHEC O157:H7 is an important cause of hemolytic-uremic syndrome in children. *Yersinia* causes a watery diarrhea in children ages 1 to 5, but it may mimic appendicitis in older children and adolescents. Important pathogens in day-care and institutional settings are the above-mentioned bacterial species, as well as *Giardia lamblia, Cryptosporidium* species, and *C. difficile*.

Patient evaluation

Most cases of acute gastroenteritis are self-limited and do not require medical attention. Physician consultation generally is advised for patients with a fever (>38.5°C [101.3°F]), dysentery (bloody stools), significant abdominal pain, dehydration, and risk factors for disease requiring intervention (e.g., elderly, pregnancy, recent antibiotic use). Initial evaluation consists of the history, physical examination, and screening stool examination. Laboratory testing and antimicrobial therapy are recommended in a limited subset of patients based on this initial evaluation, which is underscored by the

TABLE 49.4 **ETIOLOGIC AGENTS BY CLINICAL PRESENTATION**

Population	Bacteria	Viruses	Parasites	Other
Food poisoning	*Salmonella*	Norwalk	*Trichinella*	Ciguatera
	Staphylococcus aureus	Hepatitis A	*Giardia*	Histamine fish
	Shigella		*Cryptosporidium*	
	Clostridium perfringens			
	Bacillus cereus			
	Listeria			
AIDS	*Salmonella*	CMV	*Cryptosporidium*	AIDS
	Campylobacter		*Cystoisospora belli*	Enteropathy
	Shigella		Microsporidia	
	MAC			
Travelers' diarrhea	*Escherichia coli* ETEC	Rotavirus	*Giardia*	No pathogen (40%)
	Shigella		*Cyclospora*	
	Aeromonas			
	E. *coli*, other			
Acute proctitis	*Neisseria gonorrheae*	HSV	*Entamoeba*	
	Chlamydia	Condyloma, HPV	*Cryptosporidium*	
	Treponema pallidum	CMV		
	Shigella			
	Salmonella			
Day-care centers	*Shigella*	Rotavirus	*Giardia*	
	Campylobacter jejuni		*Cryptosporidium*	
Antibiotic associated	*Clostridium difficile*			*Candida albicans*
Seafood ingestion	*Vibrio* spp.		Anisakidae	

Abbreviations: AIDS = acquired immunodeficiency virus; CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex; ETEC = enterotoxigenic *E. coli*; HSV = herpes simplex virus; HPV = human papilloma virus.

fact that overall few stool cultures will be positive (1.5% to 9%), of which only a minority will have indications for antibiotic therapy.

The history should focus on the severity of disease and the risk factors for specific types of infectious diarrhea. The patient should be questioned regarding symptom duration, fever, abdominal pain, tenesmus, and dehydration. The description of the diarrhea is important: frequency, volume, and any blood, pus, or mucus. Diarrhea persisting longer than 2 to 4 weeks qualifies as chronic, with an alternate differential, and should be fully investigated. Inquiry should also be made into factors that may place the patient in a specific subgroup at increased risk for significant infection. Examples include advanced age (over 70), pregnancy, recent international travel or camping, recent antibiotic use, immunosuppression (e.g., HIV, prednisone therapy, chemotherapy), anal intercourse, seafood consumption, household contacts of day-care workers or children, and the potential for a common source outbreak (e.g., friends or relatives with similar symptoms). Short incubation periods of less than 6 hours, or 6 to 16 hours, suggest ingestion of an enterotoxin produced by *S. aureus* and *B. cereus*, or *Clostridium perfringens*, respectively. Vomiting may be the dominant complaint with viral infections and food poisoning (*S. aureus*, *B. cereus*, noroviruses [Norwalk-like]).

A broad differential diagnosis is initially appropriate as acute diarrhea may be the initial presentation of noninfectious and potentially life-threatening diseases. Important etiologies to consider include inflammatory bowel disease, mesenteric vascular disease, GI hemorrhage, and hyperthyroidism. Patients should be questioned regarding the use or recent initiation of medications that may cause diarrhea, such as ACE inhibitors, metformin, colchicine, diuretics, PPIs, magnesium-containing antacids, and sorbitol.

The physical examination is helpful to gauge the severity of the disease. Orthostasis, tachycardia, decreased skin turgor, and dry mucous membranes are signs of significant dehydration. The presence of fever, abdominal tenderness, and skin rash should be documented. All patients should undergo a rectal examination when rectal bleeding is reported.

Patients who present for medical evaluation may warrant a screening stool examination, based upon the history and physical exam. A fresh-cup specimen is preferred because there is evidence that swab and diaper specimens have decreased sensitivity.

The stool should be evaluated for fecal leukocytes and fecal occult blood. Some studies in the literature have questioned their utility, sensitivity, and specificity, but they can be helpful to suggest a bacterial etiology (Table 49.5). Fecal leukocytes are detected in the clinical laboratory either with staining techniques or with lactoferrin testing. Microscopic examination of the stool is facilitated by the methylene blue stain. A wet mount is prepared with two drops of methylene blue mixed with fecal mucus; 2 minutes should be allowed for adequate staining of the leukocyte nuclei before high-power microscopy of the cover-slipped slide. The presence of three or more fecal leukocytes per high-powered field in at least four fields is considered a positive examination. The fecal lactoferrin latex agglutination assay appears to be a more precise marker of fecal leukocytes. With fecal leukocytes, there is some overlap between the inflammatory and noninflammatory diarrheas. The finding on screening stool examination of either fecal leukocytes, lactoferrin, or occult blood has equal predictive values for diffuse colonic disease, positive stool cultures, and disease requiring antimicrobial therapy. The organisms most commonly associated with a positive screening test include *Salmonella, Shigella, E. coli* O157, *Campylobacter, Yersinia, Aeromonas, Vibrio*, and *C. difficile*.

The history, physical examination, and office stool evaluation are screening steps prior to further laboratory evaluation and consideration of treatment. As noted, most patients require only symptomatic therapy for a self-limited, noninflammatory infectious diarrhea. Laboratory evaluation is indicated in patients with the following findings or risks: severe or persistent disease (fever greater than 38.5°C, dehydration, grossly bloody stools, duration of more than 1 week), at-risk subpopulations (see above), and those with a positive stool screening examination (fecal leukocytes or occult blood). In these cases, the initial laboratory evaluation should include a complete blood count, serum electrolytes, and stool processed for bacterial culture. Stool cultures can identify *Salmonella, Shigella*, and *Campylobacter*, *E. coli* O157, *Yersinia* and *Aeromonas*. Many stool cultures are ordered inappropriately. The probability of a positive culture is less than 2% to 5% for patients without fever, occult blood, or fecal leukocytes. The yield increases to approximately 20% and 50%, respectively, when one or two of the three findings are present. Stool examination for ova and parasites is not cost-effective, and should be limited to patients with appropriate risk factors (e.g., appropriate travel history, day-care infant exposure, bloody diarrhea). Formed stools should not be sent for testing. Patients hospitalized for more than 3 days, who subsequently develop diarrhea are unlikely to have a bacterial or parasitic pathogen, and stool cultures are inappropriate, with *C. difficile* being the exception.

Additional laboratory or diagnostic evaluation will depend upon the clinical situation. Routine stool examination for ova and parasites is not recommended. Studies for parasites are indicated in the setting of persistent diarrhea, international or wilderness travel, AIDS, and infants attending a day-care center (or their caretakers). Fecal leukocyte-negative, bloody diarrhea has been associated with *Entamoeba histolytica, Schistosoma, Dientamoeba fragilis*, and *Balantidium coli*. The sensitivity of three ova and parasite examinations on three separate days is 95% to 98%. Stool testing for *C. difficile*, previously reserved for those with a history of antibiotic use or hospitalization, is now broadened with the current epidemic and advent of community-acquired infection. Differentiation of pathogenic and nonpathogenic strains of *E. coli* requires specific serotyping, although testing for *E. coli* O157:H7 is now commonplace. Commercial enzyme immunoassay kits are available for detection of rotavirus and enteric adenovirus and may be useful in the pediatric population and in elderly patients. Colonoscopy is rarely needed, but is appropriate where the differential includes ischemic colitis, inflammatory bowel disease, or other etiologies which require visualization or biopsy (e.g., immunocompromised patients, individuals with concern for *C. difficile* with negative stool studies). In addition, cross-sectional abdominal imaging (e.g., CT scan) may be helpful in complex presentations to help differentiate infectious and noninfectious causes of acute diarrhea and/or bleeding.

The initial evaluation of AIDS-associated diarrhea should include stool examination for culture, ova and parasites, and acid-fast stain. Specialized stool studies are required for the detection of *Cryptosporidium, Cyclospora*, microsporidiosis, and *Cystoisospora belli*. Mucosal biopsies are required for the diagnosis of cytomegalovirus (cytopathogenic effect) and *Mycobacterium aviumintracellulare* complex (MAC). Sigmoidoscopy may be considered for persistent or severe cases in patients with CD4 counts less than 100/μL and for those who have experienced weight loss. Colonoscopy/ileoscopy and upper endoscopy generally are reserved for refractory cases.

TABLE 49.5 **FECAL LEUKOCYTES**

Present	Variable	Absent
Campylobacter	*Salmonella*	Toxigenic bacteria
Shigella	*Yersinia*	ETEC, EPEC
EIEC, EHEC	*Clostridium difficile*	Viruses
	Vibrio parahaemolyticus	Parasites
	Noninfectious causes: ischemic colitis, IBD	

Abbreviations: EIEC = enteroinvasive *E. coli*; EHEC = enterohemorrhagic *E. coli*; IBD = inflammatory bowel disease; ETEC = enterotoxigenic *E. coli*; EPEC = enteropathogenic *E. coli*.

Management

Rehydration is the primary focus of initial management. This can be accomplished with oral fluids. Oral rehydration solutions (ORS) have decreased worldwide cholera mortality rates from 50% to 1%. The World Health Organization (WHO) ORS is made up of 3.5 g sodium chloride, 2.5 g sodium bicarbonate, 1.5 g potassium chloride, and 20 g glucose per liter of water. Rice-based ORS also may be used (e.g., CeraLyte). Prepared forms are available in solution (e.g., Pedialyte, Rehydrolyte) and packets (e.g., Orlyte). Various homemade alternatives are available, for example alternating a glass of fruit juice (8 oz) with honey (½ tsp) and salt (¼ tsp), with a second glass of water (8 oz) with baking soda (¼ tsp). Sport drinks such as Gatorade are reasonable for adults who are not dehydrated. The goal

is the passage of relatively dilute urine every 2 to 4 hours. Patients are advised to eat judiciously until stools are again formed. Cereals (rice, pasta), boiled foods (potatoes, vegetables), bananas, and crackers are recommended initial foods. Alcohol (cathartic effect), caffeine (increases intestinal motility), and carbonated drinks (gastric distension with reflex colonic contraction) should be avoided. Recommendations vary regarding dairy products, as transient lactose intolerance may occur.

In addition to rehydration, symptomatic therapy includes administering agents to control the diarrhea. These agents include bulking agents, antimotility drugs, and antisecretory medications (Tables 49.6 and 49.7). Antimotility agents should not be used if there is a possibility of a severe inflammatory bacterial diarrhea, particularly a febrile dysentery syndrome. Loperamide (Imodium) is the drug of choice in most situations because of its efficacy and safety. Bismuth subsalicylate (BSS) has antisecretory and antibacterial properties and is considered when vomiting is a significant part of the patient's presentation. It should not be used in the immunosuppressed patient, particularly the HIV population, because bismuth encephalopathy may occur. Diphenoxylate–atropine (Lomotil) has both anti-motility and antisecretory activity, but may cause central nervous system depression, especially in children. Despite their popularity, kaopectate, cholestyramine, lactobacilli, and the anticholinergics have not been shown to be consistently effective. Severe AIDS diarrhea should be treated in stepwise fashion with Imodium (2 to 4 mg PO four times daily), Lomotil (1 to 2 tablets PO four times daily), morphine (MS Contin 30 mg twice daily) or tincture of opium (DTO 0.5 to 1 mL PO four times daily), and octreotide (100 to 500 μg SC three times daily, increasing the dosage 200 μg every 3 days until response is seen).

TABLE 49.6 **SYMPTOMATIC THERAPY FOR DIARRHEA**

General	Intraluminal	Antimotility	Antisecretory
Rehydration	Bulking agents	Opiates	BSS
ORS	Psyllium	Loperamide	Octreotide
IV	Adsorbents	Diphenoxylate	
Diet therapy	Kaolin-pectin	Codeine	
	Attapulgite	Tincture of opium	
	Cholestyramine	Anticholinergics	
	Bacterial agents	Atropine	
	Lactobacillus	Scopolamine	
	Saccaromyces		

Abbreviations: ORS = oral rehydration solution; IV = intravenous; BSS = bismuth subsalicylate.

TABLE 49.7 **ANTIDIARRHEAL THERAPY**

Agent	Dosing	Comments
Loperamide[a] (Imodium)	2 mg PO q3h	Initial dose, 4 mg
		Maximum, 16 mg/day
Diphenoxylate (Lomotil)	2 tablets or 10 mL PO QID	Maximum, 8 tablets/day
BSS[b] (Pepto-Bismol)	2 tablets or 30 mL PO QID	Maximum, 8 tablets/day
Tincture of opium	0.5–1.0 ml PO q4–6h	
Octreotide	100–500 μg SC TID	

Abbreviations: BSS = bismuth subsalicylate; SC = subcutaneous.
[a] Loperamide is the drug of choice. BSS may be used in presentations with significant vomiting.
[b] BSS should not be used in patients with human immunodeficiency virus because of the risk of bismuth encephalopathy.

Antibiotic therapy is usually not indicated for patients with community-acquired acute diarrhea. Antibiotics are appropriate in a limited subset of patients, such as those with dehydration, severe travelers' diarrhea, and immunocompromised hosts, and may be appropriate for those with fever and/ or blood and those considered for hospitalization (Table 49.8). Patients with EHEC (*E. coli* O157) should not receive antibiotics, due to the reported association with HUS. Empiric therapy with a quinolone (norfloxacin, ciprofloxacin, levofloxacin) is generally recommended. Macrolides (e.g., azithromycin) may be used when drug allergies or quinolone resistance are factors, with the caveat that abdominal cramping is a common side effect. Patients with a positive stool culture or parasitic examination should be treated in specific situations: symptomatic infections with certain bacteria (*Shigella*, enteroinvasive *E. coli, C. difficile, V. cholerae*), sexually transmitted pathogens, and parasites. Therapy is reserved for subgroups of patients with *Salmonella, Campylobacter, Yersinia, Aeromonas*, noncholera *Vibrio*, and other strains of *E. coli* (EPEC, EAEC). Treatment of *Salmonella* and *Campylobacter* is indicated for patients with dysentery, systemic illness, bacteremia; or significant comorbidity (immunosuppression, malignancy, sickle cell anemia, prosthetic device, age extremes). In light of the epidemic, therapy for *C. difficile* infection is in evolution (see Chapter 51, Antibiotic-associated diarrhea).

In summary, community-acquired acute gastroenteritis, although common, is usually a self-limited disease. Oral rehydration and symptomatic therapy are appropriate for the majority of patients. Medical evaluation is advised for patients with significant fever, dysentery, abdominal pain, dehydration, or risk factors for severe disease. Laboratory evaluation and antibiotic treatment should be limited to very specific situations.

TABLE 49.8 **ANTIBIOTIC THERAPY BY ETIOLOGIC AGENT**

Etiologic agent	Therapy	Duration	Comments
Bacteria			
Empiric therapy[a]	Quinolone[b]	5–7 days	Indications:
			Fever and positive stool screen[c]
			Dysentery syndrome
			Travelers' diarrhea, severe
Campylobacter	Erythromycin, 500 mg PO bid	5 days	See text for treatment indication
	Quinolone[b]	3 days	
	Azithromycin, 500 mg PO qd	3 days	
Clostridium difficile[a]	Metronidazole, 500 mg PO tid	10–14 days	Metronidazole is the drug of choice given VRE risk.
	Vancomycin, 125 mg PO qid	10–14 days	Bactericidal but very expensive
	Fidaxomicin, 200 mg PO bid	10 days	
EIEC, ETEC[a]	Quinolone[b]	5 days	Treatment is not indicated for EHEC, including O157:H7
	TMP–SMX-DS PO BID	5 days	
EPEC	Quinolone[b]	5 days	
Salmonella	Quinolone[b]	3–7 days	See text for treatment indication
	TMP–SMX-DS PO BID	5–7 days	14 days if immunocompromised or relapsing
Shigella[a]	Quinolone[b]	3–5 days	7–10 days if immunocompromised
	TMP–SMX-DS PO BID	3 days	
	Azithromycin, 250–500 mg PO qd	3 days	
Vibrio cholerae[a]	Doxycycline, 300 mg PO	1 dose	
	Ciprofloxacin, 1 g PO	1 dose	
Yersinia	Ceftriaxone, 2 g IV qd	5 days	For severe infection
	Quinolone[b]	3 days	
Parasites			
Cyclospora	TMP–SMX-DS PO BID	710 days	
Entamoeba[a]	Metronidazole, 750 mg PO TID	10 days	Follow with cyst eradication regimen
	Tinidazole, 2 g PO qd	3 days	
Giardia[a]	Metronidazole, 250 mg PO TID	7–10 days	
	Tinidazole, 2 g PO	1 dose	
Cystoisospora	TMP–SMX-DS PO BID	7–10 days	14 days if immunocompromised
Cryptosporidium	Nitazoxanide 500 mg PO BID	3 days	

Abbreviations: VRE = vancomycin-resistant enterococcus; EIEC, = enteroinvasive *E. coli*; ETEC = enterotoxigenic *E. coli*; TMP–SMX-DS = trimethoprim–sulfamethoxazole, 160–800 mg double-strength tablet; EHEC = enterohemorrhagic *E. coli*; EPEC = enteropathogenic *E. coli*.

[a] Treatment clearly indicated. Treatment for the other listed microbes will depend on the clincal situation.

[b] Quinolone oral therapy options include: ciprofloxacin 500 mg bid, ofloxacin 300 mg bid, levofloxacin 500 mg qd.

[c] Positive stool screen: fecal leukocytes or hemoccult positive.

Suggested reading

ASGE Standards of Practice Committee, Shen B, Khan K, et al. *The role of endoscopy in the management of patients with diarrhea*. *Gastrointest Endosc*. 2010;71:887–892.

Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31:431–455.

Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis*. 2001;32:331–351.

He M, Miyajima F, Roberts P, et al. Emergence and global spread of epidemic healthcare-associated *Clostridium difficile*. *Nat Genet*. 2013;45:109–113.

Hines J, Nachamkin I. Effective use of the clinical microbiology laboratory for diagnosing diarrheal diseases. *Clin Infect Dis*. 1996;23:1292–1301.

Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012;143:1179–1187.

Thielman NM, Guerrant RL. Clinical practice. Acute infectious diarrhea. *N Engl J Med*. 2004;350:38–47.

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Food poisoning

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Foodborne illnesses are caused by ingestion of foods containing microbial and chemical toxins or pathogenic microorganisms. This chapter concentrates on toxin-mediated syndromes, usually called *food poisoning*, rather than on syndromes reflecting enteric infection, such as salmonellosis, shigellosis, vibriosis, and Shiga toxin-producing *Escherichia coli* (STEC) infection. Treatment of these infections is covered in Chapter 49, Gastroenteritis, and in chapters on the specific organisms.

Clinical presentation and diagnosis

Initially, the diagnosis of specific food poisoning syndromes is suggested by the clinical presentation, the incubation period from exposure to onset of symptoms, and the food consumed. The incubation periods, symptoms, and commonly associated foods for specific syndromes are shown in Table 50.1. Incubation periods range from a few hours or less in the case of preformed chemical and bacterial toxins, such as histamine poisoning (scombroid), staphylococcal food poisoning, and *Bacillus cereus*, to several days for bacterial infections (e.g., *Campylobacter jejuni, Salmonella, Yersinia enterocolitica*, and *E. coli* O157:H7 or other STEC) and some types of mushroom poisoning. Therefore, it is essential to obtain a diet history covering 3 to 4 days before the onset of symptoms. A careful history of illness in meal companions may help point to the responsible food. It is clinically useful to consider syndromes grouped by incubation period and symptoms.

Nausea and vomiting within 1 hour

Symptoms developing within 5 to 15 minutes of exposure that resolve over 1 to 2 hours are typical of contamination of food or drink with heavy metals or other nonspecific chemical irritants.

Nausea, vomiting, or diarrhea within 1 to 16 hours

When gastrointestinal symptoms develop 1 to 16 hours after exposure, the likely agents include *Staphylococcus aureus, B. cereus*, and *Clostridium perfringens*. Vomiting is the dominant feature of *S. aureus* and short-incubation, or emetic, *B. cereus* food poisoning. These syndromes result from preformed centrally acting toxins elaborated by the organisms in food when the food is mishandled. In contrast, abdominal cramps and diarrhea are most prominent in long-incubation, or diarrheal, *B. cereus* poisoning and *C. perfringens* food poisoning. In these syndromes, toxins are also elaborated in the small intestine. The duration of illness is usually less than 24 hours. Diagnosis of these syndromes is usually made on epidemiologic and clinical grounds. Laboratory confirmation of *S. aureus* food poisoning is based on isolation of *S. aureus* from food handlers and demonstration of more than 10^5 colonies per gram of the same strain in food or enterotoxin production by enzyme immunoassay. Laboratory confirmation of *B. cereus* and *C. perfringens* can be performed in epidemiologic investigations; it requires collection of food and stool for toxin detection or quantitative cultures.

TABLE 50.1 **INCUBATION PERIOD, SYMPTOMS, AND COMMON VEHICLES FOR MICROBIAL CAUSES OF FOOD POISONING**

Organism	Incubation period (hours) median (range)	Vomiting	Diarrhea	Fever	Common vehicles
Staphylococcus aureus	3 (1–6)	+++	++	0	Ham, poultry, cream-filled pastries, potato and egg salad
Bacillus cereus (emetic syndrome)	2 (1–6)	+++	++	0	Fried rice
Bacillus cereus (diarrheal syndrome)	9 (6–16)	+	+++	0	Beef, pork, chicken, vanilla sauce
Clostridium perfringens	12 (6–24)	+	+++	0	Beef, poultry, gravy
Vibrio parahaemolyticus	15 (4–96)	++	+++	+++	Fish, shellfish
Vibrio cholerae O1 and non-O1	24 (12–120)	++	+++	+	Shellfish
Norovirus	24 (12–48)	+++	++	++	Shellfish, salads, ice
Shigella	24 (7–168)	+	+++	+++	Egg salads, lettuce, sandwiches
Clostridium botulinum	24 (12–168)	++	+	0	Canned vegetables, fruits, sauces and fish; salted fish; bottled garlic, baked potatoes
Salmonella	36 (12–72)	+	+++	++	Beef, poultry, pork, eggs, dairy products, fruit and vegetables, sprouts
Campylobacter jejuni	48 (24–168)	+	+++	+++	Poultry, raw milk
Enterohemorrhagic *Escherichia coli* (e.g., O157:H7)	96 (48–120)	++	+++	+	Beef (especially hamburger), raw milk, salad dressings, lettuce, sprouts, apple cider
Yersinia enterocolitica	96 (48–240)	+	+++	+++	Pork, chitterlings, tofu, milk
Cyclospora cayetanensis	168 (24–336)	+	+++	++	Raspberries, basil, lettuce

Key: 0 = rare (≤10%); + = infrequent (11%–33%); ++ = frequent (33%–66%); +++ = classic (>67%).

Watery diarrhea and cramps within 16 to 48 hours

Diarrhea following a slightly longer incubation period is typical of viral foodborne illness, particularly Norovirus (Norwalk virus), and enterotoxin-producing bacteria, including enterotoxigenic *E. coli* (ETEC), *Vibrio cholerae* O1 and non-O1, and other *Vibrio* species. Most microbiology laboratories can diagnose *Vibrio* infections from stool culture provided the laboratory is aware that *Vibrio* is being considered. Diagnosis of ETEC infection requires detection of enterotoxin production by *E. coli* isolates or detection of the genes for enterotoxin and is limited to reference laboratories. Antigen detection-based enzyme immunoassays using recombinant antigens have been developed for the diagnosis of several gastroenteritis-causing viruses such as rotavirus and adenovirus 40/41; PCR testing can detect norovirus. Multiplex PCR platforms that can detect many of these organisms in one test are in advanced development.

Fever, diarrhea, and abdominal cramps within 16 to 96 hours

Bacterial infections of the gastrointestinal tract and gut-associated lymphatics with *Salmonella, Shigella, C. jejuni, Y. enterocolitica*, and STEC typically follow a longer incubation period and are marked by more prominent signs of colonic inflammation or systemic illness. Diarrhea that becomes bloody within 12 to 36 hours of onset is typical of *E. coli* O157:H7 and other STEC. These organisms are now among the most common causes of bacterial gastroenteritis in North America (see Chapter 49, Gastroenteritis).

Diarrhea, fatigue, and weight loss within 1 to 14 days

Cyclospora infection should be suspected in a patient with diarrhea of several days' duration associated with loss of appetite and weight and prominent fatigue. The incubation period is highly variable, ranging from 1 to 14 days, with a median of 7 days. Recent outbreaks have definitively shown that *Cyclospora* infections in developed countries can result from consumption of contaminated foods, notably fresh raspberries, mesclun lettuce, and basil.

Paresthesias within 6 hours

Chemical food poisoning caused by niacin, histamine fish poisoning, ciguatera poisoning, neurotoxic and paralytic shellfish poisoning, and Chinese restaurant syndrome (monosodium glutamate) present with paresthesias and other symptoms after a brief incubation period. Chinese restaurant syndrome is characterized

TABLE 50.2 **CLINICAL FEATURES OF FISH AND SHELLFISH POISONING**

Syndrome	Incubation period	Symptoms	Vehicles	Duration
Histamine (scombroid)	5 min–1 h	Facial flushing, headache, nausea, cramps, diarrhea, urticaria	Tuna, mackerel, bonito, mahi-mahi, bluefish	Hours
Ciguatera	1–6 h	Diarrhea, nausea, vomiting, myalgia, arthralgia, shooting pains, perioral and extremity paresthesias, hot–cold reversal, fatigue	Barracuda, snapper, grouper, amberjack	Days to months
Neurotoxic shellfish poisoning	5 min–4 h	Paresthesias, nausea, vomiting, ataxia	Shellfish	Hours to days
Paralytic shellfish poisoning	5 min–4 h	Paresthesias, cranial nerve weakness, ataxia, muscle weakness, respiratory paralysis	Shellfish	Hours to days
Domoic acid	15 min–38 h	Vomiting, cramps, diarrhea, confusion, amnesia, cardiac irritability	Mussels	Indefinite
Haff disease		Muscle pain, stiffness, brown urine	Buffalo fish, pomfret, burbot	2–3 days
Pufferfish (tetrodotoxin) poisoning	15 min–20 h	Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure	Pufferfish	Several days

by a burning sensation in the neck, chest, and abdomen with chest tightness and occasionally facial flushing, headache, nausea, and abdominal cramps.

The features of fish and shellfish poisoning are summarized in Table 50.2. Histamine fish poisoning (scombroid) is caused by bacterial decarboxylation of histidine in fish that are inadequately refrigerated, resulting in production of large amounts of histamine. Signs and symptoms are facial flushing, headache, nausea, and, less commonly, urticaria or diarrhea. The fish is often reported to have a peppery or bitter taste. Demonstration of high levels of histamine in the implicated fish confirms the diagnosis.

Ciguatera fish poisoning results from ingestion of fish containing toxins produced by the dinoflagellate *Gambierdiscus toxicus*. Predatory fish such as grouper, amberjack, snapper, and barracuda are usually implicated. The symptoms, which are quite distinctive, usually involve the combination of gastrointestinal and neurologic symptoms, most commonly perioral and distal extremity paresthesias, and reversal of hot and cold sensation. Other symptoms include sensation of loose teeth, arthralgias, headaches, muscle weakness, pruritus, lancinating pains, and hallucinations. Bradycardia, hypotension, and respiratory paralysis may occur. The symptoms may last from a few days to 6 months. The diagnosis is based on the clinical picture; detection of ciguatoxin in the fish by high-performance lipid chromatography (HPLC), radioimmunoassay (RIA) or enzyme-linked immunoassay (EIA), or a new neuro-2a cell-based assay is confirmatory.

Paralytic shellfish poisoning (PSP) and neurotoxic shellfish poisoning (NSP) are closely related syndromes caused by heat-stable neurotoxins produced by dinoflagellates (*Gonyaulax catenella* and *Gonyaulax tamarensis* cause PSP; *Gymnodinium breve* causes NSP). During periodic blooms of the dinoflagellates, which may cause red tides, shellfish concentrate the heat-stable toxins. PSP is more severe and occurs in colder waters. Patients develop symptoms a median of 30 minutes after exposure. Symptoms consist of paresthesias and dysesthesias, beginning with the lips, mouth, and face and progressing to the extremities, and then dysphonia, dysphagia, ataxia, muscle weakness, and, in severe cases, respiratory paralysis occur. NSP occurs primarily near warmer waters and is characterized by similar paresthesias, reversal of hot and cold sensation, nausea, vomiting, and ataxia. Toxin can be detected in samples of the shellfish by bioassay or several investigational assays. Amnesic shellfish poisoning is a recently described syndrome associated with mussels contaminated with domoic acid elaborated by *Nitzchia pungens*. In some patients, gastrointestinal symptoms are followed by memory loss, coma, cardiac arrhythmias, and death. Haff disease is a syndrome of acute rhabdomyolysis thought to be caused by palytoxin in certain bottom-feeding fish, notably buffalo fish, crayfish, pomfret, and burbot. Patients present 6 to 21 hours after ingestion with vomiting, severe myalgia, and stiffness. Elevated creatine phosphokinase (CPK) and other muscle enzyme levels confirm the diagnosis. Tetrodotoxin poisoning results from consumption of improperly prepared pufferfish, manifest as paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, and respiratory failure.

Nausea, vomiting, diarrhea, and paralysis within 18 to 36 hours

Foodborne botulism results from exposure to one of three distinct botulinum toxins, A, B, and E, produced when *Clostridium botulinum* spores germinate in food in an anaerobic environment. Gastrointestinal symptoms occur before the onset of neurologic symptoms in about 50% of patients with acute foodborne botulism. Descending paralysis begins with cranial nerve weakness manifested as dysphonia, dysphagia, diplopia, and blurred vision, followed by muscle weakness and respiratory insufficiency. Larger doses of toxin result in shorter incubation periods and more severe symptoms.

Botulism can be differentiated from acute myasthenia gravis and Guillain–Barré syndrome (which may follow *C. jejuni* infection) by botulism's normal cerebrospinal fluid protein, the descending nature of the paralysis, absence of sensory symptoms, normal nerve conduction studies, and typical electromyographic findings of increase in the action potential with rapid repetitive stimulation. Confirmation is based on detection of toxin in food or in serum or stool of patients by mouse toxicity assay or of *C. botulinum* spores in the stool by selective culture.

Mushroom poisoning syndromes

Syndromes of food poisoning from mushrooms fall into at least 10 major categories, outlined in Table 50.3. Parasympathetic syndromes, delirium, disulfiram (Antabuse)-like symptoms, hallucinations, or gastroenteritis may occur after a short incubation period. The more serious syndromes of monomethylhydrazine poisoning, hepatorenal failure from amatoxin-containing mushrooms, delayed myopathy and rhabdomyolysis, and tubulointerstitial nephritis develop after longer incubation periods and may not be suspected initially. If available, specimens of the mushrooms should be examined promptly by a mycologist or poison control expert to confirm the diagnosis. Toxins can be detected in gastric contents, blood, or urine by thin-layer chromatography.

Therapy

Nonspecific therapy

Most food poisoning syndromes are self-limited, and for the majority of episodes, nonspecific supportive therapy is all that is required. Exceptions include botulism, listeriosis, some enteric infections in infants and compromised hosts, and some types of mushroom poisoning.

The mainstay of treatment is fluid and electrolyte replacement to prevent and treat dehydration. The first step is to assess the degree of volume depletion by examining the skin turgor, mucous membranes, vital signs, and mental status. Measuring postural changes in pulse and blood pressure is also helpful in quantifying the volume loss. Slightly dry mucous membranes and thirst indicate mild dehydration (3% to 5% deficit, or 50 to 60 mL/ kg); loss of skin turgor, very dry mucous membranes, postural pulse increases, and sunken eyes indicate moderate dehydration (6% to 9%); and

TABLE 50.3 **CLINICAL SYNDROMES OF MUSHROOM POISONING**

Syndromes (toxins)	Incubation period	Symptoms	Mushrooms
Parasympathetic (muscarine)	30 min–2 h	Sweating, salivation, lacrimation, blurred vision, diarrhea, bradycardia, hypotension	*Inocybe* spp. *Clitocybe* spp.
Delirium (ibotenic acid, muscimol)	30 min–2 h	Dizziness, incoordination, ataxia, hyperactivity, visual disturbance, hallucinations, stupor	*Amanita muscaria, Amanita pantherina*
Disulfiram-like (coprine)	30 min after alcohol	Flushing, metallic taste, nausea, vomiting, sweating, hypotension	*Coprinus atramentarius, Clitocybe clavipes*
Hallucinations (psilocybin)	30–60 min	Mood elevation, anxiety, tachycardia, muscle weakness, hallucination	*Psilocybe cubensis, Panaeolus* spp., *Conocybe cyanopus*
Gastroenteritis	30 min–2 h	Nausea, vomiting, abdominal cramps, diarrhea	Various
Allergic pneumonic syndrome	3–6 h	Nausea, vomiting, rhinitis followed within days by fever, malaise, dyspnea, and reticulonodular infiltrates on chest x-ray	*Lycoperdon* spp. (puffballs)
Methemoglobin poisoning (monomethylhydrazine gyromitrin)	6–12 h	Nausea, vomiting, bloody diarrhea, abdominal pain, vertigo, convulsion, coma, liver failure, hemolysis	*Gyromitra* spp.
Hepatorenal failure (amatoxins, phallotoxins)	6–24 h	Nausea, vomiting, abdominal pain, diarrhea; then jaundice, liver and kidney failure, coma, death	*Amanita phalloides, Amanita verna, Amanita virosa, Galerina autumnalis, Galerina marginata*
Tubulointerstitial nephritis (orellanine)	36 h–14 days	Thirst, nausea, vomiting, flank pain, chills, oliguria	*Cortinarius orellanus, Cortinarius speciosissimus*
Rhabdomyolytic	24–72 h	Fatigue, muscle weakness, myalgia, rhabdomyolysis, renal failure	*Tricholoma equestre, Russula submigricans*

the additional presence of weak pulse, postural hypotension, cold extremities, or depressed consciousness indicates severe volume depletion, above 10%.

Most children and adults with diarrhea can be treated successfully with oral rehydration. This therapy is possible because of the coupled transport of glucose with water and sodium even in severely damaged small bowel. Diarrheal stool contains significant concentrations of sodium, potassium, and bicarbonate, and fluid therapy should replace these losses.

One liter of the World Health Organization's currently recommended replacement solution contains 75 mmol of sodium, 13.5 g of glucose, 20 mmol of potassium, 65 mmol of chloride, and 10 mmol of citrate (as a bicarbonate source). Commercial solutions such as Rehydralyte and Pedialyte have a slightly lower sodium concentration, but they are convenient and readily available, although expensive. A homemade approximation of the oral solution can be made by adding a pinch of salt, a pinch of baking soda, and a spoonful of sugar or honey to an 8-oz glass of fruit juice. For patients with altered consciousness or uncontrolled vomiting, intravenous rehydration with Ringer's lactate should be used initially. The estimated volume deficit should be replaced over 4 hours; after that, ongoing losses should be replaced. Gatorade and commercial soft drinks are poor choices because the low sodium content can lead to hyponatremia and the high osmolarity can exacerbate diarrhea.

Water intake should be allowed ad lib, and solid food can be introduced as soon as it is tolerated. Some patients will develop lactose intolerance after severe or protracted diarrhea, and dairy products should be avoided if they appear to exacerbate symptoms.

Antiemetics may be useful for severe or prolonged vomiting. Ondansetron (Zofran) can be used off-label, 4 to 8 mg orally or intravenously. Alternatively, promethazine (Phenergan), 12.5 to 25 mg PO, IM, IV, or PR, and prochlorperazine (Compazine), 5 to 10 mg orally or intramuscularly (IM), 25 mg rectally, or 2.5 to 10 mg IV could be used. Antidiarrheals should be used cautiously, especially in children. Pepto-Bismol 30 mL (2 tab) orally every 30 to 60 minutes (maximum 8 doses/ 24 hours) may be reasonable if an antidiarrheal is used because it has been shown to bind some enterotoxins. It generally should be avoided in children under 12 because of the salicylate content.

Specific therapy

Specific therapies for food poisoning are outlined in Table 50.4. Gastric emptying and administration of activated charcoal and cathartics (unless diarrhea is already present) are important for virtually all cases of mushroom poisoning. If vomiting has not occurred spontaneously in patients with botulism or ciguatera, the remaining food should be removed from the gut. In botulism, paralytic shellfish poisoning, and ciguatera, death from respiratory failure is the major risk, and monitoring the vital capacity can be lifesaving.

Equine-derived heptavalent antitoxin, which binds botulism toxin types A–G, has been recently approved for the treatment of patients 12 months and older. It is available in the United States through contacting the state health department's emergency line, and they will contact the CDC (770–488–7100) for release of antitoxin. It may prevent further paralysis but does not reverse established symptoms. To be effective, it should be administered early. Dosage and a protocol for administration of a skin test are listed in the package insert. Human-derived botulism immune globulin (BabyBIG) is licensed for treatment of infant botulism caused by toxin types A or B. It can be obtained from the California Department of Public Health (510–231–7600 or www.infantbotulism.org).

In ciguatera poisoning, analgesia and avoidance of unpleasant stimuli such as warm baths are usually adequate. Anecdotal reports in the literature suggest that amitriptyline, 25 to 50 mg/ day orally or gabapentin may be useful for dysesthesias. Intravenous mannitol has been reported to be effective for severe neurologic manifestations, but a single randomized control trial did not show a benefit. For histamine fish poisoning, conventional antihistamines, such as diphenhydramine, 25 to 50 mg PO, IM, or IV, are helpful. Epinephrine or albuterol should be given for bronchospasm. Intravenous cimetidine can be tried for refractory symptoms.

Atropine is a specific antidote for poisoning from muscarine-containing mushrooms, but the dosage (0.01 to 0.02 mg/kg up to a maximum of 1 mg) should be titrated to control excess respiratory secretions and bradycardia rather than other symptoms. Alternatively glycopyrrolate can be used.

Specific treatment is usually not necessary for poisoning caused by ibotenic acid-containing or muscimol-containing mushrooms. Benzodiazepines can be used to control combativeness, agitation, muscular overactivity, and seizures. Cardiac and blood pressure monitoring are necessary because hypotension and bradycardia can result.

For poisoning caused by monomethylhydrazine-containing mushrooms, pyridoxine, 25 mg/kg IV, should be given; the dose can be repeated as needed to control seizures. The methemoglobin level should be measured if possible. If there is symptomatic methemoglobinemia with central cyanosis, methylene blue, 1 to 2 mg/ kg or 0.1 to 0.2 mL/ kg of a 1% solution, should be given over 5 minutes.

The high fatality rate associated with poisoning by *Amanita phalloides* and related amatoxin-containing mushrooms makes it a special concern. Toxin removal should be attempted with activated charcoal and should be continued until 4 days following ingestion because of the extensive enterohepatic cycling. During the initial phase, gastrointestinal symptoms may cause hypotension. This first stage often is followed by a stage of apparent improvement, but hepatic transaminases usually are elevated by 24 to 48 hours. Fulminant hepatic necrosis and acute renal failure begin after 48 to 96 hours. Supportive treatment consists of careful fluid replacement and monitoring of serum glucose and renal and liver function tests. Intravenous silibinin dihemisuccinate (Legalon® SIL) has been shown to decrease mortality in amatoxin mushroom poisonings. High-dose penicillin G can be used if silibinin is not available, but is not as effective, and it does not have additional benefit when used in conjunction with silibinin (and actually has higher mortality than silibinin used alone). *N*-acetylcysteine can be used as an antioxidant to help prevent liver cell death. Liver transplant has been successful in some cases. Assistance from the regional poison control center should always be sought for help with mushroom identification and for the latest treatment information.

TABLE 50.4 **SPECIFIC TREATMENT FOR FOOD POISONING SYNDROMES**

Syndrome	First-line treatment	Comment
Staphylococcus aureus, Bacillus cereus, Clostridium perfringens, Norwalk virus	Fluid replacement, antiemetics (e.g., ondansetron [Zofran], promethazine [Phenergan], prochlorperazine [Compazine])	Oral rehydration is usually adequate if vomiting can be controlled.
Bacterial gastroenteritis	Fluid replacement; antimicrobials helpful for some syndromes	See chapters on specific organisms and Chapter 49, Gastroenteritis, for specific antimicrobial therapy
Clostridium botulinum	Gastric empying, cathartics if food is still in gastrointestinal tract; respiratory support, polyvalent antitoxin[a]	Antitoxin should be given as soon as possible
Cyclospora	Trimethoprim–sulfamethoxazole (160 mg trimethoprim component bid for 7 days)	If not treated, symptoms may be protracted and relapsing
Histamine (scombroid)	Antihistamine (e.g., diphenhydramine 25–50 mg PO, IM, or IV)	H_2 receptor antagonists (cimetidine) have been helpful for refractory symptoms
wCiguatera	Activated charcoal only if there is no vomiting and it has been <1 hour post ingestion; analgesia, antiemetics, supportive measures; atropine for symptomatic bradycardia	Amitriptyline (25–50 mg/d) may help paresthesias; mannitol infusion has been used
Neurotoxic shellfish poisoning	Supportive therapy	
Paralytic shellfish poisoning	Supportive therapy, monitor vital capacity	
Haff disease	IV hydration	Mannitol and bicarbonate have also been used to protect renal tubules
Muscarine-containing mushrooms	Gastric emptying, activated charcoal, cathartics; atropine 0.01–0.02 mg/kg IV up to 1 mg	Titrate atropine to drying of secretions; alternatively glycopyrrolate can be used.
Muscimol- and ibotenic acid-containing mushrooms	Gastric emptying, activated charcoal, cathartics; supportive measures	Benzodiazepines can be used for agitation
Hallucinogen-containing mushrooms	Reassurance, quiet room; benzodiazepines for severe agitation	
Monomethylhydrazine-containing mushrooms (*Gyromitra* spp.)	Gastric emptying, activated charcoal, cathartics; for delirium, pyridoxine, 25 mg/kg IV	For methemoglobinemia, methylene blue 1–2 mg/kg (1% solution 0.1–0.2 mL/kg) over 5 min
Amatoxin-containing mushrooms	Gastric emptying, activated charcoal; correction of fluid and electrolytes; monitoring glucose, liver, and renal function	IV silibinin[b] has been shown to decrease mortality. High-dose penicillin G can be used if silibinin is not available. *N*-acetylcysteine may help prevent liver cell death. Hemodialysis or liver transplantation may be necessary
Orellanine-containing mushrooms	Gastric emptying, activated charcoal, cathartics; cautious correction of fluid and electrolyte problems	Hemodialysis is often necessary

[a] Available through State Health Departments, or the Centers for Disease Control and Prevention (770–488–7100, 24 hours per day).
[b] (Legalon® SIL) is available directly from the principal investigator of an open NIH clinical trial (NCT00915681) by calling 1-866-520-4412.

Reporting

Reporting of suspected foodborne outbreaks to local or state health departments is an important part of management because epidemiologic investigation can clearly establish the responsible food and may prevent many additional cases.

Suggested reading

Achaibar KC, Moore S, Bain PG. Ciguatera poisoning. *Pract Neurol*. 2007;7:316–322.

Bennet SD, Walsh KA, Gould LH. Foodborne disease outbreaks caused by *Bacillus cerus*, *Clostridum perfringens*, and *Staphylococcus aureus*–United States, 1998–2008. *Clin Infect Dis*. 2013;57:425–433.

Diaz JH. Syndromic diagnosis and management of confirmed mushroom poisonings. *Crit Care Med*. 2005;33:427–436.

Gieraltowski LB, Roy SL, Hall AJ, Bowen A. Enteric diseases transmitted through food, water, and zoonotic exposures. In: Long S, Pickering L, Prober C, eds. *Principles and Practice of Pediatric Infectious Diseases*, 4th edn. Philadelphia: Elsevier Inc; 2012:392–400.

King CK, Glass R, Bresee JS, Duggan C; Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep*. 2003;52(RR-16):1–16.

Scallan E, Hoekstra RM, Angulo FJ, et al. Foodborne illness acquired in the United States–major pathogens. *Emerg Infect Dis*. 2011; 17:7–15.

Sobel J. Botulism. *Clin Infect Dis*. 2005;41: 1167–1173.

Tauxe RV. Emerging foodborne pathogens. *Int J Food Microbiol*. 2002;78:31–41.

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Clostridioides (Clostridium) difficile

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Clinical overview of *C. difficile* diarrhea and *C. difficile* colitis

Clostridioides (Clostridium) difficile is a gram-positive anaerobic spore-forming bacillus found in colon flora. The fecal carriage of *C. difficile* is asymptomatic without diarrhea. When *C. difficile* is induced to produce exotoxins (A/B) symptomatic disease (i.e., diarrhea or colitis) follows. The clinical spectrum of infection ranges from watery toxigenic diarrhea to invasive transmural colitis. *C. difficile* diarrhea is primarily an infection of adults. The terms "*C. difficile* infection," "*C. difficile* disease," or "antibiotic-associated diarrhea" should be abandoned as they are nondescriptive and not reflective of the differences in pathophysiology and severity between *C. difficile* diarrhea (CDD) and *C. difficile* colitis (CDC). *C. difficile* diarrhea and *C. difficile* colitis may be acquired in the community or hospital.

The onset of CDD is acute with the sudden onset of profuse watery diarrhea with a distinctive odor. Little or no fever is usual with CDD, as with other secretory diarrheas (e.g., cholera; fecal white blood cells [WBCs] are absent with no red blood cells [RBCs] present). CCD is a toxigenic mucosal infection that in some may progress to an invasive transmural colitis, with fever often >39°C/102°F, abdominal pain, and marked leukocytosis. Patients usually present with either diarrhea or colitis, but some CDC patients have a diarrheal component.

Beyond differences in severity, there are critical pathophysiologic differences between CDD and CDC that have important implications for anti-*C. difficile* therapy. Analogously, CDD is like ulcerative colitis (UC) in that it is a mucosal process without colon wall involvement. In contrast, CDC is like Crohn's disease, a regional enteritis (RE) in that it is a transmural process penetrating into the intestinal wall. These critical differences in pathophysiology have important therapeutic implications. Just as UC is treated differently than RE, similarly, the optimal treatment of CDD differs markedly from that of CDC. In most *C. difficile* studies, treatment is similar for both CDD and CDC, making evaluation of the relative effectiveness of each drug for diarrhea and colitis difficult to evaluate

Community acquired diarrheas (e.g., norovirus diarrhea) must be differentiated from CDD by stool PCR. However, non-CDD due to other infectious agents or medications (laxatives or stool softeners) may test positive for *C. difficile* carriage. Similarly, patients with underlying diarrheal diseases (e.g., irritable bowel syndrome [IBS], inflammatory bowel disease [IBD] due primarily to UC, and to a lesser extent to RE, sprue, Whipple's disease, etc.) occurring in *C. difficile* carriers may be PCR positive for *C. difficile*, thus mimicking CDD. Recurrent *C. difficile* may be due to inadequate therapy or reinfection with *C. difficile*. Mimics of recurrent *C. difficile* include exacerbations of IBS, IBD, or disorders associated with loose stools. Such patients should have stool PCR for *C. difficile,* which should be PCR negative. To differentiate true "recurrent *C. difficile*," from a diarrheal disorder with *C. difficile* colonization clinically, note that PCR-positive mimics have a few loose or soft stools per day versus the 20 to 30 watery movements of bona-fide CDD. If "recurrent *C. difficile*" occurs in a patient suspected of having another infectious cause of diarrhea (e.g., norovirus), then the diagnostic workup should be directed at specific stool test for the other enteropathogen.

C. difficile diarrhea

Community acquired CDD may be diagnosed in adults with otherwise unexplained acute onset of profuse diarrhea (20–30 watery or liquid stools per day), without fever or abdominal pain, and a stool PCR for *C. difficile* toxins (A/B). In terms of differential diagnosis, PCR-positive non-CDD must be differentiated clinically from bona-fide CDD by stool frequency and consistency. PCR-positive non-CDD has only a few soft or semi-formed stools per day. Such cases may be due to drug-related diarrhea (laxatives, stool softeners, macrolides) or alternately to a diarrhea-related disorder (e.g., IBS, IBD, anatomically altered GI tract, malabsorptive disorders, etc.).

Like community-acquired diarrheal disorders, hospital acquired non-CDD may be caused in a variety of ways. Many medications cause increased intestinal motility (e.g., macrolides, laxatives, and stool softeners). Additionally, enteral feeds may result in diarrhea via two mechanisms. First, some enteral feeds cause diarrhea in some patients, not others. Second, enteral feeds, if given rapidly or in high volume, may result in watery diarrhea (e.g., 80–100 mL/h). If high-volume enteral feed is suspected, cut back on the infusion to 20 to 40 mL/h, and diarrhea will decrease markedly or cease in 12 to 24 hours. Importantly, enteral feeds are protective against *C. difficile*. If stools test PCR-positive for *C. difficile* in a patient receiving an enteral feed, suspect *C. difficile* colonization (i.e., not CDD).

It is commonly assumed that "antibiotics" are always the cause of CDD, which is not the case. CDD, if due to antibiotics, may occur up to 8 weeks after antibiotic exposure. Of the many commonly used antibiotic classes, only β-lactams and clindamycin are commonly associated with *C. difficile*. Antibiotics may cause non-CDD by altering the colon flora (e.g., ceftriaxone), by increasing intestinal motility (e.g., erythromycin), or as an irritative diarrhea due to poor oral absorption (e.g., ampicillin, clavulanic acid). Some antibiotics are "protective" against CDD (e.g., doxycycline, tigecycline). In hospital patients with acute onset of CDD, discontinue those medications known to be associated with CDD, which include proton pump inhibitors (PPIs), some psychiatric drugs, and cancer chemotherapy drugs and probiotics. Probiotics may predispose (increased incidence) to CDD and also may make CDD more severe. Cancer chemotherapy is another medication that may induce toxin production in patients with asymptomatic *C. difficile* colonization. The only nosocomial infectious cause of acute onset of watery diarrhea is *C. difficile*. If a stool PCR is negative for *C. difficile*, there is no need for repeat testing. Effective therapy of CDD is manifested by a marked decrease in watery stools per day after 3 days. Repeat testing is not a test of cure, and PCR may remain positive for 8 weeks after infection.

Unless there is a break in hand-washing (from a hospital water problem) or a food-borne outbreak, community-acquired diarrheal pathogens *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Yersinia* spp., and *Escherichia coli* should not be considered in the differential diagnosis of nosocomial diarrheas. Stool cultures for community-acquired diarrheal pathogens should not be routinely done for nosocomial diarrhea since *C. difficile* is the only infectious cause of nosocomial diarrhea.

C. difficile colitis

Clinically, CDC differs fundamentally from CDD not just in severity, but also, importantly, in underlying colon pathology. There are two common presentations of CDC. In some cases, the onset of CDC is abrupt with fever (often >39°C/102°C), abdominal pain and tenderness with marked leukocytosis, and no diarrhea. Usually, the entire colon is involved (i.e., *C. difficile* pancolitis). *C. difficile* pancolitis may be mimicked by noninfectious disorders (e.g., UC) or infectious disorders (e.g., cytomegalovirus [CMV] colitis). Early CDC may present as segmental colitis. The differential diagnosis of segmental colitis includes noninfectious etiologies (e.g., ischemic colitis). Alternately, in a patient with CDD, if the profuse watery diarrhea stops abruptly, then progression to CDC is likely. Optimally treated CDD improves over a few days but does not cease suddenly. In this scenario, obtain an abdominal CT scan which confirms the presence of CDC. In contrast, CDD responding to therapy results in a gradual decrease in number of watery stools per day (e.g., 30/day to 27/day to 23/day to 19/day to 15/day to 8/day to 2–3/day, etc.) before stools become soft or semi-formed.

Overview of *C. difficile* diarrhea and *C. difficile* colitis treatment

An anti-*C. difficile* antimicrobial should have a "low resistance potential" and possess a high degree of anti-*C. difficile* activity. Aside from these concerns, the pharmacokinetic PK target of optimal *C. difficile* therapy depends on the site of infection in the colon. Being a secretory diarrhea not unlike cholera, the main PK target for anti-*C. difficile* antimicrobials is the colon mucosa. Accordingly, the aim of PK-based therapy is to provide high intraluminal concentrations of an anti-*C. difficile* antibiotic (e.g., oral vancomycin). Oral vancomycin does not penetrate into the colon wall, which is important since CDD is mucosal. Conversely, vancomycin (intravenous [IV]/oral [PO]) lacks the PK attributes to penetrate the colon wall. Increasing resistance aside, metronidazole for CDD is suboptimal because it is so well absorbed that it results in low intraluminal concentrations. CDC is an invasive process (transmural) primarily involving the colon wall. From a PK perspective, anti-*C. difficile* drugs for CDC must penetrate the colon wall to effectively treat colitis. Vancomycin (IV/PO) doesn't have the proper pKa properties to penetrate the colon wall. Therefore, unless with CDC there is also a diarrheal component, adding oral vancomycin when treating CDC makes little sense. Preferred antibiotics highly effective against *C. difficile* that also penetrate the colon wall include metronidazole, nitazoxanide, and tigecycline.

C. difficile diarrhea therapy

Because in CDD the process is intraluminal and limited to colon mucosa, the aim of therapy is to deliver high intraluminal concentrations of effective anti-*C. difficile* drugs (e.g., oral

vancomycin). Intraluminal concentrations of oral vancomycin are 1,000 to 3,000 μg/mL. Vancomycin resistance is not an issue, nor is systemic absorption. In contrast, intraluminal colon levels with oral or IV metronidazole are very low (subtherapeutic). Furthermore, metronidazole resistance to *C. difficile* is of concern.

With CDD, the effectiveness of oral vancomycin therapy is dose and time dependent: dosing matters. The minimally effective dose of oral vancomycin is 125 mg (PO) every 6 hours, but this dose often fails or results in delayed resolution or prolonged course. Fidaxomicin is considered "non-inferior" but not superior to vancomycin 125 mg (PO) every 6 hours. However, 250 mg (PO) every 6 hours is more dependably effective but also may fail or prolong resolution. The speed of resolution of CDD is "dose dependent" and has important infection control implications: more effective and more rapid resolution has important infection control implications because more rapid resolution means less *C. difficile* exposure to other patients and staff, not to mention patient hospital length of stay.

An effective approach to begin treatment of CDD is to begin with vancomycin 250 mg (PO) every 6 hours and evaluate the response (decrease in stools per day) after 3 days of treatment. If there has been a marked decrease in liquid stools per day (e.g., 16/day or 18/day), then complete 10 to 14 days of therapy with the same dose of oral vancomycin.

If there is little or no decrease in stools per day with vancomycin 250 mg (PO) every 6 hours, increase the dose to 500 mg (PO) every 6 hours and again reevaluate the response (i.e., decrease in stools per day after 3 days). At 500 mg (PO) every 6 hours essentially all patients rapidly respond to this dose.

Since resistance is not an issue, if there is no response (after 3 days) to vancomycin 500 mg (PO) every 6 hours, obtain an abdominal CT scan to rule out colitis. Metronidazole (IV/PO) is highly effective in CDC therapy, but its efficacy is questionable in CDD. Unlike oral vancomycin, oral metronidazole is well-absorbed from the mucosa of the colon, resulting in very low or subtherapeutic intraluminal concentrations. Importantly, while metronidazole is highly effective in CDC (penetrates the colon wall), it is suboptimal for CDD. The only other anti-CDD oral antibiotic comparable to oral vancomycin and superior to metronidazole is nitazoxanide. Therapy for CDD should not be tapered in response to clinical improvement. The patient should receive a full course of oral vancomycin therapy, with the optimal effective dose (500–250 mg orally q6h).

C. difficile colitis therapy

With CDC, the pKa aim of therapy is to achieve therapeutic colon wall levels. High intraluminal levels, key in CDD therapy, are of no benefit in CDC therapy because it is a transmural colon wall process. Also, pancolitis is often accompanied by microscopic translocation of colon flora from the wall into the peritoneum, causing microscopic peritonitis. Pancolitis may also result in colon perforation or toxic megacolon or perforation.

It is prudent to primarily treat the CDC and secondarily to give another antibiotic, with little or no *C. difficile* potential, that is effective against colon flora in potential peritonitis or perforation.

The cornerstone of treatment for *C. difficile* pancolitis has been metronidazole (IV/PO). Alternately, nitazoxanide is highly efficacious in both CDD (superior to metronidazole) and CDC (comparable to metronidazole). Oral or parenteral vancomycin has a limited role in the therapy of CDC and is usually added out of habit or desperation. In cases of CDC *with a diarrheal component*, oral vancomycin may be added to the colitis regimen. Oral vancomycin should not be administered by enema because it may result in colon perforation, since with colitis the colon is inflamed and friable. Early preemptive therapy for potential microbial translocation of bacteria (microscopic peritonitis) or colon perforation is prudent. Therefore, with severe pancolitis, an antibiotic effective against coliforms and *B. fragilis* is reasonable. It doesn't matter which agent is selected, but preferably select one that doesn't predispose to *C. difficile* (e.g., piperacillin/tazobactam). Aside from nitazoxanide, an effective alternate in CDC is tigecycline. Tigecycline has several advantages. First, the use of tigecycline is protective against *C. difficile*. Second, by itself, it is highly effective against *C. difficile*. Third, and importantly, it also provides preemptive therapy of microscopic or gross peritonitis. Optimal therapy for *C. difficile* pancolitis is metronidazole plus tigecycline. In severe cases of pancolitis, nitazoxanide may be given orally via nasogastric or percutaneous endoscopic gastrostomy tube. Treatment of CDC should be continued until clinical resolution on abdominal CT scan. Transition to oral therapy for completion of CDC treatment may be done with nitazoxanide. CDC accompanied by toxic megacolon or colon perforation may require surgical intervention. Should surgery become necessary, tigecycline provides optimal monotherapy for colon surgery necessitated by toxic megacolon and/or colon perforation. Alternately, combination therapy with metronidazole (*C. difficile* and *B. fragilis* coverage) plus a "low *C. difficile* potential" antibiotic (e.g., ceftriaxone for aerobic Gram negative colon flora coverage).

C. difficile diarrhea and *C. difficile* colitis recurrence and relapse

Reinfection or recurrence of CDD is defined as another episode of CDD that has occurred after previous successful treatment. Clinically, cure is manifested by cessation of CDD while stool PCR for CDD may remain positive for 8 weeks following infection. Some

CDD patients will remain colonized (asymptomatic carriage) over time. The diagnosis of reinfection with CDD is a patient who again acutely develops otherwise unexplained, profuse watery diarrhea (20–30 liquid stools per day). Recurrence is easily misdiagnosed in those with *C. difficile* carriage who develop diarrhea due to another infectious or noninfectious diarrheal disorder. Diarrhea in such cases produces few soft or semi-formed stools per day, markedly less in number and volume than with CDD. In such cases, the clinician should try to determine the cause of the non-CDD loose stools and not try to treat *C. difficile* carriage just because the stool PCR is positive. In infectious disease, in general, colonization is more difficult to eliminate than infection, and this applies to CDD as well. Recurrent CDD should be treated the same as an initial episode with oral vancomycin using 500 mg (PO) every 6 hours for a week after clinical resolution. It is prudent to avoid retreatment with oral metronidazole even if successful previously, given its resistance potential and limited effectiveness against oral vancomycin.

A more difficult therapeutic challenge is CDD relapse. Relapse implies interval improvement without cure and is usually due to inadequate treatment due to drug choice, drug dose, or treatment duration. The approach to treating CDD relapse is based on two principles: avoidance of drug "tapering" regimens. High-dose oral vancomycin (500 mg q6h) is highly effective when given for a prolonged treatment course (3 weeks) without tapering the dose. Tapering regimens often fail and are based on the notion that, in the colon, *C. difficile* spores (spores are inert and non-toxin producing) will germinate during the taper and be eliminated by the lower drug dose. In CDD, the organism in the vegetative state is actively growing and producing toxin, but not in the spore stage; this is useful for survival in adverse environmental conditions (desiccation), which clearly is not the case in active infection in the colon. Other drugs that have been used to treat recurrent CDD include rifamaxin and fidaxomicin, which are comparable but not more effective than oral vancomycin 125 mg (PO) every 6 hours.

Fecal microbiota transplants (FMTs) have been used to treat CDD. Caution is advisable since FMTs have rarely transmitted enteric pathogens to recipients. Of the available treatment options, high-dose oral vancomycin (500 mg q6h) is the most reliably effective.

In cases of relapses of CDD, a careful review of the patient's medical history should be done to be sure that any residual *C. difficile* carriage is not induced to produce toxins and result in CDD (e.g., some antibiotics with a "high *C. difficile* potential", PPIs, probiotics, laxatives or stool softeners, some anti-depressants). In the few cases where 3 weeks of high-dose oral vancomycin may fail, it may be necessary to retreat with a second or, very rarely, a third course for cure. Relapse of CDC should be first approached by being sure that the colitis is, in fact, due to *C. difficile* and not a CDC mimic (e.g., ischemic colitis, CMV colitis, ulcerative colitis) in patients with stools PCR-positive for *C. difficile.* From a treatment perspective, nitazoxanide is highly effective, preferred to metronidazole, and may be given orally until the colitis resolves (Table 51.1).

TABLE 51.1 ***CLOSTRIDIUM DIFFICILE*** **DIARRHEA AND *C. DIFFICILE* COLITIS**

Diarrhea †§	**Diarrhea**
Initial episode:	**Initial episode:**
Vancomycin 250 mg (PO) q6h × 7–10 days* If no improvement in 3 days, ↑ dose to 500 mg (PO) q6h × 7 days)	Nitazoxanide 500 mg (PO) q12h × 7–10 days
Relapse:	**Relapse:**
Vancomycin 500 mg (PO) q6h × 14 days	Nitazoxanide 500 mg (PO) q12h × 7–10 days
Recurrence:††	**Recurrence:**
Vancomycin 500 mg (PO) q6h × 1 month (***do not taper vancomycin dose*****).**	Preferred Therapy Nitazoxanide 500 mg (PO) q12h × 7–10 days
If another recurrence,	Alternate Therapy Rifaximin 400 mg (PO) q8h × 10 days
retreat with Vancomycin 500 mg (PO) q6h × 2 months.	**or**
If another recurrence, retreat with Vancomycin 500 mg (PO) q6h *x* 3 months.	Fidaxomicin 200 mg (PO) q12h × 10 days
If dose not tapered and if no colitis, If diarrhea continues, look for alternate diagnosis.	**or**
	Bezlotoxumab 10 mg/ kg × 1 dose (plus an anti-C. difficile antibiotic)
	or
	FMT (potential to transmit enteric pathogens)

* With C. difficile diarrhea (CDD) (not colitis), treatment failure is common with vancomycin 125 mg (PO) q6h and with Metronidazole at any dose.
† When treating CDD or colitis, *discontinue antibiotics with a high C. difficile potential* (e.g., clindamycin, ciprofloxacin, β-lactams *excluding* ceftriaxone).
§ Avoid anti-spasmodics in CDD; use may result in *C. difficile* colitis (CDC).
§§ Colectomy may be life-saving in severe *C. difficile* pancolitis.

Preferred therapy	Alternate therapy
Colitis	**Colitis**
Mild/Moderately severe:	**Mild/Moderately severe:**
Metronidazole 1 g (IV) q24h until cured plus ceftriaxone 1 g (IV) 124h (until associated peritonitis resolves)	Metronidazole 500 mg (PO) q6h until cured **plus either** tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h until cured or nitazoxanide 500 mg (PO) q12h until cured ± vancomycin 500 mg (PO) q6h if also with diarrhea until cured*
Severe pancolitis:§§ Metronidazole 500 mg (IV/PO) q6–8h until cured **plus** nitazoxanide 500 mg (PO) q12h × until cured **plus** tigecycline 200 mg (IV) × 1 dose, then, 100 mg (IV) q24h until cured	
	Colitis Relapse or Recurrence: Nitazoxanide 500 mg (PO) q12h until cured

* *C. difficile* colitis with no associated diarrhea, oral vancomycin of questionable benefit.
Adapted from: Cunha CB, Cunha BA (eds.) in *Antibiotic Essentials* (17th ed.), JayPee Medical Publishers, New Delhi, 2020.

Suggested reading

Barkin JA, Sussman DA, Fifadara N, Barkin JS. *Clostridium difficile* infection and patient-specific antimicrobial resistance testing reveals a high metronidazole resistance rate. *Dig Dis Sci*. 2017;62:1035–1042.

Bartlett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* infection. *Clin Infect Dis*. 2008;46:S12–S18.

Bouza E, Burillo A, Munoz P. Antimicrobial Therapy of *C. difficile* associated Diarrhea. *Med Clin North Am*. 2006;90:1141–1163.

Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to *Clostridium difficile*. *Gut*. 1986; 27:1169–1172.

Caines C, Gill MV, Cunha BA. Non-*Clostridium difficile* nosocomial diarrhea in the intensive care unit. *Heart Lung*. 1997;26:83–84.

Chandrasekaran R, Lacy DB. The role of toxins in *C. difficile* Infection. *FEMS Micro Rev*. 2017;41:723–750.

Cunha CB, Cunha BA (eds.). *Antibiotic Essentials*, (17th ed.) New Delhi: Jay Pee Publishers; 2020.

Cunha BA. C. difficile in the CCU. In Cunha CB, Cunha BA, (eds.) *Infectious Disease and Antimicrobial Stewardship in Critical Care Medicine*, 4th ed. Boca Raton, FL: CRC Press; 2020.

Cunha BA, Thekkel V, Eisenstein L. Community-acquired norovirus diarrhea outbreak mimicking a community acquired CDD outbreak. *J Hosp Infect*. 2008;70:98–100.

Cunha BA, Sessa J, Blum S. Enhanced efficacy of high dose oral vancomycin therapy in C. difficile diarrhea for hospitalized adults not responding to conventional oral vancomycin therapy. *J Clin Med*. 2018;7:PMID 29642570.

Cunha BA, Bloom J, Cunha CB. Once daily high dose tigecycline: Pharmacokinetic/pharmacodynamic based dosing for optimal clinical effectiveness: Dosing matters, revisited. *Expert Rev Anti-Infect Ther*. 2017;15:257–267.

DeFilipp Z, Bloom PP, Soto MT, et al. Drug resistant E. coli bacteremia transmitted by fecal microbiota transplant. *N Eng J Med*. 2019: 381: 2043–2050.

Dial S, Alrasadi K, Manoukian C, et al. Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: Cohort and case-control studies. *CMAJ*. 2004;171:33–38.

DiBella S, Nisii C, Petrosillo N. Is tigecycline a suitable option for *C. difficile* infection? Evidence from the literature. *Int J Anti Agents*. 2015;46:8–12.

Gergely Szabo B, Kadar B, Szidonia Lenart K, et al. Use of intravenous tigecycline in patients with severe *C. difficile* infection: A retrospective observational cohort study. *Clin Microbiol Infect*. 2016;20:476–481.

Hung YP, Lee JC, Lin HJ, Liu HC, Wu YH. Doxycycline and tigecycline: Two friendly drugs with a low association with *C. difficile* infection. *Antibiotics*. 2015;4:216–229.

Kundrapu S, Hurless K, Sunkesula VC, Tomas M, Donskey CJ. Tigecycline exhibits inhibitory activity against C. *difficile* in the intestinal tract of hospitalized patients. *Int J Anti Agents*. 2015;45:424–426.

Lowe DO, Mamdani MM, Kopp A, et al. Proton pump inhibitors and hospitalization for *Clostridium difficile* associated disease: A population-based study. *Clin Infect Dis*. 2006;43:1272–1276.

Manea E, Sojo-Dorado J, Jipa RE, Banea SN, Rodriguez Bano J, Hristea A. The role of tigecycline in the management of C. *difficile* infection: A retrospective cohort study. *Clin Micro Infect*. 2017;Sl198–Sl743X.

McVay CS, Rolfe RD. In vitro and in vivo activities of nitazoxanide against C. difficile. *Antimicrob Agents Chemother*. 2000;44:2254–2258.

Mohan SS, McDermott BP, Parchuri S, Cunha BA. Lack of value of repeat stool testing for *C. difficile* toxin. *Am J Med*. 2006;119:e7–e8.

Musher DM, Logan N, Hamill RJ, Dupont HL, Lentnek A, Gupta A, Rossignol JF. Nitazoxanide for the treatment of CDC. *Clin Infect Dis*. 2006;43:421–427.

Musher DM, Logan N, Mehendiratta V, Melgarejo NA, Garud S, Hamill RJ. CDC that fails conventional metronidazole therapy: Response to nitazoxanide. *J Anti Chemother*. 2007;59:705–710.

Mylonakis, E, Ryan ET, Calderwood SB. *Clostridium difficile* associated diarrhea: A review. *Arch Intern Med*. 2001;161:525–533.

Napolitano LM, Edmiston CE Jr. *C. difficile* disease: Diagnosis, pathogenesis, and treatment update. *Surgery*. 2017;162:325–348.

Nistico JA, Hage JE, Schoch PE, Cunha BA. Unnecessary repeat *Clostridium difficile* PCR testing in hospitalized adults with *C. difficile*-negative diarrhea. *Eur J Clin Micro Infect Dis*. 2013;32:97–99.

Saltzman T, Fazzari M, Chung S, et al. The effect of probiotics on the incidence of *Clostridioides difficile*. *Am J Inf Control*. 2020;48:184–188.

Shim JK, Johnson S, Samore MH, et al. Primary symptomless colonisation by *Clostridium difficile* and decreased risk of subsequent diarrhoea. *Lancet*. 1998;351:633–636.

Siegal DS, Syed F, Hamid N, Cunha BA. *Campylobacter jejuni* pancolitis mimicking idiopathic ulcerative colitis. *Heart Lung*. 2005;34:288–290.

Siegel DS, Hamid N, Cunha BA. Cytomegalovirus colitis mimicking ischemic colitis in an immunocompetent host. *Heart Lung*. 2005;34:291–294.

Teasley DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium difficile*-associated diarrhea and colitis. *Lancet*. 1983;2:1043–1046.

Tang DM, Urrunaga NH, von Rosenvinge EC. Pseudomembranous colitis: Not always *C. difficile*. *Clev Clin J Med*. 2016;83:361–366.

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Sexually transmitted enteric infections

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Introduction

A wide variety of microbial pathogens may be transmitted sexually by the oral–anal or genital–anal routes. Sexually transmitted enteric infections may involve multiple sites of the gastrointestinal tract, resulting in proctitis, proctocolitis, and enteritis. These infections occur primarily in men who have sex with men (MSM) and heterosexual women who engage in anal–rectal intercourse or in sexual practices that allow for fecal–oral transmission. Anorectal infections with syphilis, gonorrhea, condyloma acuminata (human papillomavirus, HPV), lymphogranuloma venereum (LGV), and granuloma inguinale (donovanosis) have been recognized for many years. Over the past two decades, other sexually transmitted pathogens such as herpes simplex virus (HSV) and *Chlamydia trachomatis* have also been recognized as causing anorectal infection. Enteric pathogens traditionally associated with food- or waterborne acquisition but that also may be transmitted sexually include *Giardia lamblia, Entamoeba histolytica, Campylobacter, Shigella*, and *Salmonella*. In patients with AIDS, other opportunistic infections, including *Candida, Microsporida, Cryptosporidium, Isospora, Cyclospora, Mycobacterium avium* complex, and cytomegalovirus (CMV), may also cause intestinal disorders.

Depending on the pathogen and the location of the infection, symptoms and clinical manifestations vary widely. Perianal lesions are usually caused by syphilis, HSV, granuloma inguinale, chancroid, and condyloma acuminata. Rectal infections cause inflammation of the rectal mucosa, commonly referred to as *proctitis*. Symptoms include constipation, tenesmus, rectal discomfort or pain, hematochezia, and a mucopurulent rectal discharge. Proctitis can be caused by gonorrhea, chlamydia, syphilis, and HSV. Proctocolitis involves inflammation extending from the rectum to the colon, and, in addition to the organisms causing proctitis, other enteric pathogens such as *Shigella, Salmonella, Campylobacter, E. histolytica*, and CMV may be involved. Enteritis is an inflammatory illness of the duodenum, jejunum, and/or ileum. Sigmoidoscopy results are often normal, and symptoms consist of diarrhea, abdominal pain, bloating, cramps, and nausea. Additional symptoms may include fever, weight loss, myalgias, flatulence, urgency, and, in severe cases, melena. Sexually transmitted pathogens usually associated with enteritis include *Shigella, Salmonella, Campylobacter, Giardia*, CMV, and, potentially, *Cryptosporidium, Isospora*, and *Microsporida*.

The large number of infectious agents that cause enteric and anorectal infections necessitate a systematic approach to the management of these conditions. While obtaining the medical history, the clinician should attempt to differentiate between proctitis, proctocolitis, and enteritis and should assess the constellation of symptoms that suggest one or another likely infectious cause. The history should be used to investigate types of sexual practices and possible exposure to those pathogens known to cause intestinal infections. Examination should include inspection of the anus, digital rectal examination, and anoscopy to identify general mucosal abnormalities. Initial laboratory tests should include a Gram stain of any rectal exudate obtained with the use of an anoscope. The demonstration of leukocytes provides objective evidence of the presence of an infectious or inflammatory disorder. Cultures for gonorrhea should be obtained from the rectum, urethra, and pharynx, and, if possible, rectal swabs for nucleic acid amplification testing(NAAT) for chlamydia and gonorrhea should be performed. Serologic tests for syphilis should be performed in all cases.

Dark-field examination of any ulcerations and a rapid plasma reagin test should be performed. Cultures for HSV should be performed if ulcerative lesions are present. If proctocolitis is present, additional stool cultures for *Campylobacter, Salmonella*, and *Shigella* should be obtained, and stool examination for *E. histolytica* is indicated. For HIV-positive patients, other pathogens, including *Microsporida*, CMV, atypical *Mycobacteria, Cryptosporidium*, and *Isospora*, should be screened for by stool examination and cultured when possible. Specific information on clinical presentation, diagnosis, and therapy is provided in other chapters on gastroenteritis, intestinal protozoa, and individual enteric pathogens.

Gonococcal proctitis

Rectal infection with *Neisseria gonorrhoeae* occurs predominantly among homosexual men and in women engaging in anal–rectal intercourse. In many cases of women, the patient has no history of rectal intercourse and the infection is thought to have resulted from contiguous spread of infected secretions from the vagina. Symptoms, when present, develop approximately 5 to 7 days after exposure. Symptoms are usually mild and include constipation, anorectal discomfort, tenesmus, and a mucopurulent rectal discharge that may cause secondary skin irritation resulting in rectal itching and perirectal erythema. Although asymptomatic or mild local disease is common, complications such as fistulas, abscesses, strictures, and disseminated gonococcal infection may occur.

Findings of rectal gonorrhea during anoscopy are nonspecific and limited to the distal rectum. The most common finding is the presence of mucopus in the rectum. The rectal mucosa may appear completely normal or demonstrate generalized erythema with local areas of easily induced bleeding, primarily near the anal–rectal junction. Diagnosis is usually made by Gram stain and culture of material obtained by swabbing the mucosa of the rectal area. The sensitivity of Gram stain of rectal exudate for identification of gram-negative intracellular diplococci is approximately 80% when obtained through an anoscope versus 53% for blindly inserted swabs. Cultures inoculated on selective media provide the definitive diagnosis; however, the precise sensitivity of a single rectal culture for gonorrhea may be no greater than 80%. DNA detection assays are now widely available for detection of gonorrhea in urogenital specimens and are equally sensitive to culture.

Due to increasing antibiotic resistance of gonorrhea to cefixime and fluoroquinolones, the Centers for Disease Control and Prevention (CDC) recommends for treatment of uncomplicated urogenital, anorectal, and pharyngeal gonorrhea combination therapy with a single intramuscular dose of ceftriaxone 250 mg plus a single dose of azithromycin 1 g orally. Clinicians who diagnose gonorrhea in a patient with persistent infection after treatment (treatment failure) with the recommended combination therapy regimen should culture relevant clinical specimens and perform antimicrobial susceptibility testing of *N. gonorrhoeae* isolates. When ceftriaxone cannot be used for treatment of urogenital or rectal gonorrhea, several alternative options are available: cefixime 400 mg orally plus azithromycin 1 g orally, or dual treatment with single doses of oral gemifloxacin 320 mg plus oral azithromycin 2 g, or dual treatment with single doses of intramuscular gentamicin 240 mg plus oral azithromycin 2 g orally in a single dose. If a patient with gonorrhea is treated with an alternative regimen, the patient should return 2 weeks after treatment for a test of cure at the infected anatomic site. For all patients with gonorrhea, every effort should be made to ensure that the patients' sex partners from the preceding 60 days are evaluated and treated for *N. gonorrhoeae* with a recommended regimen. If there is continued evidence of proctitis, further evaluation for other agents such as chlamydia, syphilis, enteric bacterial pathogens, and HSV should be considered.

Chlamydia proctitis

Rectal infection with LGV and non-LGV immunotypes of *C. trachomatis* has been well documented. LGV infections are endemic in tropical countries, but they have also been increasing in frequency among MSM in the United States and Europe. LGV infections usually cause a severe proctocolitis characterized by severe anorectal pain, bloody mucopurulent discharge, and tenesmus. Inguinal adenopathy, which is characteristic of genital LGV, is often present. Sigmoidoscopy typically reveals diffuse friability with discrete ulcerations in the rectum that occasionally extend to the descending colon. Strictures and fistulas may become prominent and can be easily misdiagnosed clinically as Crohn's disease or carcinoma. Histologically, rectal LGV may be confused with Crohn's disease because giant cells, crypt abscesses, and granulomas may be present.

The non-LGV immunotypes of *C. trachomatis* are less invasive than LGV and cause a mild proctitis characterized by rectal discharge, tenesmus, and anorectal pain. Many infected individuals may be asymptomatic and can be diagnosed only by routine cultures. However, even in asymptomatic cases, abnormal numbers of fecal leukocytes are usually present. Sigmoidoscopy results may be normal or may reveal mild inflammatory changes with small erosions or follicles in the lower 10 cm of the rectum.

Rectal *C. trachomatis* infection can be diagnosed by nucleic acid amplified tests (NAATs) and nucleic acid hybridization tests. Since chlamydia culture is not widely available for this purpose, NAATs have demonstrated improved sensitivity and specificity compared with culture for the detection of *C. trachomatis* at rectal sites and at oropharyngeal sites. Some laboratories have met Clinical Laboratory Improvement Amendment (CLIA) requirements and have validated NAAT testing on rectal swab specimens for *C. trachomatis*. Serology is useful for the diagnosis of LGV with a complement fixation titer of greater than 1:64. Azithromycin, tetracycline, and doxycycline are the drugs of choice for infection with *C. trachomatis*. Azithromycin, 1 g as a single dose, is effective for urethritis and cervicitis and has been recommended for uncomplicated rectal infections. Doxycycline, 100 mg twice a day for 7 days, is effective except for treating LGV infection, which should be treated for 3 weeks with doxycycline 100 mg orally twice a day. Patients should be followed carefully with repeat sigmoidoscopy, particularly when there is any question about the differential diagnosis of LGV versus inflammatory bowel disease.

Anorectal syphilis

Treponema pallidum can be seen in its early infectious stages with a primary anorectal lesion appearing 2 to 6 weeks after exposure to rectal intercourse. However, clinicians often fail to recognize anorectal chancres and, consequently, syphilis in MSM is diagnosed in a secondary or early latent stage much more often than in the primary stage. Careful perianal examination can reveal unsuspected perianal chancres, but digital rectal examination and anoscopy may be required to detect asymptomatic chancres higher in the anal canal or rectum. When anorectal syphilis causes symptoms, it is often misdiagnosed as a traumatic lesion, fissure, or hemorrhoiditis. When symptoms are present, they include mild anal pain or discomfort, constipation, rectal bleeding, and occasionally a rectal discharge. Primary anorectal syphilis may appear as a single or multiple, mirror-image perianal ulcer ("kissing chancres"). It can also present as an ulcerated mass typically located on the anterior wall of the rectum. Inguinal adenopathy with rubbery, nonsuppurative, painless nodes may be associated with anorectal syphilis; it helps distinguish it from fissures. Secondary syphilis may cause discrete polyps, smooth lobulated masses, mucosal alterations, and nonspecific mucosal erythema or bleeding. In secondary syphilis, condyloma lata may be found near or within the anal canal. These are smooth, warty masses and should be differentiated from the more highly keratinized condyloma acuminata.

Diagnosis of anorectal syphilis is based on serology, perirectal and digital rectal examination, and anoscopy. Detection of motile treponemes by dark-field examination is useful for evaluation of perianal and anal lesions but may be less specific for rectal lesions because pathogenic treponemes can be found in the intestine. Biopsies of rectal lesions or masses should be processed for silver staining if syphilis is suspected. Serologic diagnosis of syphilis is based on the presence of antibodies to non-treponemal and treponemal antigens. A positive Venereal Disease Research Laboratory (VDRL) test or rapid plasma reagin (RPR) test must be confirmed by a positive specific test such as the fluorescent treponemal antibody absorption test (FTA-ABS) or the microhemagglutination assay (MHA). Some clinical laboratories and blood banks now screen samples initially using treponemal tests, typically by enzyme immunoassay. Persons with a positive treponemal screening test should have a standard non-treponemal test with titer performed reflexively by the laboratory to guide patient management decisions. For most HIV-infected persons, serologic tests are accurate and reliable for the diagnosis of syphilis and for following a patient's response to treatment. However, atypical syphilis serologic test results (i.e., unusually high, unusually low, or fluctuating titers) can occur in HIV-infected persons. When serologic tests do not correspond with clinical findings suggestive of early syphilis, use of other tests (e.g., biopsy and dark-field microscopy) should be considered.

Treatment for anorectal syphilis is standard treatment for early syphilis and consists of benzathine penicillin, 2.4 million U IM. Penicillin-allergic patients may be treated with a 14-day course of doxycycline, 100 mg twice daily, or tetracycline, 500 mg four times a day for 14 days.

Shigella, *Salmonella*, and *Campylobacter* infections

Shigellosis presents with an abrupt onset of diarrhea, fever, nausea, and cramps. Diarrhea is usually watery but may contain mucus or blood. Sigmoidoscopy usually reveals an inflamed mucosa with friability not limited to the distal rectum, and histologic examination shows diffuse inflammation with bacteria scattered throughout the submucosa. *Shigella sonnei* and *Shigella flexneri* account for most of the *Shigella* infections in the United States. Diagnosis is made by culturing the organism from the stool on selective media. Treatment is usually supportive with fluid replacement, and antimotility agents should be avoided. Antibiotics are useful in the management of shigellosis because use of appropriate therapy has reportedly shortened the period of fecal excretion and limited the clinical course. However, some authorities believe that antibiotic therapy should be reserved for the severely ill only or the immunocompromised patient because the infection is typically self-limited and resistance has been common. HIV-infected patients who develop *Shigella* infections may require prolonged treatment or suppressive therapy similar to those infected with salmonella. Antibiotic therapy should be chosen according to the sensitivity pattern of the *Shigella* species isolated. Ciprofloxacin, 500 mg twice a day for 7 days, is usually effective unless resistance is evident.

Campylobacter jejuni and *Campylobacter*-like organisms such as *Helicobacter cinaedi* and *Helicobacter fennelliae* have also been associated with proctocolitis in homosexual men. Clinical manifestations of infections resulting from all *Campylobacter* species appear nearly identical. There is often a prodrome with fever, headache, myalgia, and malaise 12 to 24 hours before the onset of intestinal symptoms. The most common symptoms are diarrhea, malaise, fever, and abdominal pain. Abdominal pain is usually cramping and may be associated with 10 or more bowel movements per day. *C. enteritis* is often self-limiting with gradual improvement in symptoms over several days. Illnesses lasting >1 week occur in approximately 10% to 20% of patients seeking medical attention, and relapses are often seen in HIV-infected patients. Fecal leukocytes are uniformly present, and diagnosis is confirmed by isolation of the organisms on selective media in a microaerophilic atmosphere. Therapy consists of fluid and electrolyte replacement and antibiotic treatment. Ciprofloxacin 500 mg twice a day for 7 days or azithromycin 500 mg once daily for 3 days has been used successfully for treatment, but resistance to these antibiotics has also been increasing within recent years and antibiotic susceptibility should be reviewed.

Salmonella infections of the intestinal tract are primarily caused by *S. typhimurium* and *S. enteritidis*. Salmonella has been reported among homosexual male partners, suggesting sexual transmission,

and salmonella bacteremia in an HIV-infected individual is now diagnostic of AIDS. Clinical presentation often depends on the host immune status. In an immunocompetent person, salmonellosis is usually self-limited and causes gastroenteritis. No antibiotic therapy is recommended because symptoms fade within days, and antibiotics have been associated with prolonged salmonella intestinal carriage. In HIV-infected individuals, salmonella infections may cause severe invasive disease and often result in bacteremia with widespread infection. The fluoroquinolones are effective drugs of choice for *Salmonella* infections in immunocompromised individuals. Despite adequate therapy for bacteremia, virtually all HIV-infected patients may suffer recurrent salmonella septicemia. Ciprofloxacin, 500 to 750 mg twice daily, has been effective in suppressing recurrences in such patients.

Parasitic infections

Homosexual men engaging in sexual activities involving fecal contamination such as oral–anal sex are at increased risk for a number of parasitic infections, including *Giardia lamblia, Iodamoeba butschlii, Dientamoeba fragilis, Enterobius vermicularis, Cryptosporidium, Isospora*, and microsporidia. Of these infections, *Giardia* and *E. histolytica* appear to be the most common sexually transmitted parasitic infections. *G. lamblia* is associated with symptoms of enteritis, and *E. histolytica* may cause proctocolitis. Most *E. histolytica* infections are asymptomatic, and <10% of those infected develop invasive disease with amebic dysentery or liver abscess. Most *E. histolytica* strains isolated from homosexual men are the nonpathogenic strains not usually associated with gastrointestinal symptoms. However, when symptoms are present, they may vary from mild diarrhea to fulminant bloody dysentery. These symptoms may wax and wane for weeks to months.

Diagnosis is based on demonstration of *E. histolytica* in the stool in a wet mount of a swab or in biopsy of rectal mucosal lesions. Occasionally, multiple fresh stool examinations are necessary to demonstrate the cysts or trophozoites or *E. histolytica*. For noninvasive disease limited to the lumen only, paromomycin 25 to 30 mg/kg/d in three doses for 7 days is the regimen of choice. Invasive intestinal disease should be treated with metronidazole, 750 mg orally three times daily for 7 to 10 days.

G. lamblia also appears to be sexually transmitted through oral–anal contact. Giardiasis is typically an infection of the small intestine, and symptoms vary from mild abdominal discomfort to diarrhea, abdominal cramps, bloating, and nausea. Multiple stool examinations may be necessary to document infection with *G. lamblia*. When stool examination is negative, sampling of the jejunal mucus by the Enterotest or small-bowel biopsy may be necessary to confirm the diagnosis. Metronidazole 250 mg three times a day for 7 days is recommended. Alternative regimens include tinidazole, 2 g only single dose, or paromomycin, 10 mg/kg orally three times per day for 5 to 10 days.

Although sexual transmission of *Cryptosporidium, Isospora belli*, and *Microsporida* are commonly seen in HIV-infected homosexual men, evidence for sexual transmission is limited. These protozoa primarily infect the small bowel and cause nonspecific watery diarrhea, abdominal cramping, and bloating. Diagnosis is established by a modified acid-fast stain or fluoramine stain of the stool or by concentration and identification of the organism by the sugar-flotation method. A commercially available fluorescein monoclonal antibody assay increases the sensitivity for detection of *Cryptosporidium*. Treatment of *Cryptosporidium* or *Isospora* infections in immunocompetent patients with self-limited diarrhea is rarely required. Among HIV-infected individuals, treatment should be directed toward symptomatic treatment of the diarrhea with rehydration and repletion of electrolyte losses by either oral or intravenous route. Although several antibiotics have been used, including paromomycin and azithromycin, chronic infection and relapses are common. The most effective therapy currently is a reversal of immunosuppression with the use of highly active antiretroviral therapy. It is common for patients with severe diarrhea from *Cryptosporidium* and *Microsporida* to clear their infections by taking combination antiretroviral agents with reduction in the viral load below detectable limits. Successful treatment of the infection presumably results from a subsequent rise in CD4 count and restoration of immune competence sufficient to clear the intestinal infection.

Suggested reading

Abdolrasouli A, McMillan A, Ackers JP. Sexual transmission of intestinal parasites in men who have sex with men. *Sex Health*. 2009;6(3):185–194.

Cosentino LA, Campbell T, Jett A, et al. Use of nucleic acid amplification testing for diagnosis of anorectal sexually transmitted infections. *J Clin Microbiol*. 2012;50:2005–2008.

Davis TW, Goldstone SE. Sexually transmitted infections as a cause of proctitis in men who have sex with men. *Dis Colon Rectum*. 2009;52(3):507–512.

de Vries HJ, Zingoni A, Kreuter A, Moi H, White JA; European Branch of the International Union against Sexually Transmitted Infections; European Academy of Dermatology and Venereology; European Dermatology Forum; European Society of Clinical Microbiology and Infectious Diseases; Union of European Medical Specialists; European Centre for Disease Prevention and Control; European Office of the World Health Organisation. 2013 European guideline on the management of lymphogranuloma venereum. *J Eur Acad Dermatol Venereol*. 2015 Jan;29(1):1–6.

Hoentjen F, Rubin DT. Infectious proctitis: When to suspect it is not inflammatory bowel disease. *Dig Dis Sci*. 2012;57(2):269–273.

Lamb CA, Lamb EI, Mansfield JC, Sankar KN. Sexually transmitted infections manifesting as proctitis. *Frontline Gastroenterol*. 2013;4(1):32–40.

Levy I, Gefen-Halevi S, Nissan I, et al. Delayed diagnosis of colorectal sexually transmitted diseases due to their resemblance to inflammatory bowel diseases. *Int J Infect Dis*. 2018 Oct;75:34–38.

Mayer KH. Sexually transmitted diseases in men who have sex with men. *Clin Infect Dis*. 2011;53(Suppl 3):S79–S83.

Patel R, Green J, Clarke E, et al. 2014 UK national guideline for the management of anogenital herpes. *Int J STD AIDS*. 2015 Oct;26(11):763–776.

Pinto-Sander N, Parkes L, Fitzpatrick C, Richardson D. Symptomatic sexually transmitted proctitis in men who have sex with men. *Sex Transm Infect*. 2019 Sep;95(6):471.

Stoner BP, Cohen SE. Lymphogranuloma venereum 2015: Clinical presentation, diagnosis, and treatment. *Clin Infect Dis*. 2015 Dec 15;61(Suppl 8_:S865–873.

Vall-Mayans M, Caballero E, Sanz B. The emergence of lymphogranuloma venereum in Europe. *Lancet*. 2009;374(9686):356.

White JA. Manifestations and management of lymphogranuloma venereum. *Curr Opin Infect Dis*. 2009;22(1):57–66.

Workowski KA, Bolan G; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR-3):1–135. https://www.cdc.gov/std/tg2015/tg-2015-print.pdf

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Acute appendicitis

Bian Wu and John Maa

Background and epidemiology

Acute appendicitis is one of the most common surgical emergencies, with a lifetime incidence of approximately 7%. It can occur in males and females of all ages, but is most common in older children and young adults. The diagnosis is often delayed in younger children and the elderly due to atypical presentations.

Pathogenesis

The pathophysiology of acute appendicitis begins with obstruction of the appendicular lumen. The obstruction is commonly caused by a fecalith (impacted stool) in adults and lymphoid hyperplasia in children, but can also result from foreign bodies (undigested seeds), infections (especially parasitic), and tumors (most commonly adenocarcinoma, followed by carcinoid tumors). Luminal obstruction leads to accumulation of distal secretions and increased intraluminal pressure, which results in impairment of venous outflow and, subsequently, arterial inflow. The resulting ischemia yields bacterial translocation, mucosal necrosis, and, eventually, perforation. The natural progression and types of acute appendicitis are described in Table 53.1 (simple acute, suppurative, gangrenous, perforated, associated with abscess). The organisms most typically associated with gangrenous or perforated appendicitis are *Escherichia coli*, *Peptostreptococcus*, *Bacillus fragilis*, and various species of *Pseudomonas*, with most cases being polymicrobial.

Diagnosis

A classic presentation of acute appendicitis includes periumbilical pain that migrates to the right lower quadrant, representing a progression from visceral pain to parietal pain that may occur within a few hours or a few days. Physical examination often reveals point tenderness at McBurney's point, located two-thirds the distance from the umbilicus to the right anterior superior iliac spine. Worsening or diffuse abdominal pain or tenderness are concerning for perforation and peritonitis, as are fevers greater than 38.5°C (101.3°F). Occasionally a palpable mass may be felt in the right lower quadrant, suggestive of a walled-off abscess.

Onset of pain is classically followed by anorexia and nausea, and vomiting may occur. Absence of anorexia and repeated episodes of emesis suggest an alternate diagnosis. Importantly, the classic symptoms of acute appendicitis have limited sensitivity due to variant locations of the appendix and inflammatory irritation of nearby organs. A retrocecal appendicitis may present as flank or back pain, whereas an inflamed appendix in the pelvis may present as dysuria or be confused with testicular or gynecologic diseases. Inflammation of adjacent bowel may cause either an ileus or diarrhea, especially in cases of gross perforation or abscess.

TABLE 53.1 **TYPES OF ACUTE APPENDICITIS**

Type	Characteristics
Simple acute	Mild hyperemia, edema, appendiceal dilation, no serosal exudate
Suppurative	Edematous, congested vessels, fibrinopurulent exudate; peritoneal fluid increased, clear or turbid; may be walled off by omentum, adjacent bowel or mesentery
Gangrenous	Similar to suppurative plus areas of gangrene, microperforations, increased and purulent peritoneal fluid
Perforated	Obvious defect in wall of appendix; thick and purulent peritoneal fluid; may be associated with ileus or bowel obstruction
Abscess	Appendix may be sloughed; abscess at site of perforation: right iliac fossa, retrocecal, or pelvic; may present rectally; thick, malodorous pus

The recent advances in ultrasonography and computed tomography (CT) have markedly improved the accurate diagnosis of appendicitis, especially in "atypical" cases. Ultrasound is noninvasive and an excellent way to evaluate young children for whom avoidance of radiation is desirable. However, the usefulness of ultrasound is technician-dependent and often limited by patient habitus (ultrasound waves penetrate poorly through fat). CT, optimally with IV and PO contrast, yields excellent sensitivity and specificity, but is costly and carries the risk of radiation and contrast exposure. Many diseases may mimic acute appendicitis and it is essential to combine history, physical exam, laboratory values, and imaging studies with clinical experience and judgment to minimize the rate of misdiagnosis.

Treatment

The mainstay of treatment for simple acute appendicitis is prompt surgical removal of the appendix. To prevent progression leading to perforation, it is important to achieve timely and proper source control. While some evidence supports using antibiotics alone to treat simple acute appendicitis, it is our opinion that appendectomy remains the standard of care. Antibiotics alone carry a significant risk of primary failure leading to perforation as well as disease recurrence, and the now widespread use of laparoscopic appendectomy results in lower rates of surgical complications and shorter hospital stays than were achieved with open appendectomy.

Similarly, surgery remains the standard of care for suppurative, gangrenous, and perforated appendicitis. The exception to urgent surgical intervention for acute appendicitis is perforated appendicitis associated with a contained abscess. In such cases, percutaneous drainage together with antibiotics and interval laparoscopic appendectomy in 6 weeks may be the best treatment strategy, to avoid injury to the small bowel and colon. Antibiotic selection should be tailored to the polymicrobial nature of the disease. Typically, an antipseudomonal β-lactamase is used, such as meropenem, cefepime, or piperacillin/ taxobactam. In cases of β-lactamase allergy, combinations such as ciprofloxacin and metronidazole can be used. The most common bacteria that lead to a postoperative infection after appendectomy are: (1) *Bacteroides*, (2) *Klebsiella*, (3) *Enterobacter*, and (4) *E. coli*, although many of these infections are polymicrobial. Gram-positive cocci are less frequently isolated.

Laparoscopic appendectomy is generally recommended over open appendectomy because it results in less postoperative pain, shorter hospital stays, and a faster return to normal activities. The risk of wound infections is lower with laparoscopic surgery than with open surgery (odds ratio 0.43 with 95% confidence interval 0.34–0.54), but the risk of intra-abdominal abscesses is higher (odds ratio 1.87 with 95% confidence interval 1.19–2.93). This higher risk may be due to the more limited ability to perform peritoneal lavage with laparoscopic surgery as compared to open surgery. In fact, studies suggest there is no advantage to irrigation of the peritoneal cavity over suction alone during laparoscopic appendectomy for perforated appendicitis. Thus, open surgery may be preferred for patients with grossly perforated appendicitis. Laparoscopic surgery use is also limited in some parts of the world by the availability of laparoscopic equipment and surgeons trained in minimally invasive techniques.

Perioperative management

During workup for possible acute appendicitis, patients should be kept NPO. Once the diagnosis is made, a general surgeon should be consulted and the operation arranged. Since patients are typically volume depleted (as evidenced by tachycardia, low urine output, elevated creatinine, hemoconcentration), aggressive fluid resuscitation with an isotonic solution should be started, and electrolytes repleted. Should there be signs of perforation or frank peritonitis (as evidenced by worsening diffuse pain, rebound or involuntary guarding on exam, very high fever, findings on CT scan), the patient's operation should be further expedited.

A broad-spectrum antibiotic should be given prior to skin incision and is typically not continued postoperatively, except in cases with gross perforation. Preoperative preparation of the skin is best performed with a chlorhexidine–alcohol scrub. Postoperatively, patients undergoing laparoscopic appendectomy can typically be started on a clear liquid diet immediately and advanced to a regular diet the following morning. Patients with gross perforation and a likely associated ileus are typically kept NPO immediately postoperatively. The diet is then advanced slowly depending on the length of surgery and associated intra-abdominal inflammation or contamination. Patients should begin walking immediately postoperatively to prevent complications such as pneumonia or deep venous thrombosis.

TABLE 53.2 **TYPES OF POSTOPERATIVE INFECTION**

Type	Characteristics	Management
Superficial surgical site infection (SSI)	Cellulitis +/− infected subcutaneous fluid collection	PO or IV antibiotics +/− open skin at bedside to drain fluid followed by packing the wound with gauze
Deep surgical site infection (SSI)	Infection involving the abdominal fascia (may be associated with fascial dehiscence)	IV antibiotics +/− operative debridement
Organ space infection	Intra-abdominal abscess or gross postoperative perforation/peritonitis	IV antibiotics and percutaneous drainage or operative exploration and washout
Pylephlebitis	Infection and thrombophlebitis within the portal venous system	Intravenous antibiotics +/− systemic heparinization

Postoperative complications

Postoperative infections remain the major source of morbidity associated with acute appendicitis. Gross perforation of the acutely inflamed appendix changes the wound classification from clean-contaminated to dirty, with an associated increased risk of postoperative infection from around 10% to 40%. Classification of postoperative infections is dependent on the depth: superficial surgical site infection (SSI), deep SSI, and organ space infection (Table 53.2). While superficial SSIs can typically be managed with a short course of antibiotics with or without bedside opening of the superficial wound, deep SSIs require longer courses of antibiotics and possible return to the operating room for debridement. Organ space infections typically necessitate percutaneous drainage or operative exploration and washout, as well as an extended course of antibiotics.

To minimize the risk of superficial SSIs in cases of perforated appendicitis, the traditional approach after open appendectomy has been to close the fascia, but not the skin edges, to allow for healing by secondary intention or delayed primary closure. This is not typically performed after laparoscopic appendectomy. Laparoscopic appendectomy is associated with a lower risk of superficial and deep SSI, but a higher risk of organ space infection compared to open appendectomy. To minimize the risk of deep SSIs and organ space infections, a Jackson Pratt drain may be left in the abdomen after either open or laparoscopic appendectomy.

For cases of non-perforated appendicitis, postoperative antibiotics do not alter the incidence of superficial SSIs, deep SSIs, or organ space SSIs, but do correlate with higher rates of *Clostridium difficile* infection and urinary tract infection, as well as longer hospital stays. On the other hand, antibiotics play an important role in the postoperative management of perforated appendicitis. Patients with severe sepsis or septic shock in the postoperative period necessitate immediate transfer to the ICU and goal-directed therapy (blood cultures, IV antibiotics, IV fluids, and possible vasopressors). These patients often require return to the operating room for source control.

The presence of a postoperative hematoma significantly increases the risk of both superficial and organ space infections, thus meticulous intraoperative hemostasis is essential. Pyephlebitis (infection and thrombosis within the portal venous system) may occur with any intra-abdominal infection, but is now rare with the use of perioperative antibiotics. Other rare postoperative complications include stump appendicitis (related to incomplete resection of the appendix), cecal fistula (related to loss of seal at the resected appendicular orifice resulting in an organ space infection), and wound dehiscence (associated with deep surgical site infection).

Suggested reading

Coakley BA, Sussman ES, Wolfson TS, et al. Postoperative antibiotics correlate with worse outcomes after appendectomy for nonperforated appendicitis. *J Am Coll Surg*. 2011;213(6):778–783.

Darouiche RO, Wall MJ, Itani KMF, et al. Skin preparation in the OR: chlorhexidine-alcohol versus povidone-iodine for surgical site antisepsis. *N Engl J Med*. 2010;362(1):18–26.

Dellinger RP, Levy MM. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36(1):296–327.

Hughes MJ, Harrison E, Paterson-Brown S. Post-operative antibiotics after appendectomy and post-operative abscess development: a retrospective analysis. *Surg Infect*. 2013;14(1):56–61.

Leigh DA, Simmons K, Normal E. Bacterial flora of the appendix fossa in appendicitis and postoperative wound infection. *J Clin Pathol*. 1974;27(12):997–1000.

Liu K, Fogg L. Use of antibiotics alone for treatment of uncomplicated acute appendicitis: a systematic review and meta-analysis. *Surgery*. 2011;150(4):673–683.

Maa J, Kirkwood KS. The Appendix. In: Townsend CM Jr, Beauchamp RD, Evers BM, Mattox KL, eds. *Sabiston Textbook of Surgery*, 18th edn. Philadelphia: Saunders Elsevier; 2008:1333–1347.

Sauerland S, Lefering R, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Database Syst Rev*. 2010;6(10):CD001546.

St Peter SD, Adibe OO, Iqbal CW, et al. Irrigation versus suction alone during laparoscopic appendectomy for perforated appendicitis: a prospective randomized trial. *Ann Surg*. 2012;256(4):581–585.

Varadhan KK, Humes DJ, Neal KR, Lobo DN. Antibiotic therapy versus appendectomy for acute appendicitis: a meta-analysis. *World J Surg*. 2010;34(2):199–209.

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Diverticulitis

Matthew D. Zelhart and Ronald L. Nichols

Diverticulosis coli is an anatomic abnormality of mucosal outpouchings in the colonic wall. Colonic diverticula are often asymptomatic, and the prevalence varies greatly with such factors as geographic location, dietary habits, race, and age. In the United States, the incidence has been noted to increase with age, with up to a third of the population older than 60 being affected and more than two-thirds of the population older than 80 being affected.

The diagnosis of diverticulosis is often made incidentally in otherwise asymptomatic patients at the time of routine surveillance endoscopy or on imaging for other reasons. Most of these patients require only counseling about the need for prophylactic measures such as a fiber-rich diet, adequate fluid consumption, and the prevention of constipation. Discussion of the risk of possible infectious (up to 25% risk) or hemorrhagic complications of the disease should also be undertaken.

Symptomatic diverticulosis presents as two categories. First is bleeding, in the form of lower gastrointestinal hemorrhage. This is very rarely seen in the setting of diverticulitis. The second category of complications is from inflammation in the form of diverticulitis. This can present as perforations, fistulas, or strictures. While rare when compared to the frequency of diverticulosis in the population, clinically significant diverticular disease and its complications continue to tax the diagnostic and therapeutic skills of physicians. Physical findings range from diffuse slight abdominal tenderness to shock secondary to either massive hemorrhage or overwhelming sepsis. Even when clinical manifestations of diverticulosis occur, emergent surgical intervention is necessary in only a minority of patients. During such life-threatening emergencies, the physician must be prepared to resuscitate the patient quickly and proceed to surgical intervention without benefit of a definite diagnosis. These patients may have massive or recurrent gastrointestinal bleeding or could have generalized peritonitis from a perforation of diverticulitis.

Diagnosis of infection

It is often possible to make a presumptive diagnosis of acute diverticulitis on the basis of history, physical examination, and initial laboratory tests. These symptoms include fever, abdominal pain, and tenderness—usually in the left lower quadrant. This presumptive diagnosis allows for the expedited initiation of resuscitative measures, including empiric antibiotic therapy. If the patient is stable, it is best to perform diagnostic radiographic tests as soon as possible to confirm the presumptive diagnosis.

CT is generally thought to be superior and safer than contrast enema studies and ultrasounds for the diagnosis of diverticular disease. For those who still prefer the contrast enema for colonic imaging, water-soluble contrast materials are preferred to barium to avoid barium peritonitis in case of perforation or leakage.

Once diverticulitis has been documented radiographically, further clinical decisions depend on the resolution of signs and symptoms of infection. If they resolve completely and the patient is stable, endoscopic examination of the entire colon is required to evaluate for neoplastic disease or complications such as stricture. Colonoscopy is best performed approximately 6 weeks after symptoms of acute diverticulitis have subsided

to decrease the risk of perforation of the inflamed intestinal wall. Approximately 8% of patients diagnosed with perforated diverticulitis actually have a neoplastic process.

Management of diverticulitis

The greatest number of complications in colonic diverticular disease result from infection. They range from localized short segments of diverticulitis, to abscesses and/or fistulas, to free perforation with generalized peritonitis and overwhelming intra-abdominal sepsis (Figure 54.1). While the cause of the diverticular formation has been established as increased intraluminal pressure, the cause of diverticulitis and its related complications is not clear. Some authorities postulate that a surge in intraluminal pressure is often the cause, and others suggest ulceration, ischemia, and foreign-body perforation. Diverticulitis resulting in bowel perforation is divided into *uncomplicated* and *complicated diverticulitis* (Figure 54.2).

Uncomplicated diverticulitis

Uncomplicated diverticulitis occurs when there is local inflammation or phlegmon associated with diverticulosis but no discrete abscess or perforation (Figure 54.3). This is the most common form of diverticulitis. Penetration of mixed bacterial flora into the wall of the intestine associated with this state initiates peridiverticular infection.

Patients with uncomplicated diverticulitis usually complain of abdominal pain localized to the left lower quadrant. In some cases, however, a redundant sigmoid colon may have sufficient mobility to produce local symptoms in the right lower or right upper abdominal quadrant as well as in the mid epigastrium. These patients are often febrile and have mild leukocytosis. However, they typically respond well to bowel rest, parenteral fluids, and antibiotic therapy. Nasogastric tube insertion is usually unnecessary unless obstructive signs and symptoms are present.

Most patients require a 3- to 5-day course of appropriate parenteral or enteral antimicrobials (Table 54.1), but this has recently been called into question by recent studies that show no difference in recovery between patient treated with or without oral antibiotics;

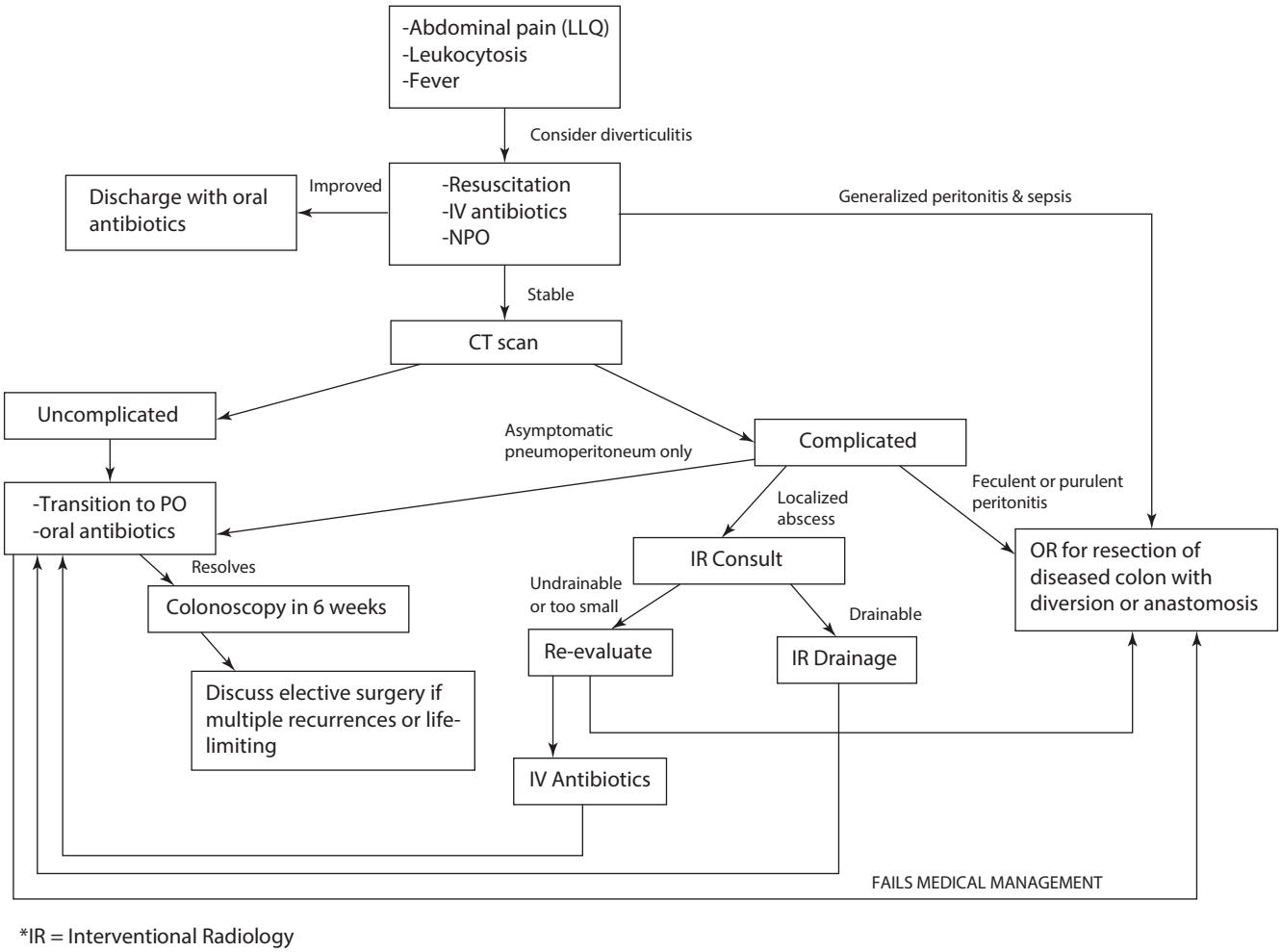

FIGURE 54.1 Algorithm for the workup and treatment of acute diverticulitis.

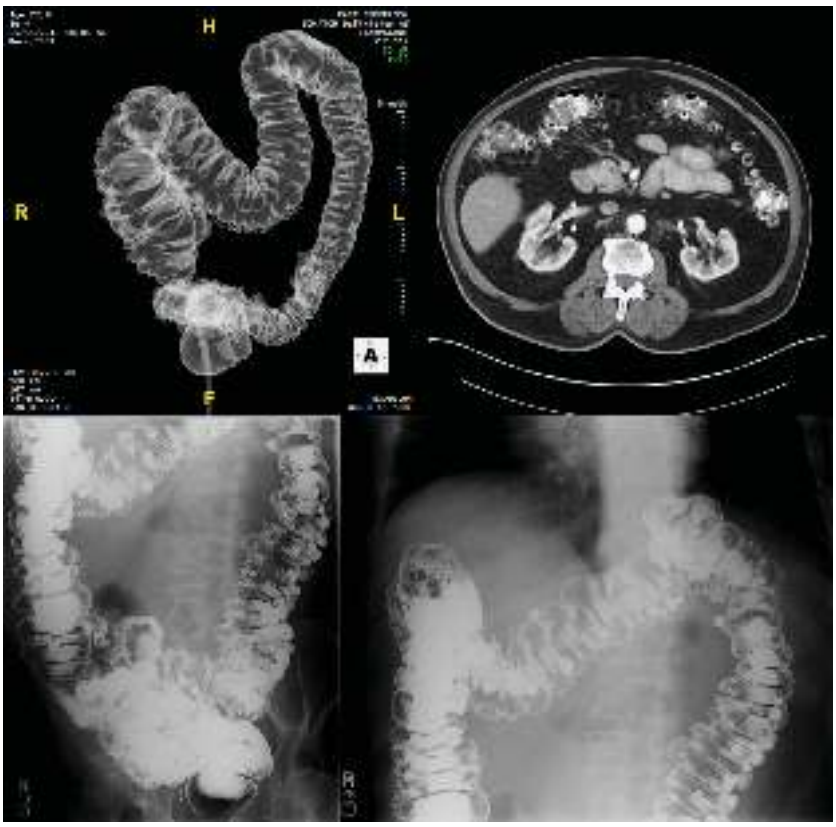

FIGURE 54.2 Representative images of diverticulosis without inflammation or perforation.

further studies are needed to elucidate this controversy. If patients continue to improve with normalization of the white blood cell (WBC) count, temperature, and abdominal examination, we advance them to a low-residue diet—one that is devoid of poorly digestible foods (e.g., whole corn)—in the acute inflammation stage.

Patients must be followed carefully after resolution of abdominal symptoms. If no disease other than diverticulosis is found on follow-up endoscopy, each patient should follow a fiber-supplemented diet with generous consumption of fluids and a recommended 30 minutes of daily cardiovascular exercise.

Surgery is not generally recommended after uncomplicated diverticulitis in otherwise healthy patients. Rather, we recommend medical therapy, and the decision for elective surgery after resolution should be made on a case-by-case basis. Some factors which may influence the decision to proceed with elective colon resection include frequency of episodes, frequent travel, life-limiting attacks, and immune status of the patient. Such resection can be performed by an open laparotomy technique or by a minimally invasive technique.

Although the medical approach rarely fails to control the signs and symptoms of uncomplicated diverticulitis, surgical resection may become necessary if the infection does not resolve with prolonged parenteral antibiotic therapy. This is normally termed "smoldering diverticulitis." However, patients with very limited symptoms and no signs of systemic sepsis normally respond to oral

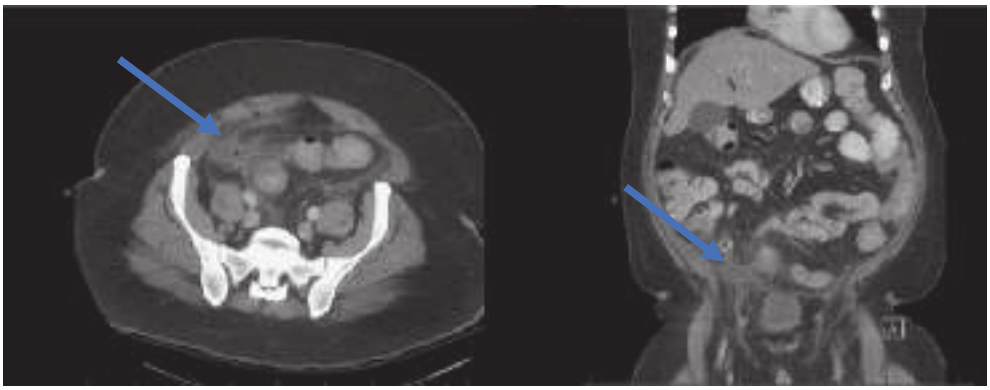

FIGURE 54.3 Diverticulitis with phlegmon and no organized abscess (*arrow*).

TABLE 54.1 **INTRAVENOUS ANTIBIOTICS FOR COVERAGE OF THE AEROBIC AND ANAEROBIC HUMAN COLONIC MICROFLORA**

Drug	Dosage	Frequency
Combination therapy		
Aerobic coverage[a]		
Amikacin	15–20 mg/kg/d	q8–12h
Aztreonam	1–2 g	q6–8h
Ceftriaxone	1–2 g	12–24h
Ciprofloxacin	400 mg	ql2h
Gentamicin	5–7 mg/kg/d	q8h
Tobramycin	5–7 mg/kg/d	q8h
Anaerobic coverage[b]		
Clindamycin	600–900 mg	q8h
Metronidazole	500 mg	q8–12h
Aerobic–anaerobic coverage (single-drug therapy)		
Ampicillin–sulbactam	1.5–3 g	q6h
Cefotetan	1–2 g	q8–12h
Cefoxitin	1–2 g	q6h
Ertapenem	1 g	q24h
Imipenem–cilastatin	500 mg	q6h
Meropenem	1 g	q8h
Piperacillin–tazobactam	3.375–4.5 g	q6h
Ticarcillin–clavulanate	3.1 g	q6h
Tigecycline	100 mg (initial dose) then 50 mg	q12h

[a] To be combined with a drug exhibiting anaerobic activity.
[b] To be combined with a drug exhibiting aerobic activity.

regimens of antibiotics aimed at covering these colonic aerobes and anaerobes (Table 54.2).

Complicated diverticulitis

Complicated diverticulitis occurs when the diverticular inflammation has progressed to a frank perforation. This can manifest itself into an abscess (Figure 54.4) or free perforation of purulent material or feces into the abdomen (Figure 54.5). Complicated diverticulitis is classified into four types by the Hinchey Classification (Table 54.3), although this plays little role in treatment. Most often, complicated diverticulitis presents as a pericolic abscess demonstrated by CT. If these studies reveal a small cavity and the patient is improving, continuation of medical therapy and antibiotics is warranted. However, in patients who are not improving or have a larger abscess cavity, percutaneous drainage may be a useful adjunct.

In patients with a history of an episode of complicated diverticulitis, a long discussion should be had about undergoing elective colon resection. Our approach to preoperative colon preparation is shown in Box 54.1. However, data have not consistently demonstrated that recurrent attacks will occur or that they will become more severe in nature. Decompressing the purulent contents of an abscess via CT-guided percutaneous catheter placement gains time to improve the patient's status with volume replacement and appropriate antibiotic therapy. Once the abscess cavity has been resolved by catheter drainage and symptoms improve, oral intake can be resumed.

TABLE 54.2 **ORAL ANTIBIOTIC REGIMENS FOR TREATMENT OF A MILD EPISODE OF ACUTE DIVERTICULITIS**

Antibiotic	Dosage (mg)	Frequency-duration
Ciprofloxacin	500	BID
Ciprofloxacin and metronidazole	500/500	BID/BID
TMP–SMX DS and metronidazole	800/500	BID/BID
Amoxicillin-clavulanic acid	250–500	TID
Doxycycline	100	q24h

Abbreviations: BID = twice a day, TID = three times a day, TMS–SMX DS = trimethoprim–sulfamethoxazole (Bactrim) double strength.

Patients with free perforations of purulence or feces, or those who do not respond to medical management, are best treated with urgent surgical intervention. There are two essential operative goals. The first is to resect the inflamed colon and control the associated septic complications; surgical resection of the infectious source is superior to simple diversion of colonic contents (colostomy) and drainage or laparoscopic lavage. The second goal is to restore intestinal continuity. Although this may require a second procedure in

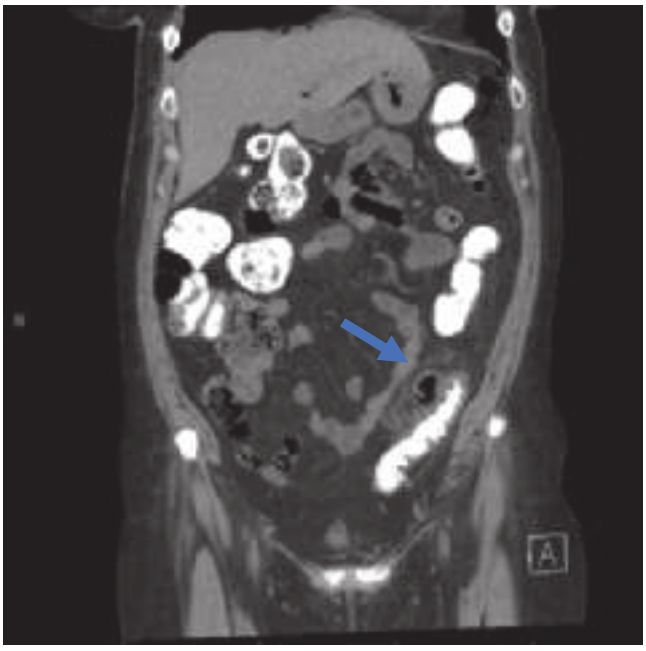

FIGURE 54.4 Perforated diverticulitis with contained abscess (*arrow*).

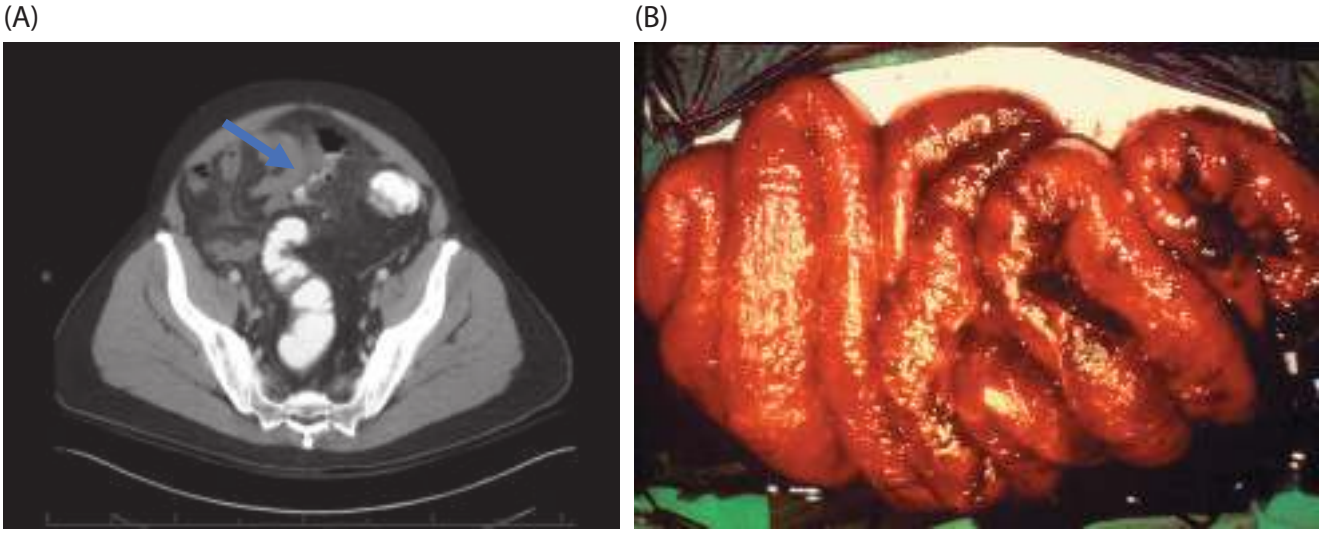

FIGURE 54.5 (A) Perforated diverticulitis with free contrast extravasation (*arrow*). (B) Photo of generalized peritonitis.

some cases, we believe it can often be accomplished safely during the same operation (single-stage procedure) in many patients. This is particularly true in individuals who are not hemodynamically compromised, who have localized diverticulitis, or who have diverticulitis with an associated mesocolonic abscess amenable to en bloc resection and with no intra-abdominal spillage of purulent material.

In summary, if urgent surgery is necessary for localized diverticulitis, we try to remove the inflamed colon, most often performing a primary anastomosis with or without a diverting ileostomy. If this is inadvisable because of hemodynamic instability or gross evidence of peritoneal contamination, we do an end colostomy with a distal pouch provided no distal obstruction is present. Diversion alone is rarely done as it has shown to result in a high mortality rate.

Generalized intra-abdominal sepsis

Patients with free perforation of purulence or feces require prompt fluid resuscitation and empiric antibiotic coverage with an agent or combination of agents that will control both aerobic and anaerobic enteric organisms (Table 54.1). If there is evidence of an unconfined perforation or if the patient is in shock, laparotomy as soon as the patient is stable is often necessary. Laparotomy often reveals fibrinous exudate, free purulence, or fecal material throughout the abdominal cavity (Figure 54.5). If we find diverticulitis, we resect the involved segment and perform a proximal colostomy. Under these conditions, we rarely perform a primary anastomosis. We prefer to leave a closed distal pouch, but only if there is no distal lesion present. Such a lesion could produce a blind-loop syndrome and leakage of the distal pouch, or could require another operation for its removal. If the distal pouch is friable or there is a compromised staple line, a large Malecot drain can be left in the rectal pouch draining exteriorly as a path of least resistance to prevent rectal stump blowout.

After resection, we copiously irrigate the abdominal cavity with normal saline. We strongly believe that if gross peritonitis is present, the skin wound should not be closed tightly. There is some merit to considering negative pressure dressings in these patients as well. Patients who have undergone such surgery usually require careful monitoring in an intensive care unit and appropriate antibiotic coverage.

TABLE 54.3 **HINCHEY CLASSIFICATION FOR COMPLICATED DIVERTICULITIS**

Hinchey stage	
Grade I	Contained pericolic abscess
Grade II	Contained distant abscess
Grade III	Purulent peritonitis
Grade IV	Fecal peritonitis

BOX 54.1

Suggested approach to preoperative preparation for elective colon resection

Two days before surgery (at home)
Low-residue or liquid diet

One day before surgery (at home or in hospital if necessary)
Admit in morning (if necessary and allowed)
1. Continue clear liquid diet, IV fluids as needed
2. Whole-gut lavage with polyethylene glycol, 1 L/h PO starting at 8 AM until diarrhea is clear (no longer than 3–4 h)No enemas

All patients receive 1 g of neomycin PO and 1 g of erythromycin base PO at 1 PM, 2 PM, and 11 PM **Day of surgery**
Operation at 8 AMA single dose of antibiotic with broad-spectrum aerobic/anaerobic activity given IV by anesthesia personnel in the operating room just before incision; repeat dosage if operation lasts >2 h

Many of these patients develop secondary intra-abdominal or pelvic abscesses, which are detectable with CT. If percutaneous drainage is not successful a repeat laparotomy will likely be necessary. Many of these patients will also have prolonged ileus and therefore may require parenteral hyperalimentation to meet the extraordinary metabolic demands of controlling intra-abdominal sepsis. Of course, enteral nutrition should be resumed as soon as possible.

Suggested reading

The Medical Letter writers. Antimicrobial prophylaxis for surgery. *Med Lett Drugs Ther*. 2016; 58:63–68.

Cannon JA, Alton LK, Deierhoi RJ, et al. Preoperative oral antibiotics reduce surgical site infection following elective colorectal resections. *Dis Colon Rectum*. 2012;55:1160–1166.

Devaraj B, Liu W, Tatum J, et al. Medically treated diverticular abscess associated with high risk of recurrence and disease complications. *Dis Colon Rectum*. 2016; 59(3):208–215.

Huston J, Zuckerbraun B, Moore L, et al. Antibiotics versus no antibiotics for the treatment of acute uncomplicated diverticulitis: Review of the evidence and future directions. *Surg Infect*. 2018, 19:7.

Migaly J, Bafford A, Francone T, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the use of bowel preparation in elective colon and rectal surgery. *Dis Colon Rectum*. 2019;62:3–8.

Nichols RL. Current strategies for prevention of surgical site infections. *Curr Infect Dis Rep*. 2004;6:426–434.

Nichols RL. Peritonitis. In Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious diseases*, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004: 723–731.

Rafferty J, Shellito P, Hyman NH, et al. Practice parameters for sigmoid diverticulitis. *Dis Colon Rectum*. 2006;49:939–944.

Zelhart MD, Hauch AT, Slakey DP, Nichols RL. Preoperative antibiotic colon preparation: Have we had the answer all along? *J Am Coll Surg*. 2014;219:1070–1077.

55

Abdominal abscess

K. Shad Pharaon and Donald D. Trunkey

Intra-abdominal infections generally occur after entry of enteric organisms into the peritoneal cavity. An abscess is the body's way of attempting to contain an infection. Intraperitoneal and retroperitoneal abscesses can develop as a result of appendicitis, diverticulitis, necrotizing enterocolitis, pancreatitis, pelvic inflammatory disease, tubo-ovarian infection, surgery, or trauma. Given the vast number of microbes in our alimentary tract, any penetration of the wall of the gastrointestinal (GI) tract as a result of a vascular, traumatic, or iatrogenic event introduces these microbes into the abdomen. The concentration of microorganisms increases with distal progression down the GI tract. The morbidity of an intra-abdominal infection is 40%. The mortality is 20% in immunocompetent patients, and can be as high as 70% in the immunocompromised. This chapter explains types of peritonitis, locations of abscesses, diagnosis, treatment, common organisms associated with community-acquired and healthcare-associated infections, and suggested use of antimicrobials.

Abdominal abscess often follows or complicates peritonitis (see Chapter 57, Peritonitis). Primary peritonitis is an infection of the peritoneal cavity without an underlying violation of the intestinal wall; the most common cause of primary peritonitis is spontaneous bacterial peritonitis (SBP). The etiology of SBP is thought to be translocation of bacteria through the intestinal wall and into the abdomen. Clinical features of SBP may be subtle or absent, but usually SBP causes abdominal pain from infected ascites. The mainstay of treatment of primary peritonitis is antibiotics. Secondary peritonitis results from perforation of hollow viscera with spillage of intestinal contents, often from appendicitis, diverticulitis, or ulceration. The patient may initially present with severe abdominal pain, tenderness, rigid abdomen, or shock. The peritonitis can be focal or diffuse. If the spillage is small, the patient may not initially seek medical attention. Over the course of a few days the body will attempt to contain it, and an abscess may develop. If the abscess is less than 3 cm, the patient may only need antibiotics. An abscess 3 cm or greater usually needs drainage, and the percutaneous approach is preferred. Some abdominal abscesses progress to severe sepsis and shock, particularly when left untreated. Immunocompromised patients may have perforation with gross contamination of their abdomen, yet be relatively asymptomatic, making diagnosis more challenging. Tertiary peritonitis is a persistent or recurrent infection following treatment of primary or secondary peritonitis and is often found in patients with pre-existing comorbidities or who are immunocompromised.

Abdominal infection is designated uncomplicated or complicated. Uncomplicated infection usually involves one organ, as in acute (non-perforated) appendicitis, cholecystitis, or diverticulitis. Surgical resection is needed for many of these early, uncomplicated infections. Patients usually improve quickly and only need 24 hours or less of antibiotic coverage. Complicated infection extends beyond one organ into the peritoneal space. These infections can be florid fecal peritonitis from a perforated appendix or diverticulum and fecal contamination will often lead to an abscess.

Abscesses can form within the peritoneal lining, usually days after an intraperitoneal infection. Intraperitoneal abscesses commonly follow a perforated appendix or diverticulum, but also occur after tubo-ovarian infection, recent surgery (particularly of the colon), pyogenic liver abscess after biliary tract disease, or splenic abscess from trauma. Patients can also develop retroperitoneal abscesses, such as a pancreatic abscess. This can occur after pancreatitis which progresses through pancreatic necrosis and on to a definable collection. Retroperitoneal abscesses are usually found in one of four spaces: anterior retroperitoneum (lower esophagus, duodenum, pancreas, bile duct, splenic vein, appendix, ascending and descending colon, and

rectosigmoid), posterior retroperitoneum (perinephric, around the ureters, gonadal vessels, aorta, and inferior vena cava), retrofascial (ileopsoas muscle and paraspinous muscles), and retroperitoneal pelvis (prevesical space, retrovesical presacral, and perirectal).

Routine history, physical exam, and laboratory studies are the initial workup of suspected intra-abdominal infection. Some patients may have an unreliable exam, such as those with obtunded mental status, recent analgesia, or immunosuppression. A plain film is useful in establishing "free air" (as a result of perforation of a hollow viscus), pneumatosis (as a result of ischemic bowel), dilated loops (as a result of *Clostridium difficile*), or obstruction as possible signs of abdominal infection. Ultrasound is useful in diagnosing abscess, but it is limited by the skill of the technician and the patient's body habitus. For patients who do not need an emergent operation, computed tomography (CT) is the best imaging modality to detect an abscess.

The cornerstones of treatment of an abscess are source control and antimicrobials. Initially, fluids are given, electrolyte derangements and coagulopathies corrected, and antibiotics started. Source control requires taking measures to eliminate a source of infection, control ongoing contamination, and restore premorbid anatomy and function. In recent years, there has been a shift from open abdominal drainage to percutaneous drainage. Interventional radiologists now approach many abscesses that previously would have been considered best approached by laparotomy. The results of percutaneous drainage are equal clinically and more cost-effective. Percutaneous drainage may result in significantly fewer physiologic alterations in patients and may eliminate or reduce the need for an open operation. An open operation may still be needed for poorly localized, loculated, complex, or diffuse fluid collections, necrotic tissue, or percutaneously inaccessible locations, such as the posterior subphrenic space or among loops of small bowel.

The CT scan findings should be discussed with a surgeon to avoid inappropriate abscess drainage in the presence of free hollow-organ perforation and peritonitis. There are some patients in whom drainage catheter placement is not appropriate, and laparotomy is the procedure of choice. Patients with diffuse peritonitis or a high clinical suspicion of a perforation should undergo surgery as soon as possible, continuing ongoing resuscitation in the operating room. Debridement is indicated in the case of intra-abdominal necrosis, such as infected necrotic pancreas. Open drainage of abdominal abscesses has been associated with enteric fistula formation, adult respiratory distress syndrome, renal failure, and liver failure. Some surgeons leave the abdomen open if source control is uncertain. In some cases, closing the abdomen is not prudent, particularly when the bowel is left in discontinuity or is too dilated to allow closure of the surgical wound, as forcing the abdomen closed can cause abdominal compartment syndrome. Instead, the abdomen can be packed open with a vacuum-assisted device. A second-look operation may be scheduled at the surgeon's discretion.

Antimicrobial treatment is an adjunct to source control. The correct antimicrobial agent started early has been shown to significantly improve outcomes. While cultures from the abscess are necessary, blood cultures are not always needed in the initial workup of patients with suspected intra-abdominal infection. However, in patients who appear toxic or immunocompromised, knowledge of appropriate coverage for potential bacteremia may be helpful in determining antimicrobial therapy. Infections are divided into community-acquired or healthcare-associated (Table 55.1). This distinction is important in determining which bacteria are the likely source and which antimicrobial to choose for initial coverage. All intra-abdominal infections show prevalence of gram positives (*Streptococcus* species, *Enterococcus faecalis*), gram negatives (*Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa*) and anaerobes (*Bacteroides* and *Clostridium*). Healthcare-associated infections are more likely to have more resistant flora, and those patients that do not respond to the initial empiric antimicrobials may have resistant *P. aeruginosa*, vancomycin-resistant enterococcus (VRE), or *Candida globrata* as their pathogen. The patients most likely to develop severe abdominal infections are those with a high Acute Physiology and Chronic Health Evaluation (APACHE) score, poor nutritional status, inability to achieve adequate source control, or immunosuppression.

TABLE 55.1 **PATHOGENS IN ABDOMINAL ABSCESS**

Community-acquired intra-abdominal infection		
Aerobes	**Anaerobes**	**Healthcare-associated intra-abdominal infection**
Escherichia coli	*Bacteroides*	*Staphylococcus epidermidis/ aureus*
Klebsiella pneumoniae	*Clostridium*	*Pseudomonas aeruginosa*
Proteus mirabilis	*Peptostreptococcus*	*Enterococcus*
Streptococcus	*Fusobacterium*	*Enterobacter*
Enterococcus	*Prevotella*	

The general consensus on antimicrobials is to "hit hard and early," meaning start broad-spectrum antibiotics immediately, and quickly narrow the antibiotics after cultures have returned. The choice of antibiotics depends on whether the infection is community-acquired or healthcare-associated. In some instances, an antifungal is needed. There are several antimicrobial choices available to treat intra-abdominal infections. Many can be treated with a single agent (Table 55.2). Methicillin-resistant *Staphylococcus aureus* (MRSA) is found in some intra-abdominal infections and should be treated with vancomycin. Linezolid, daptomycin, quinupristin–dalfopristin, and tigecycline also provide adequate coverage for MRSA. Empiric treatment of VRE is not recommended unless the patient is at very high risk for an infection due to this organism (such as a liver transplant patient with infection from the biliary tree) or is known to be colonized with VRE; this organism is usually sensitive to linezolid, quinupristin–dalfopristin, daptomycin, and ampicillin. Antifungal therapy is recommended if *Candida* is grown from intra-abdominal cultures. Fluconazole is appropriate for treatment of *Candida albicans*, but an echinocandin (caspofungin, micafungin) should be used for fluconazole-resistant *Candida* species such as *Candida globrata* or *Candida tropicalis* (Table 55.3). If the index of suspicion is high for fungal infection, such as in an

TABLE 55.2 **EMPIRIC REGIMENS FOR TREATMENT OF ABDOMINAL ABSCESS**

Community-acquired intra-abdominal infection			Healthcare-associated intra-abdominal infection	
Antibiotic(s)	**Mild to moderate infection**	**Severe infection**	**Antibiotic(s)**	**By definition, likely resistant bacteria**
Single agent	Ertapenem	Imipenem-cilastin	*Single agent*	Imipenem-cilastin
	Moxifloxacin	Meropenem		Meropenem
	Tigecycline	Doripenem		Doripenem
	Ticarcillin-clavulanic	Piperacillin–tazobactam		Piperacillin–tazobactam
	Cefoxitin			
Double agent	Cefazolin + metronidazole	Cefepime + metronidazole	*MRSA*	Add vancomycin
	Cefuroxime + metronidazole	Ceftazidime + metronidazole		Can add linezolid
	Ceftriaxone + metronidazole			Can add daptomycin
	Cefotaxime + metronidazole			Can add quinupristin–dalfopristin
	Ciprofloxacin + metronidazole			Can add tigecycline
	Levofloxacin+ metronidazole		*VRE*	Add linezolid
				Can add quinupristin–dalfopristin
				Can add daptomycin
				Can add ampicillin

Abbreviations: MRSA = Methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococcus.

immunocompromised patient or in the setting of a healthcare-associated infection, antifungal coverage should be started early, since fungal cultures often require prolonged incubation times. Antimicrobial therapy should be limited to 4 to 7 days, unless source control cannot be obtained. This is a change from previous recommendations which advised broad-spectrum antimicrobials for an empiric 14-day course. Once the patient has no fever for 24 to 48 hours, has a normal white blood cell count, and has clinically improved, the antimicrobial may be discontinued. In most cases, the antimicrobials can be stopped in 7 days or less. Probiotics can be started on patients receiving antimicrobial treatment for intra-abdominal infection.

Patients with inadequate source control, old age, higher level of organ dysfunction, or significant comorbidities are at a higher risk of treatment failure and death. Intra-abdominal infections are frequent and have significant morbidity and mortality. Patients benefit from early diagnosis with early start of antimicrobials and source control.

TABLE 55.3 **TREATMENT OF *CANDIDA***

Fungus	Antifungal
Candida albicans	*Fluconazole*
Resistant Candida, i.e, globrata	*Caspofungin Micafungin*

In most cases, a CT scan will identify the necessary cause of an intra-abdominal infection. There are several choices of antimicrobials, but treatment should start broad and then be tailored to the culture results. When patients improve, stop the antimicrobials to decrease the chance of creating multiresistant organisms. Most patients will do well with close coordination of care among specialists in surgery, radiology, critical care, and infectious disease.

Suggested reading

Brook I. Microbiology and management of abdominal infections. *Dig Dis Sci*. 2008;53:2585–2591.

Friedrich AK, Cahan M. Intraabdominal infections in the intensive care unit. *J Intensive Care Med*. 2013;0:1–8.

Hasper D, Schefold J, Baumgart D. Management of severe abdominal infections. *Recent Pat Antiinfect Drug Discov*. 2009;4:57–65.

Mazuski JE, Solomkin JS. Intra-abdominal infections. *Surg Clin North Am*. 2009;89:421–437

Sirinek KR. Diagnosis and treatment of intra-abdominal abscesses. *Surg Infect*. 2000;1:31–38.

Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect*. 2010;1:79–109.

56

Splenic abscess

Walter Dehority and Thomas R. Howdieshell

The diagnosis of splenic abscess is often overlooked because of its rarity and misleading clinical features as well as the presence of predisposing conditions that obscure its clinical presentation. Hence, it is not surprising that splenic abscess is often diagnosed during postmortem examinations (0.2–0.7% incidence in various autopsy series) even in the era of antibiotics. Contributing factors to an apparent increase in the incidence of splenic abscess include advances in radiologic imaging, comfort with nonoperative management of blunt splenic trauma, and a greater number of patients who have cancer or are otherwise immunocompromised.

Incidence and predisposing factors

Splenic abscesses occur more commonly in males (55–60% in several series), with the average age ranging from 25 to 54 years. Nelken and colleagues describe a bimodal distribution: patients >40 years of age, generally immunosuppressed or intravenous (IV) drug users, who usually present with a multilocular abscess, and patients >70 years of age who are suffering from diabetes and/or a non-endocarditic septic focus and develop a unilocular abscess.

The primary predisposing causes of splenic abscess include metastatic hematogenous infection, contiguous disease processes extending to the spleen, splenic trauma, hematologic disorders (collagen vascular diseases, hemoglobinopathies, malignancy), and immunodeficiency states (acquired, congenital). The incidence of these predisposing causes or risk factors is shown in Table 56.1.

Metastatic hematogenous infections

Infective endocarditis is the most common condition predisposing a patient to splenic abscess (Table 56.1, Figure 56.1). Although the exact incidence is difficult to determine, several studies demonstrated the occurrence of splenic embolization in 31% to 44% of patients with endocarditis. Histologic examination disclosed splenitis in at least 20% of patients. Splenic infarction occurred in 30% to 67% of patients with endocarditis during the pre-antibiotic era, and in 33% to 44% of these patients during the antibiotic era. In 1977, Pelletier and Petersdorf reported the incidence of splenic abscess in patients with bacterial endocarditis to be approximately 2.4%, although a 2012 report described an incidence of 7.3% on autopsy. Mycotic aneurysms are seen angiographically within abscesses, but whether these predispose a patient to or result from splenic abscess remains uncertain.

In addition to endocarditis, a multitude of other infections have been reported as primary causes of splenic abscess (see Table 56.1). Miscellaneous infections include dental abscess, bacteremia after dental extraction, tonsillectomy, peritonsillar abscess, acute parotitis, bronchiectasis, perinephric abscess, decubitus ulcer, complicated infectious mononucleosis, tuberculosis, yellow fever, typhoid fever, diphtheria, cat-scratch disease, and anthrax.

TABLE 56.1 **PRIMARY PREDISPOSING CAUSES OR RISK FACTORS FOR SPLENIC ABSCESS**

Factors	Percentage
Infectious etiology	**68.8**
Endocarditis	15.3
Septic syndrome	11.9
Miscellaneous	11.9
Urinary infection	7.1
Otitis	3.3
Appendicitis	2.8
Pneumonia	2.8
Brucellosis	2.3
Lung abscess	2.3
Malaria	1.9
Diverticulitis	1.9
Amebiasis	0.95
Noninfectious etiology	**31.2**
Contiguous diseases	23.0
Trauma	16.7
Hemoglobinopathies	11.9

Conditions resulting in splenic ischemia and infarct have been implicated in the development of splenic abscess, probably from hematogenous spread of pathogens. Splenic abscess has been reported after splenic artery ligation in the course of liver transplantation surgery, division of the short gastric vessels during laparoscopic Nissen fundoplication, and accidental injection of the splenic artery during endoscopic procedures for gastric bleeding.

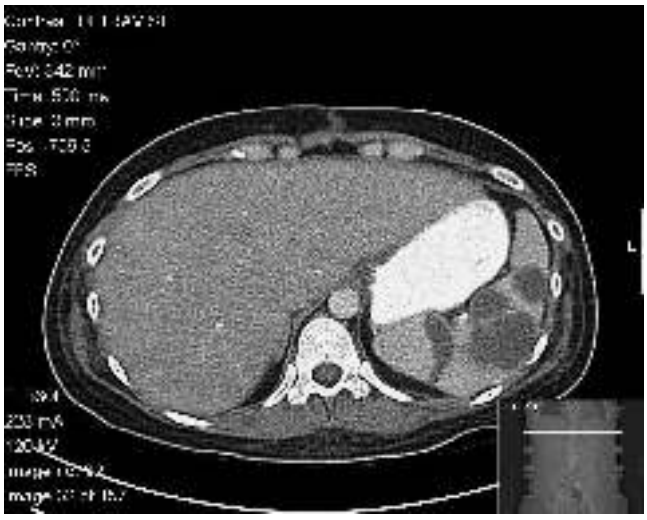

FIGURE 56.1 Multilocular splenic abscess in an intravenous drug abuse patient with bacterial endocarditis.

Contiguous infection

On occasion, splenic abscess can result from the direct extension of disease having its primary focus in adjacent organs. Contiguous extension from diverticulitis, pancreatic pseudocyst or carcinoma, gastric ulcer, carcinoma of the stomach, perihepatic abscess, perinephric and subphrenic abscess, and carcinoma of the descending colon have been reported. Splenic abscess has rarely been reported as an extraintestinal manifestation of inflammatory bowel disease.

Traumatic abscess

Traumatic abscess results from secondary infection and suppuration of contused parenchyma or of a hematoma arising from injury to splenic tissue. In a report by Phillips, the initial traumatic injury was not easily recognized or reported, and most patients developed signs and symptoms of splenic infection after a latent period of 2 weeks to 4 months after sustaining injuries to the left upper quadrant. Splenic abscess has been reported after operative repair of splenic injury (splenorrhaphy) and nonoperative management of blunt splenic injuries diagnosed by CT scan (Figure 56.2). On occasion, radiologic procedures such as splenic artery embolization for hemorrhage control following traumatic injury, splenoportography for portocaval shunt evaluation, and percutaneous transluminal coronary angioplasty have been implicated as causes of splenic abscess, sometimes up to 4 months afterward.

Hematologic disorders

Hemoglobinopathies accounted for approximately 12% of splenic abscesses reported by Alsono-Cohen. Patients with sickle cell disease have an increased risk of acquiring invasive bacterial infections as a result of hyposplenism, including functional defects in opsonization, phagocytic function, and cell-mediated immunity. If a patient with sickle cell disease and prior splenic infarcts develops a transient bacteremia, bacterial seeding of infarcted regions may occur with resultant abscess formation.

The spleen may also be a site of infection in patients with collagen vascular diseases. Splenic abscesses have been reported in patients with rheumatoid arthritis, systemic lupus erythematosus, myelodysplastic syndrome, and polyarteritis nodosa. Pathologic features of the spleen in these illnesses include capsulitis and small infarcts.

Immunodeficiency states

Splenic abscess has been reported complicating AIDS, chemotherapy, cancer (leukemia, lymphoma), bone marrow and solid organ transplantation, long-term steroid use, monoclonal antibody immunosuppressive medications, and conditions such as diabetes mellitus and alcoholism.

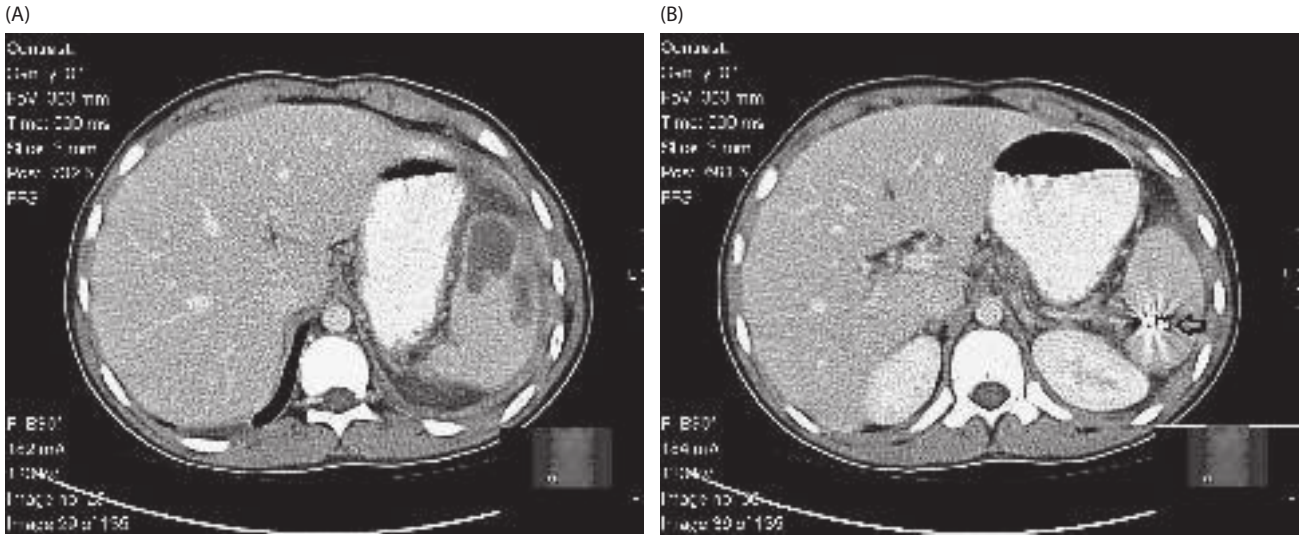

FIGURE 56.2 (A, B) Splenic abscess following nonoperative management of blunt splenic injury including splenic artery embolization. Note embolization coil (B, see *arrow*).

Diagnosis

History and physical examination

The signs and symptoms of a splenic abscess are often insidious, nonspecific, and related to the underlying disease. Table 56.2 characterizes the clinical findings in 227 patients. Fever is the most common symptom, along with pain in the left hypochondrium or vague abdominal pain. Pain is likely caused by splenitis with capsular involvement. Abscesses located in the upper pole of the spleen tend to irritate the diaphragm, causing radiation of pain toward the left shoulder (Kehr's sign) and an elevated, immobile left hemidiaphragm. Splenic rupture also commonly manifests as left shoulder pain. An abscess located in the lower pole of the spleen more often irritates the peritoneal surface, resulting in peritonitis. A deep-seated abscess that does not involve the splenic capsule may be accompanied only by nonspecific symptoms of infection without pain or other localizing signs.

TABLE 56.2 **CLINICAL FINDINGS IN SPLENIC ABSCESS**

Clinical feature	Percentage
Fever	92.5
Abdominal tenderness	60.1
Abdominal pain	57.5
Splenomegaly	56.0
Left upper quadrant pain	39.2
Pleuritic pain	15.8
Toxic syndrome	15.4
Vomiting	14.0

Laboratory findings

Leukocytosis is present in 70% to 80% of patients but is a variable finding. In several series, the white blood cell count varied between 2,400 and 41,000 cells/mm^3. In general, other serum laboratory studies were not helpful. Blood cultures demonstrated growth in 50% to 70% of patients. Of these positive blood cultures, 60% to 75% grew the same organisms as those subsequently isolated from the splenic abscess.

The microbial etiology of splenic abscesses is reported in Table 56.3, representing a compilation of three reports reviewing the microbiology of splenic abscesses from 1900 to 1995. Nearly half of all cases involved aerobic gram-negative bacilli, with *Salmonella* the most common pathogen. *Staphylococcus* spp. were also frequently reported, and at 18.8%, represented the second most common etiology. *Candida* abscesses of the spleen are seen almost exclusively in neutropenic patients with the exception of disseminated candidiasis as a complication of abdominal surgery. Fungal abscesses due to *Candida* are also more likely to complicate the use of broad-spectrum antibiotics, indwelling central venous lines, total parenteral nutrition, systemic steroids, cytotoxic chemotherapy, malignancy, or immunosuppression after organ transplantation. Organisms responsible for AIDS-related splenic abscesses include *Salmonella, Mycobacterium avium-intracellulare, Mycobacterium tuberculosis*, C*andida* spp., *Aspergillus* spp., and *Pneumocystis jirovecii* (*carinii*). A novel *Klebsiella pneumoniae* strain with hypermucoviscous properties has been reported as the cause of hepatic and splenic abscesses in otherwise healthy hosts. In several series, approximately one-fourth of patients with a splenic abscess did not have an organism cultured from the abscess cavity, possibly related to the use of IV antibiotic therapy prior to abscess drainage. In addition, polymicrobial infections may be present, particularly when anaerobic organisms are isolated.

TABLE 56.3 **MICROBIAL ETIOLOGY OF SPLENIC ABSCESSES: 505 CASES FROM 1900 TO 1995**

Organism	Number of cases (%)	
Streptococci	**57**	**(11.3)**
***Enterococcus* spp.**	**20**	**(4.0)**
Staphylococci	**95**	**(18.8)**
S. *aureus*	21	
Other or unspecified *Staphylococcus* spp.	74	
Aerobic gram-negative bacilli (GNB)	**227**	**(45.0)**
Salmonella spp.	72	
S. *typhi*	10	
Escherichia coli	49	
Pseudomonas spp.	18	
Klebsiella spp.	8	
Proteus spp.	10	
Enterobacter spp.	2	
Other or unspecified GNB	68	
Anaerobic organisms	**43**	**(8.5)**
Bacteroides spp.	7	
Propionibacterium spp.	6	
Clostridium spp.	4	
Fusobacterium spp.	1	
Other or unspecified anaerobic organisms	25	
Mycobacterium spp.	**21**	**(4.2)**
Mycobacterium tuberculosis	15	
Mycobacterium avium-intracellulare	5	
Other Mycobacterial spp.	1	
Fungi	**41**	**(8.1)**
Candida pseudotropicalis	1	
Candida albicans	9	
Candida tropicalis	6	
Aspergillus spp.	4	
Blastomyces spp.	2	
Other fungi	19	
Parasites	**1**	**(<1)**
Entamoeba histolytica	1	

Radiographic findings

The most common findings on chest radiography are an elevated left hemidiaphragm (31%), pleural effusion (28%), and left basilar pulmonary consolidation (18%). Plain abdominal films reveal an abnormal soft-tissue density or gas pattern in only 35% of patients. CT scanning, with a sensitivity of 96% and an associated specificity between 90% and 95% is currently the best diagnostic test for splenic abscess. CT scan may show a homogeneous low-density area, with or without rim enhancement; lucent areas within the spleen containing fluid levels of different densities; and intrasplenic gas formation. CT scan may also be useful for guiding percutaneous abscess drainage.

Ultrasonography has a sensitivity of 60% to 75% in the detection of splenic abscess. The ultrasound appearance of splenic abscess is characterized as a hypoechoic or nearly anechoic, ovoid- or round-shaped area in the spleen, with varying internal echogenicity,

irregular wall, and mild to moderate distal acoustic enhancement. Ultrasonic examinations are not specific, and the findings are highly variable and may be difficult to interpret. However, ultrasonography is low-cost, noninvasive, and readily repeatable to evaluate for interval change or resolution.

Differential diagnosis

The differential diagnosis should include intraparenchymal hematoma, splenic infarction, parasitic and nonparasitic splenic cysts, subphrenic abscess, pulmonary empyema, perinephric abscess, neoplasm, and leukemic infiltration. In a review of 3,372 subphrenic abscesses, Ochsner and Graves found a primary lesion in the spleen in approximately 4% of the cases. Therefore, the possibility of coexistent splenic abscess should be considered in the presence of a subphrenic abscess. Pulmonary empyema as a complication of splenic abscess (4%) may also divert the clinician's attention from the primary lesion.

Treatment

There is no place for long-term medical management of a clinically overt splenic abscess. The mainstay of treatment consists of splenectomy and appropriate antibiotics, with a success rate of 86% to 94%. Mounting evidence has shown that percutaneous drainage plus effective antibiotics is a safe and efficacious therapy. Percutaneous drainage may be used if the patient has a unilocular abscess, is in unstable condition from a recent operation, has had multiple previous operations, or has significant risks for general anesthesia or standard surgical drainage. The catheter can be removed when the drainage is minimal and the cavity has decreased in size, as evidenced by sinogram, ultrasound, or CT scan. If the patient does not improve clinically, splenectomy is recommended. Percutaneous drainage, with a reported success rate of 68% to 75%, is most likely to succeed when the abscess collection is unilocular, has a discrete wall, and has no internal septation. Abscesses containing thick, tenacious, necrotic debris are less likely to be successfully drained percutaneously, as are phlegmons, poorly defined cavities, microabscesses, multiple abscesses, and abscesses originating from a contiguous process. Complications associated with percutaneous drainage include hemorrhage, pleural empyema, pneumothorax (transpleural catheterization), and fistula.

Broad-spectrum antibiotics should be initiated when a splenic abscess is diagnosed. Empiric therapy should include agents effective against staphylococci, streptococci, and gram-negative bacilli, at least until culture results return. A semi-synthetic penicillin in conjunction with an aminoglycoside or a fourth-generation cephalosporin (cefepime) should be considered. If a contiguous abdominal process is suspected, anaerobic agents such as metronidazole should be added, or utilization of a β-lactam with broad-spectrum anaerobic and aerobic coverage, such as piperacillin-tazobactam or a carbapenem, are additional options for single-agent coverage. In immunosuppressed patients, antifungal coverage should be initiated early in the disease process. Some authors recommend continuing antibiotics for 2 to 3 weeks after splenectomy or discontinuation of percutaneous drainage.

The optimal management of fungal splenic abscess remains to be defined. Some authors suggest prolonged courses of amphotericin B, while others recommend splenectomy in conjunction with amphotericin B. The argument in support of splenectomy for fungal abscess is based primarily on reports of bacterial splenic abscess in which nonoperative therapy was associated with high mortality. However, as most cases of splenic candidiasis represent disseminated infection, splenectomy does not address the problem of *Candida* present in other tissues, most notably the liver. There are many reports of confirmed splenic fungal abscesses resolving with antifungal drugs alone. Several case reports and a recent multicenter randomized trial in patients without neutropenia or major immune deficiency indicate that fluconazole may be as efficacious as amphotericin B. Echinocandins are likely to be viable options as well. Patients suspected of having a fungal abscess should have a specific diagnosis made by percutaneous aspiration of the liver or spleen or laparoscopic or open biopsy of the lesions.

Splenic abscess may rupture into the peritoneal cavity, thus causing acute peritonitis. A mortality rate of 50% has been reported in cases of splenic abscess rupture. A splenic abscess may also drain into the stomach, colon, or pleura. However, splenic abscesses most commonly produce repeated bacteremia, which ends in septic shock if not treated. Two-thirds of all splenic abscesses in adults are solitary, and one-third are multiple. In children, however, the opposite is true. Solitary abscesses generally are easier to diagnose and treat and usually are caused by streptococci, staphylococci, or *Salmonella*. Multiple abscesses tend to be caused by gram-negative bacilli or *Candida*. The prognosis is clearly related to patient age, associated diseases, and development of multisystem organ failure.

With early diagnosis and treatment of splenic abscess, the mortality rate can be as low as 7%. Medical therapy appears appropriate for patients with mycobacterial, *P. jirovecii*, and fungal disease. Percutaneous drainage appears reasonable for patients with a singular, unilocular abscess without associated intra-abdominal disease. In patients in whom there is any question about the accessibility, locularity, or singularity of the abscess, or if there is a question of intra-abdominal pathology, splenectomy remains the treatment of choice.

Suggested reading

Alonso-Cohen MA, Galera MJ, Ruiz M, et al. Splenic abscess. *World J Surg*. 1990;14:513–516.

Chang KC, Chuah SK, Changchien CS, et al. Clinical characteristics and prognostic factors of splenic abscess. *World J Gastroenterol*. 2006;12:460–464.

Chun CH, Raff MJ, Contreras L, et al. Splenic abscess. *Medicine*. 1980;59(1): 50–66.

Ekeh AP, McCarthy MC, Woods RJ, et al. Complications arising from splenic embolization after blunt splenic trauma. *Am J Surg*. 2005;189:335–339.

Fernandez-Guerrero ML, Alvarez B, Manzarbeitia F, et al. Infective endocarditis at autopsy: A review of pathologic manifestations and clinical correlates. *Medicine*. 2012;91(3):152–164.

Johnson JD, Raff MJ, Barnwell PA, et al. Splenic abscess complicating infectious endocarditis. *Arch Intern Med*. 1983;143:906–912.

Nelken N, Ignatius J, Skinner M, et al. Changing clinical spectrum of splenic abscess: A multicenter study and review of the literature. *Am J Surg*. 1987;154:27–34.

Ooi LLPJ, Leong SS. Splenic abscesses from 1987 to 1995. *Am J Surg*. 1997;174:87–93.

Pelletier LL, Petersdorf RG. Infective endocarditis: A review of 125 cases from the University of Washington Hospitals, 1963–72. *Medicine*. 1977;56:287–313.

Phillips GS, Radosevich MD, Lipsett PA. Splenic abscess, another look at an old disease. *Arch Surg*. 1997;132:1331–1335.

Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. *N Engl J Med*. 1994;331:1325–1330.

Sreekar H, Saraf V, Pangi A, et al. A retrospective study of 75 cases of splenic abscess. *Indian J Surg*. 2011;73:398–402.

Thanos L, Dailiana T, Papaioannou G, et al. Percutaneous CT-guided drainage of splenic abscess. *Am J Roentgenol*. 2002;179:629–632.

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Peritonitis

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Peritonitis is inflammation within the peritoneal cavity. This chapter considers infectious causes of peritonitis. Two major types include: (1) primary (spontaneous or idiopathic) and (2) secondary. When signs of peritonitis and sepsis persist or recur after treatment for secondary peritonitis, the clinical entity has been termed tertiary peritonitis. In comparison with patients with other forms of peritonitis, tertiary peritonitis has significantly longer intensive care unit (ICU) and hospital stays, higher organ dysfunction scores, and higher mortality rates (50% to 70%).

Intraperitoneal abscesses can result from (1) localization of the initially diffuse peritoneal inflammatory response to one or more dependent sites (i.e., the pelvis, the right or left subphrenic spaces, which are separated by the falciform ligament, and Morrison's pouch, which is the most posterior superior portion of the subhepatic space and is the lowest part of the paravertebral groove when the patient is recumbent) or (2) at the site of the intra-abdominal source of the infection (e.g., periappendiceal, pericholecystic, or peridiverticular abscess). For management of peritoneal catheter-related peritonitis, see Chapter 96, Dialysis-related infection.

PRIMARY PERITONITIS

Primary peritonitis, also called spontaneous bacterial peritonitis (SBP), is defined as infection within the peritoneal cavity without an evident intra-abdominal source. Primary peritonitis occurs at all ages: in children, in association with postnecrotic cirrhosis and with nephrotic syndrome, and in adults, with ascites from any cause, but most commonly alcoholic cirrhosis. Rarely, primary peritonitis occurs with no apparent underlying disease.

Primary peritonitis has been reported in 10% of all hospitalized patients with alcoholic cirrhosis and ascites. The risk of developing primary peritonitis is greater in patients with more advanced cirrhosis but also increases with coexisting gastrointestinal hemorrhage, previous primary peritonitis, use of proton pump inhibitors, or low protein levels in ascitic fluid (<1 g/dL), presumably because of decreased ascitic fluid opsonic activity.

Primary peritonitis is monomicrobial and only rarely involves anaerobes; if cultures reveal a polymicrobial or anaerobic infection, secondary peritonitis should be suspected. *Escherichia coli* is the most frequently isolated pathogen, followed by *Klebsiella* species and *Streptococcus pneumoniae*.

Cases with positive ascitic fluid culture but low leukocyte counts (<250 neutrophils/mm^3) and no clinical findings of peritonitis are designated as *monomicrobial nonneutrocytic bacterascites* (MMNNB). This may represent early colonization of the peritoneal cavity because some patients progress to SBP; in others it resolves spontaneously. Conversely, some patients have clinical evidence of peritonitis, elevated leukocyte counts (greater than or equal to 250 neutrophils/mm^3) in the ascitic fluid, but negative cultures, called *culture-negative neutrocytic ascites* (CNNA); blood cultures are positive in one-third of cases.

Polymicrobial nonneutrocytic bacterascites (PMNNB) is diagnosed when Gram stain or culture of peritoneal fluid demonstrates multiple organisms and there is less than 250 neutrophilic leukocytes/mm^3. This

variant usually complicates puncture of the intestines during paracentesis, which occurs in less than 1% of paracenteses. Risk factors for this complication include ileus, intestinal adhesions, and inexperience of the operator. If the peritoneal fluid protein concentration is greater than 1 g/dL and the osponic activity of the fluid is adequate, PMNNB is reported to resolve spontaneously.

The route of infection in primary peritonitis may be hematogenous, lymphogenous, via trans-mural migration through the intact bowel wall, or, in women, from the vagina via the fallopian tubes. In addition, clearance of bacteria from blood is delayed in patients with cirrhosis due to decreased phagocytic activity within the reticuloendothelial system, impaired intracellular killing by neutrophils and monocytes, impaired opsonization, and low serum and ascitic complement levels.

The clinical features of primary peritonitis are variable. In children it is often confused with acute appendicitis. The most common sign is fever (often low grade), reported to occur in up to 80% of patients. Fever may be present without abdominal signs or symptoms, or the intraperitoneal infection may be clinically silent. Ascites predating the infection is almost always present. Other signs and symptoms include abdominal pain, nausea, vomiting, diarrhea, diffuse abdominal tenderness, rebound tenderness, and hypoactive to absent bowel sounds. Atypical signs such as hypothermia, hypotension, and unexplained decline in renal function may be present, as well as unexplained encephalopathy, hepatorenal syndrome, and variceal bleeding in cirrhotic patients. Because peritonitis may be clinically inapparent in a patient with ascites and decompensated liver disease, routine paracentesis is necessary in every hospitalized cirrhotic patient with ascites, especially if febrile, to disclose its presence.

The diagnosis of primary peritonitis requires exclusion of intra-abdominal sources of infection, usually by contrast-enhanced computed tomography (CT). Examination of the ascitic fluid is required. The ascitic fluid leukocyte count is generally greater than 250 polymorphonuclear leukocytes/mm^3. Gram stain of the fluid is commonly negative because of the low bacterial density. The diagnostic yield of ascitic fluid culture is enhanced by culturing a large volume (e.g., 10 to 20 mL). Blood cultures should also be obtained because concurrent bacteremia is present in up to 75% of these patients.

Primary peritonitis is managed medically unless secondary peritonitis is suspected, in which case either exploratory laparotomy or laparoscopy is done. Because the Gram stain is often negative in primary peritonitis, the initial choice of antimicrobial agents is empiric and is modified once results of cultures and susceptibility testing are available. Initial therapy should be directed against enteric gram-negative bacilli and gram-positive cocci. Acceptable regimens include the third-generation cephalosporins ceftriaxone and cefotaxime, the fourth-generation cephalosporin cefepime, or one of the newer generation of fluoroquinolones (e.g., levofloxacin or moxifloxacin) that have improved activity against *S. pneumoniae*, including those strains that are relatively penicillin resistant, or β-lactam antibiotic-β-lactamase inhibitor combinations (e.g., ticarcillin–clavulanate or piperacillin–tazobactam).

Fluoroquinolones should not be used for treatment of primary peritonitis if used previously to prevent primary peritonitis, because of the likelihood of a fluoroquinolone-resistant pathogen. If peritonitis develops during hospitalization or in a community where antibiotic-resistant *E. coli* or *Klebsiella pneumoniae* (e.g., extended-spectrum β-lactamase [ESBL]-producing strains) are prevalent, broader-spectrum antimicrobial therapy should be used, such as a carbapenem (e.g., ertapenem, imipenem, meropenem, or doripenem).

Streptococcus pneumoniae and group A streptococci are best treated with high-dose penicillin G, ceftriaxone, or cefotaxime. Methicillin-sensitive *Staphylococcus aureus* is best treated with a penicillinase-resistant penicillin (nafcillin) or with a first-generation cephalosporin (cefazolin). If the strain is methicillin resistant or the patient is allergic to penicillin, vancomycin is used. If *Pseudomonas aeruginosa* is isolated, an aminoglycoside can be given in combination with an antipseudomonal penicillin or cephalosporin, aztreonam, or imipenem or meropenem, or, to avoid the nephrotoxicity and ototoxicity of aminoglycosides, ciprofloxacin combined with another antipseudomonal agent should be used if results of susceptibility testing permit. Intraperitoneal antimicrobial administration is not beneficial.

A clinical response should be evident by 48 to 72 hours with appropriate antimicrobial therapy. Failure to respond should prompt an examination for an alternative or additional diagnosis. Antimicrobial therapy should be continued for 10 to 14 days if improvement is noted; however, shorter-course (5 day) therapy is efficacious if rapid clinical improvement occurs. Treatment of primary peritonitis is ultimately successful in up to 85% of cirrhotic patients, but because of the underlying liver condition, the overall mortality has been reported as high as 95% in some series. Those patients with the poorest prognosis were found to have renal insufficiency, hypothermia, hyperbilirubinemia, and hypoalbuminemia.

Patients with peritoneal fluid neutrophil counts less than 250 cells/mm^3 (MMNNB) and signs or symptoms of infection (temperature greater than 100°F or abdominal pain or tenderness) should receive empiric antibiotic therapy for primary peritonitis, while awaiting results of cultures, because symptomatic patients with MMNNB variant are prone to primary peritonitis even though at time of the paracentesis it is not known whether the cultures will yield bacteria. Because only 15% of asymptomatic patients with MMNNB progress to primary peritonitis, asymptomatic patients with the MMNB variant usually do not need antibiotics and observation is appropriate. In these asymptomatic patients the paracentesis should be repeated as soon as the first culture yields bacteria. Antibiotics are initiated only if signs or symptoms of infection develop or if the second paracentesis demonstrates neutrocytic ascites.

If the peritoneal neutrophil count was at least 250/mm^3, but the peritoneal Gram stain and culture were negative (i.e., CNNA variant of primary peritonitis), antimicrobial therapy should be continued, because CNNA has clinical, prognostic, and therapeutic characteristics similar to that of primary peritonitis, although other possible causes of neutrocytic ascites such as peritoneal carcinomatosis, pancreatitis, and tuberculous peritonitis must be ruled out.

Cirrhotic patients who have had an upper gastrointestinal bleed, ascitic fluid protein <1.5 g/ dL, or recurrent primary peritonitis are at high risk of primary peritonitis and may benefit from antibiotic prophylaxis with norfloxacin (400 mg daily), ciprofloxacin (750

mg once a week), or trimethoprim–sulfamethoxazole (one double-strength tablet once daily for 5 days each week). Prophylaxis may be an option in patients awaiting liver transplantation but may not otherwise prolong survival in patients with end-stage liver disease. Indeed long-term antibiotic use may increase risk of secondary infection with resistant pathogens.

Occasionally, peritonitis may be caused by *Mycobacterium tuberculosis*, usually from hematogenous dissemination from remote foci of tuberculous infection or extension of infection in mesenteric lymph nodes, intestine, or fallopian tubes or ovaries. The diagnosis of tuberculous peritonitis can usually be confirmed by histologic examination and culture of a peritoneal biopsy specimen and fluid. Diagnosis of *Coccidioides immitis* peritonitis can be made by wet mount of ascitic fluid, histology, and culture of the peritoneal biopsy specimen and fluid.

SECONDARY PERITONITIS

Secondary peritonitis is associated with a predisposing intra-abdominal lesion. Numerous intra-abdominal processes may give rise to secondary peritonitis; a partial list includes perforation of a peptic ulcer; traumatic perforation of the uterus, urinary bladder, stomach, or small or large bowel; appendicitis; pancreatitis; diverticulitis; bowel infarction; cholecystitis; biliary sepsis; and female genital tract infection such as septic abortion, postoperative uterine infection, endometritis, or salpingitis.

Secondary peritonitis is usually an endogenously acquired polymicrobial infection. On average, about five bacterial species are isolated, including both obligate and facultative anaerobes. The species of organisms vary with the primary source of the infection. Community-acquired peritonitis secondary to a breach in the integrity of the stomach and duodenum in the absence of obstruction usually involves mouth flora, i.e., mainly β-lactam-susceptible gram-positive cocci and anaerobic gram-negative bacilli, such as *Prevotella melaninogenica* (formerly a member of the *Bacteroides melaninogenicus* group), and *Candida* species. Community-acquired peritonitis from a breach in the integrity of the lower small bowel or colon, or a breach of more proximal portions of the gastrointestinal tract when obstruction is present, involves colonic flora with *E. coli*, *Bacteroides fragilis*, enterococci, other *Bacteroides* species, *Fusobacterium*, *Clostridium perfringens*, other clostridia, *Peptostreptococcus*, and *Eubacterium*. Similar organisms (*E. coli*, enterococci, *Clostridium*, and *B. fragilis*) are also responsible for peritonitis complicating cholecystitis and biliary sepsis. Concomitant bacteremia occurs in 20% to 30% of patients, most frequently from *E. coli* and *B. fragilis*. In patients who acquire their infection in the hospital, antibiotic-resistant organisms such as *Enterobacter*, *Serratia*, *Acinetobacter*, vancomycinresistant enterococci, and *P. aeruginosa* are frequently isolated.

The presenting symptoms are similar to those of primary peritonitis. The rapidity of onset and initial location and extent of peritoneal involvement vary with the inciting event; for example, sudden massive intraperitoneal spillage of gastric contents secondary to traumatic injury produces severe epigastric pain that, within minutes, spreads to involve the entire abdomen. In contrast, the spread of pain from a lesion such as a ruptured appendix or colonic diverticulum is more gradual and limited as the inflammatory process usually has time to wall off.

Pain is the predominant symptom. Pain and abdominal tenderness to palpation are usually maximal over the organ in which the process originated (e.g., epigastrium for a ruptured peptic ulcer, right upper quadrant for cholecystitis, right lower quadrant for appendicitis, and left lower quadrant for diverticulitis). Other findings include fever, nausea, vomiting, and abdominal distension. The patient often lies motionless with the legs drawn up to the chest; any motion is likely to exacerbate the abdominal pain. Blood pressure is usually normal early but may fall with onset of septic shock, and there may be tachypnea and tachycardia. Direct and rebound abdominal tenderness and abdominal wall rigidity are often present. Bowel sounds are absent. Rectal and vaginal examinations, and in women in whom an ectopic pregnancy is suspected, a urinary beta-human chorionic gonadotropin (β-HCG) determination, are necessary.

Often, the diagnostic evaluation must be brief because of the patient's critical condition. Laboratory studies include a complete blood count, serum chemistry profile, liver profile, and amylase and lipase determinations. Appropriate cultures should be done promptly (e.g., blood), although culture of peritoneal fluid is often delayed until the time of laparotomy. Chest radiographs should be obtained to exclude chest conditions that might simulate an intra-abdominal process. Plain radiographs of the abdomen may also be helpful, sometimes revealing free air or fluid, bowel distension, ileus, or bowel wall edema. However, CT of the abdomen and pelvis with contrast is most helpful to localize the infection and indicate its probable source.

Antimicrobial therapy is initiated early to control bacteremia and minimize the local spread of infection. Patients with hemodynamic, respiratory, renal, and other critical organ system dysfunction require immediate appropriate supportive therapy. Surgery is often necessary to drain purulent material that contains bacteria, and excessive levels of proinflammatory cytokines and adjuvants (e.g., fecal matter, food, blood, bile, barium) that would enhance the virulence of peritoneal infection; debride devitalized tissues that foster anaerobic conditions; and control continued peritoneal contamination with bacteria and adjuvants by removing the initiating process (e.g., cholecystitis, appendicitis, and diverticulitis). Optimal management also includes bowel decompression (e.g., by proximal colostomy for perforation, diverticulitis, or colonic carcinoma). Proper timing and adequacy of surgical source control is paramount. To reduce the bacterial load and inflammatory exudate, a lavage of the abdominal cavity is performed, with particular attention to areas prone to abscess formation (e.g., paracolic gutters, subphrenic area).

Some patients, who are too severely ill and unstable from septic shock or coagulopathy to have a definitive procedure at the initial operation, are resuscitated and stabilized in an ICU setting for 24 to 36 hours and returned to the operating room in a series of re-explorations for additional debridement of necrotic tissue and foreign matter, drainage of residual infectious foci, and source control. Swelling of the bowel, retroperitoneum, and abdominal wall may preclude abdominal closure after surgery. Temporary closure of the

abdomen to prevent herniation and contamination of the abdominal contents can be achieved using gauze and large, impermeable, self-adhesive membrane dressings, mesh with or without zipper- or Velcro-like closure devices, or vacuum-assisted closure devices. Advantages of this management strategy include avoidance of abdominal compartment syndrome and easy access for re-exploration. The disadvantages include significant disruption of respiratory mechanics and potential contamination of the abdomen with nosocomial pathogens.

Percutaneous catheter drainage guided by CT scan or ultrasonography may in some cases decrease the need for surgical therapy or delay surgery until the acute process and sepsis are resolved and a definitive procedure can be performed under elective circumstances. Where possible, percutaneous catheter drainage of abscesses and other well-localized fluid collections is preferable to surgical drainage if there is no evidence of uncontrolled perforation.

Antibiotic therapy should begin as soon as blood cultures are obtained but often before peritoneal fluid can be obtained for culture. Initial therapy is often empirical and must have broad-spectrum activity against the suspected pathogens. Peritoneal fluid cultures can be obtained at the time of paracentesis, percutaneous drainage of an intraperitoneal abscess, or laparotomy.

The spectrum of initial empiric antimicrobial coverage for community-acquired acute stomach and proximal jejunum perforations, in the absence of acid-reducing therapy or malignancy, should include aerobic gram-positive cocci and oral anaerobes. The spectrum of empiric antimicrobial coverage for community-acquired (1) distal small bowel-, appendiceal, and colon-derived infection, (2) more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus, and (3) biliary-derived infection if a biliary-enteric anastamosis is present should include facultative gram-negative bacilli, especially *E. coli*, and enteric streptococci, and obligate anaerobic gram-negative bacilli, especially *B. fragilis* (see Box 57.1).

Inclusion of enterococcal coverage is somewhat controversial. It is prudent to include empiric antienterococcal therapy in an attempt to improve outcome in high-risk patients and in patients with cardiac valvular lesions that place them at high risk for a bad outcome of endocarditis (e.g., prior endocarditis, prosthetic cardiac valves, or complex cyanotic heart disease) (see Box 57.1).

Empiric therapy directed against vancomycinresistant *Enterococcus* (VRE) *faecium* is not recommended unless the patient is at high risk for an infection due to this organism, such as a liver transplant recipient with an intra-abdominal infection from the hepatobiliary tree or a patient known to be colonized with VRE. Antibiotics active against VRE *faecium* include tigecycline, daptomycin, linezolid, and quinupristin–dalfopristin. For the more penicillin-susceptible VRE *faecalis*, ampicillin, linezolid, or daptomycin is appropriate (*E. faecalis* is inherently streptogramin resistant).

Similarly, treatment of *Candida* is controversial. Isolation of *Candida* from blood cultures or as the sole organism within residual or recurrent intra-abdominal infection, or as the predominant organism on Gram staining of peritoneal exudate, requires additional antifungal therapy for patients with severe community-acquired or healthcare-associated infection with either fluconazole

BOX 57.1

Empiric regimens for secondary peritonitis[a]

Single agent

1. β-lactam–β-lactamase inhibitor (piperacillin–tazobactam[b,c])
2. Moxifloxacin[b,c,d,e,f]
3. Carbapenem (imipenem[b,c], meropenem[c], doripenem[c], or ertapenem[g])[d]
4. Tigecycline[b,f,h]

Combinations

5. Cefazolin, cefuroxime, ceftriaxone, or cefotaxime plus metronidazole
6. A third- or fourth-generation cephalosporin (ceftazidime[c] or cefepime[c]) plus metronidazole
7. Levofloxacin[d,e,f] or ciprofloxacin[c,d,e,f] plus metronidazole
8. Aztreonam[c,f,i] plus vancomycin plus metronidazole[b]

[a] These regimens should be adjusted based on the results of culture and susceptibility testing.

[b] Empiric regimens with activity against *Enterococcus faecalis* are preferred for severe or nosocomial infections.

[c] Antipseudomonal

[d] The carbapenems and often fluoroquinolones, but not third-generation cephalosporins or β-lactam–β-lactamase inhibitor combinations, are active against ampC β-lactamase-producing and extended-spectrum β-lactamase (ESBL)-producing aerobic–facultative gram-negative bacilli.

[e] Fluoroquinolones are not recommended for use in patients who have received a fluoroquinolone in the past 3 months or in locales that have high rates (>10%) of fluoroquinolone-resistant *E. coli*.

[f] Tigecycline or fluoroquinolone- or aztreonam-containing regimens can be used in penicillin-allergic patients.

[g] Ertapenem does not cover *P. aeruginosa*.

[h] Tigecycline has shown increased risk of death compared to other drugs when used to treat a variety of serious infections, including complicated intra-abdominal infections.

[i] Aztreonam lacks activity against anaerobes and gram-positive cocci and must be combined with vancomycin and metronidazole.

or an echinocandin (caspofungin, micafungin, or anidulafungin) for fluconazoleresistant *Candida* species such as *Candida glabrata* and *Candida krusei*. Use of fluconazole for non-albicans *Candida* should be based on in vitro susceptibility testing. For the critically ill patient, therefore, initial therapy with an echinocandin instead of a triazole is recommended. Because of toxicity, amphotericin B is not recommended as initial therapy.

Because a significant proportion of *B. fragilis* is now resistant to clindamycin, cefoxitin, and cefotetan, and aminoglycosides have significant nephrotoxicity and ototoxicity, these drugs can no longer be recommended for empiric coverage now that more reliable and less toxic agents are available. For example, although *B. fragilis*, as well as many *Prevotella melaninogenica* are resistant to ampicillin, ticarcillin, and piperacillin, these organisms are sensitive to the β-lactam–β-lactamase inhibitor combinations piperacillin–tazobactam, and ticarcillin–clavulanate, as well as the carbapenems, the fluoroquinolone moxifloxacin, tigecycline, and metronidazole. All these antimicrobial agents, except metronidazole, will also be active against most *E. coli* and therefore can be used as single-drug therapy (see Box 57.1). Ampicillin–sulbactam is no longer recommended for use because of high rates of resistance to this agent among community-acquired *E. coli*.

Because nosocomial intraperitoneal infections are caused by more resistant flora, broader-spectrum empiric regimens are appropriate, as well as for more severe community-acquired infection or infection in immunocompromised patients (Box 57.1). Acute Physiology and Chronic Health Evaluation II (APACHE II) score >15, advanced age, low albumin levels, poor nutritional status, and concurrent malignancy increase risk for a more severe infection.

Local susceptibility profiles should be reviewed and empiric regimens modified accordingly. Empiric regimens should also be modified once results of susceptibility testing are available. However, empiric antimicrobial therapy directed against anaerobes should be maintained, even if anaerobes are not recovered, because of the unreliability of clinical anaerobic methodology.

The duration of antimicrobial therapy after adequate surgery is usually 5 to 10 days but depends on control of the source of the infection, severity of infection, clinical response to therapy, and normalization of the white blood cell count. Only a short course of antimicrobial therapy (about 24 hours) is required for sterile peritonitis that occurs around an infected but resected intra-abdominal organ, such as an appendix or gallbladder. Once the patient can tolerate oral therapy, antimicrobial agents can be given orally rather than intravenously, if oral agents are available that have antimicrobial activity equivalent to that of the intravenous regimen.

The main therapy for any intraperitoneal abscess is early and adequate drainage. Effective management depends on accurate localization of the abscess and discrimination between single and multiple abscesses. In recent years, successful therapy has been accomplished using percutaneous catheter drainage as an alternative to surgery. This method has become possible with the use of refined imaging techniques, especially ultrasonography and CT. The general requirements for CT- or ultrasound-guided percutaneous catheter drainage include (1) an abscess that can be adequately approached; (2) an abscess that is unilocular; (3) an abscess that is not vascular and the patient has no coagulopathy; (4) joint radiologic and surgical evaluation, with surgical backup for any complication or failure; and (5) the possibility of dependent drainage via the percutaneously placed catheter. CT also allows detection of an unsuspected additional intra-abdominal problem that would otherwise require surgical intervention. Percutaneous catheter drainage can be used as an initial approach in a patient too unstable to withstand immediate surgery. Definitive surgery can then be postponed until the patient is in better condition.

SUGGESTED READING

Holzheimer RG, Gathof B. Re-operation for complicated secondary peritonitis—how to identify patients at risk for peritoneal sepsis. *Eur J Med Res*. 2003;8:125–134.

Marshall JC, Maier RV, Dellinger EP, Jiminez MF. Source control in the management of severe sepsis and septic shock: an evidence-based review. *Crit Care Med*. 2004;32(Suppl 11): S513–S526.

Nathens AB, Rotstein OD, Marshall JC. Tertiary peritonitis: clinical features of a complex nosocomial infection. *World J Surg*. 1998;22:158–163.

Peralta R, Geibel J. Surgical approach to peritonitis and abdominal sepsis. Available at http://emedicine.medscape.com/article/1952823-overview#aw2aab6b7.

Runyon BA; AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology*. 2009;49(6):2087–2107.

Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010;50(2):133–164. Available at http://cid.oxfordjournals.org/content/50/2/133.full.pdf+html.

58

Whipple's disease and sprue

Amirkaveh Mojtahed and Payam Afshar

Dr. George H. Whipple, a pathologist at Johns Hopkins Hospital, described the first case of "intestinal lipodystrophy" in 1907. The patient was a 36-year-old male physician with chronic diarrhea, abdominal pain, weight loss, and chronic cough. The patient succumbed 5 years later due to cachexia. Universally fatal prior to the advent of antibiotics, this condition, now recognized as Whipple's disease, has accumulated case reports, case series, and even a prospective study. This rare disease masquerades as a multisystem condition of nonspecific symptoms, rendering the diagnosis inaccessible unless it is included in the differential. Based on the most recent prospective study, the disease is well-managed with appropriate attention to diagnosis and antibiotic therapy.

After the initial case report by Dr. Whipple, progress was made toward establishing a means of diagnosis and treatment. In 1949, periodic acid-Schiff (PAS) staining helped to identify the red appearance of glycoproteins within intestinal macrophages. Shortly afterward, the first microscopic identification of a bacteria-like organism led to the first successful treatment of Whipple's disease with chloramphenicol. Electron microscopy and the advancement of histologic staining helped to further characterize the infectious entity as a gram-positive bacterium. In 1992, polymerase chain reaction (PCR) was used to identify the ribosomal RNA of the organism, classifying it as an actinomycete. Genomic sequencing of the organism in 2003 has brought us to the current classification of this rod-shaped, gram-positive, actinomycete as *Tropheryma whipplei*.

Whipple's disease is a multisystem, exceedingly rare chronic disease. It has an approximated incidence of 1 per 1 million, with a middle-aged Caucasian male predilection. The pathogenesis of *T. whipplei* is important for the explanation of the population at risk and the multisystem nature of the disease. Occupations at risk include farmers, due to soil contact, and sewage plant workers. The mode of transmission of the disease is suspected to be through feces and less often saliva, as viable bacteria have been detected in these samples. Curiously, no reports of human-to-human transmission have been made although humans are the only carriers of *T. whipplei* to manifest clinical disease. Fluorescence in situ hybridization (FISH) has been instrumental in characterizing this as a metabolically active organism of the intestinal mucosa. Ineffectively degraded by macrophages, *T. whipplei* replicate in these mononuclear cells of the lamina propria of the intestinal tract. The persistence of the bacteria in macrophages is related to an impaired T-cell interaction with macrophages. Due to a genetic predisposition, patients with Whipple's disease have an inadequate protective inflammatory immune response compared to the more frequently encountered asymptomatic carriers. Iatrogenic immunosuppression has also been noted to expedite disease progression. Apoptosis of the macrophage initiates the cascade that leads to the multisystem pathology of Whipple's disease via invasion from the intestinal lymphatics and eventual hematogenous spread to distant tissues.

The nonspecific clinical presentation of the condition creates confusion for the clinician and latency in the diagnosis that can span for many years. However, its diagnosis may be expedited with iatrogenic immunosuppression. Whipple's disease is primarily a disease of the gastrointestinal tract with extraintestinal symptoms of arthralgia, fever, and neurologic syndromes. The classic presentation of prodromal migratory destructive peripheral arthralgias (on average 6 years prior to other symptoms), followed by gastrointestinal complaints of diarrhea and abdominal pain, should raise suspicion of Whipple's disease. The gastrointestinal symptoms may result in malabsorption, malnutrition, hypoalbuminemia with abdominal lymphadenopathy,

and eventual anasarca. The seronegative migratory peripheral arthralgia mimics autoimmune rheumatologic conditions leading to needless immunosuppressive treatment, which can result in immune reconstitution inflammatory syndrome (IRIS).

The ominous neurologic manifestations usually occur in conjunction with the gastrointestinal disorder or as disease relapse due to inadequate blood–brain barrier penetration of the antibiotic. These are variable and may include cognitive impairment, psychiatric disorder, sensorimotor impairment, and cranial nerve abnormalities, with the most notable and pathognomonic being oculomasticatory or oculofacial myorhythmias. Central nervous system (CNS) involvement in Whipple's disease, reported at 10% to 40%, is likely underestimated due to underreporting. The rare cardiac manifestations of Whipple's disease include blood culture-negative endocarditis, constrictive pericarditis, myocarditis, coronary arteritis, and congestive heart failure. Mucocutaneous Whipple's pathology includes reports of hyperpigmentation of the skin, vasculitic rash, and hemorrhagic gingivitis. Last, pulmonary complaints of chronic cough with the appearance of pulmonary nodules and endobronchial lesions with noncaseating granulomas that resemble sarcoidosis of the lungs have been reported.

The diagnosis of Whipple's disease must be supported by tissue sampling. A reliable and readily available method of diagnosis is biopsy of the duodenum, an endoscopically accessible replication site of *T. whipplei*. Experts recommend at least five mucosal biopsies including the most distal segment of the duodenum to avoid sampling error. Endoscopic findings span the spectrum from normal to lymphangiectasias, with widening of intestinal villi or more suggestive white plaques denoting lipid deposition. Routine hematoxylin and eosin staining of the intestinal biopsies identifies the foamy cytoplasm of the macrophage while PAS stain enhances the appearance of cytoplasmic granules that represent the glycoprotein component of the *T. whipplei* bacterial cell wall (Figure 58.1). Due to nonspecific PAS-positivity, as can be mimicked by mycobacterial infection, real-time PCR should be used to confirm the diagnosis and monitor response to treatment. FISH can be used in conjunction with PCR for confirmation but is not mandatory. Patients with the diagnosis of Whipple's disease should undergo cerebrospinal fluid (CSF) analysis with PCR to exclude CNS involvement, as neurologic damage may be irreversible and absence of symptoms is not a reliable marker to rule out CNS involvement. If initially positive, repeat lumbar puncture with PCR should be performed to

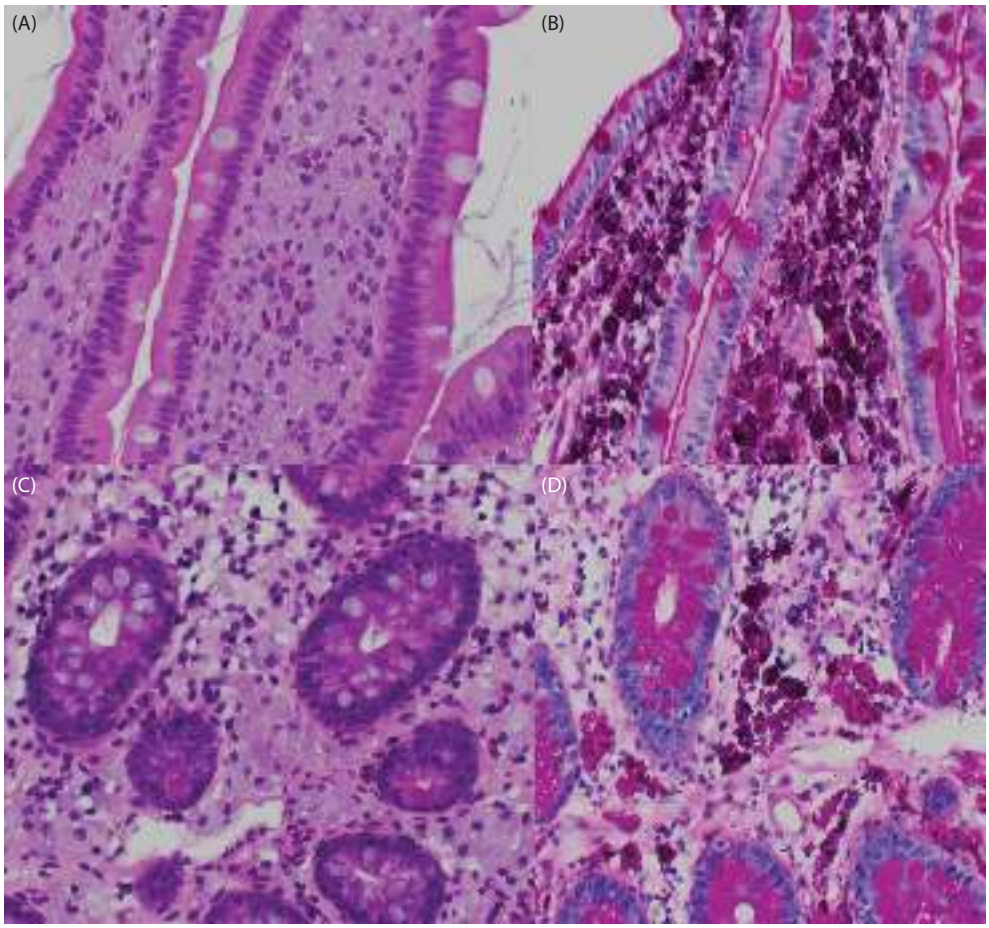

FIGURE 58.1 Histologic sections demonstrate duodenal mucosa with sheets of foamy macrophages in the lamina propria of the duodenum (A) and more uncommon finding in the colon (C) with representative periodic acid-Schiff-diastase (PAS-D) stains (B, D) highlighting the red appearance of *T. whipplei* glycoproteins.
Courtesy of Brett M. Lowenthal, MD.

ensure bacterial eradication. Patients with symptoms beyond the gastrointestinal tract should have appropriate tissue sampling (synovial fluid, cardiac valve, lymph nodes, skin, etc.) based on clinical presentation. In a recent small series publication, urine PCR testing has been shown to be an effective, noninvasive means of diagnosis, especially when other diagnostic measures have failed.

Appropriate treatment of Whipple's disease with antibiotics is essential to avoid the inevitable mortality of the condition. In addition, it is imperative that the chosen antibiotic has blood–brain barrier penetration and can obtain high CSF levels. Tetracycline had long been the drug of choice despite a relatively high relapse rate of up to 35%. Poor response in tetracycline retreatment of CNS-involved patients is likely due to poor absorption and lack of blood–brain barrier penetration. Recently, the only prospective, randomized study to examine therapy compared the efficacy of bactericidal ceftriaxone versus meropenem, followed by oral trimethoprim-sulfamethoxazole (TMP-SMZ) for 12 months due to native impaired immune response. Based on long-term follow-up of 89 months, 93% (37/40) patients maintained clinical remission. Penicillin G followed by doxycycline is also a valid therapeutic option (Table 58.1). Clinical response to therapy should occur within 1 to 3 weeks for gastrointestinal symptoms and several weeks for arthropathy. Follow-up studies with duodenal histology and PCR in patients with GI manifestations and CSF analysis with PCR in patients with CNS involvement are recommended.

Life-long prophylaxis should be considered given the known underlying genetic immunologic deficit in patients with Whipple's disease. Issues with resistance, folate deficiency, and Steven-Johnson related to TMP-SMZ have led to increasing use of doxycycline.

IRIS, a recurrence of inflammatory symptoms after an initial objective improvement with antibiotics, is the most frequent and potentially fatal complication occurring during the treatment of Whipple's disease. A protracted history of immunosuppression for a presumed rheumatologic disorder prior to the diagnosis and treatment of Whipple's disease is ubiquitously observed in patients who develop IRIS. Treatment of IRIS includes initiation of steroids and on occasion more potent immunosuppression.

The mortality rate of treated Whipple's disease is unknown, but untreated Whipple's disease is universally fatal. Even with treatment, relapses have been reported months to years after treatment. One factor may be an ongoing genetic impaired immunity to the bacteria, which leads to a relapse, sometimes with a different strain. Close follow up at 6 and 12 months with duodenal biopsies and immunohistochemistry is recommended since PAS-positive macrophages may persist despite successful eradication of the bacteria. Patients with CNS involvement are at higher stakes for relapse and should have a low threshold for retreatment if a relapse is suspected.

TABLE 58.1

Induction therapy	
Penicillin G	2 million units IV q4h for 14 days
Ceftriaxone	2 gr IV daily for 14 days
Meropenem (if penicillin allergy)	1 g IV TID for 14 days
Maintenance therapy	
Trimethoprim-sulfamethoxazole (TMP-SMX)	160/800 mg BID oral for 12 months
Doxycycline (if sulfa allergy), plus Hydroxychloroquine	200 mg once daily oral, *plus* 200 mg TID for 12 months
Lifelong therapy	
Doxycycline	200 mg once daily oral
Trimethoprim-sulfamethoxazole (TMP-SMX)	160/800 mg once daily oral

Tropical sprue

Tropical sprue (TS) is an acquired malabsorptive and likely infectious disease of unknown etiology that may affect locals and travelers in the tropics. Residence in the tropics for longer than a month with chronic diarrhea and nutritional deficiencies are the usual symptomatic hallmarks. Endemic areas include south Asia, Caribbean, Central America, and northern South America while sparing Africa and the Middle East. Most often it is a disease of local inhabitants; however, long-term visitors are also at risk. TS, initially described as a disease of low-socioeconomic populations, can also affect those with access to medical care, adequate hygiene, and nutritional diet. In North America and Europe, TS should be suspected in the long-term traveler after exclusion of common causes of chronic diarrhea and malabsorption.

Several theories for infectious mechanisms exist, but a specific organism has not been implicated. Patients with TS frequently report a preceding acute infectious diarrheal illness. This finding, in addition to a possible mechanism of small bowel injury explained by an overgrowth of aerobic coliform bacteria with resolution of symptoms after antibiotics, justifies an alternative nomenclature of TS: *postinfective tropical malabsorption*.

Patients suffer from chronic diarrhea related to malabsorption of fatty acids and carbohydrates, as well as bile salt–induced diarrhea from terminal ileal (TI) involvement. Loss of brush border enzymes (e.g., lactase), impaired fat absorption leading to steatorrhea, and nutrient deficiencies of primarily folate, vitamin D, and, as the disease progresses, B_{12} are commonly seen in TS. Macrocytic anemia from nutrient deficiency is commonly seen. Steatorrhea also leads to loss of fat-soluble vitamin absorption with subsequent vitamin deficiency clinical sequela.

Diagnosis is by exclusion of close mimics, particularly celiac sprue (CS). The incidence of TS has decreased as the serum testing for CS has improved, suggesting that many of these cases were not TS. Infectious diarrheal illnesses such as *Entamoeba*, AIDS enteropathy, Whipple's disease, *Giardia*, *Isospora*, and *Cryptosporidium* must be excluded. Mucosal scalloping, a common feature of CS, can be present on endoscopy, while biopsies of any region of the small bowel can show partial villous atrophy and intraepithelial lymphocytes. Duodenal biopsies are of highest yield as the ileum is affected in later stages. *Tropical enteropathy*, a subclinical variant of

TS without the usual symptoms, may have similar biopsy changes. A thorough workup is indicated but the diagnosis can also be confirmed by response to treatment.

Three to six months of tetracycline 250 mg four times a day with folate is the first-line treatment regimen. In several case series, initial folate (1–5 mg/d) has been shown to resolve symptoms. B_{12} should also be replaced subcutaneously if deficient. Cholestyramine may reduce diarrheal frequency if TI is involved. Recurrence or relapse can occur in 20% of cases, requiring repeat treatment. If tetracycline is contraindicated in the patient, sulfonamide antibiotics can be used based on a single study.

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) is an increased numbers of bacteria residing in the small bowel. Symptoms are linked to malabsorption and excessive bacterial degradation and can include bloating, flatulence, dyspepsia, diarrhea, and anorexia. Deficiency of B_{12} is often recognized. The gold standard is a jejunal aspirate with $>10^5$ CFU/mL bacteria; however, a lower threshold of 10^3 CFU/mL bacteria, especially if coliform, is being considered. A more popular approach is the hydrogen breath test because it is less arduous, is inexpensive, and is more clinically feasible. An abnormal early hydrogen peak is thought to suggest a positive test. Detection of abnormal methane levels is associated with delayed transit and therefore observed in patients with irritable bowel syndrome (IBS) or chronic constipation. Antibiotic reduction of methanogens has been shown to improve symptoms in this subset. Unfortunately, due to varying oro-cecal times and other factors, this form of testing continues to have many critics. Studies are ongoing to identify a more sensitive and specific diagnostic test.

Patients at risk for SIBO generally have altered gut motility or physiology. Risk factors include prior surgeries such as gastrectomy or ileocecal resection, diverticula, fistulas, proton pump inhibitor–induced or unrelated hypochlorhydria, liver disease, chronic pancreatitis, immunodeficiencies, and motility disorders associated with diabetes, scleroderma, and intestinal pseudo-obstruction. IBS patients are more frequently diagnosed with SIBO.

Treatment is primarily antibiotics, management of nutritional deficiencies, and eliminating medications that reduce transit time. Initial diet recommendations should include a lactose-free diet and consideration for a trial of the low FODMAP diet. The current mainstay of therapy is high-dose rifaximin (550 mg TID) for 10 days. Rifaximin is the most effective antibiotic for SIBO with poor absorption; it has a relatively safe side-effect profile, broad antimicrobial coverage, and achieves modulation of the microbiome. Alternatives include metronidazole, oral cephalosporins, amoxicillin-clavulanate, ciprofloxacin, doxycycline, and norfloxacin. Recurrence is common in patients with underlying anatomic or motility disorders. In these cases, repeat treatment courses and improving transit time with pro-motility agents such as low-dose erythromycin can be effective. Unfortunately, probiotics have not proved effective.

Suggested reading

Afshar P, Redfield D, Higginbottom P. Whipple's disease: A rare disease revisited. *Curr Gastroenterol Rep*. 2010;12:263–269.

Fenollar F, Puchal X, Raoult D. Whipple's disease. *N Engl J Med*. 2007;356:55–66.

Feurle G, Junga N, Marth T. Efficacy of ceftriaxone and meropenem as initial therapies in Whipple's disease. *Gastroenterology*. 2010;138:478–486.

Ghoshal UC, Ghoshal U, Ayyagari A, et al. Tropical sprue is associated with contamination of small bowel with aerobic bacteria and reversible prolongation of orocecal transit time. *J Gastroenterol Hepatol*. 2003;18:540–547.

Maldonado N, Horta E, Guerra R, et al. Poorly absorbed sulfonamides in the treatment of tropical sprue. *Gastroenterology*. 1969;57:559–568.

Moter A, Wolters M, Janneck M, et al. Potential role for urine polymerase chain reaction in the diagnosis of Whipple's disease. *Clin Infect Dis*. 2019;68:1089–1097.

Quigley E, Abu-Shanab A. Small intestinal bacterial overgrowth. *Infect Dis Clin N Am*. 2010;24:943–995.

Scarpellini E, Gabrielli M, Lauritano C, et al. High dose rifaximin for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Therapeut*. 2007;25:781–785.

Schneider T, Moos V. Changing paradigms in Whipple's disease and infection with *Tropheryma whipplei*. *Eur J Clin Microbiol Infect Dis*. 2011;30:1151–1158.

Triantafyllou K, Chang C, Pimentel M. Methanogens, methane and gastrointestinal motility. *J Neurogastroenterol Motil*. 2014;20:31–40.

Westergaard H. Tropical sprue. *Curr Treatm Opt Gastroenterol*. 2004;7:7–11.

Section 8

Clinical syndromes: Genitourinary tract

59

Urethritis and dysuria

George Pappas, Ioannis A. Bliziotis, and Matthew E. Falagas

The term urethritis refers to inflammation of the urethra, which can be attributed both to infectious and noninfectious processes. The urethral canal essentially represents the first site of the body to be exposed to a variety of sexually transmitted pathogens, and the interaction of these pathogens with the epithelial cells of the urethra gives rise to the syndrome's symptoms.

Dysuria refers to the experience of pain or burning sensation or discomfort in urination, and is a subjective symptom related to varying pathology of the urinary tract. The urethra being the terminal pathway of urine flow, its inflammation most often accounts for experience of dysuria.

Etiology

Traditionally urethritis has been divided into gonococcal urethritis (GU) and nongonococcal urethritis (NGU). *Neisseria gonorrhoeae* as a cause of urethritis has been recognized since ancient years, and in fact its name represents a description, in Greek, of the syndrome's symptoms as defined by Galen: "gono" referring to semen, which was supposed to be the main constituent of the urethral discharge, and "rrhea" a term for flow. Descriptions of urethritis exist in the Old Testament, in the Book of Leviticus, in ancient Chinese documents, and in the Hippocratic Corpus.

NGU has been often considered synonymous to *Chlamydia trachomatis* infection, although a continuously increasing number of pathogens are also implicated (Table 59.1). *Chlamydia trachomatis* is generally thought of as the commonest cause of NGU, especially in younger patients, although some studies suggest that *Ureaplasma urealyticum*, biovar 2, may be a more prevalent cause of infection. Numerous other pathogens have been associated with NGU: *Mycoplasma genitalium* as a cause of urethritis was recognized in the early 1980s; its etiologic role as a sexually transmitted pathogen has been confirmed recently. *Trichomonas vaginalis* is invariably isolated in clinical series of urethritis. *Gardnerella vaginalis* has also been considered a frequent cause of urethritis in certain series. Herpes simplex virus (HSV) is also a potent cause, both as HSV-1 and HSV-2. More rare causes include adenoviruses, lymphogranuloma venereum (*Chlamydia trachomatis* serotypes L1, L2, L3), mycobacteria, and syphilis, as well as gram-negative pathogens (e.g. *Escherichia coli* in cases of strictures or cystitis). Even rarer causes include other viral infections, cytomegalovirus (CMV) in immunocompromised patients, streptococcal species (especially *Streptococcus pyogenes*), *Neisseria meningitidis*, fungi, and anaerobes such as *Bacteroides* species.

Epidemiology

The global annual incidence of urethritis is enormous: An estimated 62 million cases of GU and 89 million cases of NGU occur annually. In the United States alone, approximately five million annual cases are reported, the great majority of which is NGU. The incidence of GU has been declining in the United States since 2000, while inverse trends have been observed for NGU. The latter are accompanied though by a

TABLE 59.1 **ETIOLOGY AND RELATIVE FREQUENCY OF INFECTIOUS URETHRITIS**

Pathogen	Reported frequency in cases of urethritis
Neisseria gonorrhoeae	12%–34%
Chlamydia trachomatis	15%–55% of NGU
Mycoplasma genitalium	3%–38% of NGU
Ureaplasma urealyticum	6%–60% of NGU
Trichomonas vaginalis	<5% of NGU
Gardnerella vaginalis	12% of NGU in a single study
Mycoplasma hominis	Rare, frequency vaguely defined
Herpes simplex virus	Rare
Gram-negative bacteria	Rare
Adenoviruses	Rare
Other: mycobacteria, syphilis, lymphogranuloma venereum, streptococci, *Neisseria meningitidis*, anaerobes, fungi	Very rare/isolated reports

Abbreviation: NGU = nongonococcal urethritis.

declining incidence of chlamydial NGU and may actually reflect the increasing recognition of other etiologies of NGU or the effect of chlamydial control programs. A steady increase of the total urethritis cases reported in males has been observed in France in recent years. The increasing availability of sophisticated diagnostic techniques in developing countries has also helped underline the magnitude of the problem.

There seems to be no racial predilection for the incidence of the syndrome but certain socioeconomic factors may apply, urethritis being more common in low-income populations. Gender predilection seems also not to exist, although the difference in the syndrome's clinical presentation between males and females may account for a larger percentage of female cases that are asymptomatic and thus not reported; on the other hand, while male urethritis is a distinct syndrome, female disease is often misdiagnosed in the context of, or coexists undiagnosed with, inflammation of other sites of the female urogenital tract, most importantly cervicitis. Due to urethritis being a sexually transmitted disease, the age group of 20 to 24 years predominates in reported cases. The use of condoms has been inversely related to the incidence of urethritis. Other risk factors include the use of spermicides (which, however, may predispose to chemical urethritis only), the number of sexual partners, homosexuality in males, unprotected anal sex for heterosexual males, and history of other sexually transmitted diseases.

Clinical manifestations

The disease is often asymptomatic, particularly so in female patients and in cases of chlamydial etiology. Up to 75% of women with chlamydial urethritis experience no symptoms. Gonococcal urethritis exhibits a shorter incubation period than NGU and a more abrupt onset, and is usually symptomatic. Incubation period lies between a few days, for gonococcal disease, and up to 2 weeks for the nongonococcal one. Urethral discharge, dysuria, and urethral pruritus are the cardinal symptoms: Discharge is a product of the polymorphonuclear cell influx in the region as part of the immune response and epithelial cell apoptosis, is usually mucopurulent, most often observed at the morning, may be blood-tinged, and is a result of the inflammatory interplay following entry of the pathogen: this inflammatory response is more pronounced in cases of gonococcal compared to chlamydial urethritis and in males compared to females. Occasionally, in women with gonococcal infection symptoms can result from endocervical infection, such as altered vaginal discharge or intermenstrual bleeding and menorrhagia. Other causes of NGU such as *M. genitalium* tend also to cause symptomatic disease whereas *Trichomonas* infection in males can range from asymptomatic to more severe clinically than GU.

Diagnosis

The diagnosis of urethritis is based on the presence of relevant clinical symptoms accompanied by laboratory findings: Gram stain microscopy of urethral secretions that exhibits five or more white blood cells (WBCs) per oil-immersion field, or a positive WBC esterase test of first-void urine, or a first-void urine sample exhibiting 10 or more WBCs per high-power field. The latter though has been considered inadequate by various studies reporting that 12% of chlamydial infections and 5% of gonococcal ones may be undiagnosed by this criterion.

Gram stain microscopy allows for initial etiologic workup, since the observation of gram-negative intracellular diplococci may allow for a rapid diagnosis of gonococcal urethritis, with a sensitivity and specificity of >95% and >99% respectively in symptomatic men. However, microscopy has poor sensitivity (around 50%) in urethral samples of asymptomatic men and urethral and cervical samples of females. Thus, absence of pathologic findings on a Gram smear does not rule out gonococcal infection, especially in the later situations. Cultures may allow for isolation of the specific pathogen and evaluation of its antimicrobial susceptibility. Due to the increase in worldwide prevalence of cephalosporin-resistant strains of *N. gonorrhoeae*, cultures and susceptibility testing have become useful for new cases of urethritis and essential for cases with recurrence after treatment for GU.

Molecular diagnostic methods have been increasingly applied to urethritis diagnosis, nucleic acid amplification tests (NAAT) being the most popular choices, since they can be performed with urine specimens as well as urethral samples. These assays have shown exquisite sensitivity and specificity both for gonococci and *Chlamydia*, but lack the ability to identify resistant strains of gonococcus. Other NAAT exist for less common pathogens, such as *M. genitalium*, but their standard application in clinical practice has been under dispute. Other diagnostic tests for NGU include a wet preparation for *Trichomonas* diagnosis and a potassium hydroxide (KOH)

TABLE 59.2 **DIAGNOSTIC TOOLS FOR PATHOGENS INVOLVED IN URETHRITIS**

Pathogen	Diagnostic tools	Comments
Neisseria gonorrhoeae	Gram stain Culture NAHT NAAT	Culture and NAHT require urethral swab specimens, whereas NAAT can be performed on urine specimens. Culture allows identification of resistant strains
Chlamydia trachomatis	Culture Direct immunofluorescence Enzyme immunoassays NAHT NAAT	NAHT require urethral swab specimens, whereas NAAT can be performed on urine samples/in females addition of cervical samples increases sensitivity NAAT more sensitive and 100% specific
Mycoplasma genitalium	NAAT	NAAT can be performed on urine samples/in females addition of cervical samples increases sensitivity
Ureaplasma urealyticum, Mycoplasma hominis	Culture	Cultures need specialized media, not performed in everyday practice Urethral swabs preferred to urine samples
Trichomonas vaginalis	Wet preparation Culture NAAT	Wet preparation is 60% sensitive, often negative in males Anaerobic culture of urethral swab or first-void urine, 95% sensitive NAAT is considered superior to cultures (97% sensitivity and 98% specificity), but needs multiple samples in males

Abbreviations: NAAT = nucleic acid amplification tests, NAHT = nucleic acid hybridization tests.

preparation for fungal infections. Table 59.2 summarizes current diagnostic facilities for each pathogen and specific data about each assay's sensitivity and specificity. After confirmation of GU or NGU diagnosis, especially in cases of high-risk populations or GU recurrence, it is advisable to test for other sexually transmitted diseases, including human immunodeficiency virus (HIV) and syphilis, and, in female patients, pregnancy should be ruled out before specific antibiotic recommendations.

Complications

The importance of urethritis as a medical entity lies not in the severity of the syndrome per se, but in its potential complications: these complications may be rare in male patients, but do include formation of strictures or abscesses, prostatitis, epididymitis, infertility, disseminated gonococcal infection, and proctitis. In female patients complications are more common, and may lead to pelvic inflammatory disease, which may be of considerable severity. Females with GU and NGU can become infertile due to symptomatic or asymptomatic infection of the upper genital tract, which may cause direct damage to the uterus or fallopian tubes. Disseminated gonococcal infection can also follow urethritis in females. In pregnant women, chlamydial infection can lead to transmission of the pathogen to neonates leading to ophthalmia neonatum. Another important parameter of urethritis is that local inflammation results in disruption of the integrity of the epithelial barrier, thus urethritis confers an increased risk for HIV transmission. Finally, Reiter syndrome is another complication of GU and NGU. It is characterized by the coexistence of arthritis, urethritis, and conjunctivitis or uveitis due to an autoimmune process after gastrointestinal or genitourinary infections.

Differential diagnosis

Differential diagnosis includes traumatic urethritis, occurring after catheterization, chemical urethritis, noninfectious prostatitis, other infections of the lower urinary tract, and autoimmune urethritis of Reiter syndrome. Dysuria should be differentiated from frequency or urgency, which point to other diagnoses. It is reported that dysuria may be aggravated by alcohol consumption, or during menstruation in females. There are no systemic symptoms such as fever, and presence of such symptoms should orientate the diagnosis elsewhere. Since dysuria may be attributed to infectious processes of the whole genitourinary tract, including prostatitis or even pyelonephritis, but also to noninfectious causes of flow obstruction (including anatomical malformations, neoplasms, or even hormonal causes such as endometriosis, and neurogenic and psychogenic conditions), the significance of this subjective symptom is mainly in localizing the clinician's interest in the genitourinary tract.

A high number of WBCs in urine, termed pyuria, can be observed both in urethritis and other lower urinary tract infections, including cystitis. Pyuria with a negative urinary culture (with $°10^2$ common uropathogenic bacteria/mL of urine) is termed "sterile pyuria". NGU is among the most common causes of sterile pyuria, which include among others tuberculosis of the urinary tract, prostatitis, nephrolithiasis, interstitial cystitis, and urinary tract malignancies.

Treatment

Box 59.1 summarizes the suggested antibiotic regimens used in the treatment of urethritis, in accordance to guidelines from Europe and the USA. Many cases of urethritis resolve spontaneously, or evolve, in cases of NGU, into asymptomatic infection. Nevertheless,

BOX 59.1

Optimal treatment of urethritis and alternative approaches[a]

Gonococcal urethritis
(*all therapies in conjunction with therapy against Chlamydia: azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days*)

- First-line regimen:
  Ceftriaxone, 250 mg intramuscularly, single dose
- Second-line, alternative regimens[b]:
  Cefixime, 400 mg orally, single dose
  Azithromycin, 2g orally, single dose (regimen for patients with cephalosporin allergy, no additional treatment for *Chlamydia* needed)
- Alternative regimens of inferior, or unproven efficacy[b]:
  Spectinomycin, 2 g intramuscularly, single dose, or
  Ceftizoxime, 500 mg intramuscularly, single dose, or
  Cefoxitin, 2 g intramuscularly, single dose, plus probenecid, or
  Cefotaxime, 500 mg intramuscularly, single dose,
  Cefpodoxime, 200 mg orally, single dose, or
  Cefuroxime axetil, 1 g orally, single dose

Chlamydial infection

- Azithromycin, 1 g orally, single dose, or
- Doxycycline, 100 mg orally, twice daily for 7 days
- Alternative regimens
  Erythromycin base, 500 mg orally, four times daily, for 7 days, or
  Erythromycin ethylsuccinate, 800 mg orally, four times daily, for 7 days, or
  Ofloxacin, 300 mg orally, twice daily for 7 days, or
  Levofloxacin, 500 mg orally, once daily, for 7 days

Mycoplasma genitalium infection

- Azithromycin, 1 g orally, single dose, or
- Doxycycline, 100 mg orally, twice daily for 7 days (possibility of resistant strains)

Ureaplasma urealyticum infection

- Azithromycin, 1g orally, single dose, or
- Doxycycline, 100 mg orally, twice daily for 7 days (possibility of resistant strain), or
- Quinolones, as used for *Chlamydia trachomatis* infection

Mycoplasma hominis infection

- Doxycycline, 100 mg orally, twice daily for 7 days (possibility of resistant strain), or
- Quinolones, as used for *Chlamydia trachomatis* infection, or
- Clindamycin, dose varying

Trichomonas vaginalis infection

- Metronidazole, 2 g orally, single dose, or
- Tinidazole, 2 g orally, single dose

Pregnancy

- Azithromycin, 1 g orally, single dose, or
- Amoxicillin, 500 mg orally, three times daily, for 7 days
- Alternatively: any erythromycin regimen, apart from erythromycin estolate

[a] Major recommendations from Workowski and Berman, 2006 and Centers for Disease Control and Prevention, 2012.
[b] The patient should return in 1 week for a test-of-cure at the site of infection.

antibiotic treatment of urethritis should always follow the diagnosis to prevent complications and further transmission of the pathogen.

Another important aspect regarding treatment is that gonococcal and chlamydial infection frequently coexist; thus, a diagnosis of gonococcal infection through a Gram smear showing gram-negative intracellular diplococci will warrant treatment of both gonococcal and chlamydial disease. This observation has further raised questions regarding the utility of sophisticated diagnostic assays when Gram smear shows gonococcal disease: it simply is cheaper to treat both for GU and chlamydial urethritis than confirm or exclude chlamydial disease through further testing.

Various antibiotics have been effective in the treatment of different forms of urethritis. Regimens for gonococcal disease include third-generation cephalosporins administered as a single dose. Ceftriaxone exhibits higher blood microbicidal levels and for a more sustained period than cefixime and should be considered as the optimal regimen (Box 59.1). Oral cephalosporins have proven inferior to ceftriaxone, and gonococcal resistance to cefixime is increasing; thus it is no longer considered a first-line therapy. Other cephalosporins have not proven advantageous compared to the aforementioned regimens. Recent European guidelines recommend an increase in the single dose of ceftriaxone to 500 mg because of resistance.

Azithromycin is efficacious against both gonococci as well as *Chlamydia*; it is thus considered sufficient monotherapy at high doses in cases of established cephalosporin allergy (Box 59.1). Similarly, according to some authors azithromycin should also be the preferred empirical therapy for *Chlamydia* when GU is diagnosed (thus used together with a cephalosporin), since tetracycline resistance is increasing among gonococcal isolates whereas azithromycin is efficacious against both microbes. Spectinomycin, although of exquisite microbiologic efficacy (>98%), is expensive and needs parenteral administration. Quinolones were viewed as potential single-dose monotherapy candidates that could treat both gonococcal and chlamydial infection, but the increasing rates of gonococcal resistance to these agents worldwide made them unsuitable for therapy of GU. On the other hand, ciprofloxacin's efficacy against *Chlamydia* is doubtful.

For chlamydial infection, azithromycin and doxycycline have proven equally successful, with microbial cure rates of 97% and 98%, respectively. Azithromycin is superior in terms of compliance since it can be directly administered upon diagnosis, but doxycycline is of considerably lower cost. Azithromycin may be superior though regarding treatment of *M. genitalium* infections. There is no difference in the percentage or severity of adverse events between the two antibiotic classes. None of the various alternatives has proven superior, although not all of them have been evaluated in randomized trials. Erythromycin is marred by low compliance due to frequent gastrointestinal adverse events.

There is increasing concern regarding emergence of resistance to azithromycin by *M. genitalium*, since recent studies have underlined therapeutic failures in cases of urethritis treated with azithromycin. These studies have shown a potent role for moxifloxacin in such cases. *Ureaplasma urealyticum* follows the susceptibility patterns of *Chlamydia*, although the risk of tetracycline resistance is significant. *Mycoplasma hominis* is resistant to azithromycin and macrolides, but sensitive to tetracyclines, quinolones, and clindamycin.

In pregnancy, gonococcal infection can be treated with the usual cephalosporin regimens, and azithromycin can be considered a safe

regimen for chlamydial infection. In addition, amoxicillin can also be administered safely and efficaciously in these patients.

Patients should be advised to abstain from sexual practices for the following week post treatment initiation, and previous sexual contacts should be traced and tested, extending to a period of 6 weeks prior to diagnosis. If the patient reports no contacts during this period, then the last sexual partner should be notified and tested. Alternatively, sexual partners can be treated on the responsibility of the patients, a practice that has been supported inconsistently as effective. Test of cure is not advisable for patients that become asymptomatic after therapy. However, this follow-up testing for microbiologic eradication is suggested for all pregnant women at 3 weeks after treatment completion and for all patients with gonococcal infection that initially received second-line treatment or alternative regimens.

Of note, there is an increased prevalence of gonococcal infections in patients with a recent previous gonococcal infection, and a similar risk exists for a new chlamydial infection after an initial one in female patients, with reinfection possessing greater potential for complications. Therefore, asymptomatic patients should be retested 3 to 12 months after treatment, although this test is distinct from a test seeking evidence of microbiologic eradication.

Recurrence of urethritis may be attributed to noncompliance with the initial treatment, initial infection by resistant strains (of great importance in GU, which should be excluded by culture upon recurrence), or re-exposure to a non-treated partner. Examples of recurrence in NGU include undiagnosed *Trichomonas* infection, which should be treated with metronidazole or tinidazole, infection by a *U. urealyticum* strain resistant to tetracycline, which should be treated with azithromycin, or *M. genitalium* resistant to tetracycline (or on rare occasions to azithromycin). Another common diagnosis in male patients may be chronic nonbacterial prostatitis, which in a significant percentage is accompanied by sterile urethral inflammation.

Prevention

Prevention through screening has been often advocated: US Preventive Services Task Force supports the annual screening for chlamydial infection in sexually active females aged 24 years or younger, and in older females who belong to certain risk groups (multiple partners, sex workers, etc.). Screening for gonococcal infection should also be advocated to the aforementioned high-risk groups of patients in addition to patients with a history of gonococcal infection or other sexually transmitted disease. On the other hand, some European authorities recommend screening for *Chlamydia* only in high-risk groups. Similarly, routine screening for *Chlamydia* in pregnancy during first visit has not been universally acceptable from a cost-effectiveness point-of-view; however, all women undergoing termination of pregnancy should be tested for chlamydial infection due to the risk of ascending infection. The active research in the field of development of a *Chlamydia* vaccine may offer further prospects in the future for control of urethritis incidence; until then though public health policies should be vigorously implemented.

Suggested reading

Bignell C, Unemo M. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. http://www.iusti.org/regions/Europe/pdf/2012/Gonorrhoea_2012.pdf.

Centers for Disease Control and Prevention. Gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2010;59:49–55.

Centers for Disease Control and Prevention. Update to CDC's sexually transmitted diseases treatment guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2012;61:590–594.

European Centre for Disease Prevention and Control. Gonococcal antimicrobial susceptibility surveillance in Europe—2010. 2012. Available from: http://ecdc.europa.eu/en/publications/Publications/1206-Gonococcal-AMR.pdf (accessed December 21, 2012).

Falagas ME, Gorbach SL. Prostatitis, epididymitis, and urethritis: practice guidelines. *Infect Dis Clin Practice*. 1995;4:325–333.

Johnson RE, Newhall WJ, Papp JR, et al. Screening tests to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections, 2002. *MMWR Recomm Rep*. 2002;51:1–38.

Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. *Sex Transmit Dis*. 2002;29:497–502.

Scottish Intercollegiate Guidelines Network (SIGN). Management of genital *Chlamydia trachomatis* infection. A national clinical guideline. Edinburgh (Scotland). SIGN publication no. 109. 2009. Available from: http://www.sign.ac.uk/pdf/sign109.pdf(accessed December 21, 2012)

U.S. Preventive Services Task Force (USPSTF) Screening for chlamydial infection: recommendation statement. *Ann Intern Med*. 2007;147:128–134.

Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep*. 2006;55:1–94.

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Vaginitis and cervicitis

Sebastian Faro

INTRODUCTION

Vaginitis and cervicitis are undoubtedly linked in many instances, to some degree. When considering cervicitis as a discrete entity, the most common causes are infections due to *Chlamydia trachomatis* and *Neisseria gonorrheae*. Other causes of cervicitis are human papillomavirus (HPV) and infrequently considered are herpes simplex virus (HSV), *Mycoplasma*, and *Ureaplasma*. The two latter bacteria are commonly found colonizing the lower genital tract in sexually active women and their role in the disease of female pelvic organs is not well understood. However, recent data have implicated the mycoplasmas and ureaplasmas in both obstetric and gynecologic pelvic infections. Other causes of cervicitis have been documented throughout the world, e.g., *Mycobacterium tuberculosis*, *Schistosoma haematobium*, Epstein–Barr virus, amoebiasis, and cytomegalovirus, but are uncommon in the United States. However, when taking a history it is important to determine if there has been recent travel outside the United States, especially to parts of the world where these diseases are prevalent. The patient's past travel experience or her sexual partner's travel experience are important when evaluating the patient with vaginitis and cervicitis. The patient's travel experience can be significant when administering empirical antimicrobial treatment, especially when treating suspected gonococcal cervicitis. *N. gonorrhoeae* acquired from Asia tends to be resistant to the antibiotics commonly administered in the United States to treat gonococcal infection. Therefore, all patients being evaluated for vaginitis should be evaluated for the coexistence of cervicitis.

Vaginitis can be divided into two broad categories: infectious and noninfectious, and either can lead to cervicitis. The most common noninfectious cause of vaginitis is bacterial vaginosis (BV) which has been shown not to be simply an alteration in the indigenous vaginal microbiota. Gram-negative bacteria, especially the obligate anaerobic bacteria, make up a large portion of the vaginal microbiota. The gram-negative bacteria cell wall contains lipopolysaccharide (LPS), which is known to stimulate the cytokine cascade and the proinflammatory response syndrome. Patients with a predominance of gram-negative bacteria, and therefore an increase in the LPS content, in the vagina, have an increased vaginal concentration of tumor necrosis factor-α (TNF-α). This finding suggests that BV is not simply an alteration in the indigenous vaginal microbiota but perhaps should be considered as a subclinical infection. Therefore, in some cases it is difficult to distinguish between vaginitis and vaginosis, e.g., in the patient with BV and trichomoniasis. Patients may have both vaginitis and cervicitis of the same etiology or of different etiologies, e.g., *Trichomonas* can cause both vaginitis and cervicitis, whereas a patient with BV can also have chlamydial cervicitis. It is possible for the patient with BV to have a complex cervicitis involving BV bacteria plus *C. trachomatis* and *N. gonorrhoeae*. These potential situations underscore the need for the physician to consider the possibility of coexisting conditions in order to initiate appropriate treatment.

Many women with vaginitis are asymptomatic and do not seek treatment until they develop symptoms. Women examined for conditions other than vaginitis or even having a well-woman examination can be found to have an abnormal vaginal discharge, which should be evaluated. This is especially important because most chlamydial and gonococcal infections are asymptomatic. Vaginitis can often cause significant health problems and negatively impact the patient's quality of life, such as disruption of personal relationships,

ability to attend work and social activities. Pregnant patients who have vaginitis and cervicitis can experience premature preterm rupture of amniotic membranes, premature delivery, and postpartum endometritis. Patients with vaginitis and cervicitis who undergo pelvic surgery are at risk for post operative pelvic infection. BV has also been associated with complex pelvic inflammatory disease. Therefore, a simple evaluation of the vagina and cervicitis can lead to proper management, resolution of vaginitis and cervicitis, and improve the patient's quality of life.

BOX 60.1

Categories of the indigenous vaginal microflora

1. Healthy vaginal microflora—*Lactobacillus* dominant
2. Aerobic vaginal microflora—dominated by facultative anaerobes
3. Bacterial vaginosis—dominated by obligate anaerobes
4. Lactobacillosis—overgrowth of *Lactobacillus*

INDIGENOUS VAGINAL MICROBIOTA

The indigenous vaginal microbiota is complex and not well understood, especially the possible relationships between the bacteria of the vaginal microbiota, as well as the indigenous bacteria and the host. However, the use of molecular microbiologic techniques, such as polymerase chain reaction (PCR) analysis, has enabled a better understanding and shed new insight in understanding the make-up of the indigenous microbiota (Table 60.1). Molecular techniques have revealed the presence of bacteria that have not been found using classical microbiologic culture techniques. The microflora consists of a vast array of facultative and obligate anaerobic bacteria, and new genera and species are being found as part of the indigenous vaginal microbiota. The indigenous vaginal bacteria can be divided into four categories based on which bacterium or bacteria are dominant (Box 60.1). A "healthy vaginal microbiota" is dominated by *Lactobacillus*; however, not all species of *Lactobacillus* are effective in maintaining a "healthy vaginal microbiota." Species of *Lactobacillus* that are important in maintaining a "healthy vaginal microbiota" are those that produce adequate levels of lactic acid, hydrogen peroxide (H_2O_2), and a bacteriocin termed lactocin. These three factors, and there are likely other factors which are unknown at this time, appear to be significant in maintaining the vaginal environment that is favorable for the growth of *Lactobacillus*. These same factors are hostile to the growth of gram-negative and gram-positive facultative and obligate anaerobic bacteria.

Lactobacillus crispatus, L. jensenii, and *L. gasseri* are the three most common species found in the vagina of women with a "healthy vaginal microflora." Patients with *L. iners*, even in the presence of *L. jensenii* and/or *L. gasseri* appear to have an unstable microflora and are likely to develop "aerobic vaginitis (AVF)" or BV. The direction in which the vaginal microflora will drift and eventually become established appears to be dependent upon whether or not *Gardnerella vaginalis* is present as a member of the indigenous vaginal microbiota.

One mechanism provided by *Lactobacillus crispatus, L. jensenii*, and *L. gasseri* is the production of lactic acid. Lactic acid results in maintaining the vaginal pH < 4.5. This acidic pH favors the growth of *Lactobacillus* and inhibits the growth of facultative and obligate anaerobic bacteria. When lactobacilli are dominant this results in a ratio of lactobacilli to pathogenic bacteria of 1000:1. The concentration of lactobacilli is ≥ 10^6 bacteria/mL of vaginal fluid. This ratio of lactobacilli to pathogenic bacteria is important when considering a surgical procedure on a patient whose vaginal microflora is dominated either by a gram-positive or gram-negative facultative anaerobe or by obligate anaerobes, i.e. when pathogenic bacteria predominate. When the vaginal microflora is disrupted in such a way, especially in the patient undergoing pelvic surgery, transvaginal ovum retrieval, cesarean section, or who has preterm premature rupture of amniotic membranes leading to delivery of a premature fetus, all such patients are at significant risk for the development of a postoperative infection. Therefore, patients undergoing pelvic surgery who have a *Lactobacillus*-dominant indigenous vaginal microflora are likely to derive benefit from surgical antibiotic prophylaxis because of their risk of infection.

A second mechanism is the production of H_2O_2 by many species of *Lactobacillus*, especially *L. crispatus*, *L. jensenii*, and *L. gasseri*; most strains of *L. iners* do not produce H_2O_2. Hydrogen peroxide is toxic to obligate anaerobes because they do not produce catalase. Hydrogen peroxide can be converted to super oxide, which can disrupt DNA. Thus, the production of lactic acid and H_2O_2 appears to work in concert with a third factor, bacteriocin, which is a low-molecular-weight protein that has antibacterial properties. The bacteriocin produced by *Lactobacillus*, known as Lactocin, has been demonstrated to inhibit the growth of *Gardnerella* and *Prevotella* as well as other bacteria.

The cause of an alteration in the indigenous vaginal microflora is unknown. However, one change in the vaginal environment that appears to be instrumental in the disruption of a

TABLE 60.1 **BACTERIA OF THE INDIGENOUS VAGINAL MICROBIOTA**

Lactobacillus crispatus	*Escherichia coli*	*Atopobium vaginae*
L. jensenii	*Enterobacter aerogenes*	*Bacteroides fragilis*
L. gasseri	*E. agglomerans*	*Bifidobacterium*
L. vaginalis	*E. cloacae*	*Prevotella bivia*
L. iners	*Klebsiella oxytoca*	*Fusobacterium*
Staphylococcus aureus	*K. pneumoniae*	*Mobiluncus*
S. epidermidis	*Morganella morganii*	*Megasphaera*
Streptococcus agalactiae	*Gardnerella vaginalis*	*Sneathia*
S. pyogenes	*Peptococcus*	*Peptostreptococcus*

Note: E. agglomerans is now known as Pantoea agglomerans.

Lactobacillus-dominant indigenous vaginal microflora is a change in the vaginal pH. When the pH rises, growth of *Lactobacillus* slows and when pH is between 4.5 and 5, this appears to be a transitional zone. If *G. vaginalis* is present the microflora is destined to develop into BV. If *Gardnerella* is not present then it may well develop into "aerobic vaginitis." This is an important concept to understand because when the gram-negative bacteria are dominant there is an increase in TNF-α in the vagina. Thus, an inflammatory state is created and conditions such as BV are associated with increased risk of an infection in the upper genitalia tract as well as an increased risk of contracting sexually transmitted diseases, e.g., HIV. This inflammatory response involves the endocervical epithelium, making this tissue more receptive to contracting sexually transmitted organisms. In addition, patients with an altered vaginal microflora, e.g., BV, are at increased risk of developing a postoperative pelvic infection when undergoing pelvic surgery.

BACTERIAL VAGINOSIS

BV can be defined as a vaginal microflora that is dominated by obligate anaerobic bacteria. The diagnosis can be established easily with very little cost to the patient and consuming no more than 5 minutes of the physician's time. The clinical criteria are rather easy to determine (Table 60.2) and differentiate the most common types of vaginitis or vaginosis, and can assist in determining proper management. The patient should be reevaluated 1 to 2 weeks after completing treatment to determine if the pH has returned to the acidic range (pH > 3.8 to ≦ 4.5) and if large bacilli are present. If the pH ≥ 5 and microscopic examination of the vaginal discharge does not reveal the presence of large bacilli, the patient's initial vaginitis or vaginosis can reoccur or a different type of vaginitis can evolve. This can occur if the patient is diagnosed with BV and treated with metronidazole or clindamycin. The antibiotic will suppress the anaerobic bacteria and may suppress lactobacilli, allowing the facultative anaerobes to flourish if the pH is not decreased to < 5.

Mycoplasma and *Ureaplasma* are commonly found to be part of the indigenous vaginal microbiota in patients with a *Lactobacillus*-dominant vaginal microflora, aerobic vaginitis, or BV. *Mycoplasma* and *Ureaplasma* are found in approximately 60% of sexually active individuals. It is not understood how or if these bacteria have a role either in maintaining a healthy vaginal microflora or acting in concert with one or more of the pathogenic bacteria to create an environment that favors the growth of the pathogenic bacteria. Thus, there is much speculation regarding the potential role of *Mycoplasma* and *Ureaplasma*; however, other than nongonococcal and non-chlamydial urethritis, and perhaps cervicitis, treatment should not be initiated for these bacteria.

An organism that has gained significant attention is *L. iners*, which seems to be common in patients with an altered vaginal microflora. In addition, *L. iners* appears to rarely be present when *L. crispatus* is dominant. *L. iners* has been reported to be present when *L. jensenii* and *L. gasseri* are dominant. In this latter situation the vaginal microflora appears to be unstable and more easily undergoes shifts in the vaginal microbiota.

BV is made up of a variety of obligate anaerobes which can reach concentrations of $>10^8$ bacteria/ mL of vaginal fluid, mainly pathogenic bacteria. Undoubtedly there are facultative anaerobes present but probably fewer than 10^5 bacteria/mL of vaginal fluid. This concentration of bacteria is important because this is an enormous inoculum and can initiate or contribute to significant infection.

Treatments of BV are not very adequate because of the high recurrence rates (Box 60.2). The typical treatments are all designed to suppress the growth of obligate anaerobic bacteria. Treatments may have a suppressive effect on lactobacilli and not suppress the facultative anaerobic bacteria. However, if the pH does not decrease (<4.5) lactobacilli will not grow and either the obligate anaerobic bacteria or facultative anaerobic bacteria will gain dominance. This is the reason that the patient should be re-evaluated within one to two weeks following treatment. The two key observations that are indicative of whether there was resolution or not are: (1) has the vaginal pH returned <4.5, and (2) are large bacilli present. If the pH ≥ 5 and no large bacilli are present then patient has not responded in a positive manner. Patients who fail to respond should be referred to a gynecologist who has an interest in vulvovaginal disease.

Patients with BV who have greater than 5 WBCs/40× magnifications (wet prep) should be considered to have an infection

TABLE 60.2 **DIAGNOSIS OF AN ALTERED VAGINAL MICROFLORA**

	Healthy	Aerobic vaginitis	Bacterial vaginosis
Bacteria	Lactobacillus	Facultative anaerobes	Obligate anaerobes
Discharge color	White to slate-gray	Dirty-gray to purulent	Dirty-gray
Odor	None	None	Fish-like (Foul)
Microscopic analysis			
Squamous cells	Cytoplasmic membrane easily identified		Clue cells present
	Nucleus easily identified		Nucleus obscured
WBC	<5/hpf	<5/hpf	<5/hpf
Bacteria	Large bacilli	May be one morphotype or multiple morphotypes	Multiple morphotypes

Abbreviations: hpf = high-power field.

BOX 60.2

Treatments for bacterial vaginosis

Metronidazole 500 mg orally twice a day for 7 days, or
Metronidazole gel 0.75%, one full applicator (5 g) intravaginally hs × 7 days, or
Clindamycin cream 2%, one full applicator (5 g) intravaginally hs × 3 days, or
Tinidazole 2 g orally once daily for 2 days, or
Tinidazole 1 g orally once daily for 5 days, or
Clindamycin 300 mg orally twice a day for 7 days, or
Clindamycin ovules 100 mg intravaginally once at hs × 3 days

CDC MMWR, Sexually Transmitted Diseases Treatment Guidelines, December 17, 2010; 59: 1–110.

and should be evaluated for *Trichomonas vaginalis, Chlamydia trachomatis*, and *Neisseria gonorrhoeae*. BV is dominated by gram-negative obligate anaerobes and probably gram-negative facultative anaerobes. The cell wall of gram-negative bacteria contains LPS, the substance that initiates a proinflammatory response. It has been shown that patients with BV have an increased concentration of TNF-α in the vaginal milieu. The increase in TNF-α indicates that BV may not be a condition that initiates a classic inflammatory response, namely a significant increase in WBCs, but is associated with a possible upregulation of the cytokine cascade. This may be significant in patients who develop an infection, e.g., pelvic inflammatory disease, or who are having significant pelvic surgery, placing the patient at significant risk for developing a postoperative pelvic infection.

AEROBIC VAGINITIS

This condition may have a variety of presentations, bacteriologically; that is, dominance can be unimicrobial, e.g., *Streptococcus agalactiae* (group B streptococcus, GBS) or *Escherichia coli* or other unimicrobial vaginitis, or polymicrobial vaginitis. This condition does not resemble BV in that there are no clue cells, often noted as a purulent discharge indicating an inflammatory reaction, and either one bacterial morphotype, e.g., cocci in chains indicating dominance by streptococci or morphologically similar small rods, e.g. *E. coli*, or a variety of morphotypes indicating a polymicrobial condition. Typically the discharge is odorless. Many gynecologists do not advise obtaining a specimen for culture because whatever bacterium or bacteria is recovered is part of the normal vaginal microflora. However, obtaining a culture does assist: (1) in differentiating BV from aerobic vaginitis, (2) in determining which bacterium or bacteria is dominant, and (3) in determining if it is a mixed gram-positive and gram-negative vaginal microbiota. Without determining the microbiology, it would be difficult to administer appropriate treatment. The treatment most frequently administered, without bacteriologic data, is either metronidazole or clindamycin, neither of which is suitable for treating "aerobic vaginitis." Aerobic vaginitis like BV places the patient undergoing pelvic surgery at risk for the development of postoperative pelvic infection. This potential for infection resides in the fact that the inoculum in BV or aerobic vaginitis is extremely high with pathogenic bacteria achieving a concentration ≥ 10^6 bacteria/mL of vaginal fluid.

Treatment for aerobic vaginitis has not been established. Again, a main factor in determining whether or not *Lactobacillus* is dominant is the vaginal pH. The pH of the vagina in patients with aerobic vaginitis is ≥ 5, similar to that seen in patients with BV. This creates an environment that is unfavorable to the growth of *Lactobacillus* and favorable to the growth of pathogenic bacteria. Since there are no studies to guide treatment regimens, the author will give his recommendations based on logic. The evaluation should begin with determining if the patient's vagina contains appropriate species of *Lactobacillus*, i.e., *L. crispatus, L. jensenii*, and/ or *L. gasseri*. If none of these species are present in the patient's vagina restoration of a healthy vaginal microbiota or a *Lactobacillus*-dominant microbiota will not be achieved. If the patient has one or more of these species of *Lactobacillus* present in the vagina, treatment can be instituted either with vaginal boric acid alone or in combination with an antibiotic such as oral first-generation cephalosporin (Box 60.3). Boric acid is administered intravaginally to lower the pH of the vagina and reduce or inhibit the growth of gram-positive and gram-negative pathogenic bacteria. First-generation cephalosporins have a broad spectrum of activity, being active against many gram-positive and gram-negative facultative anaerobic bacteria. Since there is a high concentration of pathogenic bacteria and an extremely low concentration of *Lactobacillus*, the pH of the vagina will be maintained in a range > 3.8 and < 4.5. In order for *Lactobacillus* to grow the pH must be < 4.5 and maintained long enough for *Lactobacillus* to gain a foothold and the growth of pathogenic bacteria to be suppressed. The patient should be re-evaluated within 2 to 3 weeks to determine if the vaginal microbiota has been restored to a *Lactobacillus*-dominant indigenous vaginal microflora.

TRICHOMONAS VAGINALIS VAGINITIS

Trichomonas vaginalis is a sexually transmitted flagellated protozoan that causes significant infection and is transmitted via sexual contact. Trichomoniasis can be symptomatic or asymptomatic and is frequently associated with other sexually transmitted infections

BOX 60.3

Treatment of aerobic vaginitis

Orally administer first-generation cephalosporin + intravaginal administered boric acid vaginal capsules (600 mg) twice a day for 14 days

(STIs). The clinical presentation can, initially, be mistaken as BV. The pelvic exam should be coupled with a microscopic examination of the vaginal discharge; if WBCs are present (>5 WBCs/40× magnification) and no flagellated protozoa are seen a specimen should be obtained either for culture or PCR analysis for the detection of *T. vaginalis*.

Trichomonas vaginitis typically presents with a copious discharge that is dirty gray to purulent, may or may not have a foul odor, and is often found coexisting with BV. If BV is initially the diagnosis and the microscopic examination reveals a typical picture of BV and WBCs are present, STIs such as *T. vaginalis*, *C. trachomatis*, or *N. gonorrhoeae* should be suspected. Approximately 25% of patients infected with *Trichomonas* have petechiae in the vaginal epithelium and or cervix. Microscopic analysis of the vaginal discharge reveals numerous WBCs, clue cells can be present if there is an overabundance of obligate anaerobic bacteria present, and the squamous epithelial cells are well estrogenized. If the clinical presentation is consistent with a possible *Trichomonas* infection but the protozoan is not identified a specimen should be sent for culture or PCR to determine whether or not the patient is infected with *T. vaginalis*. In general, if a patient has a vaginal discharge and complains of vaginal burning or itching or odor but no pathogen has been identified, a specimen should be submitted to the laboratory for the identification of *T. vaginalis* and *Candida*. US Food and Drug Administration (FDA)-approved tests for the identification of *T. vaginalis* are: OSOM Trichomonas Rapid Test (Genzyme Diagnostics, Cambridge Massachusetts), Affirm VP III (Becton Dickenson, San Jose California), Amplicor (Roche Diagnostic Corp.), APTIMA (ASR, Gen-Probe, Inc.).

The treatment of vaginal trichomoniasis is the administration of oral metronidazole (Box 60.4). Approximately 2% to 5% of the patients will be infected with a low-level resistant strain. Metronidazole intravaginal gel is less effective than orally administered metronidazole because it does not achieve adequate levels in the paravaginal and periurethral glands. It is estimated that metronidazole gel administered intravaginally is <50% effective.

BOX 60.4

Treatment for *Trichomonas vaginalis* vaginitis

Initial treatment

Metronidazole 2 g orally in a single dose[a], or
Metronidazole 500 mg orally twice daily × 7 days[b]

Treatment for failures or reinfection

Metronidazole 500 mg orally three times a day[b], or
Metronidazole 2 g orally daily for 7 days[a], or
Tinidazole 2 g orally in a single dose[a], or
Tinidazole 500 mg orally daily for 7 days[b], or
Tinidazole 2 g orally daily for 7 days[a]

[a] CDC MMWR Sexually Transmitted Diseases Treatment Guidelines, 2010

[b] Author's recommendations to tinidazole consultation can be obtained and susceptibility testing of *T. vaginalis* isolates can be performed by the CDC (telephone 404–718–4141; http://www.cdc.gov/std).

There is also a significant rate of reinfection; in one study 17% of treated patients were found to be reinfected. Therefore, the patient's sexual partner should be treated whether or not the partner is symptomatic. The patient should be evaluated within 2 weeks of completing therapy and probably 3 months after the completion of therapy. The patient and her sexual partner should be treated simultaneously and condoms should be used during sexual intercourse and until the first follow-up examination. This will permit evaluation and reduce the chance of reinfection during this initial management of the female patient with vaginal *Trichomonas* infection. A patient suspected of having a resistant strain can be treated by increasing the dose of metronidazole or tinidazole (Box 60.4). Strains of *T. vaginalis* that have low-level resistance tend to respond to tinidazole.

VULVOVAGINAL CANDIDIASIS (VVC)

Vulvovaginal candidiasis (VVC) is a complex condition because approximately 20% of healthy, asymptomatic women have *Candida* as part of their indigenous vaginal microbiota. Therefore, the question that arises when treating women with symptomatic vulvovaginitis is can complete eradication of the yeast be achieved or should complete eradication be a realistic goal? Approximately 75% of women will experience at least one episode of VVC in their lifetime and 40% to 45% will experience two or more episodes in their lifetime. Approximately 10% to 20% will develop complicated VVC and require a detailed evaluation, and 5% will develop chronic or recurrent VVC.

The patient with VVC presents with pruritus of the vulva, external dysuria, pain, swelling of the vulva, and erythema. Signs of VVC are vulva edema, fissures, excoriations, and a vaginal discharge that is white with a consistency that ranges from liquid to pasty; the latter is often described as "cottage cheese-like." Although these signs and symptoms are highly indicative of the presence of VVC other conditions can present with similar signs and symptoms. The diagnosis can be established by performing a microscopic examination (wet prep) of the vaginal discharge and by mixing a second aliquot of the vaginal discharge with a drop or two of 10% potassium hydroxide (KOH). A wet prep must be examined microscopically (best under 40× magnification) to determine that there are no abnormalities of the vaginal discharge. Mixing 10% KOH with vaginal discharge will dissolve all constituents in the discharge except hyphae. Fungal hyphae contain chitin and chitin is resistant to strong alkali. The microscopic appearance of yeast cells are elliptical or pear-shaped cells; some of these yeast cells will have a short hypha projecting from one end of the cell (germ tube), or there will be long branching filaments (hyphae). Determining the vaginal pH can be useful, although a particular pH is not associated with VVC; however, a pH <5 is more commonly associated with VVC than a pH >5. However, candidiasis can also be present in patients with BV, aerobic vaginitis, and trichomoniasis. A patient presenting with clinical symptoms and signs of VVC, a pH <4.5, but for whom the microscopic examination of the vaginal discharge does not reveal candidiasis should have a specimen submitted for culture of yeast,

as should the patient whose wet prep reveals the present of yeast. The yeast should be identified to species because non-albicans species tend to be resistant to the usual antimycotic agents, both prescription and over-the-counter antifungal agents. Patients treated for VVC should be re-evaluated within 2 to 3 weeks following treatment to determine if the patient's signs and symptoms have resolved (clinical cure). If the patient's signs and symptoms have resolved, microscopic examination of the vaginal discharge is not necessary. It is important to remember that 10% to 20% of healthy asymptomatic women harbor *Candida*; because of this it is not possible to eradicate yeast from the vaginal microbiota in all patients. Therefore, isolation and culture of yeast from the vagina is used to determine the species of *Candida* found in the patient's vagina for purposes for enhancing treatment.

Microscopic examination of the vaginal discharge revealing hyphae does not establish the species of *Candida* but can differentiate between the hyphae-producing species of *Candida* and *Candida glabrata*. The latter species does not produce hyphae and presents as budding yeasts. *C. glabrata* is resistant to prescription and over-the-counter antimycotic agents. Treatment of *C. glabrata* can be attempted with standard antimycotic agents but the duration of treatment should be extended to 14 days. Standard treatments for *Candida albicans* range from a single dose to 7-day dosing (Box 60.5). If standard treatment fails to resolve VVC consider that the species is other than *C. albicans*. If the patient was compliant in administering intravaginal medication or taking a complete course of oral medication, the yeast should be isolated, identified to species and if a species other than *C. albicans* is present, alternative treatment should be administered (Box 60.5). If treatment with the typical prescription and over-the-counter antimycotic agents using prolonged dosing (14 days) fails, non-fluconazole azole drugs can be administered, e.g., boric acid gelatin capsules (600 mg) administered intravaginally daily for 2 weeks. The patient's vagina can be painted with gentian violet dye, weekly until the patient's symptoms have resolved. Another approach is to administer amphotericin B (10%) vaginal suppositories twice daily for 10 days. Patients with recurrent VVC should be screened for diabetes and HIV.

BOX 60.5

Treatment regimens for VVC

Prescription agents

Butoconazole 2% cream 5 g in a single dose intravaginal × 1 dose
Nystatin 100 000 unit vaginal tablet intravaginal, daily for 14 days
Terconazole 0.4% cream 5 g intravaginal for 7 days
Terconazole 0.8% cream 5 g intravaginal for 3 days
Terconazole 80 mg vaginal suppository daily for 3 days

Oral agents

Fluconazole 100 mg tablet administered in a single dose

Over-the-counter agents

Butoconazole 2% cream 5 g intravaginal for 3 days
Clotrimazole 1% cream 5 g intravaginal for 7–14 days
Clotrimazole 2% cream 5 g intravaginal for 3 days
Miconazole:
2% cream 5 g intravaginal for 7 days
4% cream 5 g intravaginal for 3 days
100 mg vaginal suppository daily for 7 days
200 mg vaginal suppository daily for 3 days
1200 mg vaginal suppository daily for 1 day
Tioconazole 6.5% ointment 5 g intravaginally in a single application

CDC Sexually Transmitted Diseases Treatment Guidelines 2010.

CERVICITIS

Cervicitis is not a simple condition but can be a rather complex condition that can be difficult to resolve. It is now known that some bacteria are capable of forming a biofilm on tissue, e.g., *N. gonorrhoeae* and *G. vaginalis*. The two most common causes of cervicitis are due to *C. trachomatis* and *N. gonorrhoeae*. One significant problem is treating the patient with cervicitis not due *to C. trachomatis* and *N. gonorrhoeae* because the etiology is often not known. Therefore, when a patient treated for cervicitis not caused by *C. trachomatis* or *N. gonorrhoeae* fails to achieve resolution the condition becomes chronic, and more invasive treatments are undertaken, e.g., cryosurgery or laser ablation. Other bacteria that may cause cervicitis are those bacteria associated with BV, e.g., *G. vaginalis* and *Mycoplasma genitalium*.

A biofilm is a complex matrix produced by bacteria and can contain a variety of bacteria. Biofilms have been associated with several recalcitrant infections involving *E. coli*, *Helicobacter pylori*, and *Pseudomonas aeruginosa*. Recently, *G. vaginalis* and *Atopobium vaginae*, two bacteria commonly associated with BV, have been shown to form a biofilm on the vaginal epithelium of women with BV. This finding could be significant in understanding why some patients with BV fail to respond to treatment and why some patients develop persistent cervicitis, even after cryosurgery or laser ablation. The matrix of biofilms forms a protective covering for the bacteria that dwell within the matrix so that antibiotics, WBCs, immunoglobulin, and antibodies are unable to penetrate the matrix and reach the bacteria.

Diagnosis

The diagnosis of cervicitis is based on the following findings:

1. Purulent or mucopurulent endocervical discharge, bleeding easily induced by gentle palpation of the endocervical epithelium with a cotton-tipped applicator
2. Cervical bleeding associated with sexual intercourse
3. Hypertrophy of the endocervical columnar epithelium associated with detectable or undetectable infection.

The diagnosis of cervicitis is often overlooked because it may be subtle. One indicator of cervicitis is the presence of > 10 WBC/40× magnification in the absence of *T. vaginalis* vaginitis. An endocervical specimen should be obtained and submitted for the

detection of *C. trachomatis* and *N. gonorrhoeae*. Specific tests for *M. genitalium, Ureaplasma urealyticum*, and *Ureaplasma parvum* are not commercially available. Patients found to have chronic cervicitis should also be evaluated for upper genital tract infection, i.e., endometritis and salpingitis. HSV can cause cervicitis but often it is not clinically apparent. In patients with cervicitis and risky sexual practices the workup should include testing for *C. trachomatis, N. gonorrhoeae*, and HSV. The data supporting testing for herpes simplex as a cause for cervicitis are not available but (author's opinion) the workup should include all three microorganisms. Patients known to have contracted genital HSV, even though they do not have an acute outbreak, could be shedding virus asymptomatically and, therefore, an endocervical specimen submitted for HSV detection could be positive and responsible for chronic cervicitis.

Treatment

The treatment of cervicitis due to *C. trachomatis, N. gonorrhoeae*, and *H. simplex* requires two different approaches. *C. trachomatis* and *N. gonorrhoeae* are bacteria and can be treated with antibiotics. If either or both these bacteria are documented as the etiology of the patient's cervicitis, then the patient's sexual partner should be treated at the same time. The patient should be re-evaluated for bacteriologic eradication following treatment. Treatment of HSV does not result in eradication of the virus but can suppress the virus and result in resolution of the cervicitis. The sexual partner of a patient who has been found to be positive for HSV should be evaluated for acute HSV infection. If the sexual partner does not have evidence for present or past HSV infection, antiviral suppressive therapy should be administered to the patient that has a documented HSV infection. If treatment is initiated prior to having laboratory confirmation of the specific etiology, treatment should be instituted against *C. trachomatis* and *N. gonorrhoeae* (Box 60.6). It is preferred to initiate treatment when the tests for *C. trachomatis* and *N. gonorrhoeae* have confirmed the presence of these two sexually transmitted diseases (STDs). Treating the patient based on clinical findings will prevent spread of the infection to the sexual partner or partners. The patient should be advised to refrain from sexual contact until the tests results are known. If either *C. trachomatis* or *N. gonorrhoeae* or both has been detected the patient should be notified and advised that her sexual partner or partners should be informed and treated.

Quinolone resistance among *N. gonorrhoeae* strains is widely disseminated throughout the United States. Therefore in 2007, the Centers for Disease Control and Prevention (CDC) recommended that quinolones not be used to treat *N. gonorrhoeae* infections. Resistance develops rapidly to macrolides and therefore these agents should not be used empirically for the treatment of gonococcal cervicitis. Patients treated with quinolones or doxycycline or azithromycin should have: (1) confirmation of the presence of *C. trachomatis* and/ or *N. gonorrhoeae*, (2) isolates of *N. gonorrhoeae* tested for resistance against cephalosporins, especially ceftriaxone and cefepime, doxycycline, levofloxacin, ofloxacin, and azithromycin. Resistance to cephalosporins has been rare in the United States but has been reported in Asia. The CDC reported that between 1987 and 2008 only four isolates have been resistant to ceftriaxone and 48 isolates have been found to have decreased susceptibility to cefepime. Therefore, patients treated for known gonococcal cervicitis should be asked about travel to the Middle East and Hawaii. They should also be queried about the travel of their sexual contact(s).

BOX 60.6

Treatment for cervicitis

C. trachomatis
- Azithromycin 1 g orally in a single dose, or
- Doxycycline 100 mg twice a day orally for 7 days, or
- Erythromycin base 500 mg orally four times a day for 7 days, or
- Erythromycin ethylsuccinate 800 mg four times a day for 7 days, or
- Levofloxacin 500 mg orally once a day for 7 days, or
- Ofloxacin 300 mg orally twice a day for 7 days

N. gonorrhoeae
- Ceftriaxone 250 mg IM in a single dose, or
- Cefixime 400 mg orally in a single dose, or
- Azithromycin 1 g orally in a single dose, or
- Doxycycline 100 mg orally twice a day for 7 days

CDC Sexually Transmitted Diseases Treatment Guidelines 2010.

Follow-up

The CDC does not recommend follow-up test of cure for those patients treated with the recommended antibiotic regimens, except if the patient is pregnant. However, the author recommends that the patient indeed have follow-up and test-of-cure testing if the patient has one or more of the following:

1. an STD infection in the past,
2. a sexual partner who has had a previous STD,
3. multiple sexual partners, and
4. has not received ceftriaxone as part of the treatment regimen.

Since most recurrent infections occur secondary to reinfection, a detailed sexual history should be obtained to determine the risk of sexual behavior. In addition, patients found to have one or more STDs should be screened for syphilis, HIV, HSV, HPV, and hepatitis B and C.

SUMMARY

Patients with vaginitis should be evaluated for cervicitis. The presence of >5 WBCs/40× magnification in the vaginal discharge and the absence of a pathogen, e.g., *T. vaginalis*, suggests the presence of cervicitis. Cervicitis can be caused by a variety of microorganisms

and some, such as *N. gonorrhoeae* and *G. vaginalis*, can produce a biofilm. The presence of a biofilm creates a problem for the physician treating the patient because the biofilm prevents antibiotics achieving adequate levels within the matrix to eradicate the bacteria. Biofilm typically contains more than one genus and this complicates the treatment of cervicitis. Clinical findings associated with cervicitis are hypertrophy of the endocervical columnar epithelium, which bleeds easily when touched, and the presence of endocervical mucopus. Inflammation of the cervix potentiates acquisition of STDs, especially HIV. Patients who have an STD, such as trichomoniasis, *C. trachomatis*, and *N. gonorrhoeae*, should have a complete evaluation for the possible existence of other STDs. In addition, the patient should be evaluated for HPV. Patients who are positive for the strains associated with cancer need to be educated about the potential for the development of cervical, vaginal, or vulva cancer. A plan of management should be presented to the patient, emphasizing prevention. Thus vaginitis and cervicitis are not minor conditions but can have far reaching effects on the patient's well being.

SUGGESTED READING

Aroutcheva AA, Simones JA, Behbakht K, Faro S. *Gardnerella vaginitis* isolated from patients with bacterial vaginosis and from patients with healthy vaginal ecosystems. *Clin Infect Dis*. 2001;33:1022–1027.

Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. *Sex Transm Dis*. 2002;29:497–502.

Mcclelland RS, Wang CC, Mandaliya K, et al. Treatment of cervicitis is associated with decreased cervical shedding of HIV-1. *AIDS*. 2001;15:105–110.

Ross JD, Jensen JS. *Mycoplasma genitalium* as a sexually transmitted infection: implications for screening, testing, and treatment. *Sex Trans Infect*. 2006;82:269–271.

Schwebke JR. Abnormal vaginal flora is a biologic risk factor for acquisition of HIV infection and sexually transmitted diseases. *J Infect Dis*. 2005;192:1315–1317.

Schwebke JR, Barrientes FJ. Prevalence of *Trichomonas vaginalis* isolates with resistance to metronidazole and tinidazole. *Antimicrob Agents Chemother* 2006;50:4209–4210.

Simones JA, Aroutcheva AA, Shoyy S, Faro S. s. *Infect Dis Obstet Gynecol*. 2001;9:41–45.

Wang SA, Lee MV, O'Conner N, et al. Multidrug-resistant *Neisseria gonorrhoeae* with decreased susceptibility to cefixime—Hawaii 2001. *Clin Infect Dis*. 2003;37: 849–852.

Whittington WL, Kent C, Kissinger P, et al. Determination of persistent and recurrent *Chlamydia trachomatis* infection in young women: results of a multicenter cohort study. *Sex Transm Dis*. 2001;28: 117–123.

Wiessenfeld HC, Hillier SL, Krohn MA, Landers DV, Sweet RL. Bacterial vaginosis is a strong predictor of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection. *Clin Infect Dis*. 2003;30: 685–694.

Workowski KA, Berman S; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1–110.

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Epididymo-orchitis

Rebecca Fallis and Daniel Mueller

Introduction

Infectious and inflammatory processes involving the contents of the scrotum can range from those that require acute surgical intervention to findings that are benign in nature. Epididymitis and orchitis are conditions that refer to inflammation of the epididymis and testicles, respectively. Since they are relatively uncommon, clinicians who are not urologists may be unfamiliar with these problems.

Anatomy and definition

The epididymis is a tightly coiled tube on the posterior aspect of each testis that connects the efferent duct to the vas deferens. The epididymis consists of three regions for sperm storage, maturation, and transportation: the head, body, and tail.

Epididymitis involves inflammation or infection of the epididymis and is usually accompanied by pain and swelling. Acute epididymitis is characterized by symptoms that last for <6 weeks. Chronic epididymitis involves symptoms persisting for 6 weeks or longer, and the symptoms may develop more gradually over time. Overall, epididymitis is the most common cause of intrascrotal inflammation.

Orchitis, or inflammation of the testes, is less common than epididymitis. It rarely occurs in isolation except in cases of viral disease. Infection of the epididymis can spread to the adjacent testis, making it difficult to distinguish the clinical entities. Thus, the term *epididymo-orchitis* is used in reference to these combined inflammatory processes of both the epididymis and testes.

Epidemiology

The true prevalence of epididymo-orchitis is unknown, but it is relatively uncommon compared to other urologic conditions. There are approximately 600,000 cases of epididymitis per year in the United States. Epididymitis accounted for 1 in 144 outpatient visits (0.69%) made by males aged 18 to 50 years in 2002 according to the most current published data report. A prospective Canadian study demonstrated that 0.9% of men who presented to outpatient urology clinics in 2004 had epididymitis, which was less common than prostatitis or interstitial cystitis.

In children aged 2 to 13 years, the annual incidence of acute epididymitis is approximately 1.2 per 1,000 with a mean age of 11 years. One-fourth of these boys will have recurrence within 5 years. In adult men, 43% of cases occur between 20 and 30 years of age. Other studies report variable mean ages, but the incidence of epididymitis tends to peak in younger sexually active men, with the majority of cases occurring between 20 and 39 years.

In a case series study, orchitis occurred in 58% of patients diagnosed with epididymitis. Orchitis in the absence of epididymitis is uncommon except in mumps orchitis. US mumps outbreaks in 2006 and 2009–2010 have produced rates of orchitis in postpubertal males ranging from 3.3% to 10%. In the United Kingdom, mumps in postpubertal males is associated with up to 40% incidence of orchitis. Unvaccinated men, as well as those who received a single dose of the vaccine, were at higher risk of developing orchitis as a complication of mumps.

Pathogenesis and risk factors

The exact pathogenesis of epididymo-orchitis has not been clearly elucidated, but it most often occurs as a result of bacterial infection. The infecting organisms may extend to the epididymis in a retrograde fashion when urethrovasal reflux is present. Hematogenous and lymphatic spread may also occur. In children, acute epididymitis is often related to a urinary tract infection or congenital anomaly such as vesicoureteral reflux. In men aged 18 to 35, it is most commonly caused by sexually transmitted infections. The bacteria are introduced during sexual intercourse and then migrate through the genitourinary tract to the epididymis. In older men, epididymitis may be related to urinary stasis from lower urinary tract obstruction in the setting of benign prostatic hyperplasia (BPH), prostate cancer, or urethral stricture.

Risk factors for epididymo-orchitis include a history of urinary tract infections, high-risk sexual activity, genitourinary anatomic abnormalities, urinary tract surgery or instrumentation, strenuous activity, cycling, and prolonged periods of sitting. Invasive urologic procedures have been associated with epididymitis at reported rates of approximately 1% to 2%. These procedures include prostate biopsy, transurethral resection, brachytherapy, laser prostatectomy, and radical prostatectomy. Other mechanical insults such as direct trauma or pressure (e.g., from bicycle riding) have been associated with epididymitis even after vasectomy. Vasectomy itself has been associated with persistent tenderness and a nodular presence in the scrotum—presumably the result of sperm extravasation known as a "sperm granuloma."

Etiology

Infectious

In boys below the age of sexual activity, the microbial flora of epididymitis is a mix of skin and urinary flora. Epididymitis may also be a part of postinfectious syndrome from *Mycoplasma pneumoniae,* enterovirus, or adenovirus in children. Among sexually active adolescents and men <35 years old, acute epididymitis is most commonly associated with a sexually transmitted infection caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. *Mycoplasma* and *Ureaplasma* are isolated more frequently in younger men with chlamydial epididymitis than in other infectious causes of epididymitis, although the role they play in acute epididymitis is unclear. Gram-negative enteric organisms tend to cause epididymitis in older men, although sexually transmitted infections are still common. Additionally, enteric bacteria should be considered in men who practice insertive anal sex.

Many other less common infectious causes of acute epididymitis have been reported (see Table 61.1). *Mycobacterium tuberculosis* (TB) is the most common cause of granulomatous epididymitis. Tuberculosis epididymitis is rare and difficult to diagnose, and it should be suspected in patients with an exposure to TB or who are at high risk for TB, as in HIV. Patients may present with painful or painless swelling, and there is usually bilateral involvement. Seeding of the epididymis may be due to hematogenous spread. Urinalysis usually shows sterile pyuria, but secondary bacterial infection may be present. Diagnosis is made via identification of *M. tuberculosis* from the urine. Since few organisms are present in the urine, direct smears are usually negative and sensitivity of cultures may be only 50%. The sensitivity of TB urinary polymerase chain reaction (PCR) has been reported as 84% to 97%.

BCG-induced tuberculous epididymitis, or *BCGitis*, is caused by therapy with Bacillus Calmette-Guérin used to treat bladder cancer. This attenuated strain of *Mycobacterium bovis* is instilled into the bladder to cause an inflammatory response against the tumor cells. In rare cases, it has been reported to cause granulomatous epididymo-orchitis. Patients develop necrotic areas in the epididymis that may spread to the testes, causing scrotal enlargement with or without pain. Ultrasound reveals a heterogeneous, hypoechoic appearance of the epididymis.

Brucellosis is another less common cause of granulomatous epididymo-orchitis. *Brucella* is endemic to the Mediterranean and Middle Eastern countries, and epididymo-orchitis can occur in 2% to 20% of patients with brucellosis. Patients may have a history of occupational contact with animals or consuming unpasteurized dairy products. Most patients have an acute febrile illness with the most common symptoms being unilateral scrotal pain and swelling. Leukocytosis is often absent, and urinalysis and culture are often normal. Blood cultures for *Brucella* are positive in about 50% of cases, and serologic testing may aid in the diagnosis.

In patients with HIV infection or transplant recipients receiving immunomodulating drugs, various fungal and opportunistic bacterial etiologies of epididymo-orchitis are more likely to occur than in those who are immunocompetent. These include candidiasis, histoplasmosis, blastomycosis, coccidiomycosis, actinomycosis, aspergillosis, nocardiosis, and listeriosis. In males with HIV, cytomegalovirus, salmonellosis, toxoplasmosis, *Ureaplasma urealyticum*, *Corynebacterium* spp., *Mycoplasma* spp., and *Mima polymorpha* have also been implicated. In HIV-infected individuals, syphilitic orchitis caused by the bacterium *Treponema pallidum* is a rare manifestation of gumma in tertiary syphilis. *Haemophilus influenza* type B has been reported as a cause of epididymo-orchitis in adults with HIV, as well as in the pediatric and elderly populations.

Orchitis most often occurs with epididymitis but can occur alone as well. Mumps, a paramyxovirus, is a well-known cause of orchitis. However, epididymitis may develop as a complication. Although the overall incidence of mumps orchitis has fallen dramatically with the widespread use of the MMR vaccine, there have been reported

TABLE 61.1 **CAUSES OF ACUTE EPIDIDYMO-ORCHITIS**

Cause	Organism/disease
Sexually acquired	
Major	*Chlamydia trachomatis*
	Neisseria gonorrhoeae
Other	*Ureaplasma urealyticum?*
	Mycoplasma genitalium
Associated with bacteriuria	
Major	*Escherichia coli*
	Proteus spp.
	Klebsiella pneumoniae
	Pseudomonas aeruginosa
	Enterococcus spp.
Other	*Haemophilus influenzae* type b
	Salmonella spp.
	Staphylococci
	Streptococci
Other infections	
Bacterial	*Mycobacterium tuberculosis*
	Brucella spp.
	Nocardia asteroides
	Actinomyces
	Listeria
Fungal	*Blastomyces dermatitidis*
	Histoplasma capsulatum
	Coccidioides immitis
	Candida albicans
	Candida glabrata
Viral	Mumps
	Mumps vaccine
	Cytomegalovirus (in HIV)
Parasitic	*Toxoplasma gondii*
	Schistosoma haematobium
	Wuchereria bancrofti filariasis
Noninfectious causes	
Drug	Amiodarone therapy
Vasculitis	Behçet's disease
	Polyarteritis nodosa
	IgA Vasculitis
	Granulomatosis with polyangiitis
Other	Sarcoidosis
	Primary autoimmune orchitis
Idiopathic	

outbreaks in the United Kingdom and United States since 2000. They often occurred in postpubertal men in high-density settings, such as college dorms and camps, where the virus can spread through direct contact and respiratory droplets. Postpubertal men with mumps can develop unilateral or bilateral orchitis with some degree of testicular atrophy from inflammation and edema. Vaccination remains the best means to prevent infection, although it is not 100% effective. Mumps orchitis is a self-limited disease and the treatment is supportive with bed rest, scrotal support, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Additional rare infectious causes of epididymo-orchitis and orchitis have been reported. Unusual causes of epididymo-orchitis include congenital syphilis, *Mycobacterium leprae* (Hansen's disease), coxsackievirus, group B arboviruses, varicella, and herpes simplex virus. In South India, epididymo-orchitis can be a rare manifestation of scrub typhus caused by the parasite *Orientia tsutsugamushi*. It was reported as the initial presentation in a 3-year-old boy with painful testicular swelling and fever. Powassan virus was found to be the cause of prodromal epididymo-orchitis in one patient before he presented with encephalitis. The patient was a 63-year-old male from Cape Cod, Massachusetts, who was receiving rituximab for follicular lymphoma.

Noninfectious

Although most cases of epididymo-orchitis are of an infectious etiology, several noninfectious causes have been described. Amiodarone-induced epididymitis is considered a diagnosis of exclusion and is usually reversible once the offending agent is removed. Epididymo-orchitis has been reported in patients with various vasculitides, including polyarteritis nodosa (PAN), Behçet's disease, immunoglobulin A (IgA) vasculitis (formerly Henoch–Schönlein purpura), and granulomatosis with polyangiitis (formerly Wegener's granulomatosis). Sarcoidosis can affect the genitourinary system in 5% of patients. Primary autoimmune orchitis is not associated with a known systemic autoimmune disease. It is characterized by antisperm antibodies directed either to the basement membrane or seminiferous tubules in infertile men. Finally, traumatic causes of epididymo-orchitis may also occur. The etiology of the remaining cases of acute epididymitis is "idiopathic," but advances in microbiology and molecular diagnostic techniques may elucidate specific causes in the future.

Clinical features and differential diagnosis

Acute epididymo-orchitis presents with testicular pain and scrotal edema which is usually unilateral and gradually progressive over several days. Fever, rigors, and leukocytosis may also be present. Urethritis or pyuria, in the absence of bacteriuria, is usually associated with sexually transmitted acute epididymitis. Bacteriuria and voiding symptoms such as dysuria, frequency, and urgency tend to be associated with urinary obstruction and/or structural urogenital disease in

older men. However, dysuria is not always present in these cases. In a retrospective study of 121 patients with acute epididymitis, dysuria was present in 33% of patients, urethral discharge was present in only 5%, and positive urine cultures were found in <25% of patients.

The acutely painful and swollen scrotum has a broad differential diagnosis. The differential diagnosis includes acute epididymo-orchitis, spermatic cord (testicular) torsion, torsion of the appendix testis, incarcerated inguinal hernia, acute hydrocele, thrombosed varicocele, Fournier's gangrene, testicular cancer, and trauma. Pain is not typical of hydroceles or varicoceles, and testicular malignancies can cause pain in about 15% of cases. Importantly, a physician must identify testicular torsion in a timely manner as this necessitates immediate surgical intervention. Testicular torsion cannot be excluded based on physical examination alone, but a high-riding testicle and the absence of a cremasteric reflex are suggestive of the diagnosis. The Prehn sign (i.e., relief of pain with elevation of the testes) suggests acute epididymitis but does not rule out testicular torsion.

Diagnostic workup

Evaluation of suspected epididymo-orchitis is initially based on clinical suspicion of disease from patient complaints of pain and/or swelling within the scrotum. The first challenge is ruling out testicular torsion. The distinction between torsion and inflammation or infection needs to be made quickly, particularly in prepubescent boys, because untreated torsion can jeopardize the testis. Expert urologic consultation may be urgently required. Color Doppler ultrasound showing an enlarged, thickened epididymis with normal to increased testicular blood flow is 70% sensitive and 88% specific for epididymitis. In testicular torsion, the ultrasound reveals a normal-appearing testicle with decreased blood flow and is 82% sensitive and 100% specific. Radionuclide scanning is a sensitive study for torsion, but it is not routinely available. C-reactive protein (CRP) may be helpful in distinguishing torsion versus infection as patients with epididymitis have elevated CRP (96% sensitive and 94% specific). Surgical exploration should not be delayed if the diagnosis remains unclear.

If torsion is not considered likely, the best initial diagnostic study is urine collection for urinalysis and culture. A first-void specimen should be collected if a sexually transmitted infection is thought to be the etiology, whereas a midstream specimen is recommended if the cause is more likely due to an enteric pathogen. If urethral secretions are present, Gram stain is highly sensitive and specific for diagnosing urethritis and can establish gonococcal infection by demonstrating leukocytes containing intracellular gram-negative diplococci. In the era of nucleic acid amplification testing (NAAT), the Gram stain sensitivity has been increased by lowering the diagnostic cutoff for urethritis from ≥5 to ≥2 leukocytes/oil-immersion field. All sexually active men should have NAAT for the detection of gonorrhea and/or chlamydia in a urine specimen. These tests are highly sensitive for *N. gonorrhoeae* and *C. trachomatis* and have largely supplanted urethral cultures to diagnose these infections.

In patients who do not respond to empiric therapy—particularly in those who have unique risk factors based on host immune status, travel history, or geographic location—a more exhaustive workup should be performed in conjunction with urologic consultation. This may include further imaging, additional cultures (e.g., acid-fast bacillus [AFB] and fungal cultures), and direct sampling of the epididymis in some cases.

Treatment

Treatment includes antimicrobial therapy in combination with analgesics, bed rest, and scrotal elevation. Empirical therapy should be initiated before laboratory results are available. Antibiotic choice and duration should be tailored to the specific pathogen if one is identified by culture. See Table 61.2 for empiric antibiotic therapy for acute epididymitis.

TABLE 61.2 **EMPIRIC ANTIBIOTIC THERAPY FOR ACUTE EPIDIDYMITIS**

Population	Most likely causative agent	Most likely causative agent
Children <2 years	Various	Antibiotic treatment for likely underlying enteric organism and referral to a urologist
Children 2–14 years of age	Various, likely anatomic	Treat based on urinalysis or urine culture results
Sexually active adults <35 years	Gonorrhea or chlamydia	Intramuscular ceftriaxone (single 250 mg dose) *and* Oral doxycycline (100 mg BID for 10 days)
Adults who practice insertive anal intercourse	Gonorrhea or chlamydia and an enteric organism	Intramuscular ceftriaxone (single 250 mg dose) *and* Oral levofloxacin (500 mg once daily for 10 days) *or* oral ofloxacin (300 mg BID for 10 days)
Adults >35 years or who have had recent urinary tract surgery or instrumentation	Enteric organism	Oral levofloxacin (500 mg once daily for 10 days) *or* oral ofloxacin (300 mg BID for 10 days)

In the 2015 update to the Sexually Transmitted Diseases (STD) Treatment Guidelines for "epididymitis," the Centers for Disease Control and Prevention (CDC) recommends dual therapy with intramuscular ceftriaxone 250 mg as a single dose plus doxycycline 100 mg orally twice a day for 10 days. In men who practice insertive anal sex, enteric organisms should also be covered. For these individuals, intramuscular ceftriaxone 250 mg single dose plus either oral levofloxacin 500 mg/d or oral ofloxacin 300 mg/d for 10 days should be given. In men >35 years, monotherapy with levofloxacin or ofloxacin alone for 10 days is usually sufficient since sexually transmitted infections are less likely. Fluoroquinolones have good oral bioavailability, spectrum of activity, and penetration of genitourinary tissues. Other agents active against uropathogens (e.g., trimethoprim-sulfamethoxazole, amoxicillin) can be tried in the event of fluoroquinolone failure or intolerance.

Sex partners of patients with epididymitis caused by *N. gonorrhoeae* or *C. trachomatis* who had contact within 60 days of symptoms should be referred for evaluation and treatment. It is also prudent to counsel patients that sexual intercourse should be avoided until they and their sex partners have completed therapy and are without symptoms, although the optimal duration of this period of abstinence has never been studied.

Even though pain may persist for several weeks, patients should respond clinically in the first few days of treatment. Failure to improve may indicate an underlying abscess, tumor, vasculitis, or infarction. It also may indicate a resistant organism or an uncommon fungal or mycobacterial pathogen. In children <14 years being treated for acute epididymitis, a urologist should be consulted to evaluate for potential anatomic abnormalities. Men >50 years should be evaluated for urinary tract obstruction from an enlarged prostate.

Conclusion

Epididymo-orchitis is fairly uncommon compared to other urologic conditions, but it is important for a physician to be able to recognize this clinical entity. The etiology is often infectious, and the likely causative organism may vary based on the patient's age and risk factors. Pure orchitis is usually viral and should be considered in any male with mumps. Once the diagnosis of testicular torsion has been ruled out, the management of epididymo-orchitis can begin with a limited set of diagnostic tests and an empiric trial of antibiotics. For patients with more complex or chronic disease, co-management with a urologist is recommended. In patients who do not respond to initial therapy, this could indicate an unusual infection or noninfectious cause, and further workup should be pursued.

Suggested reading

Akinci E, Bodur H, Cevik MA, et al. A complication of brucellosis: epididymoorchitis. *Int J Infect Dis*. 2006;10(2):171–177.

Barskey AE, Schulte C, Rosen JB, et al. Mumps outbreak in Orthodox Jewish communities in the United States. *N Engl J Med*. 2012;367(18):1704–1713.

Clemmons N, Hickman C, Lee A et al. Chapter 9: Mumps. Centers for Disease Control and Prevention. Manual for the surveillance of vaccine-preventable diseases. 2008. https://www.cdc.gov/vaccines/pubs/surv-manual/chpt09-mumps.pdf

Centers for Disease Control and prevention (CDC). Update: mumps outbreak: New York and New Jersey, June 2009–January 2010. *MMWR Morb Mortal Wkly Rep*. 2010;59(5):125–129.

Centers for Disease Control and Prevention (CDC). Update to CDC's sexually transmitted diseases treatment guidelines, 2015. *Recomm Rep*. 2015;64(RR3):1–137.

Luzzi GA, O'Brien TS. Acute epididymitis. *BJU Int*. 2001;87:747–755.

Liu HY, Fu YT, Wu CJ, et al. Tuberculous epididymitis: A case report and literature review. *Asian J Androl*. 2005;7(3):329–332.

Masarani M, Wazait H, Dinneen M. Mumps orchitis. *J R Soc Med*. 2006;99(11):573–575.

McConaghy JR, Panchal B. Epididymitis: An overview. *Am Fam Physician*. 2016;94(9):723–726.

Nickel JC, Teichman JMH, Gregoire M, et al. Prevalence, diagnosis, characterization, and treatment of prostatitis, interstitial cystitis, and epididymitis in outpatient urological practice: The Canadian PIE study. *Urology*. 2005;66:935–940.

Rosenstein D, McAninch JW. Urologic emergencies. *Med Clin North Am*. 2004;88:495–518.

Saha A, Sarkar S, Patil A, et al. Epididymo-orchitis in scrub typhus. *Indian J Pediatr*. 2018;85(11):1035–1036.

Solomon IH, Spera KM, Ryan SL, et al. Fatal Powassan encephalitis (deer tick virus, lineage II) in a patient with fever and orchitis receiving rituximab. *JAMA Neurol*. 2018;75:746–750.

Taylor SN. Epididymitis. *Clin Infect Dis*. 2015;61(Suppl 8):S770–773.

Tracy CR, Steers WD, Costabile R. Diagnosis and management of epididymitis. *Urol Clin North Am*. 2008;35(1):101–108; vii.

62

Genital ulcer adenopathy syndrome

Allan Ronald

The control and prevention of genital ulcer disease (GUD) is an important public health priority. Ulcerative lesions may produce local genital pain, some pathogens are transmitted from mothers to their infants, and genital lesions increase the risk of HIV acquisition and transmission following sexual intercourse. Box 62.1 lists the infectious and noninfectious etiologies that may produce genital ulcerations with or without adenopathy. The most commonly transmitted GUD diagnosis and etiologies are syphilis (*Treponema pallidum*), herpes simplex (HSV-1 and-2), chancroid (*Haemophilus ducreyi*), lymphogranuloma venereum (LGV; L1, L2, and L3 serovars of *Chlamydia trachomatis*), and granuloma inguinale or donovanosis (*Calymmatobacterium granulomatis*). Trauma, erosive balanitis, and fixed drug eruptions are common nontransmissible causes of GUD. Fungal and mycobacterial infections, as well as tumors if suspected, should be excluded by biopsy. Because of the limitations of diagnostic tests, a specific etiology is obtained in only 50% to 80% of patients.

Major geographic variation exists in the etiology and prevalence of GUD (Table 62.1). In Europe and North America, about 5% of patients who present to sexually transmitted disease (STD) clinics have a genital ulcer compared with 10% to 30% presenting to similar clinics in Africa and Asia. HSV is the most common cause of genital ulcerations in Europe and North America; syphilis and chancroid have been more common cause elsewhere. However, herpetic ulcers are now more common in most settings, particularly in patients coinfected with HIV, whereas chancroid has largely disappeared. LGV is endemic regionally in the tropics and has reappeared in developed countries as an epidemic among men who have sex with men (MSM), many of whom are HIV-positive. Donovanosis was endemic in New Guinea, India, and Southern Africa but is now rare. Syphilis persists as a global pandemic that has recently reappeared with large outbreaks among MSM. Males who are circumcised have a markedly reduced probability of acquiring chancroid and, to a lesser extent, of acquiring herpes or syphilis following heterosexual intercourse. Circumcision also reduces human papilloma virus infections as well as penile neoplasms.

Clinical presentations

Clinical features of GUD are listed in Table 62.2. The incubation period is usually <1 week for genital herpes and chancroid, 1 to 3 weeks for LGV, and 2 to 6 weeks for syphilis and donovanosis. Depending on the etiology, the initial lesion can be a papule, pustule, or vesicle which erodes to form an ulcer. In men the ulcers are often located on the coronal sulcus but may also be found on the glans, prepuce, and shaft of the penis or, less often, on the scrotum or surrounding skin. Herpes and chancroid have a predilection for involving the frenulum. In women, the ulcers may occur on the labia, in the vagina, on the cervix, on the fourchette, or on the perianal area. Perianal and intrarectal ulcers are common among MSM.

BOX 62.1

Etiologies of genital ulcer disease

Infectious

Bacterial

- *Haemophilus ducreyi* (chancroid)
- *Treponema pallidum* (syphilis)
- *Chlamydia trachomatis* (lymphogranuloma venereum)
- *Calymmatobacterium granulomatis* (donovanosis)
- Balanitis (often polymicrobial but *Candida albicans* is often present)

Viral

- Herpes simplex
- Varicella zoster[a]
- Epstein–Barr virus
- Cytomegalovirus[a]

Parasitic

- *Sarcoptes scabiei*[a]
- *Phthirus pubis*[a]
- *Entamoeba histolytica*[a]
- *Trichomonas vaginalis*[a]

Noninfectious

- Trauma
- Fixed drug eruptions
- Pyoderma gangrenosum[a]
- Behçet's disease[a]
- Reiter's syndrome[a]
- Wegener's granulomatosis[a]
- Neoplasms[a]
- Unknown

[a] Unusual.

Genital herpes

HSV-1 is transmitted primarily by oral contact. In the developing world, the initial infection commonly occurs in infancy, and genital HSV-1 infections are less common. However, in the industrialized world most adolescents have not acquired HSV-1, and this virus is frequently transmitted through oral–genital sex. In all societies, HSV-2 is almost always transmitted by sex. Genital herpes due to both viruses presents as painful multiple, small vesicles that rapidly become superficial ulcers with erythematous margins. Urethral, gynecologic, or cutaneous symptoms may predominate depending on the site of vesicles. Systemic symptoms of fever, myalgias, and headache can occur with an initial infection. A prodrome of paresthesias 12 to 48 hours before the appearance of vesicles is often reported with each recurrence. Painful lymphadenopathy can be present. Following the initial infection, both HSV-1 and HSV-2 remain latent in the sensory ganglion but recur unpredictably. These are usually less severe. However, they tend to be severe and persistent in HIV-infected individuals. Large, painful, often single ulcers occur commonly, particularly in the perianal area.

TABLE 62.1 **GEOGRAPHIC VARIATION IN THE PREVALENCE OF GENITAL ULCER DISEASES IN CLINICS FOR SEXUALLY TRANSMITTED INFECTIONS**

	Southeast Asia/India	Africa	North America/ Europe
Chancroid	+/–	+/–	+/–
Syphilis	+++	+++	+++
Genital herpes	++++	++++	++++
Lymphogranuloma venereum	+	+	+
Donovanosis	+/–	+/–	+/–

Syphilis

The classical ulcer of primary syphilis is solitary, painless, and minimally tender with elevated, well-demarcated margins and an indurated nonpurulent base. Multiple ulcers occur more commonly in women. Lymphadenopathy, if present, is usually bilateral with firm, nontender nodes. All pregnant women should be screened for syphilis as well as HIV at their first prenatal visit. Secondary syphilis can have many cutaneous features, including condyloma and superficial ulcers which often occur in the genital area.

Chancroid

Chancroid typically produces painful, excavated ulcers with irregular, undetermined margins and a purulent base (Figure 62.1). The ulcers can be superficial and may resemble herpetic ulcers. Approximately 50% of the patients will develop painful inguinal lymphadenopathy, which can be unilateral. Lymph nodes may become fluctuant (buboes) and rupture. Untreated ulcers may persist for months and heal with scarring.

An epidemic in children of painful chronic cutaneous lower limb ulcers due to *H. ducreyi* is unfolding in the South Pacific, including Papua New Guinea. It has been described as well in Ghana, West Africa. The *H. ducreyi* isolates appear to be genetically identical to the species that causes chancroid. The epidemiology of its transmission is unknown. Sexual abuse and poor hygiene are possible factors. Clinically it can be confused with yaws and the Buruli ulcer due *Mycobacterium ulcerans*. The *H. ducreyi* ulcers can persist for months unless treated. The macrolides appear to be usually curative. Further information on this emerging "new" illness and strategies for its control and eradication are urgently needed.

Lymphogranuloma venereum

The ulcer of LGV is transient, usually superficial and painless. It precedes the development of inguinal lymphadenopathy by 7 to 30 days, and fewer than a third of the patients recall having had an ulcer. The lymph nodes are tender and may become fluctuant with eventual rupture and formation of draining sinuses. A "groove" sign may be present if nodes above and below Poupart's ligament are involved. Women and homosexual men may have involvement of perianal and perirectal tissues and present with proctitis. Complications

TABLE 62.2 **CLINICAL CHARACTERISTICS OF GENITAL ULCER ADENOPATHY SYNDROMES**

	Syphilis	Herpes simplex virus	Chancroid	Lymphogranuloma venereum	Donovanosis
Incubation period	9–90 d	2–7 d	1–14 d	7–21 d	8–80 d
Primary lesion	Papule	Vesicle	Papule or pustule	Papule, pustule, or vesicle	Papule
Number of lesions	Usually solitary	Multiple	Multiple	Usually solitary	Variable
Classical ulcer characteristics					
Size (mm)	5–15	1–10	2–20	2–10	Variable
Margins	Well demarcated Elevated Round or oval	Erythematous	Ragged, irregular Undetermined	Elevated Round or oval	Variable Elevated, irregular
Depth	Superficial or deep	Superficial	Excavated	Superficial or deep	Elevated
Base	Red, smooth, nonpurulent	Red, smooth, serous discharge	Purulent exudate	Variable	"Beefy" red, rough
Induration	++	–	–	–	++
Pain	–	++	++	±	+
Lymphadenopathy	++[B]	++[B]	++[U]	++[U]	–[P]
Characteristics of lymphadenopathy					
Consistency	Firm	Firm	Fluctuant	Fluctuant	–
Tenderness	–	++	++	++	–

[B] Bilateral;[U] unilateral;[P] pseudolymphadenopathy.

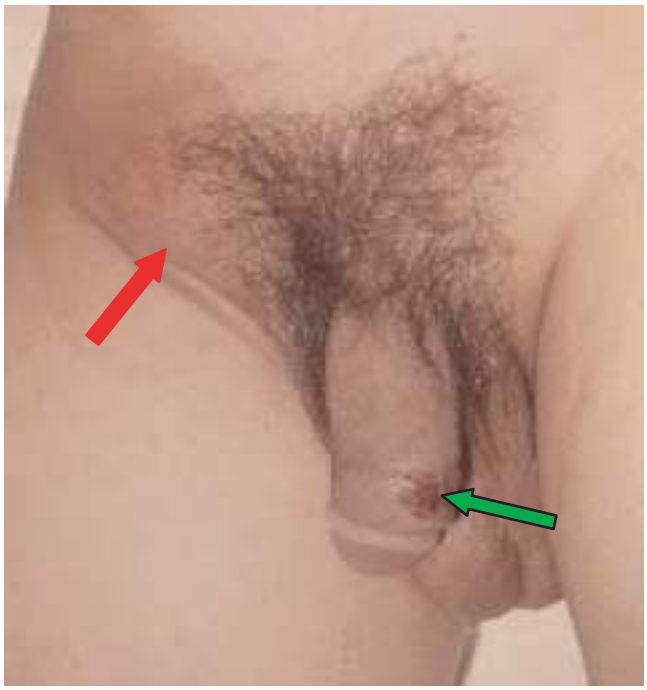

FIGURE 62.1 Chancroid; note penile lesion (*green arrow*) and inguinal adenopathy (*red arrow*).
Public Health Image Library; content provider CDC/Susan Lindsley.

of untreated infection include genital elephantiasis, rectal strictures, and perianal fistulas. Other manifestations include meningoencephalitis, hepatitis, erythema nodosum, and erythema multiforme.

Donovanosis

Patients present with a slowly progressive, painless ulceration of the genital area characterized by heaped-up granulomatous tissue. Local extension, healing, and fibrosis may occur simultaneously. Lymphadenopathy is unusual, but "pseudo buboes" caused by subcutaneous extension of the granulomatous process into the inguinal area are common. Systemic spread with involvement of liver, thorax, and bones has been reported but is rare.

Laboratory diagnosis of GUD

Clinical diagnosis of GUD is imprecise because of overlap between the clinical syndromes, the presence of mixed infections, and atypical presentations. Because of these limitations, the diagnosis must be confirmed whenever possible using the relevant laboratory tests (Table 62.3). Specimens should be collected for *H. ducreyi, C. trachomatis*, and herpes simplex cultures and, if available, DNA identification with polymerase chain reaction (PCR). If possible, a dark-field examination should be performed in all patients

TABLE 62.3 **RECOMMENDED TESTS FOR DIAGNOSING GENITAL ULCER DISEASES**

	Recommended tests	Other tests
Chancroid	Culture	Gram stain/PCR
Syphilis	Dark-field examination	PCR
	Direct fluorescent antibody test	
	Serology (e.g., RPR/VDRL, FTA- ABS, MHA-TP)	
Genital herpes	Viral culture	Antigen detection (ELISA), PCR, Serology
Lymphogranuloma venereum	PCR	*Chlamydia* culture
		Serology (complement fixation, microimmunofluorescence)
Donovanosis	Giemsa or Wright stains of tissue smears Histopathology	

Abbreviations: PCR = polymerase chain reaction; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratories; FTA-ABS = fluorescent treponemal antibody absorption; MHA-TP = microhemagglutination test for *Treponema pallidum*; ELISA = enzyme-linked immunosorbent assay.

presenting with GUD unless classical vesical lesions in clusters provide definite evidence of herpes genitalis. The ulcer base is washed with saline, dried with a cotton gauze, and squeezed between the thumb and forefinger until an exudate appears. This can be collected directly onto a coverslip for dark-field microscopy. Vesicles and pustules should be aspirated with a fine-gauge needle or de-roofed and swabbed for viral culture. Fluctuant lymph nodes should be aspirated for *H. ducreyi* and *C. trachomatis* culture. Both *Treponema pallidum* particle agglutination (TPPA) and non-treponemal rapid plasma reagin (RPR), serologic tests should be obtained in all patients with GUD to exclude syphilis. LGV diagnosis is confirmed by PCR or by rising antibody titers or a single titer of 1:64 by complement fixation or 1:512 by microimmunofluorescence.

Approach to the patient with GUD

An algorithm for investigating a patient with genital ulceration is given in Figure 62.2. The history is crucial. Information should be collected about sexual risks, demographics, medication, and travel. Risk factors such as sex work or recent prostitute contact are associated with syphilis and classical chancroid. Travel may suggest the diagnosis of an otherwise uncommon diagnosis such as donovanosis. Self-medication with topical or systemic antibiotics may lead to a false-negative dark-field examination or culture.

Treatment

The drug regimens currently recommended for treating GUD are given in Table 62.4. Treatment traditionally has been initiated only once a laboratory diagnosis has been established; however, the delay inherent in obtaining laboratory results makes it necessary to initiate empiric syndromic therapy at the time of the initial visit. The selected syndromic therapy should be effective for syphilis. Fluctuant buboes should be incised or aspirated. All patients with GUD should be tested for HIV infection.

Patients should be reassessed at 7 days to assess response to therapy. Most patients will show improvement; failure of the lesions to respond should prompt a search for an alternative diagnosis. The RPR as well as a treponemal test should be repeated in all patients. Serology can be negative in 30% of patients at first presentation with primary syphilis.

Syphilis

A single intramuscular (IM) injection of benzathine penicillin G, 2.4 million U, is the treatment of choice for both HIV-infected and -uninfected patients with primary or secondary syphilis. Doxycycline or tetracycline for 14 days can be used in patients with a documented penicillin allergy. Azithromycin resistance is now widespread, and the macrolides are no longer recommended. All patients should be followed with a quantitative RPR or VDRL at 3, 6, 12, and 24 months after treatment. Treatment failure is diagnosed if clinical signs persist or recur, a sustained fourfold rise in titer occurs, or an initially high titer (>1/8) fails to decline by at least fourfold at 6 months. Patients who fail treatment as determined by these criteria should undergo a lumbar puncture. If the cerebrospinal fluid (CSF) is normal, they should be treated with benzathine penicillin G, 2.4 million U IM weekly for 3 weeks. Patients with CSF abnormalities should be treated for neurosyphilis. Because tetracyclines are contraindicated in pregnancy, pregnant patients with a proven penicillin allergy must be desensitized and treated with penicillin. All persons who had sexual contact during the preceding 90 days should be treated and followed with serology.

Chancroid

Trimethoprim-sulfamethoxazole (TMP-SMX) is no longer recommended for the treatment of chancroid because *H. ducreyi* is generally resistant. Erythromycin, 250 mg three times daily for 7

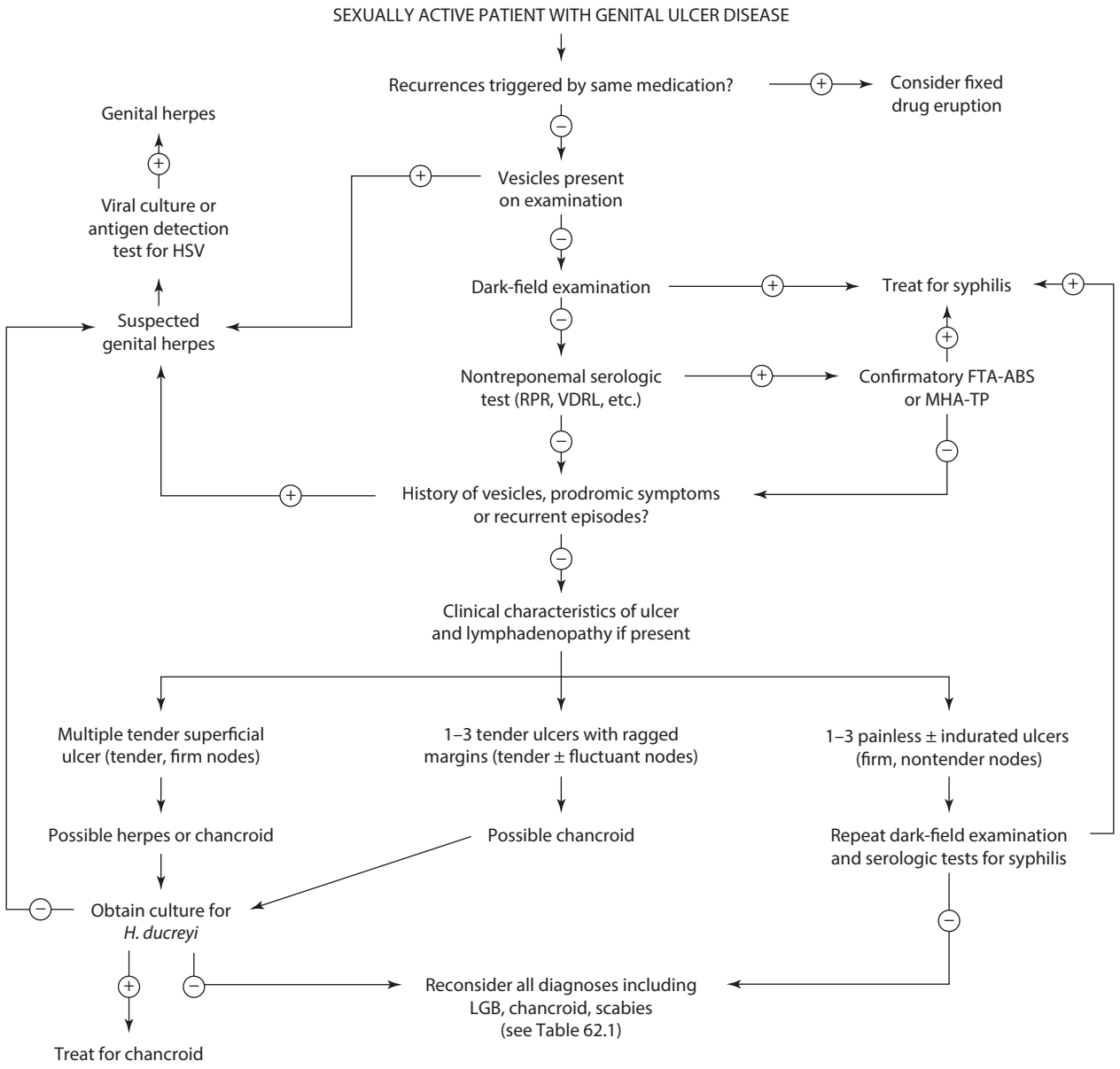

FIGURE 62.2 Diagnostic algorithm for patients with genital ulcer disease.

days, is effective in both HIV-infected and -uninfected patients. A single dose of azithromycin, 2 g or ciprofloxacin, 500 mg, is also effective, with cure rates of >95%. All chancroid patients with initially negative serologies for HIV and syphilis should have these tests repeated at 3 months. All persons who had sexual contact with the patient in the preceding 4 weeks should be treated regardless of evidence of infection.

Lymphogranuloma venereum

Doxycycline for 21 days is the treatment of choice for LGV, but treatment failures may occur, especially in the presence of proctitis, and repeated longer courses of 6 weeks should be prescribed. Pregnant patients should be treated with erythromycin. All sexual contacts within the past 4 weeks should be investigated for rectal, urethral, or cervical chlamydial infection and treated regardless of laboratory confirmation.

Donovanosis

Doxycycline (usually a 2-week course) remains the treatment of choice for donovanosis, although treatment failures occur and require a 4- to 6-week course. When doxycycline therapy fails, patients can be treated with TMP-SMX or ciprofloxacin.

Genital herpes

Acyclovir, valacyclovir, or famciclovir should be used to treat the initial clinical episode of genital herpes, and intravenous acyclovir therapy may be required in severe cases. Prophylaxis is indicated for patients with

TABLE 62.4 **TREATMENT REGIMENS FOR INFECTIOUS CAUSES OF THE GENITAL ULCER ADENOPATHY SYNDROME**

Disease	Recommended regimen	Alternative regimens	Comments
Primary syphilis	Benzathine penicillin G (2.4 million U IM)	Doxycycline (100 mg PO BID × 14 days) or Tetracycline (500 mg PO QID × 14 days)	The Jarisch–Herxheimer (J-H) reaction (acute onset of fever accompanied by headache, myalgia, malaise, nausea, and tachycardia) may occur 2–24 h after initiating therapy for syphilis. Although the J-H reaction may produce fetal distress or premature labor in a pregnant woman, this is not an indication to delay therapy
Chancroid	Erythromycin (250 mg PO QID × 7 days) Erythromycin (500 mg PO QID × 7 days)	Azithromycin (1 g PO × 1 dose) or Ciprofloxacin (500 mg PO × 1 dose) or Amoxicillin-clavulanic acid (500/125 mg PO TID × 7 days)	Single-dose regimens are contraindicated in HIV-seropositive patients because of unexpectedly high failure rates
Lymphogranuloma venereum	Doxycycline (100 mg PO BID × 21 days)	Erythromycin (500 mg PO QID × 21 days) or Sulfisoxazole (500 mg PO QID × 21 days)	Contacts may require treatment
Donovanosis	Doxycycline (100 mg PO BID)	TMP–SMX (160/800 mg PO BID) Ciprofloxacin (500 mg PO BID) Tetracycline (500 mg PO QID)	Treat until all lesions are healed (may take up to 4 wk)
Genital herpes (primary)	Acyclovir (200 mg PO 5 × daily × 10 days) Famciclovir (250 mg PO TID × 5–10 days) Valacyclovir (1 g PO BID × 5–10 days)		Recurrences require treatment only if severe

Abbreviations: HIV = human immunodeficiency virus; IM = intramuscularly; PO = orally; BID = twice a day; QID = four times a day; TID = three times a day; TMP–SMX = trimethoprim–sulfamethoxazole.

concomitant HIV infection or frequent recurrences. Acyclovir, 400 mg twice daily, famciclovir, 250 mg twice daily, or valacyclovir, 1 g once daily, each prevents 90% or more of HSV recurrences. See Chapter 185, "Herpes simplex viruses 1 and 2," for more details of treatment.

Suggested reading

Mitjà O, Lukehart SA, Pokowas G, et al. Haemophilus ducreyi as a cause of skin ulcers in children from a yaws-endemic area of Papua New Guinea: A prospective cohort study. *Lancet Glob Health*. 2014 Apr;2(4):e235–41. doi:10.1016/S2214-109X(14)70019-1. Epub 2014 Mar 27. PMID: 25103064.

Kularatne RS, Muller EE, Maseko DV, Kufa-Chakezha T, Lewis DA. Trends in the relative prevalence of genital ulcer disease pathogens and association with HIV infection in Johannesburg, South Africa. *Clin Infect Dis*. 2017;65(12):2085–2090. 10.1093/cid/cix723.

Lewis DA, Mulle E, Steele L, et al. Prevalence and associations of genital ulcer and urethral pathogens in men presenting with genital ulcer syndrome to primary health care clinics in South Africa. *Sex Transm Dis*. 2012;39:880–885.

Lautenschlager S, Kemp M, Christensen JJ, Mayans MV, Moi H. European guideline for the management of chancroid. Int J STD AIDS. 2017;28:324–329.

Mabey D, Ndowa F, Latif A. What have we learned from sexually transmitted infection research in sub-Saharan Africa? *Sex Transm Infect*. 2010;86:488–492.

Mackay IM, Jeoffreys N, Bastian I, et al. Detection and discrimination of herpes simplex viruses, Haemophilus ducreyi, Treponema pallidum, and Calymmatobacterium (Klebsiella) granulomatis from genital ulcers. *Clin Infect Dis*. 2006;42:1431–1438.

Makasa M, Buve A, Sandoy IF. Etiologic pattern of genital ulcers in Lusaka, Zambia: Has chancroid been eliminated? *Sex Transm Infect*. 2012;39:787–791.

Marks M, Fookes M, Wagner J, et al. Direct whole-genome sequencing of cutaneous strains of Haemophilus ducreyi. *Emerg Infect Dis*. 2018;24:786–789.

Orroth KK, White RG, Korenromp EL, et al. Empirical observations underestimate the proportion of human immunodeficiency virus infections attributable to sexually transmitted diseases in the Mwanza

and Rakai sexually transmitted disease treatment trials: Simulation results. *Sex Transm Dis*. 2006;33:536–544.

Peterson TA, Furness BW. The resurgence of syphilis among men who have sex with men. *Curr Opin Infect Dis*. 2007;20:54–59.

Prabhakar P, Narayanan P, Deshpande GR, et al. Genital ulcer disease in India: Etiologies and performance of current syndrome guidelines. *Sex Transm Dis*. 2012;39:906–910.

Romero L1, Huerfano C, Grillo-Ardila CF. Macrolides for treatment of Haemophilus ducreyi infection in sexually active adults. *Cochrane Database Syst Rev*. 2017;12:CD012492.

Sethi G, Allason-Jones E, Richens J, et al. Lymphogranuloma venereum presenting as genital ulceration and inguinal syndrome in men who have sex with men in London, UK. *Sex Transm Infect*. 2009;85:165–170.

Tobian AA, Quinn TC. Herpes simplex virus type 2 and syphilis infections with HIV: An evolving synergy in transmission and prevention. *Curr Opin HIV AIDS*. 2009;4: 294–299.

Van Hattem JM, Langeveld TJC, Bruisten SM, Kolader M, Grobusch MP, de Vries HJC, de Bree GJ. Haemophilus ducreyi cutaneous ulcer contracted at Seram Island, Indonesia, presented in the Netherlands. *PLoS Neglected Trop Dis*. 2018;12:0006273.

63

Prostatitis

Cheston B. Cunha and Burke A. Cunha

Clinical perspective

The most common types of prostatitis are acute bacterial prostatitis (ABP) and chronic bacterial prostatitis (CBP). ABP must be differentiated from urinary tract infections (UTIs) and CBP must be differentiated from non-bacterial (NBP) prostatitis and recurrent cystitis.

Usual uropathogens that cause ABP include common aerobic Gram negative bacilli (GNB) and group D enterococci (i.e., vancomycin-sensitive or resistant enterococci [VSE/VRE]). Patients with ABP are acutely ill with fever and chills. A history of urinary tract instrumentation (e.g., transrectal prostate biopsy) is not uncommon. Rectal exam reveals a tender prostate. If obtained early, blood cultures are usually positive. Urinalysis (UA) shows intense pyuria and urine culture (UC) is positive in high numbers ($>10^6$/hpf). Without urinary tract stones, microscopic hematuria argues against the diagnosis of ABP. ABP may be complicated by urosepsis or prostatic abscess. In contrast, CBP is an indolent relapsing UTI with or without perineal, genital, or low back pain usually accompanied by frequency, urgency, dysuria, or dysuria. Symptoms may resemble chronic non-bacterial prostatitis (NBP). The differential diagnosis of CBP and NBP is straightforward. In patients with CBP there is persistent (>25 WBCs/hpf) pyuria in the UA and a positive UC with abundant uropathogen (i.e., not *S. aureus* or coagulase negative staphylococci [CoNS]). The prostate exam in CBP is that of an often enlarged, relatively non-tender, prostate.

Differential diagnosis

Classically, a microbiologic diagnosis of CBP is made using the Stamey and Meares protocol to culture expressed prostatic secretions. Most patients with CBP do not have expressed prostatic secretions data, and the diagnosis of CBP is confirmed indirectly as described by UA and UC. Interestingly, pyuria ranges from moderate to heavy and UC shows $>10^6$/hpf uropathogens (not *S. aureus* or CoNS). A practical way to differentiate a positive UA/UC of cystitis from CBP is by the presence or absence of mucus threads in the UA. Unless there is an another explanation for these in the UA, mucus threads are indicative of CBP.

Antimicrobial therapy

CBP patients are usually referred to infectious diseases physicians for antibiotic treatment of persistent/relapsing infection. Repeated treatment failures are most often due to suboptimal (selection and duration) antibiotic therapy for CBP. Antibiotic selection is commonly based entirely on UC susceptibility data without taking into account pharmacokinetic (PK) considerations that determine optimal prostate penetration. Antibiotic susceptibilities are based on peak serum levels (PSL) and a serum pH of 7.4. However, the prostate is highly lipid in nature, and the patient with CBP typically has a prostate pH of 8.4. Ionization

TABLE 63.1 **THE DIFFERENTIAL DIAGNOSIS OF PROSTATITIS**

	Urinalysis				EPS		
	WBCs (pyuria intensity)	Mucus threads	Urine culture	Prostatic pH	WBC (pyuria intensity)	Culture	Uropathogen bacteremia
Acute uncomplicated cystitis (AUC)	+++	-	+++	pH = 6.4	NA	NA	+[a]
Acute bacterial prostatitis (ABP)	+++	-	+++	pH = 8.3	NA	NA	+[b]
Chronic bacterial prostatitis (CBP)	+++	+	+++	pH = 5.1	+++	+++	-
Chronic non-bacterial prostatitis (NBP)	-	-	-	pH = 6.5	-	-	-

EPS, expressed prostatic secretions; NA, not applicable.
[a] Only in compromised hosts with impaired B-cell function (e.g., diabetes mellitus, systemic lupus erythematosus, chronic lymphocytic leukemia, multiple myeloma).
[b] Including cases with prostatic abscess.

potential (pKa) is also a key determinant of prostate penetration in CBP since highly ionized drugs cannot cross lipid-laden epithelial cells to penetrate the prostate parenchyma by passive diffusion. Passive diffusion is determined by the concentration gradient from PSL to prostate and, importantly, by lipid solubility (V_d).

Optimal therapy of CBP is determined by these parameters in addition to appropriate spectrum for the cultured uropathogen. The antibiotic selected for CBP should have the PK properties that, when combined, have a high lipid solubility (high V_d) and an optimal ionization coefficient (pKa). There are relatively few antibiotics that have these characteristics. Since antibiotic therapy for CBP is prolonged (i.e., usually 1–3 months), oral therapy is the preferred approach (Tables 63.1–63.4). Depending on susceptibility, for prolonged oral antibiotic therapy of CBP the most useful clinically effective oral antibiotics include the quinolones (moxifloxacin, levofloxacin), trimethoprim (TMP; preferred to trimethoprim-sulfamethoxazole [TMP-SMX]), doxycycline, minocycline, and fosfomycin. Once therapy is started, if the UA/UC is somewhat improved after 3 days, complete therapy with the antibiotic selected. If there is no improvement in the UA/UC after 3 days, then change to an alternate antibiotic and repeat testing in 3 days until an effective agent is determined.

It is a common misconception that TMP-SMX is preferred for UTIs over TMP alone. Actually, only TMP has the PK properties

TABLE 63.2 **CLINICALLY INEFFECTIVE ORAL ANTIBIOTICS FOR CHRONIC BACTERIAL PROSTATITIS (CBP)**

	Effective uropathogen spectrum	Effective prostate penetration
Amoxicillin	+	-
Amoxicillin/clavulanic acid	+	-
Nitrofurantoin	+	-
Oral cephalosporins (1st, 2nd, and 3rd generation)	±	-
Methenamine salts	+	-
Macrolides[a]	-[c]	+
Clindamycin	-[b]	+

[a] Inactive at a pH = 6.4.
[b] Misses all aerobic Gram negative bacilli (GNB) and vancomycin-sensitive or -resistant enterococci (VSE/VRE).
[c] VSE are the only susceptible uropathogens.

TABLE 63.3 **KEY PHARMACOKINETIC DETERMINANTS OF EFFECTIVE PROSTATIC PENETRATION IN CHRONIC BACTERIAL PROSTATITIS (CBP)**

Major determinants	Minor determinants
1. Lipid solubility (V_d) • ↓ V_d = poor penetration • ↑ V_d = good penetration	1. Molecular size/weight[a] • Vancomycin (large molecule) = poor penetration • TMP (small molecule) = good penetration
2. Ionization coefficient (pKa) • Highly ionized = poor penetration • Nonionized = good penetration	
3. Protein binding (%) • Highly protein bound = poor penetration • Moderately protein bound = good penetration	

[a] Hydrophilic antibiotics only

TABLE 63.4 **PHARMACOKINETIC PARAMETERS IN ANTIMICROBIAL THERAPY OF CHRONIC BACTERIAL PROSTATITIS (CBP)**

Preferred oral antibiotics	Spectrum uropathogen				Lipid solubility (V_d)	Optimal antibiotic pH	Favorable ionization constant (pKa)	Protein binding (%)	Relative penetration into non-inflamed prostate
	GNB	MDR GNB	VSE	VRE					
TMP	+	±	-	-	7.3 L/kg	7.4	+	44%	+++
Levofloxacin	+	±	+	-	1.3 L/kg	5–6	+	30%	+++
Moxifloxacin	+	+	+	-	2.2 L/kg	5–6	+	50%	+++
Fosfomycin	+	+	+	+	2.0 L/kg	5–6	+	3%	+++
Doxycycline	+	±	+	-	0.75 L/kg	5–6	+	82%	+++
Minocycline	+	+	+	+	1.5 L/kg	8	+	75%	+++
Azithromycin	-	-	+	-	31 L/kg	8.1	+	50%	+++

Serum pH = 7.4
Prostatic fluid = Normal pH 6.7 (6.2–7.3)
CBP prostatic parenchyma pH = 8.1 (7.4–8.5)

pKa >8.6 = low ionization → good penetration
pKa <6.8 = high ionization → poor penetration

Abbreviations; GNB = gram-negative bacilli, MDR = multidrug resistant, TMP = trimethoprim, VRE = vancomycin-resistant enterococci, VSE = vancomycin-sensitive enterococci.

to penetrate the minimally inflamed prostate in CBP; SMX is not synergistic with TMP and prostate levels. TMP-SMX may be used, but TMP alone is preferable. Another common misconception concerns quinolone therapy of CBP. First, quinolones have the requisite PK characteristics to concentrate in the noninflamed or subacutely inflamed prostate of CBP. Second, with the exception of moxifloxacin, quinolones penetrate well into urine to effectively treat UTI (e.g., AUC due to susceptible organisms). It is not commonly appreciated that moxifloxacin not only penetrates the noninflamed prostate (e.g., providing prophylaxis for transrectal biopsy well), but also results in higher prostate levels than levofloxacin with the usual doses (e.g., moxifloxacin 400 mg [PO] q24h vs. levofloxacin 500 mg [PO] q24h).

Similarly, minocycline is not usually considered as an antibiotic for UTIs. However, if the uropathogen is susceptible, minocycline penetrates the minimally inflamed prostate even better than doxycycline using equivalent doses (i.e., 200 mg [PO] loading dose, then 100 mg [PO] q12h of either doxycycline or minocycline).

If, after initial improvement, the infection of CBP cannot be eradicated after 1 to 3 months of optimal therapy, the physician should suspect a "protected focus" of infection not usually curable using antibiotic therapy alone. In such cases, transrectal ultrasound should be done to rule out small prostatic abscesses, small prostatic calculi, or prostatic calcifications. In these situations a transurethral resection of the prostate (TURP) is usually necessary for cure in addition to carefully selected prolonged antibiotic therapy.

Suggested reading

Albert A. Ionization, pH and biologic activity. *Pharmacol Rev*. 1952:136–137.

Brannan W. Treatment of Chronic Prostatitis. *Urology*. 1975;5:626–631.

Cunha BA, Gran A, Raza M. Persistent extended-spectrum β-lactamase-positive E. coli chronic prostatitis successfully treated with a combination of fosfomycin and doxycycline. *Int J of Anti Agents*. 2015;45:427–429.

Meares EM Jr. Acute and chronic prostatitis: Diagnosis and treatment. *Infect Dis Clin N Amer*. 1987;1:855–873.

Pfau A, Perlberg S, Shapira A. The pH of the prostatic fluid in health and disease: Implications of treatment in chronic bacterial prostatitis. *J Urology*. 1978;119:384–387.

Pilmis B, Lecuyer H, Lortholary O, Charlier C. Enterococcus faecalis-related prostatitis successfully treated with moxifloxacin. *Anti Agents Chemo*. 2015;59:7156–7157.

Ristuccia A, Cunha BA. Current concepts in antimicrobial therapy of prostatitis. *Urology*. 1982;20:338–345.

Zhanel G, Zhanel M, Karlowsky J. Oral fosfomycin for the treatment of acute and chronic bacterial prostatitis caused by multidrug resistant E. coli. *Can J Inf Dis and Med Micro*. 2017; 2017:6362804.

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Pelvic inflammatory disease

William J. Ledger

Introduction

The current emphasis upon evidence-based medicine has poorly served our approach to pelvic inflammatory disease (PID). On paper, the goal of determining the best therapeutic strategy by prospective randomized double-blind studies is laudable, but it makes the assumption that patients with similar risk factors can be grouped into large study groups for such endeavors. It is increasingly apparent that this has not been the case.

PID is a classification that attempts to encompass too wide a range of clinical syndromes. It includes seriously ill women with a tubo-ovarian abscess, who require hospitalization, intravenous antibiotics, and sometimes operative intervention for a cure. In contrast, most women with PID either are asymptomatic or have such mild symptoms that they do not seek medical care. To address these concerns, the International Infectious Disease Society for Obstetrics-Gynecology (I-IDSOG-USA) suggested the term "upper genital tract disease" (UGTI) be used with the designation of the etiologic agent. In addition, the UGTI can be placed in stages, depending upon the clinical severity of the infection.

Epidemiology studies have added to the confusion about risk factors for PID. For the past two decades, study after study has shown bacterial vaginosis (BV) and douching as risk factors for the development of PID, but in separate prospective studies, on BV and douching, no increased risk was seen.

In addition, epidemiologic studies that suffer from inaccurate reporting of condom use and imperfect diagnosis of sexually transmitted disease (STD) infection have been used to bolster the faith-based emphasis upon abstinence over condoms to prevent infection.

Microbiology

The diversity of the clinical picture of PID is matched by the variety of microbiologic findings. There are infections in which a single pathogen dominates, such as *Neisseria gonorrheae*, *Chlamydia trachomatis*, and the group A *Streptococcus*. In contrast, most infections are polymicrobial with aerobes, *Mycoplasma hominis*, *Ureaplasma urealyticum*, or anaerobes involved. Gram-negative anaerobes are particularly important in those women who develop a tubo-ovarian abscess.

Clinical diagnosis

The clinical diagnosis of PID remains a work in progress. More sensitive and more specific invasive techniques to diagnose PID, including laparoscopy, endometrial biopsy, and needle culdocentesis, have been confined to research studies and are not used routinely by clinicians. There is a dependence upon clinical findings, which are variable. In some women, the diagnosis is obvious. This is particularly true in patients requiring care in urban emergency departments. When *N. gonorrheae* is one of the pathogens, the patient usually has severe lower abdominal discomfort, excruciating pain on pelvic examination, and an elevated temperature. This is what a clinician expects with a bacterial infection. Patients seen in the early stages of a gonococcal

infection, however, may present with minimal symptoms, including a new discharge, abnormal bleeding, or urinary urgency and frequency. Another group with an obvious diagnosis are those women with a pelvic abscess. These patients are usually febrile, have tender pelvic masses detected on pelvic examination and confirmed by imaging study such as a pelvic ultrasound. In contrast, women infected with *C. trachomatis* with PID have minimal or no symptoms, and are usually afebrile without an elevated white blood cell count. Many do not seek medical care. Because of this, I share the concerns of the Centers for Disease Control and Prevention (CDC) about the validity of the minimal criteria for physician diagnosis. These criteria—lower abdominal tenderness, adnexal tenderness, and cervical motion tenderness—exclude more women who do not have PID, but they also reduce the number of women with PID who are identified.

There are other signs of early infection that should be called into play by clinicians. Suspect a pelvic infection in a young sexually active woman who has either a new sexual partner or a promiscuous male partner who does not use condoms. Consider this diagnosis whenever these women complain of urgency and frequency of urination, whose urination culture shows no significant growth of bacteria, irregular vaginal bleeding with no obvious cause found on pelvic examination or, most commonly, a new vaginal discharge.

Another problem is that more relaxed physician standards that increase the likelihood of a diagnosis of PID are of no value if the patients do not present for care. The current reality in the United States is that many of these women with few or no symptoms do not consider themselves sick enough to seek medical care. We need a new direction in patient care. Women need to be educated and made aware of the risks of infection if exposed to a new male partner who does not use a condom. They also should be made aware of the subtle signs of pelvic infection and to seek medical care. One possible future strategy will be to have these women test themselves with a vaginal swab that will be polymerase chain reaction (PCR) tested for the presence of *C. trachomatis*. Studies indicate that this would be a feasible strategy.

Treatment

There are no prospective studies available with the statistical power to dictate absolute criteria to determine hospital admission or the best choice of antibiotics to prevent long-term morbidity. One study to compare inpatient versus outpatient therapy had 78.1% of the patients with well-established infections, with symptoms for more than 3 days, before treatment was begun. Well-established infections are not as responsive to antibiotic therapy. In addition, the current clinical reality of care is that treatment regimens have to be initiated before culture or PCR studies identify the pathogens present. Because of this, initial regimens should include antibiotics effective against *N. gonorrheae, C. trachomatis*, and gram-negative anaerobes. Changes in initial choices can be made if bacterial identification suggests that other agents should be used.

In Sexually Transmitted Diseases Treatment Guidelines, 2010, the CDC provide the following options: parenteral treatment (Box 64.1) and oral treatment (Box 64.2). Patients who fail to respond

BOX 64.1

Parenteral treatment

Recommended parenteral regimen A
Cefotetan 2 g IV every 12 hours
OR
Cefoxitin 2 g IV every 6 hours
PLUS
Doxycycline 100 mg orally or IV every 12 hours
Parenteral treatment can be discontinued 24 hours after a patient improves. Clinical oral therapy with doxycycline 100 mg twice a day to complete 14 days of therapy.

Recommended parenteral regimen B
Clindamycin 900 mg IV every 8 hours
PLUS
Gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) may be substituted.
Parenteral treatment can be discontinued 24 hours after a patient improves. Oral therapy should then be given to complete 14 days of therapy, either clindamycin 450 mg four times a day or doxycycline 100 mg twice a day.
Alternative parenteral regimen
Ampicillin–sulbactam 3 g IV every 6 hours
PLUS
Doxycycline 100 mg orally or IV every 12 hours

BOX 64.2

Oral treatment

Recommended oral regimen
Ceftriaxone 250 mg IM in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days

WITH OR WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Cefoxitin 2 g IM in a single dose and probenecid, 1 g orally administered concurrently in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days

WITH OR WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
PLUS
Doxycycline 100 mg orally twice a day for 14 days

WITH OR WITHOUT
Metronidazole 500 mg orally twice a day for 14 days

to systemic antibiotic treatment should be evaluated to see whether pelvic abscess formation has occurred. In women in whom an abscess is discovered aspiration can be done under direct laparoscopic vision or ultrasonographic-guided needle aspiration. The patients who fail to respond to this intervention are few in number, but they may need operative removal of infected tissue to achieve a cure.

Suggested reading

Hemsel DL, Ledger WJ, Martens M, et al. Concerns regarding the Centers for Disease Control's published guidelines for pelvic inflammatory disease. *Clin Infect Dis*. 2001;32:103–107.

Montgomery RS, Wilson SE. Intra-abdominal abscesses: image-guided diagnosis and therapy. *Clin Infect Dis*. 1996;23:28–36.

Ness RB, Soper DE, Holley RL, et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEAH) Randomized Trial. *Am J Obstet Gynecol*. 2002;186: 929–937.

Ness RB, Hillier SL, Kip KE, et al. Bacterial vaginosis and risk of pelvic inflammatory disease. *Obstet Gynecol*. 2004;104:761–769.

Peipert JF, Boardman L, Hogan JW, Sung J, Maver KH. Laboratory evaluation of acute upper genital tract infection. *Obstet Gynecol*. 1996;87:730–736.

Polaneczky M, Quigley C, Pollock L, Dulko D, Witkin SS. The use of self-collected vaginal specimens for the detection of Chlamydia trachomatis infection. *Obstet Gynecol*. 1998;91:375–378.

Rothman KJ, Funch DP, Alfredson T, Brady J, Drayer NA. Randomized field trial of vaginal douching, pelvic inflammatory disease and pregnancy. *Epidemiology*. 2003; 14(3):340–348.

Sweet RL. Role of bacterial vaginosis in pelvic inflammatory disease. *Clin Infect Dis*. 1995; 20(Suppl 2):S271–S275.

Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines 2010. *MMWR Recomm Rep*. 2010;59(RR-12): 1–110.

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Urinary tract infection

Peter Liu, Keith W. Hamilton, and Judith A. O'Donnell

Urinary tract infections (UTIs) account for a significant burden of morbidity, cost, and healthcare resource utilization in both the inpatient and outpatient setting. UTIs occur in patients of all ages, with a predilection for females throughout life and males at each end of the age spectrum. They represent approximately 8.6 million annual visits in the ambulatory setting and are a frequently diagnosed healthcare-associated infection. The term "urinary tract infection" encompasses a group of conditions that includes cystitis, pyelonephritis, and asymptomatic bacteriuria. Appropriate management of a patient with a UTI requires consideration of multiple factors, including age, sex, underlying comorbidities, pregnancy, history of prior UTIs, site of infection, anatomic aberrations, and the pathogen involved.

Determination of the location of the infection as upper versus lower tract is essential to selection of optimal therapy. *Lower urinary tract infection* is infection involving the bladder, or *cystitis*, and is characterized by dysuria, pyuria, urinary frequency, or urinary urgency. *Upper urinary tract infection*, or *pyelonephritis*, is infection involving the bladder and kidney that classically presents with fever and flank pain, with or without the symptoms of lower tract infection.

Differentiating uncomplicated from complicated UTI is also critical to developing an appropriate treatment strategy. An uncomplicated UTI is an infection occurring in an otherwise healthy individual who has no functional or structural abnormalities of the kidneys, ureters, bladder, or urethra. Most adult women with cystitis fall into this category. Complicated UTIs occur in the setting of factors that predispose to persistent or relapsing infection. These factors include functional or anatomic abnormalities of the upper or lower tract (such as urinary retention from anatomic obstruction or neurogenic bladder and nephrolithiasis), the presence of an indwelling bladder catheter, or underlying conditions such as pregnancy, diabetes mellitus, or renal transplantation. Infections with unusual or multidrug-resistant bacteria are often considered complicated. UTIs in adult men are uncommon without complicating factors (such as urinary obstruction or prostatitis), and most cases should be treated as complicated infections. These complicating factors are associated with less favorable treatment responses.

Uncomplicated lower UTIs respond well to therapy of short duration of 3 to 7 days depending on the chosen agent (see Table 65.1). Complicated infections are often associated with factors that may predispose the patient to complications or recurrence and usually require longer courses of therapy (7–14 days or more), but few studies have been performed to determine the optimal treatment courses for complicated UTIs.

Pathogenesis

The pathogenesis of most upper and lower UTIs is related to the ability of microorganisms to establish colonization in the periurethral area and to ascend into the urinary tract and cause infection. These organisms are typically derived from the gastrointestinal tract or vagina. After colonization, the ensuing events that lead to infection are not entirely understood but likely depend on virulence factors of the organism and host anatomy and immune response. Urinary catheters can facilitate both colonization and infection. They are commonly colonized by periurethral flora that migrate along the catheter surface. Interactions between

TABLE 65.1 **ANTIBIOTICS FOR UNCOMPLICATED LOWER URINARY TRACT INFECTIONS**

Drug	Dose and duration	Comments
First-line agents		
TMP-SMX	1 DS (160/800 mg) tablet BID for 3 days	First-line agent unless ≥10–20% rate of Escherichia coli resistance to TMP-SMX locally, history of antibiotic use, within past 3 months, or history of recent hospitalization FDA pregnancy category C; avoid in third trimester
Nitrofurantoin (monohydrate macrocrystals)	100 mg BID for 7 days	Consider for patients with mild to moderate symptoms, and with ≥10–20% rate of *E. coli* resistance to TMP-SMX locally, sulfa allergy, or antibiotic use other than nitrofurantoin within past 3 months FDA pregnancy category B. Alternative agent should be considered if creatinine clearance <40 given inadequate urinary concentration. Pulmonary toxicity including interstitial pneumonitis or pulmonary fibrosis has been described, in particular for patients with documented long-term use.
Fosfomycin	3 g as single dose	Consider for patients with mild to moderate symptoms, and with ≥10–20% rate of *E. coli* resistance to TMP-SMX locally, sulfa allergy, or antibiotic use other than fosfomycin within past 3 months; FDA pregnancy category B. Exhibits activity against multidrug resistant pathogens including vancomycin-resistant enterococci and extended spectrum β-lactamase (ESBL) producing gram-negative rods.
Second-line agents		
β-lactams (e.g., amoxicillin-clavulanate, cephalosporins)	3–7 days (dose depends on individual agent)	There are less efficacy data for these agents compared to data for first-line agents and fluoroquinolones
		Consider β-lactams if ≥10–20% rate of *E. coli* resistance to other agents and rates of resistance to selected β-lactams ≤20%
		Amoxicillin or ampicillin should not be used as monotherapy for empiric treatment; FDA pregnancy category B
Fluoroquinolones Ciprofloxacin Levofloxacin	400 mg BID for 3 days 750 mg/d for 3 days	Consider fluoroquinolones if ≥10–20% rate of *E. coli* resistance to TMP-SMX locally, patient allergy to other agents, and antibiotic use other than fluoroquinolones within past 3 months; FDA pregnancy category C

Antibiotic dose recommendations assume normal renal function.
Abbreviations: TMP–SMX = trimethoprim–sulfamethoxazole; DS = double strength; FDA = Food and Drug Administration.

the catheter and infecting or colonizing organisms facilitate adhesion to the catheter and production of a biofilm, which aids certain microorganisms in evading host defenses. Rarely, UTIs may occur through a hematogenous route of infection.

The majority of upper and lower UTIs are monomicrobial. *Escherichia coli* is the most common pathogen, causing 70% to 90% of all UTIs. Other members of the Enterobacteriaceae family such as *Klebsiella*, *Proteus*, and *Enterobacter* spp. are also common UTI pathogens. Among the gram-positive organisms, *Staphylococcus saprophyticus* and *Enterococcus* spp. are the most frequently identified pathogens. Other bacteria, such as *Pseudomonas* and *Serratia* can be seen more frequently in association with indwelling urinary catheters, and polymicrobial UTIs can also occur in this setting. A polymicrobial infection in the absence of a urinary catheter may suggest an enterovesical fistula or contamination during the specimen collection process. *Candida albicans* is the most common etiologic agent in fungal UTIs, but other *Candida* spp. are becoming increasingly common. Several sexually transmitted infections (STIs), including *Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis*, and genital herpes simplex virus infection, can cause urethritis, which mimics symptoms of UTI. Therefore, appropriate diagnostic evaluation for STIs should also be performed as part of a UTI workup in sexually active patients, especially if another pathogen is not isolated.

Lower UTI: Cystitis

Typical symptoms of lower UTIs include dysuria, urinary frequency, urgency, and, occasionally, hematuria or suprapubic pain. The presence of fever or flank pain should raise the concern for pyelonephritis. In addition to history and physical examination findings, laboratory tests are often used in the diagnosis of cystitis.

Diagnosis

The diagnosis of cystitis can be made using a combination of clinical and laboratory criteria. Some symptoms, including dysuria, urinary frequency, and hematuria, increase the likelihood of UTI.

The absence of dysuria or back pain and presence of vaginal irritation or discharge decrease the likelihood of UTI. Women with at least one symptom have at least a 35% to 50% likelihood of having cystitis. The presence of dysuria and urinary frequency combined with the absence of vaginal discharge increases the likelihood of UTI to >90%. Patients with a high pretest probability for cystitis and no complicating factors should be treated empirically without additional testing. Patients with a lower pretest probability should have diagnostic testing performed. In these patients, the diagnosis of cystitis can be evaluated using urine dipstick, microscopy, and/or culture.

In ambulatory settings, urine dipstick testing has largely replaced microscopy to diagnose UTI because it is cheaper, faster, and more convenient. Dipstick testing can detect the presence of leukocyte esterase, an enzyme released by white blood cells, and nitrites, byproducts of nitrate metabolism produced by Enterobacteriaceae. A positive test for either leukocyte esterase or nitrite has a sensitivity of 75% and specificity of 82%. Because of the limited sensitivity and specificity of the dipstick test, the dipstick may be most useful for rapid rule-out of UTI among women with a moderate to low pretest likelihood of infection, such as minimally symptomatic patients or those with both bladder and vaginal symptoms. Urine microscopy has a higher sensitivity and specificity compared to the dipstick test. Hemocytometer (counting chamber) measurement of urine leukocytes in an unspun specimen provides the most accurate assessment of pyuria, which is defined as a leukocyte count of ≥10 leukocytes/mm^3. Pyuria is present in almost all women with cystitis in the absence of severe neutropenia (ANC <500). Another method of urinalysis involves the microscopic examination of urine sediment from centrifuged samples. The accuracy of this method depends on the skill of the operator and the level of procedural standardization. The presence of bacteriuria on urine microscopy can also be used to assess the presence of UTI, but it is often difficult to interpret given the ease of specimen contamination with periurethral flora during collection, as well as the overgrowth of bacteria that may result from the improper handling of specimens. Therefore, bacteriuria alone in the absence of pyuria and compatible clinical symptoms should not be used to make the diagnosis of UTI.

Urine culture is not necessary in most otherwise healthy women with cystitis because the causative organisms and their susceptibility patterns are predictable. However, urine cultures should be obtained in patients with refractory symptoms, recurrent UTIs, suspected pyelonephritis, or complicated UTI. Urine cultures should also be obtained in patients with history of or risk factors for antibiotic-resistant pathogens, including in those patients with recent antibiotic use, recent hospitalization, or residence in a long-term care facility. Although suprapubic aspiration or straight catheterization has the best chance of minimizing contamination, midstream or "clean-catch" urine collection remains the most practical method of obtaining urine samples. Quantitative urine cultures are the gold standard for microbiologic diagnosis of UTIs. Growth, identification, and susceptibility testing of the pathogen can offer the most effective means for establishing infection and determining appropriate antimicrobial therapy. Traditionally, bacteriuria with $\geq 10^5$ colony-forming units (CFU) of bacteria per milliliter of urine has been considered diagnostic. This threshold was extrapolated from studies of pyelonephritis and asymptomatic bacteriuria in women. However, based on more recent studies, lower colony counts (10^2 to 10^4 CFU/mL) in association with signs and symptoms of cystitis have also been accepted as diagnostic. The quantitative threshold for UTIs in men remains unclear, but many authorities recommend a lower threshold of 10^3 CFU/mL.

Therapy

Treatment of uncomplicated cystitis can be accomplished with a short course of an effective antimicrobial agent. Because therapy is typically started in the absence of a culture or before culture results become available, understanding common pathogens and local susceptibility patterns is essential. Given that *E. coli* is the predominant UTI pathogen, its susceptibility patterns typically drive empiric antibiotic choices. Table 65.1 outlines general treatment recommendations for uncomplicated cystitis.

In many areas, resistance rates for nitrofurantoin, fosfomycin, and trimethoprim– sulfamethoxazole (TMP-SMX) are <10%. Therefore, these drugs have become the recommended first-line empiric agents for uncomplicated cystitis. However, the rates of resistance vary considerably by geographic region and can exceed 20% in some areas. In particular, the rapidly increasing rate of resistance of *E. coli* to TMP-SMX has raised significant concern about its empiric use for UTI. In vitro and mathematical modeling studies suggest that TMP-SMX should not be used when local resistance rates exceed 20%. Individual risk factors for resistance should also be considered before using TMP-SMX for empiric therapy. Studies have suggested that the highest risk of UTI caused by TMP-SMX-resistant *E. coli* is associated with recent TMP-SMX or other systemic antibiotic use. Other risk factors include recent hospitalization, residence in a long-term care facility, and travel outside the United States within the past 3 to 6 months.

The potential benefits of nitrofurantoin for UTI treatment includes a relatively narrow spectrum of activity, little evidence of in vitro resistance, and bactericidal activity in the urine at therapeutic doses. Nitrofurantoin has been studied primarily for lower UTIs, does not achieve high drug concentration levels in the upper urinary tract, and consequently should not be used to treat upper tract infections. In multiple studies, nitrofurantoin used for 5 days demonstrated similar clinical cure rates as TMP-SMX used for 3 days. It is generally well-tolerated, although hepatotoxicity, peripheral neuropathy, and pulmonary toxicity including interstitial pneumonitis and pulmonary fibrosis have been described, particularly in patients with documented long-term use. The US Food and Drug Administration (FDA) lists a creatinine clearance of <60 mL/min as a contraindication to the use of nitrofurantoin due to concerns for impaired excretion and inadequate urinary concentration. However, recent studies suggest that efficacy is retained for the treatment of lower UTIs with a creatinine clearance of at least 40 mL/min.

Fosfomycin is considered a first-line therapy for lower UTIs and has distinct advantages in certain clinical scenarios. Fosfomycin is administered in a convenient single 3 g dose regimen, achieves high concentration in the urinary bladder, and possesses a favorable side-effect profile with infrequent reports (2–6%) of self-limited nausea and diarrhea. Importantly, it retains in vitro activity against many

multidrug-resistant organisms, including extended-spectrum β-lactamase (ESBL)-producing organisms and vancomycin-resistant enterococci (VRE), and it can sometimes be prescribed for uncomplicated lower UTIs caused by these organisms, thus avoiding intravenous therapy. Several clinical studies have demonstrated high rates of efficacy in lower uncomplicated UTIs, including those due to multidrug-resistant pathogens. One potential disadvantage of fosfomycin is that most microbiology laboratories do not perform routine fosfomycin susceptibility testing and require a special request to do so, and, as such, results may not be available to inform early clinical decision-making. Additionally, robust clinical data describing outcomes in recurrent or complicated infection are lacking. Nevertheless, as multidrug-resistant organisms become more prevalent in the community, fosfomycin will likely have a more prominent role in both empiric and definitive therapy.

The fluoroquinolones have often been used as first-line empiric therapy for cystitis. Currently fluoroquinolone resistance rates in *E. coli* are highly variable depending on geography. In some areas, resistance rates to fluoroquinolones can exceed 20%. Even when resistance rates are <10%, fluoroquinolone use can select for development of multidrug-resistant organisms. Therefore, fluoroquinolones should be reserved as alternative therapy and prescribed for patients who do not tolerate or are not eligible to receive recommended first-line agents. Moxifloxacin and gemifloxacin achieve poor levels in the urine and are not approved for treatment of UTI. Levofloxacin or ciprofloxacin are the fluoroquinolones recommended for treatment of genitourinary tract infections.

Selected β-lactam agents may also be appropriate therapeutic options for uncomplicated cystitis as resistance rates for these agents are <10% in many geographic regions. As compared to TMP-SMX and the fluoroquinolones, there are far fewer clinical outcome data with these agents. Historically, β-lactam agents have been noted to be less effective than TMP-SMX and to potentially cause more disruption of the vaginal flora, leading to vaginal yeast infection. However, in the current climate of increasing resistance to TMP-SMX and fluoroquinolones, the β-lactam agents have once again become a reasonable therapeutic option in some settings. In most regions of the United States, rates of resistance of *E. coli* to amoxicillin exceed 20%, making amoxicillin a poor choice for empiric therapy. The β-lactams that may be considered as UTI treatment based on local susceptibility patterns include amoxicillin-clavulanate, second-generation cephalosporins (cefaclor), third-generation cephalosporins (cefdinir and cefpodoxime), and, in some instances, first-generation cephalosporins (cephalexin and cefadroxil). Broad-spectrum β-lactam agents should be prescribed with caution as their use has also been associated with development of drug resistance.

Patients with cystitis who may not be appropriate candidates for more traditional empiric treatment recommendations include those at higher risk for acquisition of multidrug-resistant pathogens. Patients with recent antibiotic exposure, infection with multidrug-resistant bacteria, hospitalization, or residence in a long-term care facility all carry a higher risk of resistance to first-line agents. Urine should be submitted for culture and susceptibility in such patients, and, if empiric therapy is desired prior to culture results, it should be based on prior culture results and recent antibiotic use.

Complicated UTI

A UTI is considered complicated if any of the criteria discussed in the introduction to this chapter are present. Symptoms of complicated UTI can be similar to those associated with uncomplicated cystitis, including dysuria, hematuria, urinary frequency, and suprapubic pain. However, symptoms can be atypical, especially in those patients with functional or structural abnormalities or with a urinary catheter. The management of candiduria and UTIs occurring in catheterized patients is discussed in detail in Chapter 106, "Infections associated with urinary catheters." Urine culture and sensitivity should be performed for all patients with complicated UTI. Treatment duration for complicated UTIs, including UTIs in men, is usually 7 to 14 days, depending on the choice of antibacterial therapy, due to the potential for higher rates of treatment failure and relapse in complicated infections treated for short courses.

The issues regarding antibiotic choice in light of increasing rates of resistance are similar to those discussed previously for uncomplicated UTIs; however, consideration should be given to the potentially higher risk of resistant pathogens in many populations with complicated UTIs. Therefore, TMP-SMX, nitrofurantoin, and fosfomycin are generally not recommended for the empiric treatment of complicated infections. Nitrofurantoin and fosfomycin, which both poorly penetrate into tissue of the upper urinary tract, should be avoided in situations where there is diagnostic uncertainty of upper versus lower UTI.

Because of the increased rates of resistance, likelihood of upper tract infection, and the limitations of first-line agents in complicated UTI, empiric therapy should be initiated with a broad-spectrum antibiotic such as a fluoroquinolone. Parenteral therapy may be necessary, especially in hospitalized patients or those who cannot tolerate oral medications. In these cases, reasonable choices include third- or fourth-generation cephalosporins or the fluoroquinolones. Choice of empiric therapy should be based on local susceptibility patterns and prior culture data. Therapy should be modified as needed or narrowed where possible once the culture and susceptibility results are available.

Upper UTI: Pyelonephritis

Pyelonephritis is defined as an infection of the urinary tract that ascends to involve the renal pelvis. The organisms that cause pyelonephritis are similar to those that cause cystitis. Characteristic symptoms and signs of pyelonephritis include fever, nausea, vomiting, flank pain, and costovertebral angle tenderness. Symptoms of cystitis may or may not be present. However, pyelonephritis may also mimic appendicitis, cholecystitis, and pelvic inflammatory disease. Therefore, a careful history and physical exam are essential, and a pelvic examination or dedicated imaging studies should be considered in patients who present with atypical symptoms.

As is true with other types of UTI, pyuria is almost always present. Urine dipstick tests for leukocyte esterase and nitrites can be used to screen for the presence or absence of infection, but they cannot differentiate upper from lower tract diseases. Furthermore, they are generally not sensitive enough to rule out pyelonephritis; therefore, urinalysis

should be performed. Urine culture and sensitivity should be performed in all cases of suspected pyelonephritis and therapy adjusted based on susceptibility results. The accepted diagnostic threshold for significant bacteriuria in pyelonephritis is $\geq 10^5$ CFU/mL, although colony counts as low as 10^3 CFU/mL of urine may be seen. Blood cultures should be performed in patients with fever or severe disease. Pregnancy should be ruled out in all women of childbearing age because pregnancy is a predisposing condition for pyelonephritis, and many antibiotics including fluoroquinolones, are contraindicated during pregnancy.

Many patients with uncomplicated pyelonephritis may be treated as outpatients with oral antibiotics. Indications for hospitalization include severe nausea or vomiting, signs of sepsis or severe disease (e.g., high fevers, tachycardia, and hypotension), diagnostic uncertainty, or concerns regarding ability to adhere to treatment plans or follow-up. If the patient is deemed an appropriate candidate for outpatient oral therapy, fluoroquinolones are generally recommended as the first-line agents given the variable and rising rates of resistance to TMP-SMX (Table 65.2). TMP-SMX should be used in

TABLE 65.2 **ANTIBIOTICS FOR UNCOMPLICATED PYELONEPHRITIS**

Drug	Dose and duration	Comments
Outpatient therapy[a]		
Fluoroquinolones		First line agents for treatment of pyelonephritis in the outpatient setting except when contraindicated.
Ciprofloxacin	500 mg BID for 7 days	Must follow up in 48-72 hours to assess response.
Levofloxacin	750 mg/d for 5 days	FDA pregnancy category C
TMP-SMX	1 DS (160/800 mg) tablet BID for 14 days	Use TMP-SMX only if causative organism is shown to be susceptible. If C/S not available, add single dose of parenteral agent (Ceftriaxone or aminoglycoside) pending susceptibility data. FDA pregnancy category C Avoid during third trimester
Other Agents	14 days (dose depends on individual agent)	There are less data for these agents in empiric treatment of pyelonephritis If an agent other than a fluoroquinolone is used for empiric therapy in absence of C/S, add single dose of parenteral agent (ceftriaxone or aminoglycoside) pending susceptibility data Amoxicillin and ampicillin should not be used for empiric treatment of pyelonephritis Nitrofurantoin and fosfomycin should not be used for treatment of pyelonephritis even if isolate is susceptible to these agents
Inpatient therapy[b,c]		
Fluoroquinolones		FDA pregnancy category C
Ciprofloxacin	400 mg IV BID	
Levofloxacin	250–500 mg/d IV daily	
Cephalosporins		FDA pregnancy category B
Ceftriaxone	1 g IV daily	
Cefotaxime	1 g IV q8h	
Cefepime	1 g IV q8h	
Carbapenems		FDA pregnancy category B
Meropenem	1 g IV q8h	FDA pregnancy category C
Doripenem	500 mg IV q8h	
Ertapenem	1 g daily	
Imipenem	500 mg IV q6h	
Aztreonam	1 g q8h	FDA pregnancy category B
Aminoglycosides		FDA pregnancy category D
Gentamicin	5 mg/kg IV daily	
Tobramycin	5 mg/kg IV daily	

[a] If enterococcus suspected, add amoxicillin to regimen.
[b] If enterococcus suspected, add ampicillin to regimen.
[c] Empiric use of broader spectrum agents may be necessary in severe disease or if risk factors for antibiotic-resistant bacteria are present. Streamline therapy based on culture and sensitivity data. Patient can be switched to oral agents once patient responds and if oral option available.
Antibiotic dose recommendations assume normal renal function.
Abbreviations: TMP–SMX = trimethoprim–sulfamethoxazole; DS = double strength; C/S = culture and sensitivity; FDA = Food and Drug Administration.

pyelonephritis only if culture and sensitivity results are available and if the infecting organism is known to be susceptible. There are less data for the use of oral β-lactams for the treatment of pyelonephritis, and these agents may be inferior to fluoroquinolones. If an alternative agent other than a fluoroquinolone is used for outpatient treatment or if fluoroquinolone resistance exceeds 10%, a single dose of a long-acting parenteral agent, such as ceftriaxone or an aminoglycoside, should be administered pending culture and susceptibility. If a urine Gram stain reveals gram-positive cocci (suggesting a possible enterococcal infection), amoxicillin should be added to the regimen.

Antibiotics should be narrowed or adjusted according to culture and susceptibility results. For treatment of mild cases of pyelonephritis in the outpatient setting, the duration of therapy should be 5 to 7 days if a fluoroquinolone is used. If an alternative agent is used, a 10- to 14-day duration of therapy is generally recommended. Patients usually improve within the first 48 to 72 hours of therapy, and it is important for appropriate follow-up within this period to review clinical response and culture results. In the absence of improvement, the patient should be admitted to the hospital for alternative treatment regimens and further diagnostic evaluation.

Patients requiring hospitalization for management of pyelonephritis should be treated initially with parenteral agents (Table 65.2). Local susceptibilities should drive empiric treatment decisions. Reasonable choices include fluoroquinolones, extended-spectrum cephalosporins (third- and fourth-generation), extended-spectrum penicillins (ampicillin-sulbactam or piperacillin-tazobactam), or aminoglycosides. If gram-positive cocci are observed on Gram stain, the addition of ampicillin or use of ampicillin-sulbactam is recommended. Consultation with an infectious diseases expert should be considered in cases of treatment failure or in patients with risk for or history of multidrug-resistant pathogens.

Antibiotic coverage should be narrowed if possible when culture and sensitivity results are available. A 14-day course of therapy is generally recommended for hospitalized patients. If the patient has not improved within the first 72 hours of therapy, dedicated imaging such as renal ultrasound or CT is suggested to evaluate for perinephric abscess, nephrolithiasis, obstruction, or other complication. (See Chapter 67, "Focal renal infections and papillary necrosis.")

Asymptomatic bacteriuria

Asymptomatic bacteriuria is defined as the presence of significant bacteriuria ($\geq 10^5$ CFU/mL) in the absence of signs or symptoms of UTI. The diagnosis of asymptomatic bacteriuria in women is made when *two* separate clean-catch, voided urine specimens demonstrate the same organism. Only *one* sample is required to make the diagnosis in males. In men and women with chronic catheterization, one sample with bacteriuria $\geq 10^2$ CFU/mL is considered diagnostic. Asymptomatic bacteriuria is common in certain populations. Reported prevalence rates range from 1.0% to 5.0% among healthy premenopausal women, 1.9% to 9.5% among pregnant women, and up to 16% of elderly ambulatory women. The prevalence of asymptomatic bacteriuria is even greater among persons in long-term care facilities and in patients with spinal cord injuries. The rate of asymptomatic bacteriuria approaches 100% in patients with chronic urinary catheterization.

Treatment of asymptomatic bacteriuria in most patient populations has no clinical benefit. The only patients who should be screened and treated for asymptomatic bacteriuria are pregnant women and patients undergoing an invasive urologic procedure with a reasonable risk of mucosal bleeding. Pregnant women with asymptomatic bacteriuria have an increased risk of pyelonephritis and are more likely to have premature delivery and low-birth-weight infants. Patients with asymptomatic bacteriuria undergoing urologic procedures with mucosal bleeding, such as transurethral prostate resection, have a higher rate of bacteremia and sepsis. Pregnant women ideally should be screened between weeks 12 and 16 of gestation, but may be screened later if the first prenatal visit occurs after 16 weeks.

Bacteriuria in pregnancy should be treated for 3 to 7 days. Choice of antibiotic should depend on susceptibility results of the urine culture. Fluoroquinolones are contraindicated in pregnancy. Reasonable choices for treatment in this setting include an oral cephalosporin, TMP-SMX, trimethoprim alone, or nitrofurantoin. TMP-SMX should be avoided in the final weeks of the third trimester. Nitrofurantoin should similarly be avoided during the third trimester. Pregnant women should be screened periodically for recurrent bacteriuria following treatment, but the proper screening interval is not known; many obstetricians screen monthly.

Patients undergoing urologic procedures should be screened for asymptomatic bacteriuria prior to the procedure, and treatment should be tailored based on the susceptibility results if the urine culture is positive. Antibiotics should be discontinued at the completion of the procedure unless an indwelling catheter is left in place.

Recurrent cystitis

Recurrent cystitis is defined as two episodes of cystitis over 6 months or three or more infections in a year. Recurrent cystitis can be categorized into two types: relapse and reinfection, although the distinction between the two can be difficult. A recurrent infection is considered a *relapse* if it occurs within 2 weeks of finishing treatment for the previous infection and the pathogen is the same strain. *Reinfection* is defined as recurrent infection with a different strain of bacteria or, if the infection is with the same strain, it occurs >2 weeks after finishing the last treatment course. Relapsing infections can result from inadequate length of therapy, nephrolithiasis, urinary tract obstruction, structural abnormality, perinephric abscess, and chronic bacterial prostatitis. If relapse occurs despite appropriate treatment, further investigation for these syndromes should be undertaken.

Reinfection, which represents a majority of cases of recurrent UTIs, is often multifactorial. Some associated risk factors for women with reinfection include new sex partners, spermicide use, urinary retention, and structural abnormality. Treatment strategies are aimed at modifying these risk factors.

When appropriate, behavioral modification should be the first strategy in managing women with recurrent UTI. Although postcoital voiding in women has not been studied in controlled trials, it is often recommended based on biologic plausibility and anecdotal evidence. Given the minimal costs and side effects, it is reasonable to suggest postcoital voiding to women with postcoital UTIs. Cranberry juice has long been suggested as a preventative measure for UTIs, and a natural compound present in cranberry juice has been shown to inhibit the binding of uropathogens to uroepithelial cells. No strong evidence exists on the clinical efficacy of cranberry juice and cranberry products to prevent recurrent cystitis; however, many patients and healthcare providers have anecdotal success with this preventative treatment. In women who use spermicides, alternative methods of contraception can be considered as a modification strategy to prevent recurrent UTI. Methenamine hippurate, which possesses antibacterial properties and an ability to effectively acidify urine, has also been anecdotally used with varying degrees of success. There is limited clinical data on its efficacy; however, one Cochrane review concluded that methenamine hippurate is safe and effective for short-term prevention of recurrent UTIs in patients without structural or functional urinary tract aberrations.

Loss of estrogen with menopause leads to elevated vaginal pH, loss of lactobacilli in the vagina, and uropathogen-dominant vaginal flora. In postmenopausal women with recurrent UTIs, estrogen replacement therapy has been attempted, and limited clinical data suggest that topical estrogens can help prevent recurrent UTI when compared with placebo. Topical vaginal estrogen therapy offers a reasonable management strategy in postmenopausal women when behavioral interventions fail.

In patients where reinfection affects quality of life despite more conservative interventions, various antibiotic strategies can be highly effective. These strategies include patient-initiated self-treatment, postcoital prophylaxis, and continuous prophylaxis. Patient-initiated self-treatment may be used with short-course regimens in patients with two or fewer episodes per year. Only patients who will reliably contact their physicians if their symptoms do not improve in 48 hours should be considered for this strategy. Alternatively, postcoital prophylaxis can be offered to patients who can temporally associate their UTI recurrences with sexual activity.

In the remainder of women with three or more UTIs per year, continuous low-dose antimicrobial prophylaxis can be considered. Continuous prophylaxis has been shown to be highly effective, although the benefits must be weighed against the expense and the risks of adverse drug reactions and development of antimicrobial resistance. Continuous prophylaxis may be given for 6 to 12 months, and a variety of agents may be used. In general, when prophylaxis is discontinued, women with recurrent UTI usually revert back to their baseline pattern of recurrent infection. If this occurs, prophylaxis can be reinitiated if the uropathogens remain susceptible. Recommended regimens for postcoital prophylaxis and continuous prophylaxis are listed in Table 65.3.

TABLE 65.3 **SUMMARY OF TREATMENT RECOMMENDATIONS FOR RECURRENT URINARY TRACT INFECTIONS**

Prophylaxis	Antimicrobial agent	Dose	Comments
Postcoital (single dose)	TMP-SMX	40 mg/200 mg (1 single-strength tablet)	Eliminates vaginal reservoir without disturbing other flora FDA pregnancy category C; may be used in pregnancy up until end of third trimester
	Nitrofurantoin (macrocrystals)	50–100 mg	FDA pregnancy category B
	Cephalexin	250 mg	Disrupts vaginal flora FDA pregnancy category B
	Ciprofloxacin	125 mg	FDA pregnancy category C; avoid in pregnancy
Continuous[a]	TMP-SMX	40 mg/200 mg (1 single-strength tablet)	Give daily or 3 times a week Eliminates vaginal reservoir without disturbing other flora Safe for years of use FDA pregnancy category C
	TMP	100 mg	See above
	Nitrofurantoin (macrocrystals)	50–100 mg	FDA pregnancy category B
	Cephalexin	125–250 mg	Disrupts vaginal flora FDA pregnancy category B
	Cefaclor	250 mg	Disrupts vaginal flora FDA pregnancy category B
	Ciprofloxacin	125 mg	FDA pregnancy category C

[a] All doses are given daily unless otherwise specified.
Antibiotic dose recommendations assume normal renal function.
Abbreviations: TMP–SMX = trimethoprim–sulfamethoxazole; FDA = Food and Drug Administration.

Suggested reading

Cardozo L, Lose G, McClish D, et al. A systematic review of estrogens for recurrent urinary tract infections: Third report of the hormones and urogenital therapy (HUT) committee. *Int Urogynecol J*. 2001;12(1):15–20.

Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52(5):e103–120.

Hooton TM. Uncomplicated urinary tract infection. *N Engl J Med*. 2012;306(11):1028–1037.

Johnson J, Russo T. Acute pyelonephritis in adults. *N Engl J Med*. 2018; 378:48–59.

Lin K, Fajardo K; US Preventative Services Task Force. Screening for asymptomatic bacteriuria in adults: Evidence for the U.S. Preventative Services Task Force reaffirmation recommendation statement. *Ann Intern Med*. 2008;149(1):W20–W24.

Matthews P, Barrett L, Warren S, et al. Oral fosfomycin for the treatment of urinary tract infection: A retrospective cohort. *BMC Inf Dis*. 2016; 16:556.

Mody L, Juthani-Mehta M. Urinary tract infections in older women: A clinical review. *JAMA*. 2014;311(8):844–854.

Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis*. 2005;40(5):643–654.

Sangeeta S, Doi Y. Fosfomycin: Resurgence of an old companion. *J Infect Chemo*. 2016;22(5):273–280.

Schaeffer A, Nicolle L. Urinary tract infections in older men. *N Engl J Med*. 2016;374:562–571.

Sobel JD, Kaye D. Urinary tract infections. In Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 7th edn. Philadelphia, PA: Elsevier; 2010: 957–985.

Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: A randomized trial. *JAMA*. 2000;283(12):1583–1590.

Wilson ML, Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. *Clin Infect Dis*. 2004;38(8):1150–1158.

Wright OR, Safranek S. Urine dipstick for diagnosing urinary tract infection. *Am Fam Physician*. 2006;73(1):129–130.

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Candiduria

Jack D. Sobel

Since the early 1980s, the prevalence of candiduria in hospitals has increased by 200% to 300% such that in a community hospital, 5% of urine cultures may yield *Candida*, and in tertiary care centers, *Candida* accounts for almost 10% of urinary isolates, including a quarter of Foley catheter-associated infections. Most positive *Candida* urine cultures are isolated or transient findings of little significance and represent colonization of catheters rather than true infection. Although less than 10% of candidemias are the consequence of candiduria, *Candida* urinary tract infections (UTIs) have emerged as important nosocomial infections.

Candida albicans is the most common species isolated from the urine, whereas non-*albicans Candida* species account for almost half the *Candida* urine isolates. *Candida glabrata* is responsible for 25% to 35% of infections.

Predisposing factors

Candiduria is rare in the absence of predisposing factors. Most infections are associated with use of Foley catheters, internal stents, percutaneous nephrostomy tubes, and age extremes of life. Diabetic patients, especially when their diabetes is poorly controlled, are particularly at risk primarily because of increased instrumentation, urinary stasis, and obstruction secondary to autonomic neuropathy. Concomitant bacteriuria is common and bacterial adherence to bladder epithelium may play a key role in the pathogenesis of *Candida* infection. Antimicrobials similarly play a critical role in that candiduria almost always emerges during or immediately after antibiotic therapy. Antibiotics, especially broad-spectrum agents, act by suppressing protective indigenous bacterial flora in the gastrointestinal (GI) tract and lower genital tract, facilitating *Candida* colonization of these sites with ready access to the urinary tract. Nosocomial candiduria is more common in intensive care unit (ICU)-based catheterized women with concomitant contributory vaginal *Candida* colonization. The pool of critically ill, immunosuppressed medical, and surgical patients has increased, and this increase, together with improved technology, provides an expanded population at risk of developing *Candida* infection.

Most lower UTIs are caused by retrograde infection from an indwelling catheter or genital or perineal colonization. Biofilm formation contributes to *Candida* persistence in the presence of catheters and stents. The upper urinary tract is uncommonly involved during ascending retrograde infection and then only in the presence of urinary obstruction, reflux, or diabetes. Renal candidiasis is usually the consequence of secondary hematogenous seeding of the renal parenchyma; *Candida* species have a unique tropism for the kidney and result in anterograde candiduria.

Clinical aspects

Most adult patients with candiduria are asymptomatic, especially those with indwelling bladder catheters. Only 4% to 14% of patients with candiduria have symptoms of urinary infection. Clinical manifestations depend on the site of infection. *Candida* cystitis may present with frequency, dysuria, urgency, hematuria, and

pyuria. Ascending infection resulting in *Candida* pyelonephritis is characterized by fever, leukocytosis, and rigors and is indistinguishable from bacterial pyelonephritis. Excretory urography may reveal ureteropelvic fungus balls or papillary necrosis. Renal candidiasis is difficult to diagnose when secondary to hematogenous spread and presents with fever and other signs of sepsis. By the time renal candidiasis is considered, blood cultures are usually no longer positive; however, unexplained deteriorating renal function is often evident.

In contrast to adult patients, candiduria in low-birth-weight infants, especially extreme low weight (<1000 g), is synonymous with disseminated *Candida* infection and is associated with high mortality. This patient population is not further considered in this review.

Because isolation of *Candida* from a urine specimen may represent contamination, colonization, or superficial or deep infection of the lower or upper urinary tract, diagnosis is difficult and management depends on the site of infection. Contamination of the sample is particularly common in women with vulvovaginal colonization and may be excluded by repeating urine culture with special attention to proper collection techniques. Differentiating infection from colonization may be extremely difficult if not impossible in some patients, especially if they are catheterized. Accordingly, I often rely on accompanying clinical features to determine the significance of candiduria; unfortunately these are often nonspecific in critically ill patients, and fever and leukocytosis may have several other sources.

Quantitative urine colony counts have some value in separating infection from colonization but only in the absence of a Foley catheter. The latter negates any diagnostic value of quantitative cultures. In noncatheterized patients, counts greater than 10^4 colony-forming units (CFU)/mL are usually associated with infection. It is rare for patients with invasive disease of the kidney, pelvis, or bladder to have 10^3 CFU/mL or less. No definitive cutoffs for defining candiduria have been substantiated. Most patients with urinary tract *Candida* infection have pyuria, but the value of this finding is similarly diminished in the presence of a catheter or concomitant bacteriuria and in neutropenic subjects. Serologic tests of *Candida* tissue invasion are not available. Treatment is preceded by attempts to localize the source or anatomic level of infection. Unfortunately, no reliable tests to differentiate renal candidiasis from the more frequent lower tract infections exist. The extremely rare finding of *Candida* microorganisms and pseudohyphae enmeshed in renal tubular casts is useful when present. Ultrasonography and computed tomography (CT) scans have a useful but limited role in localization. A 5-day bladder irrigation with amphotericin B may be of value in localizing the source of candiduria in catheterized subjects in that post-irrigation persistent candiduria originates from above the bladder, thus identifying patients with need for further studies. Unfortunately, the lengthy nature of this diagnostic test excludes its utility in most febrile, critically ill subjects.

Prognosis

Prognosis depends on the anatomic site of *Candida* infection and the presence of urinary drainage tubes, obstruction, and concomitant renal failure. A high mortality rate of 20% is found in candiduria patients, which is more a reflection of the multiple serious illnesses found in these patients than the consequence of candiduria per se.

Management

More important than the knowledge of antifungal agents for treating candiduria is understanding the indications and rational basis for initiating treatment. Regrettably, despite the availability of a variety of potent antifungal agents, data from controlled studies are scant.

Asymptomatic candiduria

No antifungal therapy is required for asymptomatic candiduria in catheterized adult patients, a common condition, because candiduria often is transient only, and even if persistent rarely results in serious morbidity. Moreover, relapse of candiduria following therapy is common if the patient remains catheterized: In catheterized patients, removal of the catheter and discontinuation of antibiotics often results in cessation of candiduria (40%). Change of catheter results in elimination of candiduria in only approximately 20% of patients.

In contrast, persistent candiduria in noncatheterized patients should be investigated because the likelihood of obstruction and stasis is high. Persistent asymptomatic candiduria in catheterized, low-birth-weight infants, as well as in afebrile neutropenic patients, requires anti-fungal therapy and investigation to exclude the possibility of renal or systemic involvement. Patients with asymptomatic candiduria in whom urologic instrumentation or surgery is planned should have candiduria eliminated or suppressed before and during the procedure to prevent precipitating invasive candidiasis and candidemia. Successful elimination can be achieved by amphotericin B irrigation using a concentration of 50 μg/dL of sterile water for 7 days or with systemic therapy using amphotericin B, flucytosine, or fluconazole. Fluconazole, 200 to 400 mg/day, oral therapy should continue for at least 14 days to maximize cure rates. The management of asymptomatic candiduria in the renal transplant patient is perplexing. Many recipients are diabetic, are receiving perioperative antibiotics and immunosuppressive agents, and have Foley catheters and temporary ureterocystic stents. The risk of ascending infection is high given the above and frequent reflux. Fortunately, occurrence of symptomatic renal infection and candidemia is rare. A large study by Safdar et al. found that treatment and eradication of candiduria did not enhance graft on patient survival.

Candida cystitis

Symptomatic cystitis requires treatment with either amphotericin B bladder irrigation (50 μg/dL) or systemic therapy, once again using intravenous (IV) amphotericin B, flucytosine, or oral fluconazole.

Oral azole agents ketoconazole, itraconazole, and voriconazole are poorly excreted in the urine, and there is limited and suboptimal clinical experience only. In contrast, fluconazole is water soluble, well absorbed orally with more than 80% excreted unchanged in the urine, achieving high urine concentrations, and is highly effective. The optimal dose and duration of fluconazole therapy has yet to be determined, but usually 200 to 400 mg/day is prescribed for 7 to 14 days. Similarly, the duration of therapeutic bladder irrigation with amphotericin B is arbitrary, lasting 5 to 7 days. Amphotericin B bladder irrigation is extremely labor intensive and has largely fallen out of favor, even in symptomatic patients, being replaced by oral fluconazole except in the presence of azole-resistant *Candida* strains. Flucytosine is also excreted unchanged in high concentrations in the urine and is highly active against most *Candida* species, including *C. glabrata*; nevertheless, because resistance develops rapidly to flucytosine when used alone, this agent is rarely used especially because its use is precluded in renal insufficiency.

Single-dose IV amphotericin B, 0.3 mg/kg, has also been shown to be highly efficacious in the treatment of lower urinary tract candidiasis, achieving therapeutic urine concentrations for considerable time after the single administration. More prolonged systemic IV amphotericin B (7 to 10 days) and at conventional dosage of 0.5 to 0.7 mg/kg/day is preferable for resistant fungal species.

Ascending pyelonephritis and candida urosepsis

Invasive upper UTI requires systemic antifungal therapy as well as immediate investigation and visualization of the urinary drainage system to exclude obstruction, papillary necrosis, and fungus ball formation. Previously favored therapy consisted of IV amphotericin B, 0.5 to 0.7 mg/ kg/day, for a variable duration depending on severity of infection, presence of candidemia, and response to therapy, in general 1 to 2 g total dose. However, systemic therapy with fluconazole, 5 to 10 mg/kg/day (IV or oral) for at least 2 weeks offers an effective and less toxic alternative regimen. Moreover, although the echinocandin class of antifungals (caspofungin, micafungin, and anidulafungin) achieves low urinary concentrations, they are effective for kidney parenchymal infections and particularly useful for *Candida* species resistant to azoles. Infection refractory to medical management should be treated surgically with drainage, or in cases of a nonviable kidney, nephrectomy may be indicated. An obstructed kidney with hydronephrosis requires a percutaneous nephrostomy. In some cases, nephrostomy drainage must be combined with local amphotericin B irrigation (50 μg/dL) or fluconazole, particularly with end-stage renal disease and low urinary levels of antifungal agents.

Renal and disseminated candidiasis

Management of renal candidiasis secondary to hematogenous spread is that of systemic candidiasis, including IV amphotericin B, 0.6 to 1.0 mg/kg/day, or IV fluconazole, 5 to 10 mg/ kg/ day. IV voriconazole, 4 mg/ kg twice a day, or any of the echinocandins could be used in preference to amphotericin B. Dosage modifications of fluconazole but not the echinocandins are necessary in the presence of moderate to severe azotemia. Prognosis depends on correction of underlying factors, that is, resolution of neutropenia, removal of responsible intravascular catheters, and susceptibility of the *Candida* species, but most importantly the nature and prognosis of the underlying disease per se. Systemic candidiasis involving metastatic sites of infection requires prolonged therapy for approximately 4 to 6 weeks.

Suggested reading

Achkar JM, Fries BC. Candida infections of the genitourinary tract. *Clin Microbiol Rev*. 2010;23:253–273.

Ang BSP, Telenti A, King B, et al. Candidemia from a urinary tract source: microbiological aspects and clinical significance. *Clin Infect Dis*. 1993;17:662–666.

Drew RH, Arthur RR, Perfect JR, et al. Is it time to abandon the use of amphotericin B bladder irrigation? *Clin Infect Dis*. 2005;40:1465–1470.

Fisher JF, Kavanagh K, Sobel JD, Kauffman CA, Newman CA. Candida urinary tract infection: pathogenesis. *Clin Infect Dis*. 2011;52(Suppl 6):S437–S451.

Fisher JF, Sobel JD, Kauffman CA, Newman CA. Candida urinary tract infections–treatment. *Clin Infect Dis*. 2011;52(Suppl 6):S457–S466.

Helbig S, Achkar JM, Jain N, et al. Diagnosis and inflammatory response of patients with candiduria. *Mycoses*. 2013;56:61–69.

Kauffman CA, Fisher JF, Sobel JD, Newman CA. Candida urinary tract infections–diagnosis. *Clin Infect Dis*. 2011;52(Suppl 6):S452–S456.

Kauffman CA, Vazquez JA, Sobel JD, et al. A prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. *Clin Infect Dis*. 2000;30:14–18.

Kauffman CA, Vazquez JA, Sobel JD. Candiduria. *Clin Infect Dis*. 2005;41(Suppl 6):S371.

Pappas PG. Infectious Diseases Society of America: guidelines for treatment of candidiasis. *Clin Infect Dis*. 2009;48:503–535.

Rivett AG, Perry JA, Cohen J. Urinary candidiasis: a prospective study in hospitalized patients. *Urol Res*. 1986;14: 183–186.

Safdar N, Slattery WR, Knasinski V, et al. Predictors and outcomes of candiduria in renal transplant recipients. *Clin Infect Dis*. 2005;40:1413–1421.

Shay AC, Miller LG. An estimate of the incidence of Candiduria among hospitalized patients in the United States. *Infect Control Hosp Epidemiol*. 2004;25:894–895.

Sobel JD, Fisher JF, Kauffman CA, Newman CA. Candida urinary tract infections–epidemiology. *Clin Infect Dis*. 2011; 52(Suppl 6):S433–S436.

Sobel JD, Kauffman CA, McKinsey D, et al. Candiduria—a randomized double-blind study of treatment with fluconazole and placebo. *Clin Infect Dis*. 2000;30:19–24.

Wise GJ, Silver DA. Fungal infections of the genitourinary system. *J Urol*. 1993;149: 1377–1388.

67

Focal renal infections and papillary necrosis

Ann F. Fisher and Louise M. Dembry

Focal infections of the kidney can be divided into intrarenal and perirenal pathology (Box 67.1). The classification of intrarenal abscess encompasses renal cortical abscess and renal corticomedullary abscess; the latter includes acute focal bacterial nephritis (AFBN), acute multifocal bacterial nephritis, and xanthogranulomatous pyelonephritis (XGP). Perirenal abscesses are found in the perinephric fascia external to the capsule of the kidney, generally occurring from extension of an intrarenal abscess. Papillary necrosis is a clinicopathologic syndrome that develops during the course of a variety of syndromes, including pyelonephritis; it affects the renal medullary vasculature and leads to ischemic necrosis of the renal medulla. The resultant sloughing of papillae may lead to urinary tract obstruction and potentially further renal impairment.

Renal cortical abscess

A renal cortical abscess results from hematogenous spread of bacteria from a primary focus of infection outside the kidney, often the skin. The most common causative agent is *Staphylococcus aureus* (90%). Predisposing conditions include entities associated with an increased risk for staphylococcal bacteremia, such as immunodeficiency, diabetes mellitus, hemodialysis, and injection drug use. The primary focus of infection may not be apparent in up to one-third of cases. Ascending infection is an infrequent cause of renal cortical abscess formation. On rare occasions a renal cortical abscess ruptures through the renal capsule, forming a perinephric abscess.

Patients, predominantly males, present with chills, fever, and back or abdominal pain, with few or no localizing signs (Table 67.1). Most patients do not have urinary symptoms as the process does not generally communicate with the excretory passages. Physical examination may reveal costovertebral angle tenderness and involuntary guarding of the upper lumbar and abdominal musculature. A flank mass or bulge in the lumbar region with loss of lumbar lordosis may be present.

Laboratory data vary, though leukocytosis is common. Radiologic techniques can establish the diagnosis. Ultrasonography is useful diagnostically, may guide percutaneous drainage of the abscess, and may be used to follow response to therapy. CT is the most precise noninvasive diagnostic technique and may guide percutaneous aspiration. MRI with gadolinium may help diagnose a renal abscess and define its extent with accuracy comparable to CT, but without exposure to radiation and ionizing contrast.

Renal cortical abscesses often respond to antibiotics alone without surgical intervention. If the diagnosis is suspected and bacteriologic evaluation of the urine or aspirated abscess fluid reveals large, gram-positive cocci or no bacteria, anti-staphylococcal therapy should be started promptly (Table 67.2). The choice of empiric therapy depends on the susceptibility patterns of *S. aureus* in the community. If methicillin susceptible *S. aureus* (MSSA) is suspected, a semisynthetic penicillin (e.g., oxacillin or nafcillin) or a first-generation cephalosporin, such as cefazolin, is appropriate empiric therapy. Vancomycin should be reserved for patients with a severe immediate β-lactam allergy. If the prevalence of methicillin-resistant *S. aureus* (MRSA) is high,

BOX 67.1

Focal renal infections

Intrarenal abscesses
Renal cortical abscesses (renal carbuncle)
Renal corticomedullary abscesses
- Acute focal bacterial nephritis (acute lobar nephronia)
- Acute multifocal bacterial nephritis
- Xanthogranulomatous pyelonephritis

Perinephric abscesses

empiric therapy with vancomycin should be initiated. In the absence of occult bacteremia, parenteral antibiotics are administered for 10 to 14 days, followed by oral anti-staphylococcal therapy for at least 2 to 4 more weeks. Fever generally resolves after 5 to 6 days of antimicrobial therapy. If there is no response to therapy in 48 hours, percutaneous aspiration should be considered, and, if unsuccessful, open drainage should be undertaken. The prognosis is good if the diagnosis is made promptly and effective therapy is instituted immediately.

Renal corticomedullary abscess

Renal corticomedullary abscesses occur most commonly as a complication of bacteriuria and ascending infection accompanied by an underlying urinary tract abnormality. The most common abnormalities include obstructive processes, genitourinary abnormalities associated with diabetes mellitus or primary hyperparathyroidism, and vesicoureteral reflux. Immunodeficiency conditions, such as HIV/AIDS and renal transplantation, are also risk factors. Enteric aerobic gram-negative bacilli, including *Escherichia coli, Klebsiella*, and *Proteus* species, are common causative organisms. Corticomedullary abscesses can extend and result in perinephric collections. A severe form of acute bacterial interstitial nephritis involving a single renal lobe, AFBN, represents focal inflammation of the kidney without frank abscess formation and may be an early transition phase from acute pyelonephritis to acute multifocal bacterial nephritis or renal abscess. XGP, often clinically indistinguishable from acute pyelonephritis, is an uncommon but severe chronic infection of the renal parenchyma. It is defined by a granulomatous process containing lipid-laden macrophages (i.e., foam cells). It may be related to a combination of obstruction of the renal collecting system due to nephrolithiasis and chronic urinary tract infection. Other

TABLE 67.1 **CLINICAL AND LABORATORY FINDINGS OF RENAL AND PERIRENAL ABSCESSES**

	Renal cortical abscess	Renal corticomedullary abscess	Perinephric abscess
Epidemiology	Males 3× more than females, 2nd–4th decades, hematogenous seeding of kidneys	Frequency is equal in males and females (though 70% of XGP cases are female), incidence increases with age, underlying abnormality of the urinary tract, diabetes mellitus, or immunodeficiency	Males = females, 25% of patients are diabetic, rupture of intrarenal suppurative focus into perinephric space
Clinical presentation	Fever, chills, localized back or abdominal pain	Fever, chills, flank or abdominal pain, nausea and vomiting (65%), weight loss	Insidious onset over 2–3 weeks: fever (early), flank pain (late)
Urinary symptoms	None[a]	Dysuria/other urinary tract symptoms variably present	Dysuria 40%
Physical exam	Flank mass	Unilateral flank mass in 60%, hepatomegaly in 30%	Flank or abdominal mass in ≤50%, 60% have abdominal tenderness
Organisms	*S. aureus*	Enteric aerobic gram-negative rods (*Escherichia coli*, *Klebsiella* spp., *Proteus mirabilis), Pseudomonas, S. aureus.* XGP: 25% are culture negative	Enteric aerobic gram-negative rods with *Proteus* predominance and *S. aureus*; occasionally *Pseudomonas* spp., gram-positive bacteria, obligate anaerobic bacteria, fungi, mycobacteria; 25% polymicrobial
Urinalysis	Normal[a]	Abnormal in 70%	Abnormal in 70%
Urine cultures	Negative[a]	Positive in 60%	Positive in 60%
Blood cultures	Often negative	Often positive	Positive in 40%
Radiologic Findings	Ultrasound: hypoechoic/anechoic mass with internal debris; CT with contrast: enhanced collection	AFBN: Ultrasound demonstrates renal mass with decreased echogenicity. CT scan: hypo perfused wedge/round lesion with no capsule. 1/3 have ascites. XGP: Bear paw sign (CT)	CT scan: rim enhanced collection, central hypoattenuation (rind sign), thickened perinephric fascia and stranding

[a] If there is no communication between the abscess and the collecting system.

TABLE 67.2 **THERAPY OF RENAL AND PERIRENAL ABSCESSES**

	Empiric therapy[a]	Duration[a]	Drainage	Surgery
Renal cortical abscess	Anti-staphylococcal penicillin: oxacillin or nafcillin (1–2 g IV q4–6h) or first-generation cephalosporin: cefazolin (2 g IV q8h) or vancomycin (15 mg/kg IV q12h) if severe immediate β-lactam allergy or if MRSA is suspected	Intravenous antibiotics for 10–14 days followed by 2–4 weeks oral anti-staphylococcal agent depending on antibiotic susceptibility testing	If no response to treatment after 48 h, percutaneous drainage followed by open drainage if no response	
Renal corticomedullary abscess				
Acute focal bacterial nephritis	Extended-spectrum penicillin (piperacillin–tazobactam 3.375 g IV q6h), extended-spectrum cephalosporin (ceftriaxone 1 g IV q24h, fluoroquinolone (ciprofloxacin 200–400 mg IV q12h), ampicillin (1 g IV q4–6h) with gentamicin or cefazolin (1 g q8h) with gentamicin	Intravenous for 24–48 h after resolution of symptoms and fever followed by 2 weeks oral antibiotics based on results of susceptibility testing (cefpodoxime 200 mg q12h or ciprofloxacin 500 mg q12h)	Generally not necessary	
Acute multifocal bacterial nephritis	Same as acute focal bacterial nephritis	Same as acute focal bacterial nephritis	If slow response to antibiotics or large abscess, presence of obstructive uropathy, urosepsis, or advanced age	
Xanthogranulomatous pyelonephritis	Same as acute focal bacterial nephritis	Same as acute focal bacterial nephritis		Surgical excision usually necessary for cure (partial nephrectomy or total nephrectomy)
Perinephric abscess	Initiate broad spectrum gram negative coverage such as piperacillin–tazobactam 4.5 g IV q6h, cefepime 2 g IV q12h, or ceftazidime 2 g IV q8h). Empiric Vancomycin should be included if staphylococcal infection suspected. For β-lactam allergy: ciprofloxacin 200–400 mg IV a12h and. For ESBL-producing organisms, use a carbapenem.	Initial parenteral therapy until clinical improvement, change to appropriate oral therapy until radiographic studies indicate resolution of process	Requires percutaneous drainage followed by open surgical drainage if no resolution	Nephrectomy in cases that do not resolve with antibiotics and drainage

[a] Dosages based on normal renal and hepatic function.
ESBL, extended-spectrum β-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*.

predisposing factors include urinary obstruction, lymphatic obstruction, renal ischemia, alterations in lipid metabolism, abnormal host immune response, diabetes mellitus, and primary hyperparathyroidism. Due to the insidious nature of XGP, extrarenal fistulas and psoas abscess may also be present at the time of diagnosis. These lesions can mimic renal tumors and often require differentiation through pathologic testing.

Patients typically present with fever, chills, and flank or abdominal pain. Two-thirds of patients have nausea and vomiting, and dysuria may not be present. In some patients, symptoms may be subtle thus delaying the diagnosis. Patients may have a history of recurrent urinary tract infections or prior genitourinary instrumentation. The majority of patients have renal calculi, of which 50% are staghorn calculi. Patients may have a flank mass and/or hepatomegaly on exam. The urinalysis is often abnormal with bacteriuria, pyuria, proteinuria, and hematuria. Patients with acute focal or multifocal bacterial nephritis are frequently bacteremic. Many patients are anemic and have liver function abnormalities.

The nonspecific clinical presentation is associated with a variety of renal processes, including renal cortical abscess, perinephric

abscess, renal cysts, and tumors. Radiographic techniques are necessary to differentiate these various space-occupying lesions. Gray-scale ultrasonography and CT scanning are both used for diagnosing renal corticomedullary abscesses except for XGP, for which gray-scale ultrasound is less specific than CT. For XGP, CT scanning will often demonstrate dilated calyces, a thin parenchyma, and central calculus: the "bear paw sign." More recent validation of contrast-enhanced ultrasound has increased sensitivity in evaluating these lesions as well as allowing the avoidance of nephrotoxic contrast materials and radiation exposure. Alternatively, MRI may be considered for patients with renal insufficiency or allergy to iodinated contrast material.

Determination of empiric antimicrobial treatment should take into consideration the type of renal infection suspected as well as patient factors such as previous urine culture isolates and previous antimicrobial exposure. Fluoroquinolone-resistant and ESBL-producing *E. coli* urinary tract infections are increasing in frequency worldwide. Knowledge of risk, such as healthcare exposure, types of antimicrobial exposure, and travel to endemic areas, can inform the decision to use a carbapenem. It is also recommended to consider the possible risk of carbapenem resistance based on local resistance patterns and patient risk factors. Most patients with acute focal and multifocal bacterial nephritis respond to antibiotic treatment alone within 1 week of starting therapy. Radiologic techniques should be used early for slow response assessment and to ensure resolution of the parenchymal abnormalities after clinical resolution. An intensive trial of appropriate antibiotic therapy can be attempted before considering surgical drainage for lesions localized to the renal parenchyma. A large, well-established abscess may be more difficult to treat successfully with antimicrobial agents alone. Most intrarenal abscesses <3 cm respond to antimicrobial therapy alone, whereas abscesses >3 cm often require percutaneous or surgical drainage. Parenteral antimicrobial agents and intravenous hydration should be administered promptly when the diagnosis is considered. Empiric antimicrobial therapy is directed against the common bacterial organisms in this setting, including *E. coli, Klebsiella*, and *Proteus* spp. (Table 67.2). An extended-spectrum penicillin (e.g., piperacillin–tazobactam) or cephalosporin (e.g., ceftriaxone or cefotaxime) or ciprofloxacin are all appropriate choices. Empiric fluoroquinolones should be avoided as a single agent if local *E. coli* resistance is >10%. Antimicrobial therapy should be modified based on the results of culture and sensitivity testing. Duration of therapy should be individualized. Parenteral antimicrobial therapy should be continued for at least 24 to 48 hours after improvement of symptoms and resolution of fever. Oral antibiotic therapy, based on antimicrobial susceptibility results and oral bioavailability of the agent, is then administered for an additional 2 weeks.

AFBN typically responds to antimicrobial therapy alone, with follow-up radiographic studies showing complete resolution of the intrarenal lesion. Only occasionally is a drainage procedure necessary. Factors associated with failure to respond to antimicrobial therapy alone include large abscesses, obstructive uropathy, advanced age, and urosepsis. Percutaneous abscess aspiration, sometimes with repeated aspirations, combined with parenteral antibiotics has been successful. If obstructive uropathy is present, prompt drainage by percutaneous nephrostomy until the patient is stable and afebrile is appropriate, at which time the lesion should then be corrected. Nephrectomy is reserved for patients with diffusely damaged renal parenchyma or patients requiring urgent intervention for survival in the setting of sepsis.

Patients with XGP generally require surgical excision of the xanthogranulomatous process for cure, although there have been case reports of successful treatment without surgical intervention. Once the tissue is removed, the xanthogranulomatous process ceases and does not recur; however, bacteriuria may recur and require treatment. After excision, the prognosis in those without other urinary pathologic conditions is excellent.

Perinephric abscess

The common etiologic agents of intrarenal abscesses, *E. coli, Proteus* species, and *S. aureus*, are also the common organisms associated with perinephric abscesses. Other gram-negative bacilli associated with this entity are *Klebsiella*, *Enterobacter*, *Pseudomonas*, *Serratia*, and *Citrobacter* species. Occasionally enterococci are implicated, and anaerobic bacteria may account for culture-negative abscesses. Fungi, particularly *Candida* spp., are also important, as is *Mycobacterium tuberculosis*.

A perinephric abscess is a collection of suppurative material in the perinephric space between the renal capsule and Gerota's fascia. Most perirenal abscesses result from the rupture or direct extension of an intrarenal abscess into the perinephric space; chronic or recurrent pyelonephritis, particularly in the presence of obstruction; and XGP. Predisposing conditions for perinephric abscesses are similar to those for intrarenal abscesses. Most patients have underlying urinary tract abnormalities. Patients with polycystic kidney disease, neurogenic bladder, or chronic or recurrent urinary tract infections, with or without calculi, and immunodeficiency may also be at increased risk.

The symptoms of perinephric abscess develop insidiously over a period of 2 to 3 weeks (Table 67.1). Fever is present in 50% of patients. Unilateral flank pain is common (70–80%), whereas chills and dysuria are less common (40%). Costovertebral angle tenderness is often present on exam, and 60% of patients may have abdominal tenderness. Half the patients have a flank or abdominal mass.

The diagnosis should be strongly considered in any patient with a febrile illness and unilateral flank pain that does not respond to therapy for acute pyelonephritis. Contrast-enhanced CT is the radiographic study of choice as it identifies the abscess and defines its extent beyond the renal capsule and the surrounding anatomy, including extension into the psoas muscle. Classic findings are a rim-enhanced collection with central hypoattenuation, "the rind sign," with thickened perinephric fascia and stranding. MRI is an acceptable imaging modality when avoidance of exposure to radiation and iodinated contrast is desired. Ultrasound may identify the abscess structure and extent, although sensitivity is less than with CT imaging.

Early recognition and management contribute to decrease the mortality associated with this entity. Antimicrobial therapy alone is usually inadequate, and percutaneous drainage should be considered. Surgical drainage is considered when an abscess is multilocular, percutaneous drainage fails, or is contraindicated. Most cavities

spontaneously resolve after drainage and antimicrobial therapy. Acute nephrectomy is occasionally indicated. Empiric antimicrobial therapy should be directed against the most common gram-negative pathogens and *S. aureus* (Table 67.2). An aminoglycoside and an anti-staphylococcal β-lactam (e.g., oxacillin, nafcillin), or cephalosporin (i.e., cefazolin) are appropriate initial antibiotics. If MRSA is suspected, vancomycin should be used instead of an anti-staphylococcal β-lactam. A broad spectrum β-lactam may be used in place of an aminoglycoside for gram-negative coverage. When *Pseudomonas aeruginosa* is identified, an anti-pseudomonal β-lactam (e.g., piperacillin–tazobactam, cefepime, or ceftazidime) should be included with or without an aminoglycoside. Alternatively, the aminoglycoside may be discontinued and ciprofloxacin given. If an ESBL-producing gram-negative organism is suspected a carbapenem should replace a β-lactam. If enterococcus is isolated, ampicillin plus gentamicin is the treatment of choice. Therapy should be modified based on culture and antimicrobial susceptibility testing results. Perinephric abscesses caused by mycobacteria and fungi are treated with appropriate antimicrobial agents based on the organism and antimicrobial susceptibility testing.

Perinephric abscesses may cause ureteral compression leading to hydronephrosis. Even after drainage, ureteral stenosis from periureteritis may evolve during the healing process, a late complication of this disease.

Renal papillary necrosis

Renal papillary necrosis is an uncommon severe complication of pyelonephritis (2–5%) that occurs most often with underlying structural renal abnormalities or host immunocompromise (more than half of patients are diabetic) (Box 67.2). Additionally, minimal ischemic insults can result in necrosis due to the limited vasculature of the renal papillae. When papillary necrosis is caused by infection, both kidneys are frequently affected with one or more pyramids involved. As the lesion progresses, a portion of the necrotic papilla may break off, producing a calyceal deformity that results in a recognizable radiologic filling defect. The sloughed portion may be voided and can be recovered from the urine.

Patients present with worsening symptoms of preexisting pyelonephritis. They may have lumbar pain, hematuria, and fever. The diagnosis should be considered in diabetic patients with active pyelonephritis who experience a rapid clinical deterioration and/or worsening renal function. Multiphasic helical CT is helpful in identifying early papillary necrosis. CT may reveal the "ring sign," an area of contrast surrounding a crescent-shaped papilla.

Therapy is directed toward control of infection generally caused by common uropathogens including *E. coli, Proteus*, and *Klebsiella* species (Table 67.2, renal corticomedullary abscess treatment). If the patient does not respond promptly to appropriate antimicrobial therapy, obstruction cannot be alleviated, and infection is subsequently not controlled, nephrectomy may be needed.

BOX 67.2

Conditions associated with development of papillary necrosis

Diabetes mellitus
Pyelonephritis
Obstruction
Analgesic abuse
Sickle cell disease
Renal transplantation

Suggested reading

Al-Delfi F, Herrera GA. Xanthogranulomatous pyelonephritis. *Pathology Case Rev*. 2015;20:256–259. https://journals.lww.com/pathologycasereviews/toc/2015/11000

Buanaiuto VA, Marquez I, De Toro I, et al. Clinical and epidemiological features and prognosis of complicated pyelonephrosis: A prospective observational single hospital-based study. *BMC Infect Dis*. 2014;14:639–747.

Campos-Franco J, Macia C, Huelga E. Acute focal bacterial nephritis in a cohort of hospitalized adult patients with acute pyelonephritis. Assessment of risk factors and a predictive model. *Eur J Intern Med*. 2017;39:69–74.

Chaudhary HM, Abou Karam A, Calleros-Macias, JE. Everyday practice: Spectrum of urinary tract infections. *Contemp Diagn Radiol*. 2016;39:1–5. https://journals.lww.com/cdronline/toc/2016/09150

Fontanilla T, Minaya J, Cortes C, et al. Acute complicated pyelonephritis: Contrast-enhanced ultrasound. *Abdom Imaging*. 2012;37(4):639–646.

Gardiner RA, Gwynne RA, Roberts SA. Perinephric abscess. *BJU Int*. 2011;107(Suppl 3):20–23.

Hooten J. Urinary tract infections in adults. In Feehally J, Floege J, Tonelli M, Johnson RJ, eds. *Comprehensive clinical nephrology* (6th ed.). Philadelphia, PA: Elsevier; 2018:626–638.

Johnson JR, Russo TA. Acute pyelonephritis in adults. *N Engl J Med*. 2018;378(12):48–59.

Kim YK, Seo MR, Kim SJ. Usefulness of blood cultures and radiologic imaging studies in the management of patients with community-acquired acute pyelonephritis. *Infect Chemother*. 2017;49(1):22–30.

Nanda N, Dembry LM. Renal and perirenal abscesses. In Coffman TM, Falk RJ, Molitoris BA, Neilson EG, Schrier RW, eds. *Schrier's Diseases of the Kidney* (9th ed.). Philadelphia, PA:Wolters Kluwer Health; 2012:725–737.

Ruiz-Mesa JD, Marquez-Gomez I, Sena G. Factors associated with severe sepsis or septic shock in complicated patients. *Medicine*. 2017;96(43):e8371.

Schneeberger C, Holleman F, Geerlings S. Febrile urinary tract infections: Pyelonephritis and urosepsis. *Curr Opin Infect Dis*. 2016;29(1):80–85.

Sieger N, Kyriazis I, Schaudinn, et al. Acute focal bacterial nephritis is associated with invasive procedures: A cohort of 138 cases extracted through a systematic review. *BMC Infect Dis*. 2017;17(1):240–249.

Talan DA, Takhar SS, Krishnadasan A, et al. Fluoroquinolone-resistant and extended-spectrum β-lactamase-producing *Escherichia coli* infections in patients with pyelonephritis, United States. *Emerg Infect Dis*. 2016;22(9):1595–1603.

Wang PS. Xanthogranulomatous pyelonephritis. *Ultrasound Q*. 2016;32(3):310–311.

Section 9

Clinical syndromes: Musculoskeletal system

68

Infection of native and prosthetic joints

Shahbaz Hasan and James W. Smith

Native joint infections

Infections of native joints generally occur in patients with predisposing factors such as trauma, underlying arthritis, immunosuppressive therapy, diabetes mellitus, malignancies, intravenous drug abuse, and other infections (e.g., endocarditis, skin infections, and urinary tract infections). Hematogenous spread of the organism through the highly vascular synovial space leads to an influx of polymorphonuclear leukocytes (PMLs) into the synovium and then to a release of enzymes that destroy the articular surface.

Diagnosis

Patients present with pain and limited motion of the joint. Fever may be mild, with only a few patients having a temperature higher than 39°C (102.2°F). Joint tenderness can be minimal to severe, but most patients have swelling as a result of joint effusions in response to the infection. Involvement of multiple joints is seen in 10% to 20% of cases, especially in viral arthritis and rheumatoid arthritis. Laboratory findings suggestive of septic arthritis include an elevated erythrocyte sedimentation rate and synovial fluid cell counts exceeding 50 000/mL, with more than 75% PMLs. In no individual case do any of these findings distinguish infected from inflammatory arthritis, such as rheumatoid or crystalline arthropathy, so the diagnosis is based on cultures of synovial fluid. On occasion, blood cultures may be positive. In patients with a chronic monoarticular process caused by mycobacterial or fungal organisms, synovial tissue cultures provide a better yield than synovial fluid cultures. Serum antibody tests provide the diagnosis of Lyme or viral arthritis. Polymerase chain reaction (PCR) assay of the joint fluid may yield the diagnosis in partially treated patients or in patients' infections caused by fastidious organisms such as *Mycoplasma, Chlamydia*, or *Borrelia burgdorferi* (Lyme disease). Plain radiographs are seldom of use diagnostically. Computed tomography (CT) and magnetic resonance imaging (MRI) provide more detail of the surrounding soft tissue and may reveal adjacent osteomyelitis. Radionuclear scans may be needed to visualize the sacroiliac joint; however, they are unable to distinguish septic arthritis from other inflammatory arthritis.

Staphylococcus aureus is the most common organism isolated in native bacterial arthritis. However, a variety of other gram-positive and gram-negative organisms have been reported as agents in monoarticular bacterial arthritis. *Neisseria gonorrhoeae* is the main cause of bacterial arthritis in sexually active individuals with no underlying joint disease. It presents with a syndrome of fever, skin lesions, and polyarticular involvement, often with associated tenosynovitis. Any of a number of mycobacterial and fungal organisms can cause a chronic, slowly progressive infection of a single joint with tenosynovitis. Viral agents commonly associated with arthritis include rubella and parvovirus B19 (erythema infectiosum or fifth disease) in women and mumps in men. Hepatitis B infection may manifest as a prodromal syndrome consisting of arthritis and urticaria that disappear with the onset of jaundice.

Therapy

Empiric antimicrobial therapy for suspected bacterial arthritis is started after obtaining appropriate fluid specimens for analysis and culture. The choice of antibiotics depends on the patient's age, risk factors, and results of the synovial fluid Gram stain (Figure 68.1). The antibiotics are modified after obtaining the culture results. The usual course of antibiotics is 2 weeks. Infections from staphylococci and gram-negative bacilli require 3 weeks of treatment. Mycobacterial and fungal infections are treated for up to a year. Initial therapy by causative organism is given in Table 68.1.

Infected joint effusions require repeated needle aspirations of recurrent joint effusions during the first 5 to 7 days of antimicrobial therapy. Most patients respond to needle aspiration. If the volume of fluid and number and percentage of PMLs decrease with each aspiration, no drainage is required. However, if the effusion persists for more than 7 days or the cell count does not decrease, surgical drainage is indicated. Surgical drainage is also indicated when effective decompression with needle aspiration is unlikely (hip joint) or when the joint is not accessible for aspiration (sternoclavicular and sacroiliac joints); if the joint space has become loculated as a result of formation of adhesions; or if thick, purulent material resisting aspiration is encountered. Arthroscopic drainage is an alternative to open drainage for the knee, shoulder, and ankle joints.

Prognosis

Bacterial arthritis is associated with a mortality of 10% to 15%. Up to 25% to 50% of surviving patients are left with residual loss of joint function. Poor outcomes are commonly seen in the elderly and those with severe underlying joint disease, hip infections, or infections caused by mycobacterial or fungal agents.

Prosthetic joint infections

Prosthetic joint surgery has been used with increasing frequency over the past 4 decades. About 1 000 000 arthroplasties are performed in the United States each year. Although most procedures involve the hip and knee joints, arthroplasties of the elbow, shoulder, and wrist are also being performed. Primary indications for surgery generally include rheumatoid arthritis, degenerative joint disease, fractures, and septic arthritis.

Ten-year implant survival rates of 70% to 90% are being achieved at most centers. Most failures result from aseptic loosening of the prosthesis, with infectious complications accounting for fewer than 1% of implant failures. These prosthesis infections necessitate extensive surgical procedures and prolonged use of antibiotics, all of which result in increased cost, morbidity, and rarely, mortality. Risk factors for the development of prosthesis infection include rheumatoid arthritis, previous surgeries at the joint, postoperative wound infection, hematoma, and unhealed or draining wounds at hospital discharge. Other risk factors include sinus tracts to the surgical site, obesity, age, use of immunosuppressive therapies, diabetes mellitus, and distant site infections, especially urinary tract and skin infections. Varying frequency of infection is noted with different joints: Incidence of infections for hip arthroplasties is less than 1%; for knees 1% to 2%; and for elbows 4% to 9%.

Direct inoculation of the joint at the time of surgery and intraoperative airborne contamination probably account for most infections. Evidence of the importance of this is demonstrated by the preponderance of infections caused by skin commensals (Table 68.2) and by reduction in frequency of infection that accompanies the use of prophylactic antibiotics. Hematogenous seeding of the implants is implicated in infections occurring more than 2 years postoperatively.

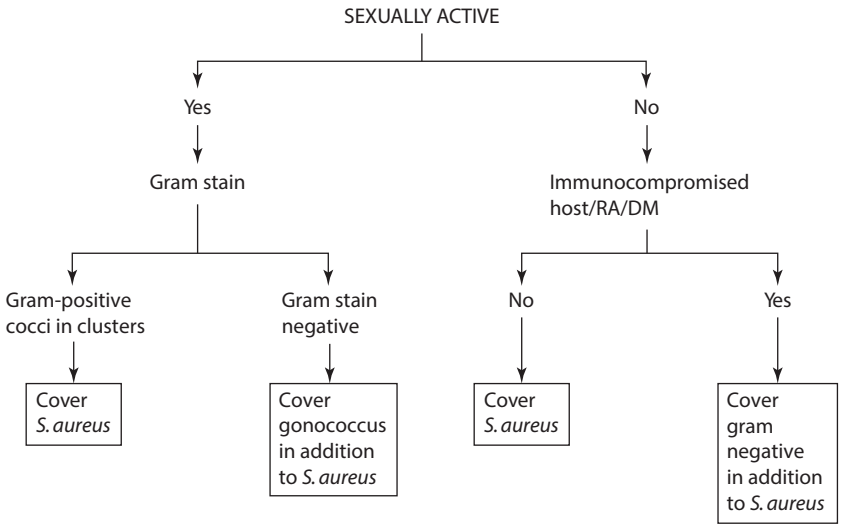

FIGURE 68.1 Empiric antibiotic coverage for nontraumatic, acute monoarticular arthritis. RA = rheumatoid arthritis; DM = diabetes mellitus.

TABLE 68.1 **THERAPY FOR BACTERIAL ARTHRITIS OF NATIVE JOINTS**

Microorganism/infection	Treatment	Duration
Staphylococcus aureus	Penicillinase-resistant penicillins,[a] first-generation cephalosporin,[b] or cefuroxime, 1.5 g q8h	3–4 wk
Methicillin-resistant S. aureus or patient allergic to penicillin	Vancomycin, 1 g q12h daptomycin 4–6 mg/kg/d, or linezolid 600 mg q12h	3–4 wk
Streptococci	Penicillin G, 4 million units q6h, or first-generation cephalosporin[b] or clindamycin, 300 mg q8h	2 wk
Gram-negative bacilli	Antipseudomonal cephalosporins,[c] carbapenem,[d] quinolone[e]	3–4 wk
Disseminated gonococcal infection	Ceftriaxone, 1 g q24h until response, then cefixime, 400 mg PO BID	7–10 d
Septic gonococcal arthritis	Ceftriaxone, 1 g q24h	3 wk
Lyme arthritis	Doxycycline, 100 mg PO BID, or ceftriaxone, 2 g q24h IV	4 wk, 2 wk
Mycobacterium tuberculosis	Isoniazid, 300 mg/d, plus rifampin, 600 mg/d, with ethambutol, 15 mg/kg/d, and pyrazinamide, 1500 mg/day for the first 2 mo	1 y
Fungal arthritis	Amphotericin B, 0.5–0.7 mg/kg/d for a total of 2 g, then itraconazole, 200–400 mg/d PO, or fluconazole, 200–400 mg/d PO	1 y

[a] Nafcillin, 2 g q6h IV.
[b] Cefazolin, 1 g q8h IV, or cephalothin, 1–2 g q6h IV.
[c] Ceftazidime, 2 g q8h IV, or cefepime, 1 g q12h IV.
[d] Imipenem–cilastatin, 500 mg q6h IV, or meropenem, 500 mg q8h IV.
[e] Ciprofloxacin, 400 mg q12h IV, or levofloxacin, 500 mg q24h IV.
Abbreviations: PO = orally; BID = twice a day; IV = intravenously.

Diagnosis

The diagnosis of acute prosthetic joint infection is suspected in those who develop pain and fever within 6 months of the procedure. These findings are similar to those of acute septic arthritis in a native joint. However, most infections tend to be indolent and manifest with local pain and mechanical loosening of the prosthesis. Clinical features, laboratory tests, and imaging techniques may be insufficient to differentiate between aseptic and septic complications (Table 68.3). Hence, the diagnosis of an infection often has to be confirmed on the basis of the intraoperative appearance of the tissues and the presence or absence of acute inflammatory reaction on the intraoperative histopathology specimens. Given the heterogeneity of organisms (see Table 68.2), the joint fluid and tissues must be submitted for aerobic and anaerobic bacterial, fungal, and mycobacterial cultures. Microbiologic culture yield is improved if sampling of tissues is performed with the patient being off antimicrobials for 1 to 2 weeks.

TABLE 68.2 **MICROBIOLOGY OF PROSTHETIC JOINT INFECTIONS**

Organism	Percentage
Staphylococcus aureus	25
Coagulase-negative staphylococci	25
Streptococci	5–10
Enterococci	3–5
Gram-negative bacilli	8–10
Anaerobes	5–10
Mixed	10–15
Others (fungi, mycobacteria, actinomyces, brucella)	1–2

Therapy

The object of successful management of prosthetic joint infections is 2-fold: eradication of infection and maintenance of functional integrity of the joint. Two-stage reimplantations offer the best possible chance for eradication of infection. However, not all patients may be suitable candidates for this extreme surgical undertaking either because of poor bone stock, inability to withstand prolonged immobilization, or inability to eradicate the infectious agent. Such cases may call for other salvage techniques that usually sacrifice joint function for microbiologic cure (Table 68.4). Antibiotic selection is based on the susceptibility pattern of the organisms isolated. The antibiotics of choice for the isolated organisms are similar to those used in native joint infections (see Table 68.1). Unlike native joint infections, the most common organisms isolated in prosthetic joint infections are coagulase-negative staphylococci (see Table 68.2). Therefore this organism should not be considered a contaminant but should be treated. If the prosthesis is removed, parenteral antibiotics are administered for 6 to 8 weeks; however, if management includes retention of the prosthesis, a prolonged course of oral antibiotics (6 months to 1 year) should be given after the completion of the course of parenteral antibiotics. With regard to staphylococci, 2 to 6 weeks of parenteral antibiotics in combination with rifampin is followed by a further 6 weeks of oral agents. Oral agents may include quinolones, if susceptible, such as ciprofloxacin, 750 mg twice daily, or levofloxacin, 500 mg once daily, combined with rifampin, 600 mg once daily. Other alternatives include minocycline or doxycycline, 100 mg twice daily.

TABLE 68.3 **DIAGNOSTIC FEATURES OF PROSTHETIC JOINT INFECTIONS**

	Suggestive findings	Comments
History	Rest pain; lack of postoperative pain-free interval; difficult wound healing; fever	These findings are not specific; they may also be found in aseptic loosening of the prosthesis. Infected prosthesis may be asymptomatic
Physical findings	Swelling; tenderness; limitation of motion; fever; sinus tract	As above
Laboratory tests	Leukocytosis; elevated ESR or CRP	Elevations in these parameters noted in most acute infections but may be normal in chronic, indolent infections
Radiology	Periostitis; endosteal scalloping; focal or diffuse osteolysis	Radiologic findings may be normal. Cannot distinguish mechanical loosening from septic arthritis
Nuclear imaging	Enhanced uptake in the region of the prosthesis	Subjective and reader dependent. Sequential bone and tagged white cell scans provide greater sensitivity and specificity than if done alone. Provides no information about organisms
Joint aspiration	Positive cultures	Sensitivity 60%–80%; specificity 85%–95%; dry taps 10%–15%. More useful in symptomatic cases; provides specific information about organisms and sensitivities; detection of previously undetected infections. Yield improved if patient is off antibiotics for 2 weeks

Abbreviations: ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

Prevention

Perioperative antibiotic coverage includes agents directed against the most common causative agents, that is, gram-positive cocci. A first-generation cephalosporin will achieve this. The antimicrobial agents are administered within 30 to 60 minutes of surgery and are continued for up to 24 hours postoperatively. For patients known to be colonized with methicillin-resistant *S. aureus* (MRSA), an additional dose of vancomycin should be administered. Antibiotic-impregnated beads and cement have also been used extensively because they have the advantage of delivering high local levels of antibiotics with minimal systemic toxicity. Laminar air-flow devices and body exhaust suits have been recommended to prevent intraoperative contamination; however, it is unclear whether these considerably expensive techniques are cost-effective.

There is no convincing evidence of benefit of routine prophylaxis with antibiotics for patients with prosthetic joints undergoing uncomplicated dental, urinary, or gastrointestinal procedures. The risk of infection is similar to that of endocarditis developing in the general population. In a joint advisory statement, however, the American Dental Association and the American Academy of Orthopedic Surgeons have suggested prophylaxis regimens similar to those set out by the American Heart Association for endocarditis in certain high-risk patients undergoing high-risk dental procedures.

TABLE 68.4 **TREATMENT OPTIONS FOR PROSTHETIC JOINT INFECTIONS**

Technique	Method	Comments
Reimplantation (exchange arthroplasty)	Removal of prosthesis and cement, immediate reimplantation (one stage) or delayed reimplantation (two stages)	Technique of choice. Excellent functional results and good microbiologic cure. Patient must be physically able to undergo major surgery and prolonged immobilization. Adequate bone stock necessary for reimplantation
Resection arthroplasty	Removal of prosthesis and cement, extensive debridement of adjacent bone	Used if reimplantation not possible because of major bone loss, recurrent infections, poorly responsive organisms (e.g., fungi) and patient mobility not essential/necessary for reimplantation Provides good microbiologic cure at the expense of joint function
Arthrodesis	Removal of prosthesis and cement and fusion of joint	If mobility is needed but patient cannot undergo reimplantation May require prolonged immobilization
Amputation		Radical treatment may be necessary following multiple revision attempts, intractable pain, or life-threatening infection
Implant salvage	Chronic antibiotic suppression, alone or with local debridement and retention of prosthesis	Indicated if patient is unable or refuses to undergo major surgery. May be successful provided duration of symptoms ≤ 3 wk, no sinus drainage, no radiologic evidence of loosening, and the microorganism is highly susceptible to antibiotics

Suggested reading

Berbari EF, Osman DR, Duffy MC, et al. Outcome of prosthetic joint infection in patients with rheumatoid arthritis: impact of medical and surgical therapy in 200 episodes. *Clin Infect Dis*. 2006;42:216–223.

Donatto KC. Orthopedic management of septic arthritis. *Rheum Dis Clin North Am*. 1998;24:275–286.

Kaandorp CJE, Van Schaardenburg D, Krijnen P, et al. Risk factors for septic arthritis in patients with joint disease: a prospective study. *Arthritis Rheum*. 1995;38:1819–1825.

Lentino JR. Prosthetic joint infections: bane of orthopedists, challenge for infectious disease specialists. *Clin Infect Dis*. 2003;36:1157–1161.

Marculescu CE, Berbari EF, Hanssen AD, et al. Outcome of prosthetic joint infections treated with debridement and retention of components. *Clin Infect Dis*. 2006;42:471–478.

Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: Clinical practice guidelines by the Infectious Diseases *Society of America*. *Clin Infect Dis*. 2013;56(1):e1–e25.

Smith JW, Piercy E. Infectious arthritis. *Clin Infect Dis*. 1995;20: 225–230.

69

Bursitis

Richard H. Parker

Inflammation of bursal sacs, or bursitis, is a common condition. Bursa are fluid-filled sacs that act as cushions between tendons and either bone or skin. There are more than 150 bursae in the human body. Most cases of bursitis involve either the olecranon or the prepatellar bursa, and the majority are related to trauma. At most 20% to 30% are infected either primarily or secondary. A much smaller percent are the result of inflammation associated with rheumatologic disorders. Possibly the most common scenario for septic arthritis is a needlestick for corticosteroid injection into a bursa as therapy for nonseptic bursitis. Septic bursitis can also occur as a complication of bacteremia without a history of trauma to the involved area. Septic bursitis is less common in the pediatrics patient but does occur and is usually associated with acute trauma such as sports-related injuries.

Septic and nonseptic bursitis of superficial bursae such as at the olecranon and prepatellar sites may present as both red and tender areas (Figure 69.1). Clinical features, including fever or infection at another site, may help differentiate infected from noninfected. Bursitis of deeper bursae, such as trochanteric bursitis is usually not infectious but tuberculous bursitis of the greater trochanter and other deeper sites has occurred. Microorganisms from the skin cause most infectious bursitis. *Staphylococcus aureus* may cause about 90% of infected bursa. However, any microorganism (hemolytic streptococci, gram-negative bacilli, or fungi) if introduced can infect these spaces. As with other infectious diseases, the immunocompromised host may be infected with unusual opportunistic microorganisms.

Diagnosis of septic bursitis requires aspiration of fluid for microscopy, culture, cell counts, and glucose (Table 69.1).

Therapy

Therapy is started following a decision as to whether the inflammation is infectious or noninfectious (Figure 69.2). Noninfectious bursitis is treated with immobilization, heat, and anti-inflammatory agents and referred to orthopedics depending on the severity or response to therapy. Septic bursitis might require hospitalization for surgical drainage and intravenous antimicrobial therapy. However, most patients are not septic, toxic, or immunocompromised and may be considered compliant and therapy can be initiated with oral antimicrobial agents and the patient is followed closely as an outpatient. Home intravenous infusion therapy is an option but should be restricted to therapy of methicillin-resistant *S. aureus* (MRSA) or other pathogens that require use of drugs that can be given only intravenously or when patients cannot tolerate oral medications.

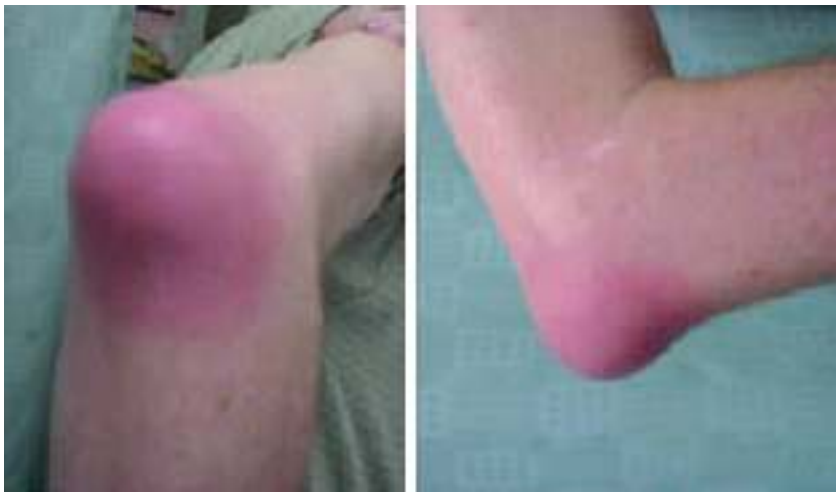

FIGURE 69.1 Red, swollen olecranon bursa. (From *Resident and Staff Physician*, March 2006.)

Initial therapy must use a good antistaphylococcal agent and may be oral therapy for nonseptic patients. In one report of 82 cases, a cloxacillin-based regimen resulted in cure of all but one patient. All patients received intravenous therapy until afebrile, including gentamicin in 35 patients. In areas where MRSA is common, intravenous vancomycin, daptomycin, or linezolid should be initiated. Linezolid has excellent bioavailability with equal efficacy for MRSA either IV or orally. Clindamycin may be useful in community-acquired MRSA provided inducible clindamycin resistance has been ruled out by appropriate studies. Therapy to cover an infection caused by gram-negative bacilli and/or anaerobes should be started if the septic bursitis occurs in the lower extremity or in an immunocompromised patient. Oral antimicrobial agents, if not started initially, can be used within 48 to 72 hours. Well-tolerated, once-a-day therapy is considered preferable for compliance. Total duration of therapy is usually 3 to 4 weeks. The recurrence of fluid after initial aspiration requires reaspiration and consideration for surgical drainage or bursectomy.

TABLE 69.1 **FINDINGS IN BURSAL FLUID RELATED TO CAUSES OF BURSITIS**

Finding	Normal	Trauma	Sepsis	Rheumatoid inflammation	Microcrystalline inflammation
Color	Clear yellow	Bloody xanthochromic	Yellow, cloudy	Yellow, cloudy	Yellow, cloudy
WBC	0–200	≤ 5000	1000–200 000	1000–20 000	1000–20 000
RBC	0	Many	Few	Few	Few
Glucose	Normal[a]	Normal[a]	Decreased	Decreased (slight)	Variable
Gram stain, culture	Negative	Negative	Positive	Negative	Negative

Abbreviations: WBC = white blood cell; RBC = red blood cell.
[a] Fluid glucose/blood glucose = 0.6–1.

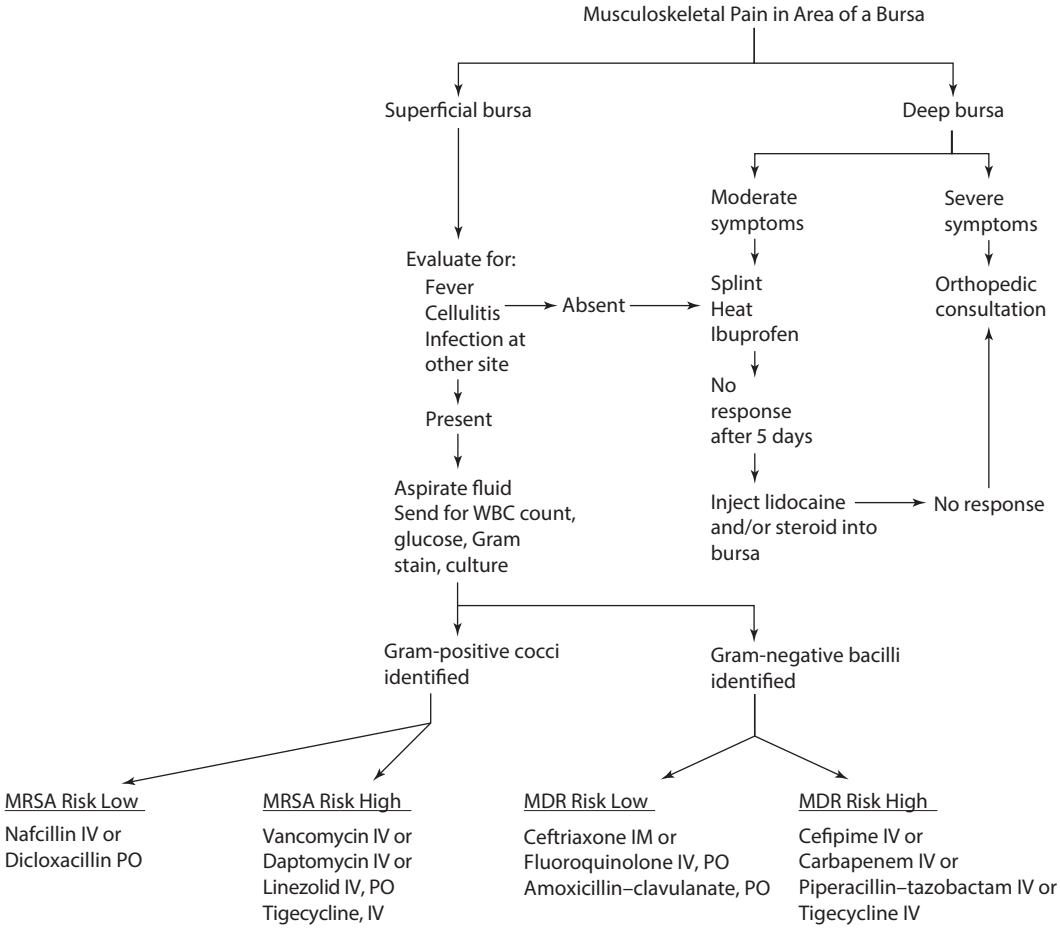

FIGURE 69.2 Algorithm for the management of musculoskeletal pain in the area of a bursa. MRSA = methicillin-resistant *Staphylococcus aureus*; MDR = multidrug resistance.

Suggested reading

Barham GS, Hargreaves DG. *Mycobacterium kansasii* olecranon bursitis. *J Med Microbiol*. 2006;55:1745–1746.

Garcia-Porrua C, González-Gay MA, Ibañez D, et al. The clinical spectrum of severe septic bursitis in northwestern Spain: a 10 year study. *J Rheumatol*. 1999;26:663–667.

Hanrahan JA. Recent developments in septic bursitis. *Curr Infect Dis Rep*. 2013;15(5):421–425.

Harwell JI, Fischer D. Pediatric septic bursitis: case report of retrocalcaneal infection and review of the literature. *Clin Infect Dis*. 2001;32:E102–E104.

Khazzam M, Bansal M, Fealy S. Candida infection of the subacromial bursa. *J Bone Joint Surg*. 2005;87:168–171.

Martinez-Taboada VM, Cabeza R, Cacho PM, Blanco R, Rodriquez-Valverde V. Cloxacillin-based therapy in severe septic bursitis: retrospective study of 82 cases. *Joint Bone Spine*. 2009;76:665–669.

Small LN, Ross JJ. Suppurative tenosynovitis and septic bursitis. *Infect Dis Clin North Am*. 2005;19:991–1005.

70

Acute and chronic osteomyelitis

Ilona Kronig, Pierre Vaudaux, Domizio Suvà, Daniel Lew, and Ilker Uçkay

Introduction, epidemiology, and clinical manifestations

Osteomyelitis is a common term for bone infection, although noninfectious inflammation of bones and adherent structures exist. Strictly speaking, osteomyelitis implicates affection of bone and marrow. The term osteitis would be often more appropriate because no one knows how much infection is inside the marrow in a given episode. As for any infection, physicians like to create big groups of disease headed as acute (AO) and chronic osteomyelitis (CO), although this distinction does not much determine daily clinical practice. For physicians, a commonly accepted definition of AO is a recent bone infection with systemic inflammatory response, while CO requires minimal symptom duration of 6 weeks to 3 months. Another classification system is the presence of a sinus tract, sequestra, or involucra, which are anatomicopathologic hallmarks of chronic infection. Finally, surgeons have their classification schemes, based on practical aspects of the surgical approach, of which the Cierny-Mader classification is one of the most frequent. The terms acute or chronic are not used in this classification. Generally, surgeons understand a CO as infection requiring surgery, with already established sequestra and bone deformities.

AO is a hematogenous infection that occurs mostly in prepubertal children and in the elderly and is usually located in the metaphyseal area of long bones (children) or in the spine (elderly). It is the result of a local proliferation of bacteria within bone after a septicemic storm. Alternatively, AO can originate locally following trauma or orthopedic surgery (surgical site infection). In contrast, CO has two origins. It may result from either a neglected sequel of AO, or from the continuous spreading of chronic ulcers in paraplegics, bedridden patients, or diabetic patients with foot problems. Epidemiology of osteomyelitis is heterogeneous with variability among involved bones, pathogens, and settings. For example, resource-poor countries may reveal a higher proportion of tuberculous osteomyelitis or CO due to post-traumatic origin compared to resource-rich countries, as well as a higher prevalence of foot osteomyelitis among elderly patients.

Pathogenesis in detail

Every chronic infection begins with an acute phase. Bacteria adhere to bone matrix and orthopedic implants via receptors to fibronectin and other structural proteins, then hide intracellularly by developing a biofilm. Patchy ischemic bone necrosis occurs when the inflammation occludes the vascular tunnels. Segments of bone devoid of blood supply can become separated and are called sequestrate. This creates an ideal culture medium for bacteria and at 48 hours, abscesses are formed. Meanwhile, osteoblastic activity occurs, in some cases exuberantly, causing periosteal apposition and new bone formation, named involucrae. When sequestrate or involucrae become fibrotic, sclerosis may result. Bone sclerosis usually indicates infection present for more than 1 month.

Microbiologic and pathologic criteria

Infection is almost exclusively of bacterial origin, much less due to fungi (in intravenous drug abusers or in skull osteomyelitis in immunesuppressed individuals) or parasites (e.g., echinococcosis). For all categories of osteomyelitis except for the jaw, *Staphylococcus aureus* is the prominent pathogen, contributing up to two-thirds or three-quarters of the study population, followed by streptococci and gram-negative pathogens such as *Pseudomonas aeruginosa*. As for any infection, virtually any bacteria can cause osteomyelitis. Skin commensals such as coagulase-negative staphylococci, propionibacteria, corynebacteria, or *Bacillus* spp. are mostly encountered in implant-related infections, but almost never alone in AO or CO without implants. Polymicrobial infection is frequent in trauma and long-lasting ulcerations, but not in hematogenous infections.

Diagnosis

Clinical signs (sinus tract with or without discharge) and radiographs (sequestra, involucra, fistulas) are suggestive for diagnosis of CO, but no noninvasive test can definitively establish or exclude infectious osteomyelitis. That is why it is extremely important to get adequate sampling of infected bone for bacteriologic or molecular identification by polymerase chain reactions (PCR). Swabs, even if taken from a deep area, should be avoided. The ultimate proof of infection requires growth of the same pathogen in several, at least two, (intraoperative) bone samples. In case of pretreatment with antimicrobial agents or suspicion of slow-growing pathogens such as in tuberculosis, brucellosis, or nocardiosis, the incubation time might be prolonged beyond the usual 5-day period and other, nonstandard laboratory tests, performed. Histology may help to confirm the clinical suspicion.

Treatment

The mainstays of management include adequate debridement, obliteration of dead space, wound protection, and targeted antimicrobial therapy.

Surgical therapy

Debridement *sensu latu* summarizes different surgical approaches: sequestrestomy, necrosectomy, intramedullary reaming, and removal of orthopedic material (when possible or indicated), except those essential for stability. Debridement must often be repeated for the removal of all nonviable tissue (second look). Surgeons know how extensively they were able to perform this debridement. There are no exact possibilities to estimate the completeness of such a debridement. A variety of techniques has been used such as cancellous bone grafting and implantation of acrylic beads impregnated with antibacterial agents. In case of vascular insufficiency, restoration of a good blood flow is performed by vascular bypass or endovascular stenting. If the stability of the bone is compromised, a two-stage procedure might be required. The first stage consists in extensive debridement, dead space management (eventually with antibiotic-containing beads or cement), bone stabilization with external fixation, and coverage with dressings. After 3 weeks of antibiotic treatment comes the second stage: new debridement, removal of the beads or cement, filling in of the dead space with bone graft, bone stabilization with internal fixation (plate and/ or intramedullary nail), and soft-tissue coverage. Local administration of antibiotics, e.g., by gentamicin beads, has long been advocated because of the benefit of a local diffusion limited in time and space. However, at present, the use of local antibiotic delivery in combination with systemic antibiotic prescription has not yet shown any supplementary beneficial effect in terms of remission rates. The major disadvantage of local beads is the presumed need for a subsequent surgical removal. Small dead space is left unchanged if the soft-tissue coverage is good. Large dead spaces are filled to reduce the likelihood of continued infection and stability loss. If a cavity cannot be filled by surrounding soft tissue, a local muscle flap or free tissue transfer obliterates the space. Autologous bone grafts usually enhance stability after 6 to 8 weeks. As a last resort, the Ilizarov fixation device is used in patients with chronic extensive and difficult to treat CO. The Ilizarov technique may bridge bone defects as long as 15 cm by continuous traction that can be started 10 days after implantation of the device.

Antimicrobial therapy

In contrast to surgical science with many related publications, the optimal antibiotic treatment post-debridement for implant-free, nondiabetic long bone osteomyelitis among adults is not well defined. Most studies primarily focused on the choice of antibiotic agents, rather than their duration, dosing, or route of administration. Usually, single-agent chemotherapy is adequate for the treatment of osteomyelitis (Table 70.1). In the past decades, according to experimental models, antibiotics were parenterally administrated on a mostly empirical basis for 4 to 6 weeks, followed by an oral course of antimicrobials for several weeks or months. Without doubt, bone penetration of antibiotic agents is optimized by parenteral administration, with a serum bioavailability per definition of 100%. On the other hand, parenteral medication should be limited to save unnecessary costs, prevent catheter-related complications, and to increase patient and nursing comfort. The estimated proportion of complications attributed to a prolonged IV course ranges around 15%. Recent studies allowed new approaches to antimicrobial therapy based on experimental models and clinical validations. Thus, there is a growing consensus for a switch to the oral route after 2 weeks of IV treatment. Several antimicrobial agents have already proven clinical efficacy upon oral intake: quinolones, linezolid, clindamycin, trimethoprim–sulfamethoxazole (TMP–SMX), and fusidic acid combined with rifampin. These drugs have oral bioavailabilities of 90%.

TABLE 70.1 **ANTIBIOTIC TREATMENT OF OSTEOMYELITIS[A]. LOCAL RECOMMENDATIONS AT GENEVA UNIVERSITY HOSPITALS**

Parenteral treatment	(Duration 0–2 weeks) Antibiotics	Alternatives
Staphylococcus aureus		
Methicillin resistant	Vancomycin 2 × 15 mg/kg	Teicoplanin (400 mg q24h, first day q12h)
		Daptomycin 6–10 mg/kg/d
		Linezolid 2 × 600 mg/d
Methicillin susceptible	Flucloxacillin 2 g q6h	Cephalosporins of I or II generation
Streptococci	Penicillin G (3 Mio U q4–6h)	Cephalosporins of I or II generation
Gram-negatives	Ceftriaxone	Ceftazidime, cefepime
Anaerobes	Amoxicillin-clavulanate	Metronidazole, carbapenems, clindamycin
Oral treatment	**(Duration 6–12 weeks)**	
Gram-positives	Clindamycin 3 × 600 mg	Levofloxacin 2 × 500 mg
		Trimethoprim–sulfamethoxazole 2 cp forte (2 × 960 mg)
		Linezolid 2 × 600 mg
		Fusidic acid 3 × 500 mg (not as monotherapy)
Gram-negatives	Ciprofloxacin 2 × 750 mg	Trimethoprim–sulfamethoxazole 2 × 960 mg
		Levofloxacin 2 × 500 mg
Anaerobes	Metronidazole 3 × 500mg	Clindamycin 3 × 600 mg

[a] Adapted from: Uçkay I, Buchs NC, Seghrouchni K, et al. Bacterial osteomyelitis: etiopathogenesis and management. In: Signore A, ed. *Management of Osteomyelitis*, 1st edn. Chapter 2. Rome, Italy: University of Rome; 2013:15–26.

Total duration of antibiotic therapy

In general practice, the duration of antibiotic administration is standard for most pathogens with few exceptions: pathogens for which the literature provides long-lasting antibiotic treatments (tuberculosis, other mycobacteria such as in buruli ulcer, fungi, Q fever, nocardiosis, or brucellosis). There are no clinical studies or documented records indicating the superiority of the 4- to 6-week course over shorter durations. In the retrospective study of Rod-Fleury et al., the duration of total post-debridement antibiotic treatment or its initial parenteral part only played no role on the remission incidences. One week of IV therapy had the same success as 2 to 3 weeks or more. Four weeks of total antibiotic treatment led to the same outcome as 4 to 6 weeks or more than 12 weeks. Less than 6 weeks was equal to more than 6 weeks. Haidar et al. listed small individual reports in animals and humans that obtained remission of osteomyelitis with antibiotic durations ranging from 1 to 4 weeks.

Intravenous agents

The most frequently used antibiotic agents, the β-lactam antibiotics, ubiquitously show low oral bioavailability and a low intra-osseous penetration. Since the bone penetration of vancomycin is only about 15% to 30% of the serum concentration, minimal trough serum levels of 20 to 25 mg/ L are believed to treat bone infections best. In continuous perfusion, the changes in serum concentrations are much lower than in intermittent application. However, continuous perfusion does not guarantee a better outcome in terms of remission. Daptomycin depolarizes bacterial membranes and yields a rapid, dose-dependent bactericidal effect. It is only available in parenteral form and administered once a day at a dose of 6 to 8 mg/kg. This makes it suitable for an outpatient treatment. Aminoglycosides are less active in synovial fluid or in bone.

Oral agents

Linezolid can be administered orally at a dose of 600 mg BID, due to its high bioavailability of 100%. Besides an expensive price, it is associated with reversible bone marrow suppression, e.g., thrombopenia. Optic neuropathy and non-reversible peripheral neuropathy have been reported in 2% to 4% of patients with prolonged administration. A severe serotonin syndrome in co-medication with certain antidepressive drugs, such as monoamine oxidase inhibitors, has been described. TMP–SMX is an inexpensive folate antagonist. However, one reason for failure in severe osteoarticular infections might be the amount of thymidine released from damaged host tissues and bacteria. Thymidine may antagonize the antistaphylococcal effects of TMP–SMX. Hence, TMP–SMX failure may well depend on the amount of tissue damage and bacteria burden. Oral fusidic acid 500 mg tid has demonstrated efficacy in CO. Most experts do not recommend fusidic acid in monotherapy because of development of resistance. The antibiotic can be combined with rifampin. For anaerobic, streptococcal, and staphylococcal clindamycin-sensitive osteomyelitis, bacterial protein synthesis inhibition by clindamycin 600 to 900 mg TID is an option, as is metronidazole for anaerobic

disease and quinolones for gram-negative infection. *Pseudomonas aeruginosa* and other nonfermenting gram-negative rods may rapidly develop resistance during quinolone monotherapy. Therefore, a combination with another parenteral drug for prolonged IV treatment in pseudomonal osteomyelitis would be wise, but antibiotic treatment adjusted to this situation has not been studied so far.

In acute flare-ups of CO that cannot be operated on due to various reasons (polymorbid patient, extended lesions compromising mechanical stability or gait), antibiotic therapy can aim for palliation. In these circumstances, a targeted antimicrobial therapy can be prescribed for 10 to 20 days, in order to calm down the situation, and not to cure. Hyperbaric oxygen therapy consumes very substantial resources. It provides oxygen to promote collagen production, angiogenesis, osteogenesis, and healing in the ischemic or infected wound. Several authors have suggested that adjunctive hyperbaric oxygen therapy might be useful in the treatment of human CO, even if the results are not consistent. The adjunctive role of hyperbaric oxygen in osteomyelitis is difficult to assess because of the multiple confounding variables of patient, surgery, organism, bone, and antibiotic therapy. Today, although recognized for reimbursement by some healthcare systems, the evidence base for hyperbaric oxygen therapy for diabetic foot care still remains weak.

Special features

Vertebral osteomyelitis (in conjunction with spondylodiscitis)

Apart from nosocomial infection after spine surgery, hematogenous spread is generally the most common origin of vertebral osteomyelitis and/or spondylodiscitis. The incidence is estimated at 0.2–to 2 annual cases per 100 000 patients involving mostly patients in the mid-ages with a male to female ratio of 2:1 for which the reason remains unclear. Usually, the management of a vertebral osteomyelitis is essentially conservative, but may require early drainage surgery and stabilization of the spine. The indications of surgery are failure of medical treatment, abscess formation, impending instability, or neurologic signs of spinal cord compression. The needle biopsy through CT guidance is currently the process of choice to obtain micro-biologic and histologic samples. In the absence of clinical sepsis, a second biopsy should be repeated when the first one is negative (by withholding antibiotic therapy). If the culture is still negative, most physicians propose an empirical therapy or request a surgical biopsy for diagnosis. No randomized controlled studies have evaluated antibiotic regimens for vertebral osteomyelitis. Practically, the choice of antibiotic agents is not different from any other osseous infections, except that an initial parenteral treatment of at least 3 to 4 weeks is usually suggested by experts. Prolonged antibiotic treatment beyond 4 or 6 weeks is only recommended for patients with abscesses that have not been drained.

Diabetic foot osteomyelitis

A diabetic foot problem is practically always a good example for multidisciplinary diagnosis and therapy. Suspicion of osteomyelitis is confirmed by microbiology or radiologic destruction in the case of toe osteomyelitis. Bone biopsy (with histology if sufficient material) is valuable for establishing the diagnosis and for defining the pathogenic organism(s). Concomitant treatment includes proper wound cleansing, debridement of callus and necrotic tissue, and offloading of pathologic pressure. There are no data to support the superiority of any particular route of delivery of systemic antibiotics or the optimal therapy duration. Therapy aimed solely at aerobic gram-positive cocci may be sufficient for mild to moderate infections in patients who have not recently received antibiotic therapy. Broad-spectrum empirical therapy is required in severe infections. Bioavailable oral antibiotics are sufficient in most mild and moderate osteomyelitis. In severe diabetic foot infections, antibiotics are given initially IV to achieve maximal tissue concentrations in an area already compromised by arteriopathy, although no evidence for a superiority of IV medication exists. The results of conservative therapy with prolonged courses of oral antibiotics challenge conventional advice that excision of infected bone is essential. Conservative success rates are cited as 75% and as 77% over a median period of follow-up of 2 years. However, conservative treatment might not reverse the high incidence of a second episode of osteomyelitis in a long-term follow-up, since the cause has not been removed by conservative treatment in most cases. A corrective surgery or an amputation for toe and mid-foot osteomyelitis is often indicated, providing the level of amputation does not compromise walking and does not require prostheses.

Sacral osteomyelitis

This disease is chronic and related to decubitus in patients with multiple comorbidities and/or neurologic disorders. It is particularly difficult to treat, since there is no remission if the reason for CO cannot be reversed. In these chronic decubitus patients, the infected sacral bone often cannot be excised and the patient cannot be improved neurologically. Prevention is of outmost importance. A thorough daily nursing care and debridement is the key to success. In ameliorated cases, plastic surgeons may graft on the naked bone. The ideal duration of antibiotic administration is unknown. The aim is not to eradicate bone infection, but to control it. More data are needed in this field of osteomyelitis.

Jaw osteomyelitis

Chronic mandibular osteomyelitis occurs after dental procedures, trauma, or in very poor settings of noma disease. There has not been much research in the past. The causative pathogens are often polymicrobial and stem from the oral flora. *Actinomyces* spp. are particular pathogens that may mimic neoplasm. Treatment consists of maxilla-facial surgery, often repeated, and of long-lasting oral antibiotic therapy for which the choice of amoxicillin–clavulanate covers the majority of the oral flora.

Clinical follow-up during therapy

Osteomyelitis patients must be regularly followed up throughout the treatment, for early detection of complications, adverse events, and control of wounds. A substantial quality improvement of care would be the use of diagnostic imaging to judge how long therapy

remains necessary; for example by repeated positron emission tomography (PET) scans (which has to be investigated yet). Indeed, the duration of antibiotic administration for CO is usually decided from the start and kept thereafter; independently of the individual case and markers. C-reactive protein (CRP) is widely used in the follow-up of patients with localized bone and implant infections, but trauma or surgery may result in its transient elevation. Indeed, many CO cases have a normal CRP level even before treatment.

Particularities of pediatric osteomyelitis

As a general principle, pediatric AO and CO cases are similar to those of adults. However, epidemiologically speaking, there are more primary AO than among adults, affecting 8 per 100 000 children, predominantly boys. The long bones are most frequently infected. CO of the adult may originate several years after bone contamination from an infant AO source, e.g. after bone trauma in childhood. Primary AO is mainly due to *S. aureus* (70% to 90% of cases), and rarely due to other pathogens, with one exception: *Kingella kingae* is a pathogen mostly encountered in osteoarticular infections among infants around 3 to 6 years of age. Specific PCR for *K. kingae* detection is available. *Haemophilus influenzae*, another infant pathogen, is much rarer, and declined considerably after the implementation of vaccination programs all around the world.

In terms of therapy, most infant AO cases are hematogenous without sequestrae. These cases can usually be treated without surgical debridements purely conservatively, while the duration is shorter than for adult disease. Indeed, review suggests that early transition from intravenous to oral therapy, after 3 to 4 days in patients responding well, followed by oral therapy to a total of 3 weeks may be as effective as longer courses for uncomplicated AO. This recommendation does not apply to neonates. The choice of the antibiotic agents is similar to that for adults, with a few exceptions that should be avoided (according to the manufacturer) among infants: quinolones and tetracyclines.

Outcome of treatment

Many experts advocate that if the bone is infected, it may remain infected throughout the life and even beyond, unless amputation is performed. Recurrences of osteomyelitis after several years, if not decades, have been reported and there is no internationally accepted minimal follow-up duration. Some authors suggest that "arrest" or "remission" is a more appropriate term than "cure" for defining outcome in CO. According to current literature, remission is "defined" as the resolution of all signs and symptoms of active infection after a minimal follow-up period of 1 to 2 years. Generally, remission rates for CO among adults oscillate between 40% and 90% with a peak of success around 80%, almost independently of the surgical technique, the duration of intravenous or total antibiotic therapy, or the causative pathogen.

Future

The future will probably provide a firm place in the antibiotic armamentarium for some of today's investigational agents such as dalbavancin, telavancin, and other compounds under development. It should not be forgotten that most, if not all, new molecules might be equivalent to established antibiotics in terms of remission rates in vivo. Additional prospective trials need to be performed before innovative approaches are proposed. As an example, bacteriophage therapy is a challenging approach and may prove to be superior to established combined antibiotic therapies. Finally, it is very difficult to evaluate osteomyelitis in small clinical studies or single centers. Sample size and international definitions need to be improved. Hopefully, future data will be collected from prospective and multicenter human cohort studies.

Suggested reading

Lew DP, Waldvogel FA. Osteomyelitis. *N Engl J Med*. 1997;336:999–1007.

Lew DP, Waldvogel FA. Use of quinolones in osteomyelitis and infected orthopaedic prosthesis. *Drugs*. 1999;58:85–91.

Lew DP, Waldvogel FA. Osteomyelitis. *Lancet*. 2004;364:369–379.

Ceroni D, Dubois-Ferriere V, Cherkaoui A, et al. Detection of *Kingella kingae* osteoarticular infections in children by oropharyngeal swab PCR. *Pediatrics*. 2013;131:230–235.

Haidar R, Der Boghossian A, Atiyeh B. Duration of post-surgical antibiotics in chronic osteomyelitis: empiric or evidence-based? *Int J Infect Dis*. 2008;14:752–758.

Howard-Jones AR, Isaacs D. Systematic review of duration and choice of systemic antibiotic therapy for acute haematogenous bacterial osteomyelitis in children. *J Paediatr Child Health*. 2013;49:760–768. doi: 10.1111/ jpc.12251.

Lazzarini L, Lipsky BA, Mader JT. Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials? *Int J Infect Dis*. 2005;9:127–138.

Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2004;39:885–910.

Rod-Fleury T, Dunkel N, Assal M, et al. Duration of post-surgical antibiotic therapy for adult chronic osteomyelitis: a single-centre experience. *Int Orthop*. 2011;35:1725–1731.

Uçkay I, Buchs NC, Seghrouchni K, et al. Bacterial osteomyelitis: etiopathogenesis and management. In: Signore A, ed. *Management of Osteomyelitis*, 1st edn. Rome, Italy: Wiley online library; 2013:15–26.

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Polyarthritis

Kathryn H. Dao and John J. Cush

The co-occurrence of fever and arthritis educes a broad set of diagnostic considerations, especially infection. Yet most forms of infectious arthritis typically involves one to three joints (monarthritis to oligoarthritis). The presence of a greater number of joints involved (polyarthritis) with fever evokes a more unusual and challenging range of diagnostic possibilities. Knowledge of prevalent forms of polyarthritis capable of fever can facilitate an early, accurate diagnosis and appropriate therapy.

Polyarthritis is defined as inflammatory pain with swelling affecting four or more joints. The distribution, chronology of joint inflammation, and host factors (e.g., demographics, comorbidities, geography) help refine the diagnostic possibilities. The presence of fever is unique as most polyarticular conditions do not manifest substantial or sustained fever. Nevertheless, fever or pyrexia is further evidence of an inflammatory, infectious, or autoimmune disorder. This chapter examines the diagnostic approach to polyarthritis and pyrexia.

History and physical exam

The diagnosis of any disease relies heavily on the history and physical examination. Eliciting an accurate history will identify those who are at risk for significant morbidity and mortality. The goals of the encounter are to (1) relieve symptoms, (2) identify and treat the underlying disease, and (3) avoid irreversible organ damage. Characteristics distinguishing arthritis from arthralgia include warmth, erythema, swelling, or joint effusion localized to the joint capsule. Inflamed joints often will have restricted range of motion (or contracture), muscle strength weakness, and limited function. The key diagnostic elements from the history and physical exam are algorithmically portrayed in Figure 71.1.

Demographics

Age, sex, and geography are important clues. Gout and reactive arthritis (ReA) are more common in men. Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are more prevalent in women. Septic arthritis is more likely in the young, elderly, and immunosuppressed. Giant cell arteritis (GCA) is unlikely in patients <50 years. Opportunistic infections, parasites, and chikungunya fever should be considered in travelers with fever and polyarthritis.

Symptom onset

It is important to acknowledge how and under what circumstances symptoms first manifest. Provocations, such as antecedent infection, drugs, trauma, or travel should be identified. Abrupt onset of symptoms, occurring in hours/days, may indicate infection or gout/pseudogout. ReA or parvovirus infection should be considered in a patient who initially presents with a viral illness then develops acute oligo- or polyarthritis.

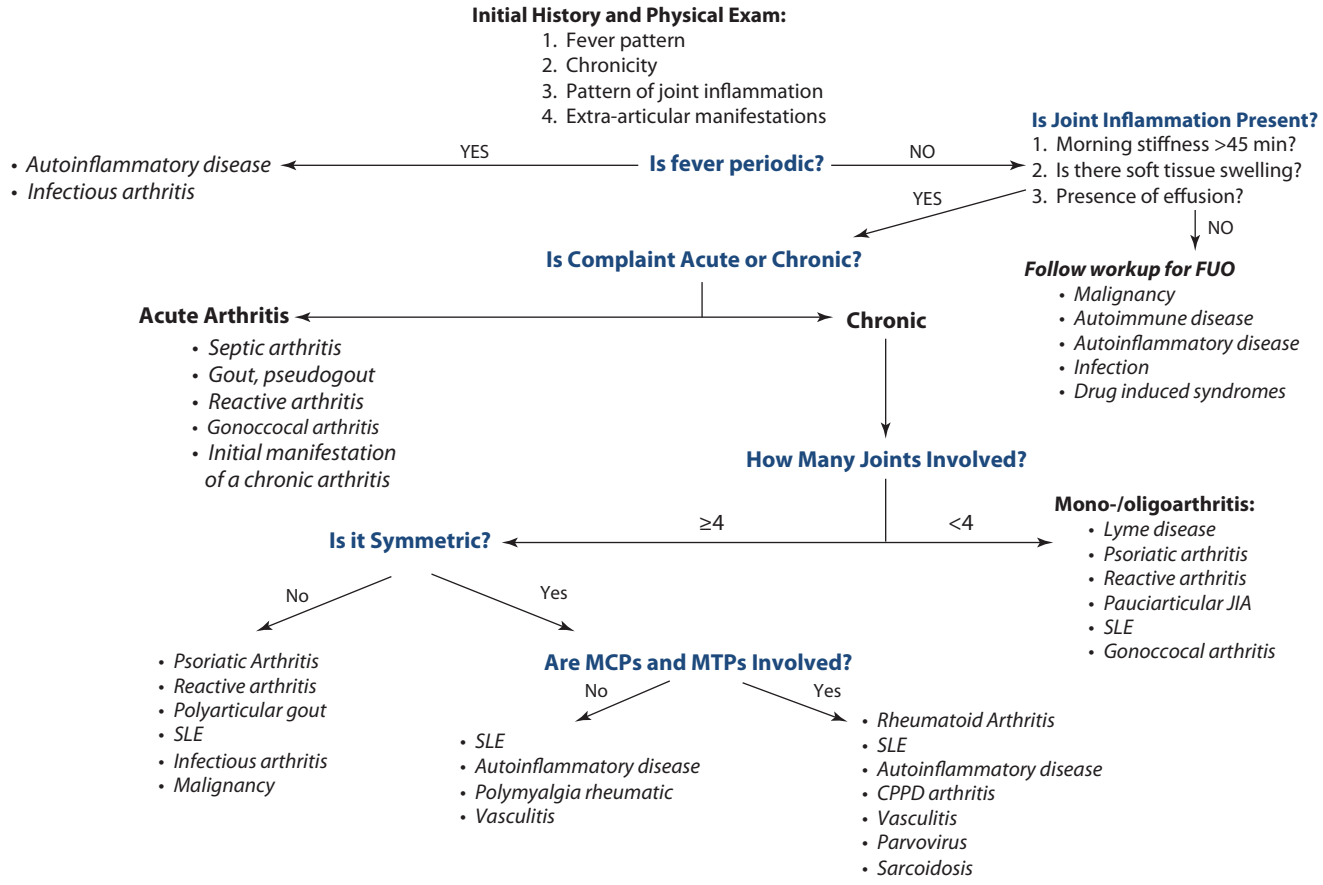

FIGURE 71.1 Algorithm for assessing fever and polyarthritis.

CPPD, calcium pyrophosphate dihydrate; FUO, fever of unknown origin; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

Arthritis lasting ≥12 weeks indicates a chronic disorder, such as autoimmune disease, chronic infection, or malignancy.

Pattern of joint involvement

Observe the number, location, and symmetry of joint involvement. Acute monarthritis is common in patients with ReA, septic arthritis, and gout, whereas a chronic monarthritis should be considered to be tuberculous, fungal, or neoplastic in origin. In contrast, patients who have diffuse symmetrical polyarticular involvement (e.g., hands, wrists, shoulders, knees, ankles) are likely to have a chronic systemic disease such as SLE, chronic viral infections, or RA. Spinal involvement may be a manifestation of tuberculous infections or a spondyloarthritis. Shoulder and hip girdle pain with high inflammatory markers should alert the consideration of polymyalgia rheumatica (PMR) or septic arthritis.

The timing of joint involvement is also useful. Varying patterns of presentation have been described, including *intermittent/episodic pattern* with flares punctuated by periods of complete remission (e.g., gout, pseudogout, autoinflammatory diseases), *additive pattern* where symptoms begin with a few joints and progress to involve more joints with time (e.g., RA, SLE, hepatitis B, parvovirus), or *migratory pattern* where certain joints are affected for a time then remit, only to reappear elsewhere in other joints (e.g., gonococcal arthritis, acute rheumatic fever).

Fever pattern

Fever is a nonspecific significant feature of inflammation driven by a specific immune, infectious, or noxious stimuli. Fever can manifest in patterns that may suggest certain diagnoses and can be described as continuous or sustained, intermittent, relapsing, periodic (e.g., quotidian, tertian, quartan), spiking, or low-grade. Studies have examined the significance of fever pattern and found that few fever curves convey any significance.

Most drug reactions, vasculitides, and viral infections present with continuous fevers; the double quotidian fever curve with spikes twice a day has been associated with visceral leishmaniasis (kala-azar) and malarial infections. Patients with systemic-onset juvenile idiopathic arthritis (soJIA) or adult-onset Still's disease (AOSD) display quotidian (or double-quotidian) fever that is truly circadian, occurring at the same hour each day (usually late afternoon or evening). The magnitude of fever has not been shown to correlate with the degree of disease severity; however, infectious etiologies should

be strongly considered in patients with temperatures of >38.9°C/102°F. Despite extensive research on the topic of fever and fever patterns, their predictive value is often less than stated in textbooks.

Differential diagnoses for polyarthritis and fever

Most causes of polyarthritis and fever can be classified into one of the following categories: infection, rheumatologic diseases (e.g., autoimmune, autoinflammatory, and crystalline diseases), or neoplastic illness (Box 71.1). While literature reviews indicate infections account for the majority of fevers of unknown origin (FUO), rheumatologic diseases and malignancies each account for a minority (~20% to 25%) of cases.

Pyrexia and polyarthritis may become an issue in patients with an *existing* rheumatic disorder who are hospitalized for (1) fever, (2) musculoskeletal trauma, (3) a new medical comorbidity (e.g., infection, neoplasm), or (4) disease flare. Importantly, rheumatic patients are less likely to be admitted for their rheumatic disease, but they are much more likely to be hospitalized for a new medical problem, comorbid condition, or complication of drug therapy.

Infections

Bacteria, viruses, and atypical microorganisms can cause polyarthritis directly as a pathogen (e.g., tuberculous arthritis) or indirectly through an immune-mediated response (e.g., reactive arthritis with *Chlamydia*, *Yersinia*, *Salmonella*, *Shigella*, *Campylobacter*, *Ureaplasma urealyticum*, and *Clostridium difficile*). Septic arthritis can result from hematogenous seeding of the synovial membrane due to bacteremia, direct introduction from a penetrating trauma (e.g., animal bite or joint injection), or extension from a contiguous focus of infection. Chapter 68, "Infection of native and prosthetic joints," details further information on evaluating the septic joint. It is estimated that 20% of septic arthritis will have a polyarticular presentation that may be severe and more likely in the immunosuppressed.[1] Other risk factors for developing polyarticular septic arthritis include corticosteroid use, age, prior septic arthritis, diabetes, chronic renal or hepatic disease, gout, and RA.

Microbes commonly cultured directly from infected joints have included staphylococci, streptococci, enterococci, *Neisseria* spp., *Borrelia* spp., and gram-negative bacilli. While conventional cultures from joint tissue or fluid are considered the gold standard in detecting septic arthritis, the16S rRNA gene PCR combined with sequencing (16SPCR) method is finding a place in clinical practice, particularly in detecting prosthetic joint infections.[2] The rationale of using 16SPCR is that the16S ribosomal subunit is conserved in all bacterial ribosomal genes (rDNA); real-time polymerase chain reaction (rt-PCR) followed by DNA sequencing will allow the detection, amplification, and identification of any bacterial DNA in the sample. Conventional cultures may be difficult to interpret, and they have poor specificity in distinguishing contaminants in tissue specimens; rates of false positives and false negatives are high especially with a single sample obtained during a surgery or if patients have been treated with empiric antibiotics.[3]

BOX 71.1

Differential diagnoses of polyarthritis and fever

Infections
- Bacterial endocarditis
- Staphylococcal infections
- Streptococcal infections
- *Escherichia coli* infections
- *Pasteurella* spp.
- Gonococcal and meningococcal infections
- Brucellosis
- *Streptobacillus moniliformis*
- Parvovirus B19
- Viral hepatitis
- Cytomegalovirus
- Epstein–Barr virus
- Human immunodeficiency virus
- Enteroviruses
- Chikungunya and other alphaviruses
- Rickettsial infections
- Secondary syphilis
- Tuberculosis
- Atypical mycobacterial infections
- Fungal infections

Autoimmune diseases
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Vasculitis (e.g., MPA, GCA, GPA)
- Reactive arthritis (from prior exposure to: *Chlamydia, Yersinia, Salmonella, Shigella, Campylobacter, Ureaplasma urealyticum*, and *Clostridium difficile*)
- Sarcoidosis

Autoinflammatory diseases
- Adult onset Still's disease (AOSD)
- Systemic-onset juvenile idiopathic arthritis (SoJIA)
- Muckle–Wells syndrome (MWS)
- Familial Mediterranean fever (FMF)
- Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
- Behçet's
- Crystalline diseases (gout, CPPD, calcium hydroxyapatite)

Malignancies
- Lymphoma
- Leukemia
- Paraneoplastic syndromes
- Multiple myeloma
- Solid tumors ± metastases

Miscellaneous
- Serum sickness
- Thyrotoxicosis
- Rheumatic fever
- Cryoglobulinemia
- Drug-induced syndromes
- Poststreptococcal arthritis
- Cryoglobulinemia

Abbreviations: MPA = microscopic polyangiitis; GCA = giant cell arteritis; GPA = granulomatous polyangiitis; CPPD = calcium pyrophosphate dihydrate.

Multiple tissue sampling may improve the predictive value of the cultures,[4] but the advantages of 16SPCR are many, including (1) rapid results, usually within 24 hours; (2) greater specificity than conventional cultures; (3) the ability to detect infection in a single sample rather than having to have multiple samples; and (4) the capacity to identify infection even in patients who have been on empiric antimicrobial therapy. 16SPCR should be consider a tool to complement routine cultures. When cultures of microorganisms are unsuccessful, rt-16SPCR has proved helpful. Rt-PCR has improved sensitivity in detecting *Borrelia burgdorferi* in synovial fluid of patients with Lyme arthritis where serologic bands for Lyme disease have been nondiagnostic; in addition, it also has been used to diagnose *Tropheryma whipplei* (Whipple's disease) in elderly white males who present with weight loss, fever, arthritis, and gastrointestinal symptoms.

Viruses also have been linked to polyarthritis, including parvovirus B19, mumps, rubella, hepatitis B and C viruses, cytomegaloviruses, Epstein–Barr virus, HIV, enteroviruses, and insect-transmitted arboviruses. In some patients, a detailed travel history will guide the diagnostic considerations and specific testing needed to detect these infections. Severe cases of debilitating polyarthritis have been associated with the alphaviruses: Chikungunya, Zika, O'nyong-nyong virus, Sindbis virus, Ross River virus, and Mayaro virus.[5] Due to global expansion and urbanization, these viruses have been able to travel with their vectors to new geographic locations and are now considered a growing threat to developed countries. Patients infected by these viruses can develop chronic rheumatic manifestations that persist for months to years.

For example, Chikungunya and Zika viruses share the common mosquito vector, *Aedes aegypti*; both may cause fever, rash, and polyarthritis and tend to be reported among those dwelling in or visiting the Caribbean and tropics. Chikungunya characteristically causes fever >39°C/102°F, headache, myalgia, rash, and severe joint pain that may become a chronic polyarthritis resembling seronegative RA. Similarly, the onset of a Zika infection may herald symptoms of fever, rash, arthritis, myalgias, and conjunctivitis, yet prolonged fevers and polyarthritis are less likely.

Autoimmune and autoinflammatory diseases

Endogenous pyrogens released by an aberrant immune system drive the pathology in autoimmune and autoinflammatory diseases. SLE, sarcoidosis, and vasculitis are examples of autoimmune diseases manifesting with polyarthritis and fever, but rarely does RA present with fever. Typically, other clues are present suggesting an autoimmune diagnosis. Patients with SLE may have a history of a photosensitive rash, alopecia, or serositis. In sarcoidosis, fever may accompany the triad of arthritis, erythema nodosum, and hilar adenopathy (Löfgren syndrome) or have features of uveitis or parotitis. Granulomatosis with polyangiitis (GPA), polyarteritis nodosa (PAN), and other vasculitides often present with malaise, weight loss, or upper or lower respiratory or renal manifestations, at times with multiorgan involvement.

In most autoimmune diseases, fever is low grade (e.g., <38°C/100°F) and indolent, in contrast to the *autoinflammatory* diseases where fever is impressive (e.g., ≥39°C/102°F) and recurrent. High-titer autoantibodies and antigen-specific T cells that are typically absent in autoinflammatory diseases are prominent features with autoimmunity.

Familial Mediterranean fever (FMF), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), and Still's disease (including both soJIA, and AOSD) are but a few examples of the autoinflammatory diseases. Among these, Still's disease is the most common autoinflammatory and autoimmune cause of FUO). Most autoinflammatory disorders have unprovoked, recurrent episodes of fever, serositis, arthritis, and cutaneous inflammation resulting from specific genetic mutations affecting the innate immune system. In cryopyrin-associated periodic syndromes (CAPS), which include familial cold autoinflammatory syndrome (FCAS) and Muckle–Wells syndrome (MWS), mutations in the NLRP3 gene affect components of inflammasomes (e.g., cryopyrin) which are important in recognizing microbial products and endogenous danger signals. Interestingly, recent evidence suggests genes in the same NLR family may be implicated in gout.

Gout and crystalline diseases

Polyarticular gout and pseudogout may manifest high fevers during acute attacks of monarticular or polyarticular gout. The frequency of fever during gout attacks is unknown but is unlikely to affect the majority of patients. Distinguishing between septic arthritis and acute gout is difficult in some: both may present as acute monarthritis with fever and have a similar laboratory profile (extreme neutrophilia, high acute phase reactants), and both may coexist in the same patient simultaneously. An accurate diagnosis may be confounded because up to 50% of gout patients can have a normal serum uric acid level during the acute attack. Synovial fluid analysis can identify crystals, but empiric antibiotics may still be necessary until Gram stain/cultures are reported. While gout tends to manifest as podagra or as a lower extremity monarticular or oligoarticular arthritis, those with arthropathy from calcium pyrophosphate dihydrate (CPPD) may present with acute oligoarticular or polyarticular upper extremity and lower extremity disease. Sometimes, pseudogout may declare as a chronic seronegative inflammatory polyarthritis with chondrocalcinosis confirmed by positively birefringent rhomboid crystals. Patients presenting with crowned dens syndrome (CDS) related to calcium hydroxyapatite crystal deposition (CPPD) in the periodontoid ligaments of the atlas can exhibit high fever, severe occipital headache, and neck stiffness that mimic aseptic meningitis.

Malignancy

Paraneoplastic syndromes with rheumatologic features have been described in most cancers. Lupus-like syndromes with fever, arthritis, and rash have been associated with ovarian cancer, breast cancer, and hairy cell leukemia. PMR symptoms have been described with multiple myeloma and solid tumors. Carcinomatous polyarthritis is often confused with RA but generally has an explosive onset and asymmetric disease pattern. Rheumatic symptoms may coincide or antedate the diagnosis of malignancy. Typically, paraneoplastic manifestations do not respond to standard rheumatologic doses of

steroids or disease-modifying agents but will resolve as the underlying cancer is treated.

The urgency to distinguish a rheumatic condition from malignancy is paramount in children. Seventy-five percent of childhood acute lymphoblastic leukemia (ALL) will present with fever and musculoskeletal pain before blasts appear in the peripheral smear. Several studies examined the predictive factors for malignancies versus JIA based on clinical and laboratory data in children with musculoskeletal pain. Highly predictive factors for malignancy were elevated lactate dehydrogenase (LDH), anemia, and neutropenia. An increased LDH greater than twofold was found exclusively in children with malignancies. Musculoskeletal pain was observed at similar frequencies in children with JIA and neoplasia, though fever tended to be recurrent in those with malignancy.

Drug-induced syndromes

Certain medication adverse effects manifest as a musculoskeletal complaint with fever. Best characterized are medications that can cause drug-induced lupus, such as hydralazine, procainamide, isoniazid, propylthiouracil, sulfonamides, quinidine, TNF inhibitors, and minocycline. Symptoms may include joint/muscle pain, fever, skin rash, pleural disease, and cytopenias which can appear weeks to months after exposure to the offending drug; remission will occur upon withdrawal of the agent.

The advent of a novel class of chemotherapy, the immune checkpoint inhibitors (i.e., ipilimumab, nivolumab, pembrolizumab, etc.), has resulted in a new syndrome and wide array of immune-related adverse events (irAEs). Drug-related irAEs may manifest as musculoskeletal symptoms (arthralgias, myalgias, arthritis), rheumatic conditions (seronegative RA, psoriatic arthritis, PMR, myositis, Sjögren's syndrome, GPA, lupus), or other organ disease (colitis, thyroiditis, pneumonitis, hypophysitis, neuropathy), but are uncommonly febrile.[6]

Laboratory tests and radiologic investigations

Routine labs

While the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) provide surrogate measures of inflammation, they do not discriminate well between infection, rheumatologic diseases, or malignancy. Other laboratory measures often are used to suggest the diagnosis. Patients with soJIA or AOSD often have high ferritin and abnormal liver function tests. SLE may manifest with hypocomplementemia, lymphopenia, and thrombocytopenia. A low haptoglobin with elevated LDH may suggest hemolysis, but high elevations in LDH should be investigated further and malignancy excluded, particularly in children or patients with concomitant weight loss, fever, and lymphadenopathy. Blood cultures are important in endocarditis and systemic infection due to bacteria and fungi.

Serologies

Autoantibodies are found in various autoimmune diseases. The presence of the rheumatoid factor (RF) and antinuclear antibody (ANA) are nonspecific and can be seen in patients with infection, malignancy, and rheumatologic disorders. Other serologic markers offer better specificity and diagnostic utility. The anti-citrullinated peptide antibodies (anti-CCP) carry the same sensitivity as RF for RA, but with better specificity (>90%). When present with the RF, the anti-CCP has a positive predictive value for RA of >99%. The cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) is also highly specific; its presence indicates GPA; similarly, double-stranded DNA and anti-Smith antibodies are specific for SLE. Antibodies against microbial antigens should be obtained when suspicion is high for infection based on contact or travel history. Relevant assays available to evaluate for infections causing fever and polyarthritis include serologies to parvovirus B19, cytomegalovirus, hepatitis B and C, streptolysin O, *Borrelia* spp., and *Brucella* spp. Further information about testing for these infections is covered in other chapters.

Synovial fluid analysis

Arthrocentesis with synovial fluid analysis is a useful adjunct to diagnosing patients and relieving symptoms. Evaluation of synovial fluid should include cell count, crystal analysis, and Gram stain/cultures for routine and atypical (e.g., acid-fast bacilli, fungi, spirochetes, gonococci) microorganisms. Inflammatory fluid is usually yellow and turbulent; white blood cell counts (WBC) range from 5,000 to 50,000 cells/mm^3, with predominance in neutrophils. In the presence of infection or gout, WBC may exceed 50,000 cells/mm^3. Synovial fluid from septic arthritis and gout generally has a higher percentage of neutrophils (>85%) compared to other inflammatory arthritides. Prompt evaluation under polarized microscopy will maximize the yield for crystal identification. Consider obtaining a 16SPCR on tissue or synovial fluid specimens in patients with suspected joint infections but in whom routine cultures are negative.

Radiography

Radiographic changes early in disease often are absent, but sometimes characteristic x-ray findings of inflammatory arthritis are found: soft-tissue swelling, joint effusion, juxtaarticular osteopenia, joint space narrowing, chondrocalcinosis, and bony erosions. Identification of these abnormalities is important as studies have shown that radiographic damage correlates with loss of productivity and increased disability.

Other imaging modalities such as MRI and ultrasound (US) have proved sensitive for detecting synovitis, abscesses, and vasculitis where clinical exam and conventional x-rays have failed. Their advantages include the ability to detect subtle inflammatory abnormalities as well as permitting more accurate placement of the needle in diagnostic arthrocentesis or tissue biopsy. Before ordering any tests, the potential benefits should be weighed against limitations of long examination times, availability of equipment, costs, and skills of the observer to interpret pathology.

Overreliance on laboratory testing to establish a diagnosis is ill-advised; the strength of laboratory testing and imaging is greatly enhanced when they are used to confirm a reasonably strong clinical suspicion garnered from the history and examination.

Conclusion

Fever and joint inflammation pose a diagnostic challenge as infection, rheumatologic disease, and malignancy can present similarly. Assess the demographics, chronology, and pattern of fever and joint involvement when formulating a differential diagnosis. Prompt evaluation, early referral, and expedient initiation of therapy are paramount to reducing morbidity and mortality associated with polyarthritis and pyrexia.

References

1. GG. Long B, Koyfman A, Gottlieb M. Evaluation and management of septic arthritis and its mimics in the emergency department. *West J Emerg Med*. 2019 Mar;20(2):331–341.
2. Marín M, Garcia-Lechuz JM, Alonso P, et al. Role of universal 16S rRNA gene PCR and sequencing in diagnosis of prosthetic joint infection. *J Clin Microbiol*. 2012 Mar;50(3):583–589.
3. Bernard L, et al. The value of bacterial culture during clean orthopedic surgery: A prospective study of 1,036 patients. *Infect Control Hosp Epidemiol*. 2004;25:512–514.
4. Atkins BL, Athanasou N, Deeks JJ, et al. Prospective evaluation of criteria for microbiological diagnosis of prosthetic-joint infection at revision arthroplasty. The OSIRIS Collaborative Study Group. *J Clin Microbiol*. 1998 Oct; 36(10):2932–2939.
5. Wesula Lwande O, Obanda V, Bucht G, et al. Global emergence of Alphaviruses that cause arthritis in humans. *Infect Ecol Epidemiol*. 2015;5:10–3402/iee.v5.29853.
6. Benfaremo D, Manfredi L, Luchetti MM, Gabrielli A. Musculoskeletal and rheumatic diseases induced by immune checkpoint inhibitors: A review of the literature. *Curr Drug Saf*. 2018;13(3):150–164.

Suggested reading

Bernheim HA, Block LH, Atkins E. Fever: pathogenesis, pathophysiology, and purpose. *Ann Intern Med*. 1979;91(2):261–270.

Cush JJ, Dao K. Polyarticular arthritis. In Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, eds. *Kelley's textbook of rheumatology*, 9th ed. Philadelphia: Elsevier Saunders; 2013: 587–598.

Cunha BA. The clinical significance of fever patterns. *Infect Dis Clin North Am*. 1996;10(1):33–44.

Franssila R, Hedman K. Infection and musculoskeletal conditions: Viral causes of arthritis. *Best Pract Res Clin Rheumatol*. 2006;20(6): 1139–1157.

Hirschmann JV. Fever of unknown origin in adults. *Clin Infect Dis*. 1997;24(3):291–300.

Jones OY, Spencer CH, Bowyer SL, et al. A multicenter case-control study on predictive factors distinguishing childhood leukemia from juvenile rheumatoid arthritis. *Pediatrics*. 2006;117(5):e840–e844.

Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: The molecular pathophysiology of autoinflammatory disease. *Annu Rev Immunol*. 2009;27:621–668.

Rose CD, Eppes SC. Infection-related arthritis. *Rheum Dis Clin North Am*. 1997;23(3):677–695.

Szekanecz Z, Szekanecz E, Bakó G, Shoenfeld Y. Malignancies in autoimmune rheumatic diseases: A mini-review. *Gerontology*. 2011;57(1):3–10.

72

Infectious polymyositis

Shanthi Kappagoda and Upinder Singh

Infectious polymyositis is a rare entity in which there is generalized muscle damage (rhabdomyolysis) caused by an infectious agent. The syndrome of rhabdomyolysis results from muscle necrosis and is characterized by muscle pain, elevated serum creatinine phosphokinase (CPK) concentrations, and myoglobinuria, which may lead to renal dysfunction. The muscle injury in rhabdomyolysis occurs in a generalized pattern and lacks the specific focus of infection as seen in pyomyositis. The entity of pyomyositis is discussed in "Chapter 22, Deep soft-tissue infections: Fasciitis and myositis."

A variety of factors can lead to rhabdomyolysis. These include crush and compression injuries, drug and alcohol ingestion, metabolic and electrolyte disturbances, hypothermia and hyperthermia, envenomation, and a variety of infections. This review focuses on infectious causes of rhabdomyolysis. It is important to distinguish rhabdomyolysis caused by a pathogen from that caused by sepsis, hypotension, or electrolyte imbalances that accompany a severe systemic infection.

Viral infections

The wide spectrum of viral infections that have been reported to cause rhabdomyolysis are listed in Box 72.1. Influenza is the most common viral cause of rhabdomyolysis, followed by HIV and enteroviral infection. Whether the higher incidence with influenza results from a predilection of the virus for muscle tissue or from the more frequent reporting due to physician awareness and ease of diagnosis is unclear. Pandemic H1N1-induced rhabdomyolysis was not clearly associated with an increased incidence or severity when compared to seasonal influenza A; however, patients with higher CPK levels fared worse and had longer ICU stays.

Renal dysfunction in rhabdomyolysis secondary to influenza infection is common and not related solely to the level of CPK elevation. The precise mechanism predisposing to renal damage from influenza-induced rhabdomyolysis is unclear; however, aggressive measures should be taken to preserve renal function in these individuals.

Rhabdomyolysis adds to the spectrum of clinical presentations of HIV infection. Many musculoskeletal syndromes associated with HIV infection have been documented, ranging from myopathy to rhabdomyolysis. Muscle damage can occur in a variety of clinical scenarios in association with HIV infection, including acute seroconversion and antigenemia, end-stage disease with myopathy, and myositis resulting from medication side effects. Muscle biopsies of patients with HIV-induced rhabdomyolysis reveal a nonspecific inflammatory myopathy with focal necrotic areas and regenerating fibers.

The precise pathophysiology underlying virus-induced rhabdomyolysis is unknown; however, three mechanisms have been postulated: direct viral invasion, toxin generation, or an autoimmune response to the virus. Some authors have suggested that direct viral invasion of muscle fibers causes muscle necrosis. Data to support this hypothesis include the identification of viral inclusions, viral DNA, and the isolation of viruses in tissue culture from the muscles of infected patients. In addition, electron microscopy has identified viral particles, and biopsies reveal a lymphocytic infiltrate in the infected muscles. This evidence strongly suggests

BOX 72.1

Viral causes of rhabdomyolysis

Seasonal influenza virus A and B
Influenza A H5N1 (avian) and HINI (swine)
Human immunodeficiency virus
Coxsackievirus
Herpesviruses (HSV, VZV, CMV, EBV, HHV-6)
Echovirus
HTLV-1
Adenovirus
Parvovirus B19
Parainfluenza virus
RSV
Mumps
Measles virus
Hepatitis B and C
Severe acute respiratory syndrome (SARS)-associated coronavirus
Flavivirus (dengue virus; West Nile virus)
Chikungunya virus
Rotavirus
Ebola virus

Abbreviations: HSV = herpes simplex virus; VZV = varicella-zoster virus; CMV = cytomegalovirus; EBV = Epstein–Barr virus; HHV-6 = human herpesvirus 6; HTLV-1 = human T-lymphotropic virus 1; RSV = respiratory syncytial virus.

that direct viral invasion may have a causative role in precipitating rhabdomyolysis. However, various reports documenting normal muscle biopsies or hyaline degeneration and myonecrosis but no viral particles by immunofluorescence and electron microscopy are used to refute this theory. Biopsies of clinically affected musculature that are essentially normal raise the possibility of a circulating "toxin" or cytokine causing rhabdomyolysis. However, to date, no putative toxins have been isolated.

Bacterial infections

Many bacterial agents have been reported to cause rhabdomyolysis (Tables 72.1 and 72.2). The most common associations are with *Legionella* spp., followed by *Streptococcus* spp., *Francisella tularensis*, and *Salmonella* infections. An increasing number of bacterial agents are being associated with this entity due to better diagnostic techniques, an increasing population of immunocompromised individuals, and increasing physician awareness. Individuals with bacterial infections resulting in rhabdomyolysis have significant morbidity (57% with renal failure in one study) and mortality (38% in one series).

Two proposed mechanisms of muscle injury by bacteria include toxin generation and direct bacterial invasion. *Legionella* is believed to release an endotoxin or exotoxin that causes rhabdomyolysis.

TABLE 72.1 **BACTERIAL CAUSES OF RHABDOMYOLYSIS**

Gram-positive bacteria	Gram-negative bacteria
Streptococcus pneumoniae	*Legionella* spp.
Staphylococcus aureus	*Francisella tularensis*
Group B streptococcus	*Salmonella* spp.
Streptococcus pyogenes	*Vibrio* spp.
Listeria spp.	*Brucella* spp.
Staphylococcus epidermidis	*Escherichia coli*
Bacillus spp.	*Pantoea agglomerans*
Clostridium spp.	*Klebsiella* spp.
Viridans streptococci	*Aeromonas* spp.
Streptococcus suis	*Haemophilus influenzae*
β-hemolytic streptococci	*Neisseria* spp.
Streptococcus gallolyticus	*Coxiella burnetii*

Biopsies that are negative for the organism by immunofluorescence support this hypothesis. Organisms such as *Streptococcus* and *Salmonella* cause muscle damage by direct bacterial invasion as well as by decreasing the oxidative and glycolytic enzyme activity of skeletal muscle and activating lysosomal enzymes. A number of bacterial pathogens, including *Staphylococcus aureus, Streptococcus pyogenes, Vibrio* spp., and *Bacillus* spp., have been demonstrated in muscle biopsy specimens, lending credence to the hypothesis of direct bacterial invasion. Rickettsial illnesses such as Rocky Mountain spotted fever can cause muscle injury through vasculitis as well as direct muscle invasion. A variety of cytokines, such as tumor necrosis factor-α and interleukin-1, released during systemic infections from a broad range of infections, can result in skeletal muscle proteolysis.

Fungal, parasitic, and mycobacterial infections

While fungal myositis with the rare progression to rhabdomyolysis is uncommon and occurs primarily in the immunocompromised host, there are a variety of parasitic infections known to cause myositis that may progress to rhabdomyolysis even in the normal host. In particular, organisms such as *Trichinella* that encyst in muscle following initial infection may result in severe myositis depending on the initial organism burden. This classically occurs in the extraocular muscles but can progress to other striated muscles and result in severe muscle weakness. *Plasmodium falciparum* has been linked to myositis with severe rhabdomyolysis resulting in renal failure with higher frequency than in the non-falciparum strains. Muscular complications of *Mycobacterium tuberculosis* and nontuberculosis mycobacterial infections are uncommon and most often are the result of contiguous spread of *M. tuberculosis* to the psoas muscles from vertebral osteomyelitis (Tables 72.2 Boxes 72.2, 72.3).

TABLE 72.2 **MISCELLANEOUS BACTERIAL CAUSES OF RHABDOMYOLYSIS**

Spirochetes	Rickettsial	Other
Leptospira spp. *Borrelia burgdorferi*	*Rickettsia conorii* *Orientia tsutsugamushi* *Ehrlichia equi* *Ehrlichia chaffeensis* *Anaplasma phagocytophilum*	*Mycoplasma pneumoniae* *Mycobacterium tuberculosis* *Mycobacterium avium complex* *Mycobacterium haemophilum* *Mycobacterium bovis* *Mycobacterium leprae* Intravesical instillation of Bacillus Calmette–Guérin

BOX 72.2

Fungal causes of rhabdomyolysis

Candida spp.
Aspergillus spp.
Mucor spp.

BOX 72.3

Parasitic causes of rhabdomyolysis

Plasmodium spp.
Toxoplasma gondii
Trypanosoma cruzi
Microsporidia
Trichinella spp.
Taenia solium

TABLE 72.3 **ENVENOMATIONS REPORTED TO CAUSE RHABDOMYOLYSIS**

Snakes	Other
South American rattlesnake	Brown recluse spiders
Tiger snake	Widow spiders
Mojave rattlesnake	Bees
Russell's viper	Hornets
Pit vipers including *Protobothrops flavorviridis*	Wasps
Taipan	Desert centipede

Envenomations and drug toxicity

Envenomations reported to cause rhabdomyolysis are listed in Box 72.3. Snake bites are commonly reported to cause muscle injury and include bites inflicted by, among others, the Mojave rattlesnake, Russell's viper, *Crotalus durissus terrificus* (South American rattlesnake), Australian snake, tiger snake, and seasnake. These patients present with swollen, tender muscles and high CPK levels. In contrast to viral and bacterial causes of rhabdomyolysis, envenomations generally cause a larger myotoxic insult. A large proportion of these patients also subsequently develop acute renal failure, presumably directly related to the increased renal toxicity from myoglobin. Spider bites of the brown recluse spider (loxoscelism) and the widow spiders (latrodectism) are also associated with rhabdomyolysis. The mechanism of muscle damage in these cases appears to be a direct myotoxic activity of the various venoms.

It is also important to remember the role of drugs, including antimicrobials, when evaluating the cause of rhabdomyolysis. Daptomycin is the most widely known drug with this side-effect profile; however, a multitude of other antimicrobials have been linked to rhabdomyolysis. Box 72.4 lists some of these agents.

Renal failure in rhabdomyolysis

The renal dysfunction associated with rhabdomyolysis arises from a variety of interrelated factors. In muscle injury, both myoglobin and heme proteins are released, although neither is directly toxic to the glomerulus. Heme protein can result in renal tubular injury through a variety of mechanisms: (1) renal vasoconstriction, (2) direct renal tubular cell cytotoxicity, or (3) intraluminal cast formation and tubular obstruction. Therapeutic measures that increase renal blood flow and decrease tubular obstruction are useful in preventing renal injury in these patients.

BOX 72.4

Antimicrobials and rhabdomyolysis

Daptomycin
Raltegravir
Bactrim
Colistin
Fluoroquinolones
Linezolid
Fusidic acid
Clarithromycin
Voriconazole

Therapy and management

The general management of rhabdomyolysis includes supportive care and treatment of the underlying predisposing condition or infection. The general approach is as follows: (1) maintenance of a high degree of suspicion for rhabdomyolysis in the appropriate clinical setting; (2) appropriate diagnostic workup, including CPK levels, urinalysis, and urine myoglobin levels; (3) rapid institution of organism-specific drug therapy; and (4) supportive renal care. Renal function can be protected by maneuvers such as volume expansion and possibly urine alkalinization. Other metabolic disturbances resulting from muscle injury, such as hyperkalemia and metabolic acidosis, also may need specific therapy.

Suggested reading

Bosch X, Poch E, Grau J. Rhabdomyolysis and acute kidney injury. *N Engl J Med*. 2009;361:62–72.

Crum-Cianflone NF. Bacterial, fungal, parasitic, and viral myositis. *Clin Microbiol Rev*. 2008;21:473–494.

Holder K, Myalgias and myopathies: Drug-induced myalgias and myopathies. *FP Essent*. 2016:440:23–27.

Huerta-Alardin AL, Varon J, Marik PE. Bench-to-bedside review: Rhabdomyolysis–an overview for clinicians. *Crit Care*. 2005;9:158–169.

Joshi MK, Liu HH. Acute rhabdomyolysis and renal failure in HIV-infected patients: Risk factors, presentation, and pathophysiology. *AIDS Patient Care STDS*. 2000;14:541–548.

Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: An evaluation of 475 hospitalized patients. *Medicine*. 2005;84:377–385.

Nauss M, Schmidt E, Pancioli A. Viral myositis leading to rhabdomyolysis: A case report and literature review. *Am J Emerg Med*. 2009;27:372.e5–372.e6.

Singh U, Scheld WM. Infectious etiologies of rhabdomyolysis: Three case reports and review. *Clin Infect Dis*. 1996;22:642–649.

Watanabe T. Renal complications of seasonal and pandemic influenza A virus infections. *Eur J Pediatr*. 2013;172:15–22.

Zimmerman JL, Shen, MC. Rhabdomyolysis. *Chest*. 2013; 144:1058–1065.

73

Iliopsoas abscess

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Overview

Iliopsoas abscess (IPA) is a rare condition defined by a collection of purulence in the iliopsoas muscle compartment. IPA is classified in two distinct varieties based on the etiology of the disease. IPA can be either *primary* wherein the infection spreads via a hematogenous or lymphatic route, or *secondary* when it is a contiguous extension of another infection, most often musculoskeletal, intra-abdominal, or genitourinary.

Symptoms can consist of a classic triad of back/flank pain, fever, and a limp on ambulation (flexion deformity); however, all three are rarely present and more generalized symptoms of malaise and weight loss may be present. The common presentation with more vague and general symptoms often leads to a delay in diagnosis and treatment that significantly worsens associated morbidity and mortality. Early and effective management is key to a successful recovery.

While IPA classically is associated with *Mycobacterium tuberculosis* infection, in actual practice it is much more frequently related to *Staphylococcus aureus* in primary IPA, often with methicillin-resistant strains (MRSA). Secondary IPAs are more frequently associated with enteric organisms that have extended outside the gastrointestinal or genitourinary tract.

Anatomy

The iliopsoas muscle group is comprised of two distinct muscles, the iliacus and the psoas major. Their function is as primary hip flexors. An additional accessory psoas muscle may be present in anywhere from 10% to 65% of the population. The iliacus muscle inserts along the superior portion of the iliac fossa, passes under the inguinal ligament, and inserts onto the lesser trochanter of the femur. The psoas major arises from the spinal processes between T12 and the five lumbar vertebrae and passes along the retroperitoneum and under the inguinal ligament where it ultimately inserts onto the lesser trochanter as well. Due to their common tendinous insertion on the lesser trochanter they are frequently grouped together as a single iliopsoas muscle; however, when considering IPA pathology it is likely best to consider them as two distinct structures with different pathologies and outcomes depending on location of infection. The psoas fascia invests the muscle group and runs from the lumbar vertebrae to the iliopubic eminence.

The blood supply of the two groups differs, with the supply for the psoas major derived from four lumbar arteries with outflow via lumbar veins. The iliacus is supplied by the medial circumflex femoral artery and the iliac branch of the iliolumbar artery. Both have a rich blood supply and are adjacent to the retroperitoneal lymphatics which may contribute to *primary* IPAs. The nerve supply of the psoas major is via the lumbar neural plexus from L1 to L3, and the iliacus is innervated by L2, L3, and branches of the femoral nerve.

As a group, the iliopsoas is in close proximity to the colon, appendix, kidneys, ureters, quadratus lumborum, and the transverse spinous processes of the lumbar vertebrae. All of these may be sources of contiguous infection leading to *secondary* IPA (Figure 73.1).

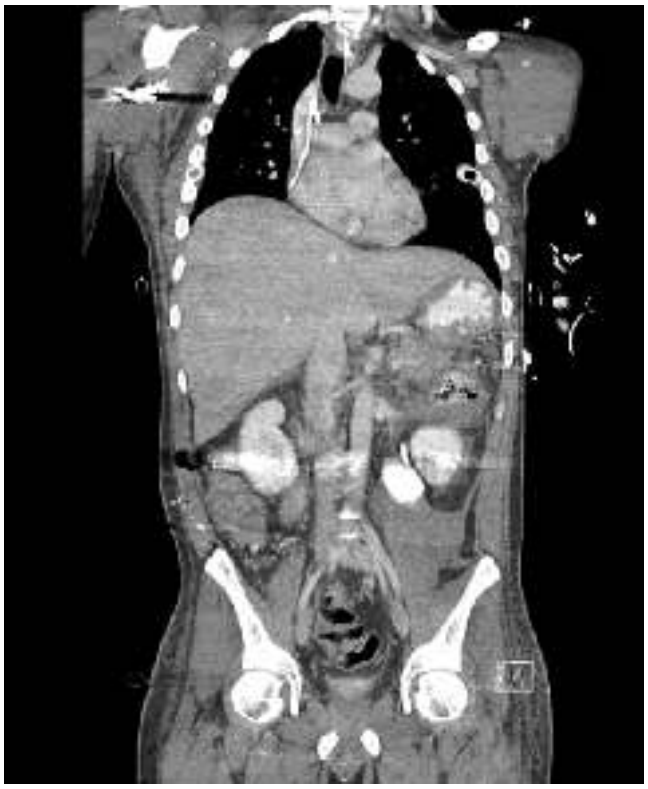

FIGURE 73.1 Coronal views of a CT scan with oral and intravenous contrast agents demonstrating a left-sided iliopsoas abscess. The patient suffered multiple gunshot wounds to the abdomen. Contrast is seen within the psoas, and the distal ureter is visualized. A collection in the left upper quadrant with air bubbles but no contrast is seen beneath the gastric bubble.

Etiology

Primary IPA occurs when a distant infection seeds to the iliopsoas via hematogenous or lymphatic spread. This typically results from intravenous drug use (IVDU), neoplasms, immunodeficient states, and chronic immunosuppressive disease states such as renal failure or diabetes mellitus. Primary IPA is more frequently the source in bilateral infections. Other sources of primary IPA include endocarditis, infected aortic aneurysms, infected vascular grafts, and femoral artery catheterization. In short, in populations at risk of circulating microbes, IPA is a potential infection.

Secondary IPA represents a contiguous extension of another infection into the iliopsoas muscle group. Previously these were primarily thought to occur from gastrointestinal disease such as fistulizing Crohn's disease, diverticulitis, or a perforated cancer. Newer case series, however, demonstrate a greater incidence of disease resulting from adjacent musculoskeletal structures, with psoas muscle abscesses typically in the form of spondylodiscitis of the lumbar spine and iliacus abscesses from sacroiliac (SI) joint or hip infections. Urologic sources of secondary IPA include urinary tract infections, nephrolithiasis, urinary tract cancers, and genitourinary tract instrumentation. Gynecologic causes include tubo-ovarian abscess, perforated uterus from septic abortion, or intrauterine contraceptive device complications. Rarer etiologies include trauma, infected vascular grafts in the retroperitoneum, mycotic femoral aneurysm/pseudoaneurysm, and septic hip arthritis.

Causative organisms vary significantly between primary and secondary IPA. Typically, the abscesses are not polymicrobial, and in primary IPA the most common organism identified is *S. aureus*. Secondary IPAs with a gastrointestinal or urinary source typically will have enteric bacteria, most commonly *Escherichia coli*; however, frequently implicated organisms include *Bacteroides, M. tuberculosis, Streptococcus viridans, Enterococcus faecalis,* and *Peptostreptococcus*. There are also case reports of a number of other atypical bacterial infections resulting in IPA as well.

Patients with HIV/AIDS most typically will present with a primary IPA from *M. tuberculosis* or less commonly *S. aureus*. Primary IPA from *M. tuberculosis* may be the result of hematogenous spreading from a primary respiratory infection. HIV patients presenting with a secondary IPA will most often have a lumbar spondylodiscitis or genitourinary source, again often from *M. tuberculosis*.

Epidemiology

IPA remains a rarely encountered condition, and to date there is no definitive worldwide series estimating the incidence of the disease. Based on published case series, large tertiary care hospitals in the developed world can expect to see on the order of 3 or 4 cases per year. As an example, Alonso et al. evaluated 15 years of admissions at the Johns Hopkins Hospital in Baltimore, Maryland, in the United States and identified a total of 61 cases of IPA, equating out to roughly 4 cases per year. In resource-poor and tropical countries younger patients may present with undetected staphylococcal bacteremia, while in developed countries secondary presentation with gastrointestinal disease has been more common. However, in countries where HIV disease and drug use is more common, primary IPA may dominate.

The rate of diagnosis of IPA is increasing, with the earliest published literature suggesting a dramatically lower incidence (Ricci et al. estimated global incidence at 3 cases globally per year, though this is likely secondary to underreporting). Increasing use of CT scan and MRI has likely increased the detection of cases. Increasing numbers of immunosuppressed patients secondary to posttransplantation status and HIV/AIDS and increasing rates of IVDU has increased the at-risk population for IPA. This increase may have increased the actual incidence of the disease.

The incidence of primary versus secondary IPA was initially thought to vary widely based on geography, with IPA cases in Africa and Asia largely being primary. Secondary IPA cases likely represent around 80% of cases in the developed world. The previously mentioned case series by Alonso et al. demonstrated a sharp increase in incidence from 0.5 cases per 10,000 admissions between 1993 and 2004 and 6.5 cases per 10,000 admissions from 2005 to 2007. Of those admissions, 80% were noted to be secondary, with the contiguous source most often skeletal (48%) or intra-abdominal (23%). The causative organism was identified as MRSA in 25% of all cases

and in 37% of the cases that had definitive microbiologic diagnosis. Within this study, risk factors for IPA included IVDU (21%), neoplasm (18%), diabetes mellitus (15%), and HIV (15%). Only 11% had an inflammatory bowel disease, and 10% had suffered trauma within the preceding 30 days.

A larger, multicenter (11 hospital) review of 124 IPA cases in Spain was published by Navarro et al. in 2009. Of those patients, only 21.8% of patients had a primary IPA while 78.2% were secondary. The main sources of secondary IPA were 50.5% musculoskeletal, 24.7% intra-abdominal gastrointestinal tract, and 17.5% urinary tract. Definitive microbiologic diagnosis was achieved in 75% of cases, most typically yielding *S. aureus, E. coli,* and *Bacteroides*. In patients with a musculoskeletal origin, 42.9% were ultimately the result of *S. aureus* infection, while in patients with urinary or gastrointestinal sources *E. coli* represented 61.5% and 42.1% of the infections, respectively. Only 21.5% of cases were polymicrobial. Risk factors included diabetes mellitus in 18.5% of patients, chronic liver disease in 16.1% of patients, neoplasm in 11.3% of patients, and HIV in 6.3% of patients. Regarding outcomes, 5% died due to complications from IPA, and 15.8% had some form of recurrent infection. Risk factors of mortality included advanced age and *E. coli* infection.

There also appears to be clinical significance in whether the offending organisms are gas-forming or not. Hseih et al. performed a retrospective review of 88 cases in Taiwan between July 2007 and February 2013. In this study, 31% of cases had gas-forming organisms, and that group of patients experienced a much higher mortality rate than those with non–gas-forming organisms (44% vs 16.4%). Moreover, they identified that in patients with gas-forming organisms both percutaneous drainage and antibiotic therapy alone were associated with very high mortality, whereas open drainage had very good outcomes. Specifically, only 2 out of 13 gas-forming IPA patients who had percutaneous drainage had a good outcome, and only 1 of 6 gas-forming IPA patients who were treated with antibiotics alone survived. Conversely, 7 of 8 patients who underwent surgical drainage had a good outcome.

Diagnosis

A focused history and physical is essential for the diagnosis of IPA. History should focus on immunosuppression, inflammatory bowel disease, IVDU, recent surgery or hardware (such as a hip prosthesis or lumbar fusion), and recent infections. There is a classic triad of IPA symptoms consisting of back/flank pain, fever, and a limp (flexion deformity): however, this triad is only seen in 10% to 30% of cases. Active contraction and passive extension of the iliopsoas muscle group may be painful, so patients tend to flex and externally rotate the thigh to minimize discomfort. A classic psoas sign may be present on examination. Additional symptoms may be vague, such as night sweats, malaise, and weight loss. Abdominal pain or a mass in the back, flank, or groin may all suggest IPA as well. Immunocompromised patients may be particularly difficult to diagnose based on history and symptoms as they may have few or no symptoms. In one recent report Takada et al. in 2015 reviewed 15 patients and noted that the time from presentation to diagnosis was an average of >20 days.

Laboratory testing should include a CBC, a comprehensive metabolic panel, C-reactive proteins, and erythrocyte sedimentation rate. Frequently patients with IPA will manifest a leukocytosis and potentially elevated blood urea nitrogen, creatinine, or electrolyte disturbance. Blood cultures, and if identified, abscess aspirate, can be critical in identifying the causative organism and tailoring antibiotic therapy to the patient. Direct aspirate is superior to blood cultures due to higher yield and greater specificity.

The preferred imaging modality for IPA is with CT scan with intravenous contrast and oral contrast if a gastrointestinal source may be contributing. CT scan approaches 100% sensitivity for IPA, but it can struggle to differentiate from hematoma. In patients with a very short interval of time between initial symptoms and non-enhanced CT scan, an abscess may not yet be identified but instead diffuse swelling of the muscle is seen. In the paper by Takada et al. sensitivity from days 1 to 5 ranged from 33% to 50% on CT and MRI, but was 100% for all patients after day 6. Delayed washout of intravenous contrast with a rim-enhancing lesion increases the specificity for abscess. Additional findings may suggest an etiology aside from IPA, for instance irregular lesion margins may suggest neoplasm (67% sensitivity), and diffuse involvement of the muscle may suggest hematoma (88% sensitive). The CT scan is particularly strong at diagnosing the associated pathology in secondary IPA and can also be used to help plan for and guide needle aspiration and drainage of the abscess collection.

MRI can also be effective at detecting IPA with rim-enhancing fluid collections on post-contrast images suggesting IPA. Alterations of T1 signal within the lesion may help differentiate the age of the lesion. MRI, however, can also struggle to delineate abscess from hematoma. Furthermore, MRI struggles at identifying and defining gastrointestinal disease that may be the source of a secondary IPA and can lead to delay in surgical treatment that may otherwise be appropriate.

Ultrasound may be a reasonable screening tool in the emergency department, but it is operator dependent and lacks sensitivity and specificity compared to other examinations. It is, however, noninvasive and cost-effective. A positive ultrasound finding should be followed up with a definitive CT study.

Treatment

Initial treatment of a patient presenting with IPA should consist of standard sepsis bundle care. This should include adequate fluid resuscitation, collection of blood cultures, and early implementation of broad-spectrum antibiotics. Antibiotic therapy should cover *S. aureus* as well as enteric organisms. Given rising rates of MRSA, the authors suggest appropriate coverage with vancomycin depending on local resistance patterns as well as for critically ill patients and high-risk patients. Culture sensitivities should ultimately be used to guide antibiotic therapy in a targeted fashion as soon as available.

In cases where the etiology of secondary IPA is readily apparent, antibiotic therapy can be targeted early on to cover the most likely

offending organisms. Table 73.1 shows pathogens implicated in IPA by etiology.

Primary IPA empiric coverage should include antibiotics for *S. aureus,* coagulase-negative *Staphylococcus, M. tuberculosis,* and *Mycobacterium avium.* Vancomycin should be the initial choice for any critically ill patient with risk factors for MRSA. Other options would include oxacillin or clindamycin with an aminoglycoside.

In cases of secondary IPA, enteric organisms should be covered including *E. coli, Klebsiella, Bacteroides, Peptostreptococcus, Proteus, Clostridium,* and *Salmonella.* Treatment options include monotherapy with ertapenem or cefotetan; however, in critically ill patients the authors would advise piperacillin-tazobactam, imipenem, or meropenem. In penicillin-allergic patients, clindamycin combined with an aminoglycoside, a third-generation cephalosporin, aztreonam, or a fluoroquinolone may be adequate initial therapy.

Initial treatment of either form of IPA should be with intravenous antibiotics and can be de-escalated to oral regimens once culture and sensitivity data are available. Table 73.2 shows treatment options for IPA by classification. Table 73.3 shows the clinical signs and symptoms of patients with an iliopsoas abscess.

Antibiotic therapy alone may be sufficient for smaller abscesses; however, many cases will require either percutaneous drainage or operative incision and debridement. Percutaneous aspiration is significantly less invasive than open drainage and may be a safer option for critically ill patients. As such, CT-guided aspiration by interventional radiology has become the mainstay of interventional management for most cases of IPA. During CT-guided drainage abscess fluid should be sent for Gram stain and culture. A pig-tail catheter drain should be retained, and a sinogram (or drain study) should be performed to confirm cavity obliteration prior to removal of the drain. Yacoub et al. describe an algorithm for CT-guided drainage and antibiotic therapy and report on 41 patients with a 90% success rate for resolution of IPA without surgery. The described algorithm involves CT scan for initial diagnosis. If the abscess is <3 cm, antibiotics alone were employed. If >3 cm, percutaneous image-guided drainage was utilized in addition to antibiotics. A study of 7 patients who were not surgical candidates demonstrated percutaneous drainage was effective in 71%, drained an average of 62 cc (10–130 cc), and retained their drainage catheters for a mean of 8 days. Two of the 7 patients required a second drainage procedure (Table 73.4).

Despite recent advances in interventional radiology-guided drain placement, some cases remain appropriate for surgical intervention. Hseih et al. published a report from Taiwan that suggested that patients who have gas-forming pathogens should be treated with a surgery-first approach, while patients with non–gas-producing pathogens appear to do equally well with either percutaneous or laparoscopic or open approaches. Cases that have either failed to resolve with image-guided drainage procedures or have an intra-abdominal pathology driving a secondary IPA that requires correction of the offending source organ to resolve should be considered for operative therapy. Additional factors that may drive open drainage include

TABLE 73.1 **PATHOGENS FOUND IN ILIOPSOAS ABSCESSES**

Iliopsoas etiology	Pathogen
Primary	
Intravenous drug abuse Immunocompromised	*Staphylococcus aureus*, coagulase-negative Staphylococcus, especially methicillin-resistant *S. aureus, Mycobacterium tuberculosis, Mycobacterium avium* Occasional gram-negatives
Secondary	
Gastrointestinal, e.g., Crohn's disease, fistula, cancer, pancreatic, recent operation	*Escherichia coli, Klebsiella, Enterococcus* sp., *Proteus* sp., *Bacteroides* sp., *Peptostreptococcus, Clostridium*, *Salmonella enteritidis*
Genitourinary	*E. coli, M. tuberculosis, Enterococcus* sp.
Lumbar/Back	*M. tuberculosis, S. aureus*, coagulase negative staphylococcus
Trauma	Enteric and *Staph* organisms *Edwardsiella tarda*

TABLE 73.2 **ANTIMICROBIAL TREATMENT OPTIONS FOR ILIOPSOAS ABSCESSES**

Iliopsoas etiology	Treatment option
Primary	
Intravenous drug abuse Immunocompromised	Initial coverage should include specific coverage for *S. aureus* but should also include gram-negative coverage until the final organism(s) are known. *Options*: Oxacillin (or nafcillin) and aminoglycoside, cephalosporins, especially cefepime, fluoroquinolones, clindamycin, and aminoglycoside. Vancomycin should be considered for critically ill patients and those with high risk of methicillin resistance.
Secondary	
Gastrointestinal, e.g., Crohn's, fistula, cancer, pancreatic, recent operation Genitourinary Lumbar/Back Trauma	Initial empiric coverage for all secondary abscesses should be broad spectrum and should include gram-negative aerobes and anaerobes. *Options: Monotherapy: Moderate Illness*: Cefotetan (cefoxitin), ertapenem, piperacillin–tazobactam; *Severe illness*: Piperacillin–tazobactam, imipenem, meropenem, *Combination Therapy*: Clindamycin + aminoglycoside, clindamycin and third-generation cephalosporin (cefotaxime, ceftriaxone), clindamycin and aztreonam, clindamycin and fluoroquinolone

TABLE 73.3 CLINICAL SIGNS AND SYMPTOMS OF PATIENTS WITH AN ILIOPSOAS ABSCESS

Clinical sign or symptom	Percentage of patients with sign or symptom
Fever	82–90
Pain	64–100
Abdominal	35–100
Flank/Back	30–35
Hip	29
Psoas sign	100
Unilateral flexion deformity	29
Mass	18–80
Swelling or erythema	24
Nausea and vomiting	30
Chills and night sweats	6
Elevated white blood cell count	90–100
Positive blood cultures	70

multiple loculations within the abscess or need for debridement of extensive areas of necrotic muscle or tissue. The typical surgical approach is a lower abdominal, muscle-splitting, extraperitoneal incision to access the retroperitoneum. Surgical planning should be guided by CT imaging. If there is an intraperitoneal process driving a secondary IPA a midline laparotomy may be required for source control. Incision and drainage via the groin, thigh, or back is not recommended.

TABLE 73.4 COMPARISON OF DIFFERENT CT FEATURES IN DISTINGUISHING ABSCESSES FROM NEOPLASMS AND HEMATOMAS OF THE ILIOPSOAS COMPARTMENT

CT feature	Sensitivity (%)	Specificity (%)	Accuracy (%)
Enlargement of both psoas and iliacus muscle	29	52	41
Low attenuation of the lesion	100	43	70
Diffuse involvement of the entire muscle by lesion	19	52	36
Irregular lesion margins	52	43	48
Fat infiltration	62	48	55
Fascial disruption	57	57	57

Abbreviation: CT = computed tomography
Modified from Lenchik L, Dogvan DJ, Kier R. CT of the iliopsoas compartment: Value in differentiating tumor, abscess, and hematoma. *AJR Am J Roentgenol*. 1994;162:83–86.

Outcome

Current mortality rates for IPA appear to range between 3% and 5%, though the relative rarity of this disease process combined with its frequently occult nature may lead to underestimations for mortality. Ricci et al. initially published an overall mortality rate of 2.5% for primary IPA, but an 18.9% mortality rate for secondary IPA. The primary cause of death was sepsis, with delayed or inadequate treatment of sepsis being the largest risk factor. More recent studies by Alonso et al. noted only 2 patient deaths out of 61 cases identified, and the 2009 case series from Spain by Navarro et al. had an overall mortality rate of 6.6%, with 5% being due to complications of IPA. Risk factors of mortality included advanced age (>65), bacteremia, and *E. coli* growth on cultures. A 2013 study by Hsieh et al. identified 88 patients with IPA and reported a mortality rate of 25%.

Outcome is largely determined by early diagnosis, appropriate management of sepsis with adequate fluid resuscitation, collection of blood cultures, initiation of broad-spectrum antibiotics, and prompt source control (Table 73.5).

Conclusion

- Primary IPA occurs when the iliopsoas muscle abscess forms as the result of hematogenous or lymphatic seeding. Secondary IPA occurs as the direct extension of a nearby infection, most often musculoskeletal, intra-abdominal, or genitourinary in nature.
- *S. aureus* is the most commonly isolated organism in primary IPA. Enteric organisms, including *E. coli*., are the most commonly isolated organisms in secondary IPA.

TABLE 73.5 PATHOGENS FOUND IN ILIOPSOAS ABSCESSES

Iliopsoas etiology	Pathogen
Primary	
Intravenous drug abuse	*Staphylococcus aureus*, coagulase-negative Staphylococcus, especially methicillin-resistant
Immunocompromised	*S. aureus, Mycobacterium tuberculosis, Mycobacterium avium* Occasional gram-negatives
Secondary	
Gastrointestinal, i.e., Crohn's disease, fistula, cancer, pancreatic, recent operation	*Escherichia coli, Klebsiella, Enterococcus* sp., *Proteus* sp., *Bacteroides* sp., *Peptostreptococcus, Clostridium*, *Salmonella enteritidis*
Genitourinary	*E. coli, M. tuberculosis, Enterococcus* sp.
Lumbar/Back	*M. tuberculosis, S. aureus*, coagulase-negative staphylococcus
Trauma	Enteric and *Staph* organisms

- The classic triad of back/flank pain, fever, and flexion deformity or limp is only present in 10% to 30% of cases. Additional symptoms of malaise and weight loss may be present.
- Risk factors for primary IPA include immunosuppression/HIV, IVDU, and chronic disease. Secondary IPA risk factors include lumbar spondylodiscitis, inflammatory bowel disease, and neoplasm.
- CT scan is the preferred imaging modality for diagnosis.
- Treatment of small collections may consist of antibiotics alone; larger collections may require image-guided percutaneous drainage. In rare cases operative intervention may be required. Secondary IPA may require an operative intervention for source control of the inciting infection.
- Early diagnosis and effective treatment with antibiotics and percutaneous drainage (if indicated) is critical to reducing morbidity and mortality related to IPA.

Suggested reading

Baier PK, Arampatizis, Imdahl A, Hopt UT. The iliopsoas abscess: Aetiology, therapy and outcome. *Lagenbecks Arch Surg*. 2006;391:411–417.

Cantasdemir M, Kara B, Cebi D, Selcuk ND, Numan F. Computed tomography-guided percutaneous catheter drainage of primary and secondary iliopsoas abscesses. *Clin Radiol*. 2003;58(10):811–815.

Chern CH, Hu SC, Kao WF, Tsai Y, Yen D, Lee CH. Psoas abscess: Making an early diagnosis in the ED. *Am J Emerg Med*. 1997;15:83–88.

De U, Pal DK. Seventy cases of non-tubercular psoas abscess at a rural referral centre in South Bengal. *Trop Doct*. 2006;36(1):53–54.

Hsieh MS, Huang SC, Loh EW, et al. Features and treatment modality of iliopsoas abscess and its outcome: A 6-year hospital-based study. *BMC Infect Dis*. 2013;13(1).

Lenchik L, Dogvan DJ, Kier R. CT of the iliopsoas compartment: Value in differentiating tumor, abscess, and hematoma. *AJR Am J Roentgenol*. 1994;162:83–86.

Macgillvray DC, Valentine RJ, Johnson JA. Strategies in the management of pyogenic psoas abscesses. *Am Surg*. 1991;57:701–705.

Mallick IH, Thoufeeq MH, Rajendran TP. Iliopsoas abscess. *Post Grad Med J*. 2004;80:459–462.

Mückley T, Schutz T, Kirschner M, et al. Psoas abscess: The spine as a primary source of infection. *Spine*. 2003;28(6):E106–E113.

Navarro Lopez V, Lopez Garcia F, Gonzalez Escoda E, Gregori Colome J, Munoz Perez A. Psoas abscess in patients infected with the human immunodeficiency virus. *Eur J Clin Microbiol Infect Dis*. 2004;23(8):661–663.

Neufeld D, Keidar A, Gutman M, Zissin R. Abdominal wall abscesses in patients with Crohn's disease: Clinical outcome. *J Gastrointest Surg*. 2006;10:445–449.

Santaella RO, Fishman EK, Lipsett PA. Primary vs. secondary iliopsoas abscess presentation. *Microbiol Treat Arch Surg*. 1995;130:1309–1313.

Song J, Letts M, Monson R. Differentiation of psoas muscle abscess from septic arthritis of the hip in children. *Clin Orthopaed Rel Res*. 2001;391:258–265.

Takada T, Terada K, Kajiwara H, Ohira Y. Limitations of using imaging diagnosis for psoas abscess in its early stage. *Intern Med*. 2015;54(20):2589–2593.

Ricci MA, Rose FB, Meyer KK. Pyogenic psoas abscess: Worldwide variations in etiology. *World J Surg*. 1986;10:834–843.

Walsh TR, Reilly JR, Hanley E, Webster M, Peitzman A, Steed DL. Changing etiology of iliopsoas abscess. *Am J Surg*. 1992;163:413–416.

Wells RD, Bebarta VS. Primary iliopsoas abscess caused by community-acquired methicillin-resistant Staphylococcus aureus. *Am J Emerg Med*. 2006;24(7):897–898.

Section 10

Clinical syndromes: Neurologic system

74

Bacterial meningitis

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Introduction

Meningitis is an inflammation of the meninges, mainly the inner meninges comprised of the arachnoid and pia mater, which surround the brain and spinal cord and through which cerebrospinal fluid (CSF) flows. Meningitis can be caused by viral, bacterial, fungal, or parasitic infections or by noninfectious etiologies such as medications, inflammatory diseases, and malignancies, as well as by autoimmune disorders. Bacterial meningitis occurs most commonly by hematogenous spread but can also occur by direct invasion from the sinuses, ear, or postoperatively.

Rates of bacterial meningitis in the Unites States have declined significantly in the past decades, with the overall incidence of bacterial meningitis being 1.38 cases per 100,000 across all age groups. This trend is largely due to availability of effective vaccines against the most common pathogens and education of high-risk populations. Despite this decline, the case fatality rate of bacterial meningitis in the United States has remained fairly stable at around 14.3% but varies depending on pathogen and host factors.

Clinical presentation

The classic clinical presentation in patients with bacterial meningitis is that of fever, headache, meningismus, and signs of cerebral dysfunction (confusion, delirium, or a declining level of consciousness) (Table 74.1). In a review of 493 cases of acute bacterial meningitis in adults, the classic triad (i.e., fever, nuchal rigidity, and change in mental status) was found in only two-thirds of patients, but all had at least one of these findings. In another review of 696 episodes of community-acquired bacterial meningitis, the triad of fever, neck stiffness, and altered mental status was present in only 44% of episodes, although almost all patients (95%) presented with at least two of the four symptoms of headache, fever, stiff neck, and altered mental status. A recent prospective study from the Netherlands of 1,412 episodes of bacterial community-acquired meningitis in adults demonstrated the classic triad in 41% of patients, with the most common presenting symptoms being headache (83%), fever (74%), neck stiffness (74%), and altered mental status (71%). The meningismus may be subtle, marked, or accompanied by Kernig and/or Brudzinski signs. However, in a prospective study that examined the diagnostic accuracy of meningeal signs in adults with suspected meningitis, the sensitivity of these findings was only 5% for Kernig sign, 5% for Brudzinski sign, and 30% for nuchal rigidity, indicating that they did not accurately distinguish patients with meningitis from those without meningitis, and the absence of these findings did not rule out the diagnosis of bacterial meningitis. Cranial nerve palsies and focal cerebral signs are seen in 10% to 20% of cases. In an observational study of 696 patients with community-acquired bacterial meningitis, cerebral infarction occurred in 25% of episodes, and, in 36% of those, specifically with pneumococcal meningitis. Seizures occur in about 30% of patients. Papilledema is observed >5% of cases early in infection, and its presence should suggest an alternative diagnosis. As meningitis progresses,

TABLE 74.1 **PRESENTING SIGNS AND SYMPTOMS IN ADULTS WITH BACTERIAL MENINGITIS**

Signs or symptoms	Relative frequency (%)
Headache	≥85
Fever	≥80
Meningismus	≥80
Altered sensorium	≥75
Classic Triad (headache, meningismus and altered sensorium)	≥40
Vomiting	~35
Seizures	~30
Focal neurologic findings	10–35

patients may develop signs of increased intracranial pressure such as coma, hypertension, bradycardia, or palsy of cranial nerve III.

To further characterize the accuracy and precision of the clinical examination in adult patients with acute meningitis, patient data on 845 episodes of acute meningitis (confirmed by lumbar puncture or autopsy) in patients aged 16 to 95 years were reviewed. The results demonstrated that individual items of the clinical history (i.e., headache, nausea, and vomiting) had a low accuracy for the diagnosis of meningitis in adults. However, on review of the accuracy of physical examination findings, the absence of fever, neck stiffness, and altered mental status effectively eliminated the likelihood of acute meningitis; the sensitivity was 99% to 100% for the presence of one of these findings in the diagnosis of acute meningitis. Despite these findings, physicians should have a low threshold for performance of lumbar puncture in patients at high risk for bacterial meningitis.

Certain symptoms or signs may suggest an etiologic diagnosis in patients with bacterial meningitis. About half of the patients with meningococcemia, with or without meningitis, present with a prominent rash that is localized principally to the extremities. The rash typically is macular and erythematous early in the course of illness, but it quickly evolves into a petechial phase with further coalescence into a purpuric form; the rash may evolve rapidly, with new petechiae appearing during the physical examination. Patients with *Listeria monocytogenes* meningitis have an increased tendency toward focal deficits and seizures early in the course of infection; some patients may present with ataxia, cranial nerve palsies, or nystagmus as a result of rhombencephalitis. A prodrome of fever, headache, myalgias, chills, gastroenteritis, and other systemic symptoms may occur on average 3 to 4 days prior to presentation. Fever is the most common presenting symptom (>90%), followed by altered mental status (66%) and headache (46%); one-half to two-thirds of patients have nuchal rigidity. In addition, many patients with bacterial meningitis have predisposing illnesses; up to 40% of patients with pneumococcal meningitis have preceding ear, sinus, or lung infections.

Furthermore, certain patient populations may not present with many of the classic symptoms or signs of bacterial meningitis. Neonates often do not have meningismus and may present with a number of nonspecific signs such as temperature instability, change in affect or level of alertness, lethargy, irritability, vomiting, diarrhea or respiratory distress. Young children, aged 1 to 4 years, most commonly present with fever, vomiting, and nuchal rigidity. Elderly patients, particularly those with underlying medical conditions (e.g., diabetes mellitus, cardiopulmonary disease), may present insidiously with lethargy or obtundation, no fever, and variable signs of meningeal inflammation. In one 30-year study of 185 patients 65 years and older, the diagnosis of community-acquired bacterial meningitis was more difficult because of the absence of characteristic meningeal signs. Immunocompromised patients, such as those with prolonged neutropenia, AIDS, certain malignancies, or receiving immunomodulating therapies, may also present in a subtle manner because of the impaired ability of the patient to mount a subarachnoid space inflammatory response. In patients with head trauma, the symptoms and signs consistent with meningitis may be present as a result of the underlying injury and not meningitis. In all of these subgroups of patients, altered or changed mental status should not be ascribed to other conditions unless bacterial meningitis has been excluded by CSF examination.

Diagnosis

Bacterial meningitis is diagnosed by examination of CSF obtained via lumbar puncture. In virtually all patients with bacterial meningitis, the opening pressure is elevated (>180 mm H_2O), with values >600 mm H_2O suggesting the presence of cerebral edema, intracranial suppurative foci, or communicating hydrocephalus. The CSF white blood cell count is elevated (usually 1,000–5,000 cells/mm^3, with a range of ≤100 to >10 000/mm^3); patients with low CSF white blood cell counts (from 0 to 20/mm^3), despite high CSF bacterial concentrations, tend to have a poor prognosis. There is usually a neutrophilic predominance (≥80%), although approximately 10% of patients with acute bacterial meningitis will present with a lymphocytic predominance in CSF (more common in neonates with gram-negative bacillary meningitis and patients with *L. monocytogenes* meningitis). A decreased CSF glucose concentration (≤40 mg/dL) is found in about 60% of patients; a CSF-to-serum glucose ratio of <0.23 is observed in about 70% of patients. The CSF protein is elevated in virtually all cases (usually 100–500 mg/dL). Gram stain examination of CSF permits a rapid, accurate identification of the causative microorganism in about 60% to 90% of patients with bacterial meningitis; the specificity is nearly 100%, and the likelihood of detecting the organism is greater with higher CSF bacterial densities. CSF cultures are positive in 80% to 90% of patients with community-acquired bacterial meningitis; the yield of culture is decreased in patients who have received prior antimicrobial therapy. Elevated CSF lactate concentrations may help differentiate between bacterial and aseptic meningitis with a sensitivity and specificity reported as high as 97% and 96%, respectively. However, the accuracy is lowered in patients pretreated with antimicrobial therapy prior to lumbar puncture or in those with other CNS diseases such as head trauma or stroke.

In patients without a positive CSF Gram stain or culture, the diagnosis of bacterial meningitis can be difficult to establish or

reject. A number of studies have examined a combination of clinical features, with or without test results, to develop models to predict the likelihood of bacterial meningitis compared to other potential agents, usually viruses. Despite positive results in a number of studies utilizing prediction models, clinical judgment should continue to be used in decisions for administration of empiric antimicrobial therapy in patients with suspected bacterial meningitis.

In patients with bacterial meningitis and a negative CSF Gram stain, several rapid diagnostic tests that can be considered for detection of specific bacterial antigens in CSF have been developed to aid in the etiologic diagnosis. Polymerase chain reaction (PCR) has been used to amplify DNA from patients with meningitis caused by several meningeal pathogens. The clinical utility of PCR for the diagnosis of bacterial meningitis was assessed in one study with a broad range of bacterial primers, yielding a sensitivity of 100%, specificity of 98.2%, positive predictive value of 98.2%, and negative predictive value of 100%. Another study demonstrated the sensitivity of broad-based PCR to be 59% (standard culture was 43%) with a specificity of 97% (standard culture was also 97%). Consequently, broad-based PCR can be used to detect the most common microorganisms with only one test, can be done within 2 hours in most industrialized countries, and has adequate sensitivity and excellent specificity. Further refinements are needed, however, before this technique can be used in patients with presumed bacterial meningitis when CSF Gram stain and cultures are negative. Currently available latex agglutination techniques have a sensitivity ranging from 50% to 100% (although these tests are highly specific) and detect the antigens of *Haemophilus influenzae* type b, *Streptococcus pneumoniae, Neisseria meningitidis, Escherichia coli* K1, and *Streptococcus agalactiae*. However, the routine use of latex agglutination for the etiologic diagnosis of bacterial meningitis has recently been questioned and is no longer routinely recommended because bacterial antigen testing does not appear to modify the decision to administer antimicrobial therapy, and false-positive tests have been reported. An immunochromatographic test is also available for detection of *S. pneumoniae* in CSF; the overall sensitivity was 95% to 100%.

TABLE 74.2 **RECOMMENDED ANTIMICROBIAL THERAPY FOR ACUTE BACTERIAL MENINGITIS BASED ON PRESUMPTIVE IDENTIFICATION BY POSITIVE GRAM STAIN**

Microorganism	Therapy
Streptococcus pneumoniae	Vancomycin plus a third-generation cephalosporin[a,b]
Neisseria meningitidis	Third-generation cephalosporin[a]
Listeria monocytogenes	Ampicillin or penicillin G[c]
Haemophilus influenzae type b	Third-generation cephalosporin[a]

[a]Ceftriaxone or cefotaxime.
[b]Addition of rifampin may be considered; some experts would add rifampin if dexamethasone is also given.
[c] Addition of an aminoglycoside should be considered.

Therapy

Initial approach to management

In patients with the clinical presentation of acute bacterial meningitis, the initial management includes obtaining blood cultures and performing a lumbar puncture. If the CSF formula is consistent with the diagnosis of bacterial meningitis, targeted antimicrobial therapy and adjunctive dexamethasone (see later discussion) should be initiated based on results of Gram stain (Table 74.2). However, if no etiologic agent can be identified on initial CSF analysis, empiric antimicrobial therapy and adjunctive therapy should be initiated rapidly based on the patient's age (Table 74.3). In patients with a clinical presentation of bacterial meningitis in whom there is a delay in performance of lumbar puncture or if there is suspicion of an intracranial mass lesion that is causing their neurologic presentation (i.e., those with focal neurologic deficits, abnormal level of consciousness, new-onset seizure, or papilledema on funduscopic examination or those who are immunocompromised or have a history of CNS disease), a noncontrast CT scan of the head should be performed before lumbar puncture. In these patients, blood cultures must be obtained and appropriate antimicrobial and adjunctive therapy given prior to lumbar puncture or before the patient is sent to the CT scanner to potentially reduce the increased morbidity and mortality associated with bacterial meningitis when initiation of appropriate antimicrobial and adjunctive therapy is delayed. Although there are no prospective data on the timing of administration of antimicrobial therapy in patients with bacterial meningitis, a retrospective cohort study in patients with community-acquired bacterial meningitis demonstrated that a delay in initiation of antimicrobial therapy after patient arrival in the emergency room was associated with an adverse clinical outcome when the patient's condition advanced to a high stage of prognostic severity, thus supporting the assumption that treatment of bacterial meningitis before it advances to a high level of clinical severity improves clinical outcome. While the yield of positive CSF cultures may decrease with initiation of antimicrobial therapy prior to obtaining CSF for analysis, the pretreatment blood cultures, CSF formula, and/or Gram stain will likely provide evidence for or against a diagnosis of bacterial meningitis.

Adjunctive therapy

Dexamethasone is the only adjunctive therapy recommended for certain bacterial causes of meningitis. By reducing the subarachnoid space inflammatory response, which leads to cerebral edema and elevated intracranial pressure, adjunctive dexamethasone administered prior to the initiation of antimicrobial therapy has been demonstrated to improve outcome in patients with meningitis caused by *S. pneumoniae* and *H. influenzae* in developed countries. A meta-analysis confirmed the benefit of adjunctive dexamethasone (0.15 mg/kg q6h for 2–4 days) for *H. influenzae* type b meningitis and, if commenced with or before parenteral antimicrobial therapy,

TABLE 74.3 **COMMON BACTERIAL PATHOGENS AND EMPIRIC THERAPEUTIC RECOMMENDATIONS BASED ON AGE IN PATIENTS WITH MENINGITIS**

Age or predisposing condition	Common bacterial pathogens	Empiric antimicrobial therapy
<1 month	*Streptococcus agalactiae* *Escherichia coli* *Listeria monocytogenes*	Ampicillin plus cefotaxime, ampicillin plus cefepime, or ampicillin plus an aminoglycoside
1-23 months	*S. agalactiae* *E. coli* *Haemophilus influenzae* *Streptococcus pneumoniae* *Neisseria meningitidis*	Vancomycin plus a third-generation cephalosporin[a,b,c]
2-50 years	*S. pneumoniae* *N. meningitidis*	Vancomycin plus a third-generation cephalosporin[a,b,c]
>50 years	*S. pneumoniae* *N. meningitidis* *L. monocytogenes* aerobic gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin[a,c]
Immunocompromised state	*S. pneumoniae* *N. meningitidis* *L. monocytogenes* aerobic gram-negative bacilli	Vancomycin plus ampicillin plus either cefepime or meropenem
Head trauma or after neurosurgery	*Staphylococci* Diphtheroids *Pseudomonas aeruginosa* *S. pneumoniae* *Acinetobacter baumannii*[d] ESBL gram-negative bacilli[d]	Vancomycin plus either ceftazidime, cefepime, or meropenem

[a]Ceftriaxone or cefotaxime.
[b] Add ampicillin if meningitis caused by *L. monocytogenes* is suspected.
[c] Some experts would add rifampin if dexamethasone is also given.
[d]If considered, would use meropenem as part of the empiric regimen.

suggested benefit for pneumococcal meningitis in childhood. Evidence of clinical benefit was strongest for hearing outcomes. In adults with acute bacterial meningitis, a prospective, randomized, placebo-controlled, double-blind multicenter trial in 301 patients demonstrated that patients randomized to receive adjunctive dexamethasone were less likely to have unfavorable outcome and death; benefit was most evident among the subgroup of patients with pneumococcal meningitis. Based on the available evidence, adjunctive dexamethasone (0.15 mg/kg q6h for 4 days with the first dose administered 10–20 minutes before, or at least concomitant with, the first dose of an antimicrobial agent) should be utilized in adults with suspected or proven pneumococcal meningitis. Adjunctive dexamethasone should not be given to adults who have already received antimicrobial therapy because administration in this setting is unlikely to improve patient outcome. The data are inadequate to recommend adjunctive dexamethasone in adults with meningitis caused by other meningeal pathogens; continuing dexamethasone in patients with culture-proven meningococcal meningitis did not lead to improvement in rates of unfavorable outcome, although its use was not associated with harm. Additionally, a recent prospective study of patients with invasive *L. monocytogenes* infection in France demonstrated that 31 (13%) of 252 patients with *L. monocytogenes* meningitis who received adjunctive dexamethasone had a statistically significant lower survival than those who did not (17 [53%] of 32 vs. 157 [73%] of 216), although this outcome has not been observed in other studies of patients with *Listeria* meningitis. Some authorities would initiate dexamethasone in all adults because the etiology of meningitis is not always ascertained at initial evaluation, given that *S. pneumoniae* accounted for 58% of all cases of meningitis in the United States between 1998 and 2007.

Despite the positive benefits of adjunctive dexamethasone in patients with *S. pneumoniae* or *H. influenzae* meningitis, its routine use in patients in the developing world has been controversial. In one randomized, double-blind, placebo-controlled trial from Malawi in adults, there were no significant differences in mortality, although almost 90% of the patients in this trial were infected with HIV and likely had advanced disease. In a Cochrane meta-analysis of 24 studies involving 4,041 participants, adjunctive dexamethasone did

not reduce overall mortality, but there was a trend to lower mortality rates in adults; corticosteroids were associated with lower rates of severe hearing loss, any hearing loss, and neurologic sequelae, but these benefits were only seen in studies from high-income countries.

In addition, the use of adjunctive dexamethasone is of concern in those with pneumococcal meningitis caused by highly penicillin- and cephalosporin-resistant strains, in which patients may require antimicrobial therapy with vancomycin. In this instance, a diminished CSF inflammatory response after dexamethasone administration might significantly reduce vancomycin penetration into CSF and delay CSF sterilization. The published trials have not examined outcome in patients with these resistant isolates who have received adjunctive dexamethasone, and it is unlikely that this question will be definitively answered in the near future given the difficulty in enrolling adequate numbers of patients with these resistant strains into clinical trials. However, CSF vancomycin penetration was not reduced by dexamethasone in a study in which a continuous infusion of vancomycin (at a dose of 60 mg/kg/d) was utilized. For any patient receiving adjunctive dexamethasone who is not improving as expected, a repeat lumbar puncture 36 to 48 hours after initiation of antimicrobial therapy is recommended to document sterility of CSF.

Antimicrobial therapy

Once the infecting meningeal pathogen is isolated and susceptibility testing known, antimicrobial therapy can be modified for optimal treatment (Table 74.4). Recommended antimicrobial dosages for meningitis in adults with normal renal and hepatic function are shown in Table 74.5. The following sections review recommendations for use of antimicrobial therapy in patients with bacterial meningitis based on the isolated meningeal pathogen.

TABLE 74.4 **SPECIFIC ANTIMICROBIAL THERAPY FOR ACUTE BACTERIAL MENINGITIS**

Microorganism	Standard therapy	Duration of therapy
Streptococcus pneumoniae		10–14 d
Penicillin MIC ≤0.06 μg/mL	Penicillin G or ampicillin	
Penicillin MIC ≥0.12 μg/mL		
Ceftriaxone or cefotaxime MIC <1.0 μg/mL	Third-generation cephalosporin[a]	
Ceftriaxone or cefotaxime MIC ≥1.0 μg/mL	Vancomycin plus a third-generation cephalosporin[a,b]	
Neisseria meningitidis		7 d
Penicillin MIC <0.1 μg/mL	Penicillin G or ampicillin	
Penicillin MIC 0.1–1.0 μg/mL	Third-generation cephalosporin[a]	
Listeria monocytogenes	Ampicillin or penicillin G[c]	≥21 d
Streptococcus agalactiae	Ampicillin or penicillin G[c]	14–21 d
Haemophilus influenzae		7 d
β-lactamase – negative	Ampicillin	
β-lactamase – positive	Third-generation cephalosporin[a]	
Escherichia coli and other Enterobacteriaceae	Third-generation cephalosporin[a,d]	21 d
Pseudomonas aeruginosa	Cefepime or ceftazidime	21 d
Staphylococcus aureus		10–14 d
Methicillin-sensitive	Nafcillin or oxacillin	
Methicillin-resistant	Vancomycin	
Staphylococcus epidermidis	Vancomycin[e]	10–14 d

[a] Ceftriaxone or cefotaxime
[b] Consider addition of rifampin if the ceftriaxone MIC is >4 μg/mL.
[c] Addition of an aminoglycoside should be considered.
[d] Choice of a specific antimicrobial agent must be guided by in vitro susceptibility test results.
[e] Addition of rifampin should be considered.
Abbreviation: MIC = minimal inhibitory concentration.

TABLE 74.5 **RECOMMENDED DOSAGES OF ANTIMICROBIAL AGENTS FOR MENINGITIS IN ADULTS WITH NORMAL RENAL AND HEPATIC FUNCTION**

Antimicrobial agent	Total daily dose (IV)	Dosing interval (h)
Amikacin[a]	15 mg/kg	8
Ampicillin	12 g	4
Aztreonam	6–8 g	6–8
Cefepime	6 g	8
Cefotaxime	8–12 g	4–6
Ceftazidime	6 g	8
Ceftriaxone	4 g	12–24
Chloramphenicol[b]	4–6 g	6
Ciprofloxacin	800–1,200 mg	8–12
Gentamicin[a,c]	5 mg/kg	8
Meropenem	6 g	8
Moxifloxacin[d]	400 mg	24
Nafcillin	12 g	4
Oxacillin	12 g	4
Penicillin G	24 million U	4
Rifampin	600 mg	24
Tobramycin[a]	5 mg/kg	8
Trimethoprim-sulfamethoxazole[e]	10–20 mg/kg	6–12
Vancomycin[f,g]	30–60 mg/kg	8–12

[a] Need to monitor peak and trough serum concentrations.
[b] Higher dosage recommended for pneumococcal meningitis.
[c] Intrathecal dosage is 1–8 mg; usual daily dose is 1–2 mg for infants and children, and 4–8 mg for adults. Intrathecal dosing should always be used in combination with a parenteral agent.
[d] No data on optimal dose needed in patients with bacterial meningitis.
[e] Dosage based on trimethoprim component; many authorities utilize a dose of 5 mg/kg every 8 hours.
[f] Maintain serum trough concentrations of 15–20 μg/mL.
[g] Intrathecal dosage is 5–20 mg; most studies have used a 10-mg or 20-mg dose.

Streptococcus pneumoniae

The recommended therapy of pneumococcal meningitis has been changed based on pneumococcal susceptibility patterns. Pneumococcal strains with minimal inhibitory concentrations (MICs) of ≤0.06 μg/mL are considered susceptible to penicillin and those with MICs of ≥0.12 μg/mL are considered resistant. Resistant strains have been reported from many countries throughout the world, including the United States, where the prevalence of penicillin-nonsusceptible *S. pneumoniae* ranges from 25% to >50%. Because initial CSF concentrations of penicillin are only approximately 1 μg/mL after parenteral administration of standard high dosages, penicillin cannot be recommended as empiric antimicrobial therapy when *S. pneumoniae* is considered a likely infecting pathogen in patients with purulent meningitis. Of additional concern is that pneumococcal strains resistant to the third-generation cephalosporins have been described in patients with meningitis. Several alternative agents have been examined for the treatment of meningitis caused by penicillin-resistant pneumococci. Chloramphenicol is one agent that has been studied, although clinical failures with chloramphenicol have been reported in patients with penicillin-resistant isolates. Vancomycin has also been evaluated, but as a single agent is likely to be suboptimal for therapy of pneumococcal meningitis.

Based on these data, it is recommended that, for empiric therapy of suspected pneumococcal meningitis, the combination of vancomycin and a third-generation cephalosporin (either ceftriaxone or cefotaxime) should be used pending in vitro susceptibility results. This combination was synergistic in a rabbit model of penicillin-resistant pneumococcal meningitis and was synergistic, or at least additive, in the CSF of children with meningitis. If the organism is sensitive to penicillin (MIC ≤0.06 μg/mL), penicillin is the drug of choice. For penicillin-resistant strains (MIC ≥0.12 μg/mL), in vitro susceptibility to the third-generation cephalosporins should be determined. If the MIC to ceftriaxone or cefotaxime is <1.0 μg/mL, a third-generation cephalosporin is used. However, if the MIC to ceftriaxone or cefotaxime is ≥1.0 μg/mL, vancomycin plus the third-generation cephalosporin are continued for the entire treatment period. Some investigators have also recommended the addition of rifampin, although no clinical data support this recommendation; rifampin should be added only if the organism is susceptible and there is a delay in the expected clinical or bacteriologic response. In patients not responding, intrathecal or intraventricular vancomycin remains a reasonable option.

Several other antimicrobial agents appear promising for the therapy of penicillin-resistant pneumococcal meningitis. Meropenem, a carbapenem with less proconvulsant activity than imipenem, has been utilized in children and adults with bacterial meningitis, including cases caused by *S. pneumoniae*, with microbiologic and clinical outcomes similar to those following treatment with cefotaxime or ceftriaxone. However, in one study of 20 cefotaxime-resistant pneumococcal isolates, 4 were intermediate and 13 were resistant to meropenem, suggesting that meropenem may not be a useful alternative agent for treatment of pneumococcal isolates that are highly resistant to penicillin and cephalosporins. Newer fluoroquinolones (e.g., moxifloxacin) that have excellent in vitro activity against *S. pneumoniae* have also been shown to have efficacy in experimental animal models of penicillin-resistant pneumococcal meningitis, although only trovafloxacin has been shown in a clinical trial to be as efficacious as ceftriaxone, with or without vancomycin, in children with bacterial meningitis. Although trovafloxacin is no longer used because of concerns of liver toxicity, these data suggest the potential usefulness of the newer fluoroquinolones in the treatment of bacterial meningitis. Although further clinical trials are needed before these agents can be recommended as first-line therapy for patients with bacterial meningitis, a combination of a third-generation cephalosporin plus a newer generation fluoroquinolone may emerge as the treatment of choice for pneumococcal meningitis in the future.

Neisseria meningitidis

The antimicrobial agent of choice for therapy of *N. meningitidis* meningitis is penicillin G or ampicillin. These recommendations may change in the future as a result of the emergence of meningococcal strains that are resistant to penicillin G, with a MIC range of 0.1 to 1.0 μg/mL. In a population-based surveillance study for invasive meningococcal disease in selected areas of the United States, 3 of 100 isolates had penicillin MICs of 0.125 μg/mL. However, the clinical significance of these isolates is unclear because patients with meningitis caused by these organisms have recovered with standard penicillin therapy. Some authorities would treat patients with meningococcal meningitis with a third-generation cephalosporin (either ceftriaxone or cefotaxime) pending susceptibility testing of the isolate. Single-dose ceftriaxone was also found to be noninferior compared with chloramphenicol when used against epidemic meningococcal meningitis in one study, suggesting that this agent should be utilized during meningococcal epidemics in the developing world.

Listeria monocytogenes

Despite their broad range of in vitro activity, the third-generation cephalosporins are inactive against *L. monocytogenes*. Therapy for *Listeria* meningitis should consist of ampicillin or penicillin G, with addition of an aminoglycoside considered in proven infection because of documented in vitro synergy. In in vitro studies, β-lactams are bacteriostatic for *L. monocytogenes*, and the addition of an aminoglycoside has been shown to synergistically enhance killing. However, there are mixed data with regards to benefit of aminoglycosides in both animal and clinical studies. A number of retrospective studies did not show improved outcomes with aminoglycoside synergy, and one showed higher mortality with aminoglycoside use. Other large studies, including a recent prospective study, showed statistically significant increased survival. Subsequently, both US and European guidelines for the treatment of *L. monocytogenes* meningitis recommend the consideration of adding an aminoglycoside rather than a formal recommendation for combination therapy.

In the penicillin-allergic patient, trimethoprim-sulfamethoxazole, which is bactericidal against *Listeria* in vitro, should be used. Meropenem may also be used as an alternative agent, although rare treatment failures have been reported. Despite favorable in vitro susceptibility results, chloramphenicol and vancomycin are associated with unacceptably high failure rates.

Haemophilus influenzae

The therapy of bacterial meningitis caused by *H. influenzae* type b depends on whether the strain produces β-lactamase. For β-lactamase–negative strains, ampicillin is recommended, and for strains that produce β-lactamase, a third-generation cephalosporin (i.e., ceftriaxone or cefotaxime) should be used. In addition, a third-generation cephalosporin should be used as empiric therapy in all patients in whom *H. influenzae* type b is a possible pathogen. Chloramphenicol is not recommended because chloramphenicol-resistant isolates have been reported throughout the world, and, even in patients with chloramphenicol-sensitive isolates, a prospective study found chloramphenicol to be bacteriologically and clinically inferior to ampicillin, ceftriaxone, or cefotaxime in the therapy of childhood bacterial meningitis caused predominantly by *H. influenzae* type b. Although cefuroxime, a second-generation cephalosporin, initially appeared to be efficacious in the therapy of *H. influenzae* type b meningitis, a study comparing cefuroxime with ceftriaxone for childhood bacterial meningitis documented delayed CSF sterilization and a higher incidence of hearing impairment in the patients receiving cefuroxime. Cefepime has been compared with cefotaxime in a prospective randomized trial for treatment of meningitis in infants and children; cefepime was found to be safe and therapeutically equivalent to cefotaxime and can be considered a suitable therapeutic alternative for treatment of patients with this disease.

Aerobic gram-negative bacilli

Outcome from meningitis caused by aerobic gram-negative bacilli has been greatly improved with the availability of the third-generation cephalosporins (cure rates of 78% to 94%). Ceftazidime, a third-generation cephalosporin with enhanced in vitro activity against *Pseudomonas aeruginosa*, led to a cure in 19 of 24 patients with *P. aeruginosa* meningitis in one study when used alone or in combination with an aminoglycoside. Similar results were observed in a study of pediatric patients in which seven patients were cured clinically and nine were cured bacteriologically when receiving ceftazidime-containing regimens. In patients with aerobic gram-negative bacillary meningitis not responding to conventional parenteral antimicrobial therapy, concomitant intraventricular or intrathecal aminoglycoside therapy should be considered, although this mode of therapy was associated with a higher mortality rate than systemic therapy alone in infants with gram-negative meningitis and ventriculitis.

Several other antimicrobial agents (e.g., imipenem, meropenem, cefepime, aztreonam, colistin) have been successfully used in isolated case reports and in small series of patients with meningitis caused by aerobic gram-negative bacilli. Imipenem has been efficacious, although a high rate of seizure activity (33% in one study) limits its usefulness in patients with bacterial meningitis. The fluoroquinolones (e.g., ciprofloxacin) have also been used in some patients with bacterial meningitis, although their primary usefulness is for therapy of meningitis caused by multidrug-resistant gram-negative organisms or when the response to conventional therapy is inadequate; these agents should not be used as first-line empiric therapy in patients with meningitis of unknown etiology because of their poor in vitro activity against *S. pneumoniae* and *L. monocytogenes*. For empirical treatment of *Acinetobacter* meningitis, intravenous meropenem, with or without an aminoglycoside administered by the intrathecal or intraventricular route, has been recommended; if the organism is found to be resistant to carbapenems, colistin (usually formulated as colistimethate sodium) or polymyxin B should be substituted for meropenem and may also need to be administered by the intrathecal or intraventricular route.

Staphylococci and streptococci

Meningitis caused by *Staphylococcus aureus* should be treated with nafcillin or oxacillin; vancomycin is used for patients who are allergic to penicillin or when the organism is methicillin resistant. For meningitis caused by coagulase-negative staphylococci (e.g., *S. epidermidis*), vancomycin is recommended; rifampin should be added if the patient fails to improve. Daptomycin, linezolid, or trimethoprim-sulfamethoxazole is considered an alternative agent in patients with staphylococcal meningitis. Ceftaroline has been used to successfully treat two patients with methicillin-resistant *S. aureus* (MRSA) meningitis and one with a ventriculoperitoneal shunt infection. In patients with meningitis caused by *S. agalactiae*, ampicillin plus an aminoglycoside is recommended based on documented in vitro synergy and because of the emergence of penicillin-tolerant strains; alternatives include ceftriaxone and vancomycin.

Prevention

Immunoprophylaxis

Streptococcus pneumoniae

The 13-valent pneumococcal conjugate vaccine (PCV13) four-dose primary series is recommended in children at 2, 4, and 6 months of age, with a fourth dose given between age 12 and 15 months. The routine use of the prior 7-valent pneumococcal conjugate vaccine (PCV7) beginning in 2000 demonstrated a 79% reduction overall in invasive pneumococcal disease in children <5 years and a 99% reduction in disease caused by the seven serotypes in PCV7. There was a 30.1% percentage decrease in the rate of pneumococcal meningitis in all ages. An indirect effect of the PCV7 vaccine program was a decline in rates of invasive pneumococcal disease in unvaccinated adult populations. Currently, PCV13 is recommended to be given in conjunction with PPSV23 as a one-time dose in those at higher risk for invasive pneumococcal disease and persons over age 65 years.

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended for all adults over the age of 65 and those at higher risk for pneumococcal disease. Due to its poor immunogenicity in young children, it is only approved for those over the age of 2 years.

Neisseria meningitidis

Quadrivalent conjugate vaccines against meningococcal disease caused by serogroups A, C, W, and Y have been in use in the United States since 2005. The two available in the United States are Menactra and Menveo. Current recommendations are for vaccination of children between 11 and 18 years of age with a booster at age 16 in those who receive the first dose prior to age 12 years. Special populations such as college students aged 19 to 21 years residing in dormitories; those living in hyperendemic regions; those with prolonged risk of exposure; those with asplenia, sickle cell disease, HIV, or complement deficiencies; and those residing in a region with an ongoing meningococcal outbreak should also be vaccinated. Long-term immunogenicity is unknown.

There are two vaccines, Bexsero and Trumenba, licensed in 2015 and 2014, respectively, in the United States, against meningococcal disease caused by serogroup B. These are both approved for use in persons aged 10 to 25 years at increased risk for meningococcal serogroup B disease.

Haemophilus influenzae

In the United States, there are currently three monovalent vaccines approved by the Food and Drug Administration (FDA)—ActHIB (PRP-T), Hiberix (PRP-T), and PedvaxHIB (PRP-OMB)—and one combination vaccine (Pentacel). The monovalent vaccines can be administered as early as 6 weeks of age but are usually given in a primary series starting at 2 months of age with a booster dose at 12 to 15 months of age. More than 95% of infants who receive the full primary series of vaccine develop protective antibodies, and immunity is thought to be long-term. Routine vaccination of infants against *H. influenzae* type b has been largely effective in reducing the overall incidence of *H. influenzae* type b meningitis by 90%.

Chemoprophylaxis

It has become clear in recent years that the spread of several types of bacterial meningitis can be prevented by chemoprophylaxis of contacts of patients with meningitis. The rationale is for eradication of nasopharyngeal colonization, thereby preventing transmission to susceptible contacts and the development of invasive disease in those already colonized. Chemoprophylaxis is recommended for contacts of a case of meningococcal meningitis. The definition of a "close contact" has not been clearly elucidated, but usually refers to persons who have had prolonged exposure of 8 hours or longer while in proximity of 3 feet or less of the index case and include household contacts, daycare center members, and anyone directly exposed to the patient's oral secretions (e.g., through kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management); the index case may also need to receive prophylaxis if he or she is treated with an antimicrobial agent (e.g., penicillin or chloramphenicol) that does not reliably eradicate meningococci from the nasopharynx of colonized patients. Chemoprophylaxis should also be administered to close contacts who have received the quadrivalent meningococcal conjugate vaccine because the vaccine does not confer protection against serogroup B meningococcus. The optimal regimen to prevent invasive meningococcal disease is controversial. At present, the US Centers for Disease Control and Prevention (CDC) recommend rifampin, ciprofloxacin, or ceftriaxone, which are all 90% to 95% effective at eradicating nasopharyngeal carriage. Rifampin (600 mg in adults, 10 mg/kg in children beyond the neonatal period, and 5 mg/kg in infants <1 month of age) is given at 12-hour intervals for 2 days, whereas ciprofloxacin (500 mg in adults) or ceftriaxone (250 mg IM in adults) only requires one dose. However, three cases of ciprofloxacin-resistant *N. meningitidis* were reported in North Dakota and Minnesota, leading the CDC to no longer recommend ciprofloxacin for meningococcal prophylaxis in

selected counties of those states; decreased susceptibility of meningococci to the fluoroquinolones has also been reported in South Africa, indicating the need for continued surveillance. Ceftriaxone is probably the safest alternative in the pregnant patient. Azithromycin (500 mg orally once) was also shown to be as efficacious as the four-dose regimen of rifampin in the eradication of meningococci from the nasopharynx. Widespread chemoprophylaxis to low-risk contacts should be discouraged because of the concern over emergence of resistant organisms and possible future limitations on this approach.

Suggested reading

Bijlsma MW, Brouwer MC, Kasanmoentalib ES, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: A prospective cohort study. *Lancet Infect Dis*. 2016;16:339–347.

Brouwer MC, McIntyre P, de Gans J, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2010;9:CD004405.

Brouwer MC, Thwaites GE, Tunkel AR, van de Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet*. 2012;380:1684–1692.

Cabellos C, Verdaguer R, Olmo M, et al. Community-acquired bacterial meningitis in elderly patients. Experience over 30 years. *Medicine (Baltimore)*. 2009;88:115–119.

Charlier C, Perrodeau E, Leclerq A, et al. Clinical features and prognostic factors of listeriosis: The MONALISA national prospective cohort study. *Lancet Infect Dis*. 2017;17:464–466.

Hasbun R, Abrahams J, Jekel J, et al. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med*. 2001;345:1727–1733.

Hsu HE, Shutt KA, Moore MR, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. *N Engl J Med*. 2009;360:244–256.

McGill F. Heyderman RS, Panagiotou S, et al. Acute bacterial meningitis in adults. *Lancet*. 2016;388:3036–3047.

McIntyre PB, Berkey CS, King SM, et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. *JAMA*. 1997;278:925–931.

Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. *N Engl J Med*. 2011;364:2016–2025.

Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267–1284.

Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis*. 2017;64:e34–e65.

van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in treatment of bacterial meningitis. *Lancet*. 2012;380:1693–1702.

van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. *N Engl J Med*. 2010;362:146–154.

Weisfelt M, van de Beek D, Spanjaard L, et al. Clinical features, complications, and outcome in adults with pneumococcal meningitis: A prospective case series. *Lancet Neurol*. 2006;5:123–129.

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Aseptic meningitis

Burt R. Meyers and Dalilah Restrepo

Aseptic meningitis syndrome is associated with symptoms, signs, and laboratory evidence of meningeal inflammation with spinal fluid findings that suggest a viral or noninfectious origin. Clinically, patients present with headache, nausea, meningismus, and photophobia, symptoms that are also common in patients with bacterial meningitis. A stiff neck, with or without a Brudzinski or Kernig sign, may be observed. Patients usually appear nontoxic but may have changes in mental status, including irritability. Other signs of possible viral infection may include pharyngitis, adenopathy, morbilliform rash, and evidence of systemic viral infection, including myalgia, fatigue, and anorexia. There are usually no signs of vascular instability, and the course is often self-limiting.

Aseptic meningitis is a syndrome of multiple etiologies, both infectious and noninfectious (Table 75.1). Infections are usually of viral origin but also may be due to mycobacteria, fungi, rickettsiae, and parasites. Group B Coxsackieviruses (mostly serotypes 2 through 5) and echoviruses (mostly serotypes 4, 6, 9, 11, 16, and 30) are responsible for >90% of cases of viral meningitis. Herpesvirus, arboviruses, lymphocytic choriomeningitis virus (LCM), Lyme disease, leptospirosis, and acute HIV are the etiologic agents that make up most of the remaining infectious cases. Noninfectious causes include drug reactions, collagen vascular diseases (i.e., lupus erythematosus, granulomatous arteritis), sarcoidosis, cerebral vascular lesions, epidermal cysts, meningeal carcinomatosis, serum sickness, and nonfocal lesions of the central nervous system (CNS). Specific syndromes (i.e., Mollaret's meningitis, Still's disease) may produce a similar clinical picture. The etiologic diagnosis of aseptic meningitis is often complicated by the numerous possible causes and the lack of specific diagnostic tests.

Etiology

Infectious agents

The most common causes of viral meningitis are the enteroviruses, herpesviruses, and HIV. Some viruses passively enter through the skin or respiratory, gastrointestinal, or urogenital tract and may cause initial infection at the entrance site. Some viruses spread through nerve endings by retrograde transmission via neuronal axons (i.e., poliovirus, rabies virus, herpesvirus). Enteroviruses, LCM, mumps, and arthropod-borne viruses replicate initially in muscle cells or mesodermal cells. Other viruses enter via the nose, cause infection of the submucosa, and then enter the subarachnoid space. Most viruses probably enter the CNS following viremia with primary replication at the site of entry and dissemination into the systemic circulation to either anchor and grow in the choroid plexus or pass directly through it into the CNS. Enteroviruses and HIV are carried by this route.

Enteroviruses are the most common cause of viral meningitis, occurring mostly during summer and fall but may continue to cause CNS infection throughout the winter. The presentation is not distinctive, and the disease presents with abrupt onset and fever, nausea, vomiting, and photophobia. Rash and upper respiratory symptoms may be present. Another increasingly common cause of viral meningitis is represented

TABLE 75.1 CAUSES OF ASEPTIC MENINGITIS

Infectious	
Enterovirus	Echovirus Coxsackievirus A and B Poliovirus Enterovirus 68–71
Herpesvirus	Herpes simplex virus (HSV) 1 and 2 Varicella-zoster virus Epstein–Barr virus Cytomegalovirus HSV-6
Paramyxovirus	Mumps virus Measles virus
Togavirus	Rubella virus
Arbovirus	Eastern equine encephalitis virus Western equine encephalitis virus Venezuelan encephalitis virus
Flavivirus	Japanese encephalitis virus Murray Valley encephalitis virus St. Louis encephalitis virus West Nile virus Powassan Dengue virus Zika virus
Bunyavirus	California encephalitis virus LaCrosse encephalitis virus Jamestown Canyon virus Oropouche virus
Reovirus	Colorado tick fever virus: Coltivirus
Arenavirus	Lymphocytic choriomeningitis virus
Rhabdovirus	Rabies virus
Retrovirus	Human immunodeficiency virus Human T-cell lymphotropic virus (HTLV)-I
Adenovirus	
Mycoplasma	*Mycoplasma pneumoniae*
Fungi	*Cryptococcus neoformans* *Coccidioides immitis* *Histoplasma capsulatum* *Candida* spp. *Aspergillus* *Blastocystis* *Sporothrix schenckii*
Mycobacteria	*Mycobacterium tuberculosis*
Rickettsia	*Rickettsia rickettsii* *Anaplasma*
Spirochetes	*Treponema pallidum* (syphilis) *Borrelia burgdorferi* (Lyme) *Borrelia recurrentis* (relapsing fever) *Leptospira* spp. (leptospirosis)
Parasites	*Angiostrongylus cantonensis* (eosinophilic meningitis) *Toxoplasma gondii* *Gnathostoma spinigerum* *Taenia solium* (cysticercosis) *Trichinella spiralis* *Taenia canis* (visceral larva migrants) *Negiceria fowleri* *Acanthamoeba* spp.
Bacteria	Partially treated bacterial meningitis *Listeria monocytogenes* *Brucella* *Nocardia* Acute or subacute bacterial endocarditis Parameningeal focus (brain or epidural abscess) *Chlamydia* spp. *Actinomyces* spp.
Noninfectious	
Drug reactions	Nonsteroidal anti-inflammatory agents Antineoplastic agents (Daratumumab) Antibiotics (trimethoprim-sulfamethoxazole, amoxicillin, isoniazid) Immunosuppressants (orthoclone, azathioprine) Immunoglobulin IV Vitamin B
Malignancy	Primary medulloblastoma Metastatic leukemia Hodgkin's disease
Collagen vascular disease	Lupus erythematosus Behçet's/adult-onset Still's disease
Trauma	Subarachnoid bleed Traumatic lumbar puncture neurosurgery
Chemicals	Lead, mercury Contrast agents Disinfectants, glove powder
Neurologic disorders	Cerebral vascular lesions Epidermal cysts Brain tumors
Systemic disorders	Sarcoidosis Vasculitis Autoimmune disorders, anti-NMDA encephalitis
Miscellaneous	Serum sickness Mollaret's meningitis Meningeal carcinomatosis Vaccination Postinfectious viral syndromes Posttransplantation lymphoproliferative disorder Kikuchi syndrome

by herpes simplex virus (HSV). Although HSV encephalitis is mostly caused by HSV-1, meningitis is generally caused by HSV-2. In patients presenting with HSV meningitis genital lesions may be present, and one-quarter of the cases presenting with primary genital herpes have meningeal involvement. However, in the case of recurrent Mollaret's meningitis, which is due to HSV-2 in 80% of cases, genital lesions are usually absent. Primary HIV can present as aseptic meningitis with headache, nausea, vomiting, fever, and stiff neck. This disease is self-limiting and can be the only manifestation of HIV for many years. Unfortunately, if patients are not diagnosed at the time of their acute illness, they may infect a number of sexual partners before the diagnosis is established. Interestingly, early onset of aseptic meningitis has not been associated with late neurologic manifestations in HIV-1 infection, and treatment is symptomatic. Other than during the acute phase, aseptic meningitis may also be present during different stages of the disease. The diagnosis may be later complicated by the fact that cerebrospinal fluid (CSF) pleocytosis is less common with advanced immunosuppression. Exposure to excretions of rodents can cause exposure to the LCM, a human zoonosis caused by a rodent-borne arenavirus. The infection, more common during the winter, presents often as an influenza-like syndrome.

Nonviral causes of meningitis often have a more complicated course than viral meningitis and must be recognized because they may have specific therapy. Agents such as bacteria, mycobacteria, and fungi enter the body through the respiratory tract, including the pharynx, sinuses, skin, or lung, and travel to the CNS via the bloodstream. Pneumonitis may be followed by fungemia or bacteremia. Coccidioides meningitis has to be considered in patients with indolent symptoms such as persistent fever and headache who live or traveled from the Southwestern United States and Central or South America. Meningitis is frequently not recognized in this population and may be lethal. *Treponema pallidum* and *Borrelia burgdorferi* enter the CNS after bloodstream invasion.

Infections with flaviviruses can manifest with encephalitis. In the case of Dengue, this is part of the systemic disorder associated with hemorrhagic fever, but it can also be directly neuroinvasive or appear as a neuromuscular complication (e.g., Guillain-Barré syndrome or transient muscle dysfunctions) or with neuro-ophthalmic involvement.

West Nile virus (WNV) is a bird virus and is spread within the avian reservoir by mosquitoes. The main vectors, *Culex pipiens*, *C. restuans*, and *C. tarsalis*, are abundant and ubiquitous in water in puddles and containers, sewers, storm drains, and catch basins. It usually causes mild flu-like symptoms 3 to 14 days after infection. However, 1 in 150 cases will develop serious manifestations, mainly meningoencephalitis, meningitis, or encephalitis. CSF invariably shows a pleocytosis, with a predominance of neutrophils in up to half of these patients. Laboratory diagnosis involves testing serum or CSF for viral-specific neutralizing antibodies. Several WNV immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) kits are available in the United States.

Because the ELISA can cross-react between flaviviruses (e.g., systemic lupus erythematosus, dengue, yellow fever, WNV, Zika, Chikungunya), it should be viewed as a screening test only. Initial serologically positive samples should be confirmed by neutralization test.

Noninfectious agents

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a severe autoimmune disorder characterized by severe psychiatric symptoms, seizures, decreased consciousness, autonomic dysregulation, and dyskinesias.

Anti-NMDA receptor encephalitis has been regarded as the second most common immune-mediated cause of aseptic meningitis after acute disseminated encephalomyelitis and is more prevalent than all antibody-associated encephalitides. It is most common in young women and children.

Diagnostic workup

In establishing a diagnosis, clues in the history, physical examination, and CSF examination (Box 75.1) are important.

History

Many viral infections are seasonal, occurring during late summer and early fall (e.g., the enteroviruses), whereas mumps and LCM peak during winter and spring. Other viruses such as HSV-2 and HIV occur in any season. WNV and equine-associated meningoencephalitis outbreaks occur from late summer to early fall. Avian (for WNV) or equine sources (for equine encephalopathy) with spread via mosquitoes is the presumed route of infection to humans. Furthermore, a history of exposure to patients with known viral illness often suggests enteroviral infection. Similar presentation in association with genital lesions should suggest HSV-2 meningitis, although genital lesions are absent in about 15% of the cases.

Exposure to mice and rodents suggests LCM, less commonly *Leptospira* species, or hantavirus, which may cause a severe pulmonary syndrome. History of sexual contacts should be elicited because HSV, syphilis, and HIV may present with aseptic meningitis. All patients, including the elderly, should be questioned about risk factors for HIV infection, including sexual promiscuity, intravenous (IV) drug use, sexual preference, and history of transfusions with blood or blood products. Human T-cell lymphotropic virus (HTLV)-I infection may also present with the diagnosis of spastic paraparesis.

Syphilitic meningitis is an important cause of aseptic meningitis, especially prevalent given the soaring incidence of this infection in recent years, as per surveillance by the US Centers for Disease Control and Prevention (CDC). Syphilitic meningitis may coexist with the primary or secondary infection or may follow it by as much as 2 years.

Geographic location, both domicile and travel history, should be evaluated. Exposure to insects such as the tsetse fly in Africa could suggest trypanosomiasis, and mosquito bites in a traveler to India, the Caribbean, or South America associated with fever and rash may suggest chikungunya (CHK) or Zika virus. *Histoplasma*

BOX 75.1

Diagnostic workup for aseptic meningitis syndrome

Clinical evaluation

History
Season (summer, enteroviruses, Rocky Mountain spotted fever)
Geographic area (Colorado tick fever, Babesia, *Anaplasma*, Lyme disease)
Exposure to other patients (mumps, varicella)
Tick, mosquito bites (malaria, Lyme disease), tsetse fly (trypanosomiasis)
Exposure to animals (rabies, hantavirus, LCM)
Sexual history (HIV, HSV, syphilis)
IVDU (endocarditis)
Drug reactions (immunoglobulin, OKT-3, NSAIDs, antibiotics)

Physical examination

Spinal fluid
Opening pressure
Leukocyte count predominance
a. Neutrophils (initial echo, polio, HSV, Mollaret's, TB)
b. Lymphocytes (Coxsackie, enterovirus)
c. Eosinophils (*Angiostrongylus*, *Gnathostoma*)
d. Abnormal cells (Mollaret's, lymphoma, WNV)
Protein ≤40 mg/dL
Glucose ≤40 mg/dL or ≤50% serum
Gram stain, AFB smear, Papanicolaou stain (Mollaret's meningitis)
Cryptococcal antigen, India ink
Immunoelectrophoresis ± Autoimmune antibodies; anti-NMDA
Wet mount (toxoplasmosis, amebae)
Bacterial, mycobacterial, fungal cultures
PCR for enterovirus, HSV, VZV (in immunocompromised patients), CMV, EBV, Zika virus (epidemiologic exposure)
Antibodies to *Borrelia burgdorferi*, *Brucella*, *Histoplasma capsulatum* antigen and anti-histoplasma antibody testing by complement fixation, beginning with undiluted CSF, complement-fixing IgG antibodies, or immunodiffusion tests for IgM and IgG for *Coccidioides immitis* (chronic or recurrent presentation)

Serologic testing

Cryptococcal antigen
Histoplasma urinary and serum antigen (MiraVista Diagnostics)
Lyme disease ELISA, Western blot
Rocky Mountain spotted fever indirect fluorescent antibody test (state health departments)
ANA
HIV-I/HIV-2 antibody
HTLV-1
Serum and CSF VDRL
Autoimmune antibodies (Anti-NMDA)

Other

PPD
Quantiferon Gold
Chest x-ray film
CT, MRI
Echocardiogram

Abbreviations: LCM = lymphocytic choriomeningitis virus; HIV = human immunodeficiency virus; HSV = herpes simplex virus; IVDU = intravenous drug use; OKT-3 = orthoclone; NSAIDs = nonsteroidal anti-inflammatory drugs; TB = tuberculosis; WNV = West Nile virus; AFB = acid-fast bacilli; PCR = polymerase chain reaction; VZV = varicella-zoster virus; CMV = cytomegalovirus; EBV = Epstein–Barr virus; CSF = cerebrospinal fluid; ELISA = enzyme-linked immunosorbent assay; ANA = antinuclear antibody; HTLV-1 = human T-lymphotropic virus type 1; VDRL = Venereal Drug Research Laboratory.

capsulatum, *Coccidioides immitis*, and *B. burgdorferi* occur mainly in certain sections of the United States. Recent contact with a pet or camping suggests *Rickettsia*, *Anaplasma*, or *Borrelia* related to a tick bite. Mosquito bites may result in WNV infection or equine meningoencephalitis virus infection. Rabies, although rare, should be considered if the patient had contact with the secretions of an infected skunk, raccoon, dog, fox, or bat. Drinking untreated water on backpacking trips may result in *Leptospira* infection, ingestion of unpasteurized milk and cheeses may cause brucellosis, and contaminated processed meats (i.e., frankfurters) may cause *Listeria monocytogenes* infection in pregnant women, elderly, and immunocompromised hosts.

Meningitis due to fungi is a consideration primarily in patients affected by HIV and in those who have organ transplantation, immunosuppressive chemotherapy, or chronic corticosteroid therapy. However, the most common pathogen, *Cryptococcus neoformans*, can occur in immunocompetent hosts, including a rare case reported in a daily cannabis smoker without evidence of immunodeficiency.

Vasculitides found in patients of Mediterranean origin include Behçet's disease and familial Mediterranean fever. Certain drugs, including IV immunoglobulin (IVIG), trimethoprim-sulfamethoxazole, nonsteroidal anti-inflammatory drugs (NSAIDs), and immunosuppressants, have been associated with aseptic meningitis syndrome. Intracranial infections often present with headache and fever. Brain, epidural, or subdural abscesses may be present in patients with a history of upper respiratory tract infection (i.e., otitis media, sinusitis) or infection of the teeth or gums. CT scan or MRI may aid in this diagnosis. Aseptic meningitis syndrome has been associated with subacute bacterial endocarditis; physical stigmata, including conjunctival petechiae, cardiac murmurs, retinal lesions, and evidence of embolic phenomenon, may be found. Infection with either mycobacteria or fungi or a history of malignancy must be considered.

It is important to investigate recent antibiotic use. Partially treated bacterial meningitis should be suspected if the patient has received prior oral antimicrobial therapy and has persistently low CSF glucose or pleocytosis with a negative Gram stain. Consideration of any medication including supplements and vitamins, in particular excess vitamin B, has been associated with neurologic signs. Recurrent bouts of meningitis with a benign clinical picture and unknown etiology suggest Mollaret's meningitis.

Physical examination

A physical examination may elicit findings that may suggest a specific agent. Generally the patient is febrile and nontoxic, pulse and respiration normal, with or without evidence of meningismus. Examination of the skin may reveal a morbilliform or vesicular rash consistent with enteroviral infection, primary HIV or syphilis, or evidence of a tick bite. However, a rash can be observed also in some cases of meningococcemia. The scalp should be examined carefully, especially the area behind the ears. Petechiae on the hands and feet usually suggest rickettsial infection. Examination of the eyes for conjunctival petechiae and funduscopic examination may reveal lesions typical of infectious endocarditis. In the right epidemiologic exposure, diffuse petechiae should raise suspicion for severe Dengue. Other lesions usually found by funduscopic examination are associated with cytomegalovirus (CMV) or *Toxoplasma*, especially if there is suspicion of HIV. The oral cavity may show thrush with or without cervical adenopathy. Presence of parotid or testicular swelling enlargement is consistent with mumps meningitis. The chest examination is usually normal, but a murmur in this setting suggests endocarditis; a pericardial rub suggests coxsackievirus infection or a collagen vascular syndrome. Hepatomegaly, splenomegaly, or adenopathy may suggest a systemic disease, including disseminated viral or fungal infection. Genital ulcerative lesions may be present in vascular syndromes such as lupus erythematosus and may also be consistent with HSV-2 infection. Examination of the neck may reveal evidence of stiffness on flexion and a positive Brudzinski and/or Kernig sign. Focal or multiple cranial nerve involvement suggests lesions such as a brain, subdural, or epidural abscess; embolic phenomena may also produce these lesions. Asymmetric flaccid paralysis suggests WNV infection, as well as a macular papular rash which can occur in up to 50% of patients with WNV infection and meningitis. Physical examination may also reveal a typical malar rash or other signs of collagen vascular disease.

Laboratory data

The CSF should be examined and opening pressure recorded; in aseptic meningitis the CSF is clear with a normal or mildly increased opening pressure. The white blood cell (WBC) count is usually <500/mL, but it can reach 1,000/mL with a predominance of lymphocytes. However, CSF differential cell counts may reveal a predominance of polymorphonuclear leukocytes mostly with echovirus, poliovirus, mumps, HSV, *Mycobacterium tuberculosis*, and Mollaret's meningitis. A shift toward a lymphocyte predominance during the first week of the disease occurs. Pleocytosis has been reported in 25% of patients with enteroviral infection. Eosinophils in the CSF suggest parasitic disease secondary to *Angiostrongylus*, *Taenia* spp., or *Schistosoma japonicum* or *Paragonimus westermani*. Meningeal carcinomatosis is suggested when abnormal cells are seen, and large granular cells with indistinct cytoplasm suggest Mollaret's meningitis. Fat droplets have been seen following epidermoid cyst rupture. Spinal fluid glucose should be compared with simultaneously drawn blood glucose. Normal levels of CSF glucose (40 mg/dL or >50–66% of the blood levels) suggest viral meningitis. However, the glucose content may be lower than normal in 18% to 33% of cases, and viruses such as herpes, mumps, LCM, and polio can cause hypoglycorrhachia (Table 75.2). A study of CSF from 334 cases of WNV infection showed that it usually presents with CSF pleocytosis, increased protein, and normal glucose. The protein levels in aseptic meningitis are usually normal or slightly elevated; levels >800 mg suggest CSF block with infection or tumor although this has also been associated with chemical meningitis. A wet prep of CSF should be examined to look for *Toxoplasma gondii* or amebae (e.g., histolytica). Gram stain and bacterial culture should be performed because a partially treated bacterial infection or infection with *L. monocytogenes* may occasionally present with a predominance of lymphocytes. Acid-fast smears, culture, and polymerase

TABLE 75.2 **DIFFERENTIAL DIAGNOSIS OF CEREBROSPINAL FLUID (CSF) GLUCOSE CONCENTRATIONS**

Normal CSF glucose concentration	Decreased CSF glucose concentration
Enteroviruses	Partially treated bacterial meningitis
Mumps virus	*Listeria monocytogenes*
Arthropod-borne viruses	*Mycobacterium tuberculosis*
Herpes simplex virus-1 and -2	*Candida*
Human immunodeficiency virus	*Cryptococcus neoformans*
Influenza virus types A and B	*Coccidioides immitis*
Measles, subacute sclerosing panencephalitis	*Histoplasma capsulatum*
Varicella-zoster virus	*Blastomyces dermatitidis*
Cytomegalovirus	Herpes simplex virus-1
Treponema pallidum	Mumps virus
Borrelia burgdorferi	Lymphocytic choriomeningitis virus
Leptospirosis	Poliovirus
Rickettsia rickettsii	Sarcoidosis
Human monocytic ehrlichiosis	Leptomeningeal carcinomatosis
Anaplasma phagocytophilum	
Behçet's disease	
Migraine	
Vasculitis	
Postinfectious encephalomyelitis	
Nonsteroidal anti-inflammatory agents	
Orthoclone	
Azathioprine	
Trimethoprim-sulfamethoxazole	
Isoniazid	
Intravenous immunoglobulin	

chain reaction (PCR) (non-US Food and Drug Administration [FDA]-approved) should be done to rule out mycobacterial infections, and India ink stain or determination of cryptococcal antigen in the CSF should be performed.

The CSF should also be sent for routine fungal and mycobacterial cultures. With the increasing use of the nucleic acid detection tests, viral cultures from CSF are not useful and should not be performed routinely. Viral cultures are laborious and time-consuming, and they need to be performed in four different cell lines that are then evaluated daily for cytopathic effect. The findings are then confirmed by a neutralizing or an immunofluorescence antibody test. The overall sensitivity of virus isolation from the CSF of patients with aseptic meningitis is between 3% and 40%. In a recent review of more than 20,000 CSF viral cultures, 0.1% or fewer recovered species were non–enteroviruses and non-herpesvirus, suggesting that when nucleic acid amplification testing is performed, viral cultures have no additional benefit. If indicated, simultaneous viral cultures are obtained from throat washings and stool specimens.

CSF should be sent for PCR, which is available for the detection of a range of pathogens, particularly viruses. This technique is highly sensitive and specific, with results available within 24 hours and requiring only small volumes of CSF. PCR is the best assay for the detection of HSV-1, HSV-2, varicella-zoster virus (VZV), human herpesvirus 6 and 7, CMV, Epstein–Barr virus (EBV), enteroviruses, respiratory viruses, and HIV in CSF samples. CSF IgM antibody tests for WNV are positive usually by the seventh to eighth day of infection. Zika virus RT-PCR assay and IgM is available for serum and CSF. PCR for *Chlamydia pneumoniae* can also be performed from a CSF sample. Respiratory viruses, *C. pneumoniae*, and *Mycoplasma pneumoniae* can also be detected from throat samples and enterovirus nucleic acid from stool samples; however, these cannot confirm the etiology of the meningitis. The use of PCR for the diagnosis of infectious origins of aseptic meningitis has resulted in increased identification of the enterovirus, which allows the discontinuation of antimicrobial therapy, decreases hospital length of stay and costs, and enables patients to return to their usual environments.

The use of multiplex PCR facilitates assay of multiple viruses on the same sample. The sensitivity and specificities of this technique are similar to those of the single PCR. Examination of the peripheral blood reveals a WBC count that is usually normal or may be $<5{,}000/mm^3$. The differential is also normal, although occasionally a left shift of polymorphonuclear leukocytes has been observed. Eosinophilia has been described in parasitic infections and in drug and serum sickness reactions. Leukopenia associated with thrombocytopenia may suggest *Anaplasma* and *Rickettsia* infection, and nonspecific changes in hepatic enzymes may be found in viral infections. Sedimentation rate may be normal or elevated. Blood cultures should always be performed, because *L. monocytogenes*, *Brucella*, and rarely some typical pathogens, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*, may present with a predominance of lymphocytes in the CSF. Infectious endocarditis from either bacteria or fungi can be considered in the appropriate clinical setting when a patient has positive blood cultures.

If fungal disease is suspected, serologic studies should be performed for cryptococcal antigen and *C. immitis*. *Histoplasma capsulatum* urinary antigen should be tested. PCR for *M. pneumoniae* is also warranted. A Venereal Disease Research Laboratory (VDRL) test should be performed on CSF. PCR tests have been developed using a variety of syphilitic antigens. They are quite specific but do not distinguish live from dead organisms. When rickettsial diseases are suspected (i.e., Rocky Mountain spotted fever or Lyme disease), appropriate serologic tests should be performed, but therapy should not be delayed while tests are pending. If rabies is suspected, an immunofluorescence test on conjunctival scrapings or subcutaneous neck fascial biopsy is the best method for establishing the diagnosis. Other serologic tests include antinuclear antibody (ANA) to rule out systemic lupus erythematosus. Given the appropriate clinical setting, HIV testing may be warranted. The virus in CSF may be detected through PCR. Low CSF lactate levels may distinguish

aseptic meningitis from bacterial meningitis, though pretreatment with antibiotics may reduce the clinical accuracy.

If vesicular lesions are present, immunofluorescent staining for HSV-1, HSV-2, and VZV and viral culture from the lesion should be performed. If lesions other than vesicular lesions are found, careful examination by dark field may reveal evidence of *T. pallidum*. Petechial lesions should be stained and cultured for bacteria and stained with immunofluorescence antibody for *Rickettsia rickettsii*. Throat and stool cultures should be obtained for confirmation of enteroviral infection.

A chest roentgenogram specifically looking for diffuse infiltrates, cavitation, and pleural or pericardial involvement may suggest mycoplasma, mycobacterial, or fungal infection, in that order. Evidence of a mass lesion in this setting suggests carcinoma and possibly meningeal carcinomatosis. With physical findings of focal involvement, an MRI scan should be performed to look for evidence of an intracranial infection or malignancy. In cases of anti-NMDA encephalitis, an abdominal ultrasound should be done because more than half of these patients have an associated tumor, most commonly an ovarian teratoma.

Therapy

The diagnosis and treatment of the aseptic meningitis syndrome is a challenge because differentiating between infectious and noninfectious etiologies can be difficult. For patients with a suspected bacterial etiology or partially treated meningitis, antibiotic therapy should be promptly initiated. In case of aseptic meningitis in an elderly or immunocompromised patient or in case of an unclear picture, antibiotic therapy should be empirically initiated and discontinued if the patient improves symptomatically and cultures are negative. If the patient deteriorates without a clear diagnosis, a repeat lumber puncture may be indicated. Although the management of patients with aseptic meningitis of viral origin includes supportive care in most cases, specific therapy exists for some viral pathogens. Acyclovir may be used to treat meningitis caused by HSV and VZV, and ganciclovir is used for CMV infection. Acyclovir, 10 mg/kg every 8 hours, is used for HSV and VZV; ganciclovir, 5 mg/kg twice a day, is the regimen for CMV. The newer oral antiviral compounds valacyclovir and famciclovir have a fivefold higher bioavailability than acyclovir, allowing less frequent dosing.

No antiviral therapeutic agent for enteroviruses has demonstrated improved outcome in controlled clinical trials. The administration of γ-globulin helps patients with agammaglobulinemia and chronic enteroviral meningitis as well as neonates with enteroviral sepsis and meningitis. Pleconaril is an orally administered antiviral agent that inhibits enteroviral replication by binding the viral capsid. This drug may reach much higher concentrations within the CNS, suggesting its potential use to treat CNS infection. However, pleconaril induces CYP3A enzyme activity and has not been FDA approved because of its potential for drug interactions for only a modest benefit in patients with more severe disease. Pocapavir, another oral capsid inhibitor, is under development to treat chronic enterovirus in immunocompromised persons. There is no specific treatment for WNV infection. At the moment, only supportive care is available in humans, although IVIG and WNV-specific IVIG has been used in severe cases in immunocompromised patients, and interferon and ribavirin have had conflicting data.

Most viral meningitides are benign and require no therapy. For bacterial, fungal, and spirochetal disease, antimicrobial therapy directed against the offending agent is required (see specific chapters) and should not be delayed while awaiting the results of CSF assay. Treatment with doxycycline in association with two other agents may be indicated for patients suspected of having *Brucella*, and doxycycline or chloramphenicol is used for Rocky Mountain spotted fever. Specific therapy with ampicillin plus gentamicin is suggested when *L. monocytogenes* is the suspected agent, especially in elderly and immunocompromised hosts.

Because the differential diagnosis of aseptic meningitis syndrome is so broad, the initial evaluation of the patient in conjunction with the results of CSF studies will determine whether the patient requires antimicrobial therapy pending culture results from blood and CSF PCR. Patients who are toxic appearing, in the extremes of life, or with serious underlying disease should be hospitalized and treated empirically until a clear diagnosis is made. Isolation precautions for contagious diseases should be instituted.

Suggested reading

Anderson JF, Rahal JJ. Efficacy of interferon alpha-2b and ribavirin against West Nile virus in vitro. *Emerg Infect Dis*. 2009;8 (1):107–108.

Ben-Nathan D, Gershoni-Yahalom O, Samina I, et al. Using high titer West Nile intravenous immunoglobulin from selected Israeli donors for treatment of West Nile virus infection. *BMC Infect Dis*. 2009;9:18.

Carod-Artal FJ, et al. Neurological complications of dengue virus infection. *Lancet Neurol*. 2013 Sep;12(9):906–919.

Chavanet P, Schaller C, Levy C, et al. Performance of a predictive rule to distinguish bacterial and viral meningitis. *J Infect*. 2007;54:328–336.

Desmond RA, Accortt NA, Talley L, et al. Enteroviral meningitis: Natural history and outcome of pleconaril therapy. *Antimicrob Agents Chemother*. 2006;50:2409–2414.

Galindo Bonilla PA, et al. Aseptic meningitis induced by vitamin B complex. *J Investig Allergol Clin Immunol*. 2012;22(3):215–235.

Hamrock DJ. Adverse events associated with intravenous immunoglobulin therapy. *Int Immunopharmacol*. 2006;6:535–542.

Khetsuriani N, Lamonte-Fowlkes A, Oberst S, et al. Enterovirus surveillance: United States, 1970–2005. *MMWR Surveill Summ*. 2006;55:1–20.

Kimaya R, et al. Aseptic meningitis as a complication of daratumumab therapy clinical lymphoma, myeloma and leukemia. 2018;18(8):e333–e335.

Lee BE, Davies HD. Aseptic meningitis. *Curr Op Infect Dis*. 2007;20:272–277.

Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: Association with clinical and laboratory features. *J Infect Dis*. 2004;189:369–376.

Petersen LR, et al. West Nile Virus: Review of the literature. *JAMA*. 2013;310(3):308–315

Polage CR, Petti CA. Assessment of the utility of viral culture of cerebrospinal fluid. *Clin Infect Dis*. 2006;43:1578–1579.

Romero-Alvarez D, et al. Oropouche fever, an emergent disease from the Americas, *Microbes Infect*. 2018:135–146.

Sejvar JJ. The long-term outcomes of human West Nile virus infection. *Clin Infect Dis*. 2007;44(12):1617–1624.

Shapiro BB MD, MPH, et al. Cryptococcal meningitis in a daily cannabis smoker without evidence of immunodeficiency. *BMJ Case Rep*. 2018 Jan 26;2018.

Wang RJ, Chen BD, Qi D. Anti-N-methyl-D-aspartate receptor encephalitis concomitant with multifocal subcortical white matter lesions on magnetic resonance imaging: A case report and review of the literature. *BMC Neurol*. 2015 Jul 8;15:107.

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Viral encephalitis

John J. Halperin and David N. Irani

Introduction

Textbook chapters and clinical medicine often work in opposite directions—a mismatch that can be particularly problematic in neurologic and infectious diseases. This chapter focuses on the pathophysiologically defined entity of viral encephalitis. Patients—and the physicians taking care of them—are focused on their fever, headaches, and changes in nervous system function—ranging from mild somnolence to coma, from focal deficits to seizures. Differentiating encephalitis from meningitis from encephalopathy can be challenging at best; determining whether it is due to a specific virus, bacteria, or fungus can be life-saving.

Since different infectious agents have different tropisms, different pathophysiologies, and different clinical manifestations, it is helpful to start by defining the various types of nervous system involvement. Encephalitis is inflammation of the brain parenchyma. As such, it typically directly alters brain function by either impairing functions normally mediated by the damaged area or triggering seizures from it. When the inflammation affects the brainstem or substantial portions of the cerebral hemispheres, level of consciousness is depressed, up to and including coma. In contrast, meningitis, inflammation in the subarachnoid space, by definition does not affect the substance of the brain and therefore should not have a significantly greater impact on brain function than other systemic illnesses. While this is usually true in viral meningitis, bacterial and fungal meningitis often involve the blood vessels traveling through the subarachnoid space to supply the brain, or directly invade the brain, causing a meningoencephalitis with changes in nervous system function. Finally, the word "encephalopathy" is commonly used to denote altered neurobehavioral function secondary to a systemic process that does not involve the nervous system directly. While this categorization is heuristically helpful, clinical medicine is rarely that simple. Patients with sepsis often have altered consciousness, usually on a toxic/metabolic basis but sometimes from central nervous system (CNS) seeding. For example, malaria causes a congestive vasculopathy significantly impairing brain function. Since different etiologies are likely to underlie each of these disease processes, quickly sorting through these overlapping possibilities has important therapeutic and prognostic implications.

Although it is possible to create a long list of microorganisms that can infect the CNS (Tables 76.1 and 76.2), the number responsible for the overwhelming majority of infectious encephalitides is actually remarkably limited. The CNS is extremely well protected—mechanically by the skull, physiologically by the blood–brain barrier. For infection to involve the CNS it must first gain access. Bacteria and fungi typically accomplish this in one of three ways: mechanically, through trauma or neurosurgery; by contiguous spread from infected sinuses or mastoids; or by vascular obstruction causing endothelial damage and extravasation. However, virtually all viruses that cause encephalitis have developed highly specialized mechanisms to penetrate the CNS. Most probably specifically bind to endothelial cells and then penetrate the blood–brain barrier. Polio, rabies, and herpes viruses bind peripheral nerve receptors, then are transported within axons to infect the CNS.

TABLE 76.1 **SIGNIFICANT CAUSES OF ACUTE VIRAL ENCEPHALITIS IN HUMANS**

Herpesviridae	*Reoviridae*
Herpes simplex virus	*Picornaviridae*
Varicella-zoster virus	Echovirus
Cytomegalovirus	Coxsackievirus
Epstein–Barr virus	Poliovirus
Human herpesvirus 6	Enterovirus 71
B virus	*Retroviridae*
Bunyaviridae	Human immunodeficiency virus, type 1
California serogroup viruses	
La Crosse virus	*Papovaviridae*
Jamestown Canyon virus	JC virus
Snowshoe hare virus	*Orthomyxoviridae*
Togaviridae (alphaviruses)	Influenza virus
Eastern equine encephalitis virus	*Paramyxoviridae*
Western equine encephalitis virus	Measles virus
Venezuelan equine encephalitis virus	Mumps virus
Chikungunya virus	Nipah virus
Flaviviridae	Hendra virus
Japanese encephalitis virus	*Miscellaneous viruses*
St. Louis encephalitis virus	Adenovirus
West Nile virus	Lymphocytic choriomeningitis virus
Tick-borne encephalitis viruses	Rabies viruschoriomeningitis virus
Dengue fever virus	Rabies virus
Powassan and deer tick virus	
Colorado tick fever virus	

TABLE 76.2 **NONVIRAL CAUSES OF AN ACUTE ENCEPHALITIS-LIKE CLINICAL PRESENTATION**

Infectious	**Noninfectious**
Bacterial	**Parainfectious/autoimmune**
Acute bacterial meningitis	Paraneoplastic disorder
Brain abscess	Reye's syndrome
Parameningeal infection	Post infectious encephalomyelitis
Subdural empyema	Post vaccination encephalomyelitis
Venous sinus thrombophlebitis	
CNS Lyme disease	**Neoplastic**
Neurosyphilis	Neoplastic meningitis
Whipple's disease	
Bacterial toxin-mediated process	
Fungal	**Cerebrovascular**
Fungal meningitis	Acute ischemic stroke
Fungal brain abscess	Subdural hematoma
Parasitic	CNS vasculitis
Toxoplasma gondii abscess	**Systemic**
Cerebral malaria	Metabolic encephalopathy
Human African trypanosomiasis	Connective tissue disease
Amebic	Drug intoxication
Naegleria fowleri	**Epileptic**
meningoencephalitis	Seizures/postictal state
Acanthamoeba	**Traumatic**
meningoencephalitis	Acute head injury

Diagnosis

Since viral encephalitis is rare and early symptoms are often confusing (déjà vu, olfactory hallucinations, dysphasia) or nonspecific ("confusion"), the single most important step is to think of the diagnosis. While emergency departments are well known for having a low threshold for obtaining brain CTs in any possible neurobehavioral disorder, these are often uninformative in encephalitis, particularly early in the disease process. Blood cultures are often informative in bacterial meningitis, as they can be in sepsis-related encephalopathy, but peripheral blood testing is not usually informative in viral encephalitis—particularly if diagnostic confirmation is needed in a timely fashion. Definitive diagnosis requires cerebrospinal fluid (CSF) examination. Yet this is often delayed, often for fear that a lumbar puncture (LP) might trigger brain herniation in a patient with cerebral edema—problematic since delaying the diagnostic LP for imaging studies can significantly negatively impact outcome,[1,2] Unfortunately, data on LP risk in encephalitis are limited. Infectious Diseases Society of America (IDSA) encephalitis guidelines emphasize the "essential" nature of a CSF exam but state that it should be obtained "unless contra-indicated"—without stating the contra-indications.[3] Bacterial meningitis guidelines[4] suggest risk of herniation is highest—and therefore pre-LP imaging necessary—if there are focal neurologic deficits or altered mental status; although subsequent studies suggest changes in mental status do not inform risk.[5] Unfortunately, in encephalitis, focal deficits and altered mental status are the norm, thus limiting the applicability of this guidance. Since CT scans are often uninformative early in encephalitis, one might conclude that MRI imaging is needed emergently, even further delaying an LP. Fortunately, while MRI is typically more definitive in supporting the actual diagnosis, a CT scan is sufficient to identify the sort of substantial focal cerebral edema that might pose a risk for an LP.

Delays in a diagnosis of encephalitis are particularly problematic with herpes simplex virus (HSV), both because initial symptoms may be confusing and because delayed treatment can

negatively impact outcome. Fortunately, unlike bacterial cultures, diagnostics in viral encephalitis typically rely on nucleic acid testing or antibodies, neither of which is immediately impacted by antiviral therapy; thus rapid institution of anti-HSV treatment before the LP has little effect on diagnostic testing over the next few days—and should be the norm in any case of suspected infectious encephalitis.

CSF in viral encephalitis typically demonstrates a modest pleocytosis, typically dozens to hundreds of leukocytes per milliliter, rarely >1,000. Although ultimately lymphocytic and monocytic, in the first few days neutrophils may predominate. Protein is usually modestly elevated, typically not exceeding several hundred milligrams per deciliter. CSF glucose is usually normal, although in herpes significant hypoglycorrhachia may occur. Historically CSF antibody testing, particularly detection of immunoglobulin M (IgM) antibody, formed the basis for diagnosis but now PCR for herpes viruses has become quite robust. More recently multiplex nucleic acid tests have become available to assist in diagnosis of CNS infections.[6] Although not perfect, they probably provide the best noninvasive tool to identify specific causative pathogens. Recent studies have used next-gen genomic sequencing[7,8] to identify the agents responsible in particularly difficult to diagnose cases. Although still too cumbersome and expensive to be used outside a research setting, as technology advances this testing may well play an increasingly important role.

Despite the limited therapeutic implications of diagnostic testing, timely diagnosis does provide insights that are important therapeutically, prognostically, and epidemiologically. Patients with presumptive encephalitis are usually started on anti-HSV treatment immediately as early treatment of this infection is critical to outcome. However, one would not want to give 3 weeks of nephrotoxic drugs unnecessarily; hence, excluding this diagnosis can decrease risk of iatrogenic complications. Likewise, identification of arthropod-borne infections has important public health implications, indicating the presence of infected arthropods in the ecosystem and indicating that others are at risk.

Neuroimaging, specifically MRI scanning, cannot provide proof of the specific etiologic agent but can be highly informative. Fluid attenuated inversion recovery (FLAIR) sequences can be highly useful in demonstrating the anatomy of the extracellular edema associated with infection and reactive inflammation. Underappreciated is the role of diffusion weighted imaging. While often presumed to be specific for ischemia, this technique actually provides evidence of cellular edema and is frequently abnormal in infectious processes—as it is in Creutzfeldt–Jacob disease, where it presumably provides evidence of the cellular vacuolization occurring in that disorder. Gradient echo sequences can provide evidence of hemorrhage, often seen in HSV-1 encephalitis. Contrast enhancement supports a diagnosis of active inflammation.

Using these techniques, several anatomic patterns can inform the diagnosis. Very early in HSV-1 encephalitis, changes are typically seen in the medial temporal or frontal lobes. Abnormal signal in the thalamus or basal ganglia (T/BG) is quite suggestive of an infectious etiology[9]; this is identified in a third of encephalitis patients with T/BG findings, but only in a fifth of those without. Importantly, this difference is almost entirely due to differences in children, where a specific infectious etiology is identified in about 40% of children with these findings, but only 20% of children—or adults—without them, and the same 20% in adults with T/BG changes. Among children T/BG abnormalities are preferentially associated with respiratory and West Nile viruses (WNV). Although they may occur in HSV-1 and other viral infections, this is not a preferential site of involvement. Curiously, T/BG involvement is disproportionately unlikely in enteroviral infections. In adults, T/BG findings occur but no more frequently than elsewhere. Importantly, a third of adults with these findings have Creutzfeld–Jacob disease; no other etiology disproportionately has findings in T/BG. Although not evident in large systematic studies, T/BG abnormalities do appear to be suggestive of flavivirus encephalitis, occurring in adults and children with WNV, Japanese encephalitis, tick-borne encephalitis (TBE), and Powassan infection, among others. Spinal cord MRI has also proved useful, particularly in flavivirus infections with flaccid paralysis.

Historically, electroencephalography (EEG) played an important role, particularly in HSV-1 encephalitis, where periodic lateralized epileptiform discharges were recognized as an early, fairly characteristic abnormality. While these findings often preceded CT scan changes, with early findings being common on MRI brain imaging and rapidly available results of sensitive and specific nucleic acid-based diagnostics, this has become less important diagnostically. However continuous video EEG has become a very important element in the management of these patients as subclinical status epilepticus is not uncommon in encephalitis, and this is the best tool available both for initial diagnosis and for monitoring treatment response.

Etiology

An etiology can be identified in about 70% of cases of encephalitis—viral in half, autoimmune in 20%.[10] Although numerous viruses can cause encephalitis (Table 76.1), a small number account for the overwhelming majority. From a pragmatic perspective these are most easily conceptualized as *endemic* (herpes, HIV), transmitted human to human, and *epizootic*, transmitted among species by bites of infected arthropods (insects [mosquitoes] and arachnids [ticks]) or animals (rabies). Endemic viruses tend to occur sporadically without seasonal or geographic propensity. Arboviruses follow the pattern of their vectors—in temperate climates, increasing in incidence over the course of the summer and fall, dropping when cold weather kills or immobilizes vectors, and following the geographic distribution of infected host animals (Figure 76.1). Rabies follows the geographical distribution of infected animals, without a temporal pattern.

HSV is the most common cause of endemic encephalitis. With 1,000 to 2,000 cases a year in the United States, it is about as prevalent as WNV encephalitis. Other flaviviruses predominate worldwide, with the TBE complex being widely prevalent throughout Europe and Asia; its cousins, Powassan and deer tick virus are now being recognized as rare causes of encephalitis in the northeast United States.[11] To give perspective, in the United States in 2015,[12] the Centers for Disease Control and Prevention (CDC) confirmed

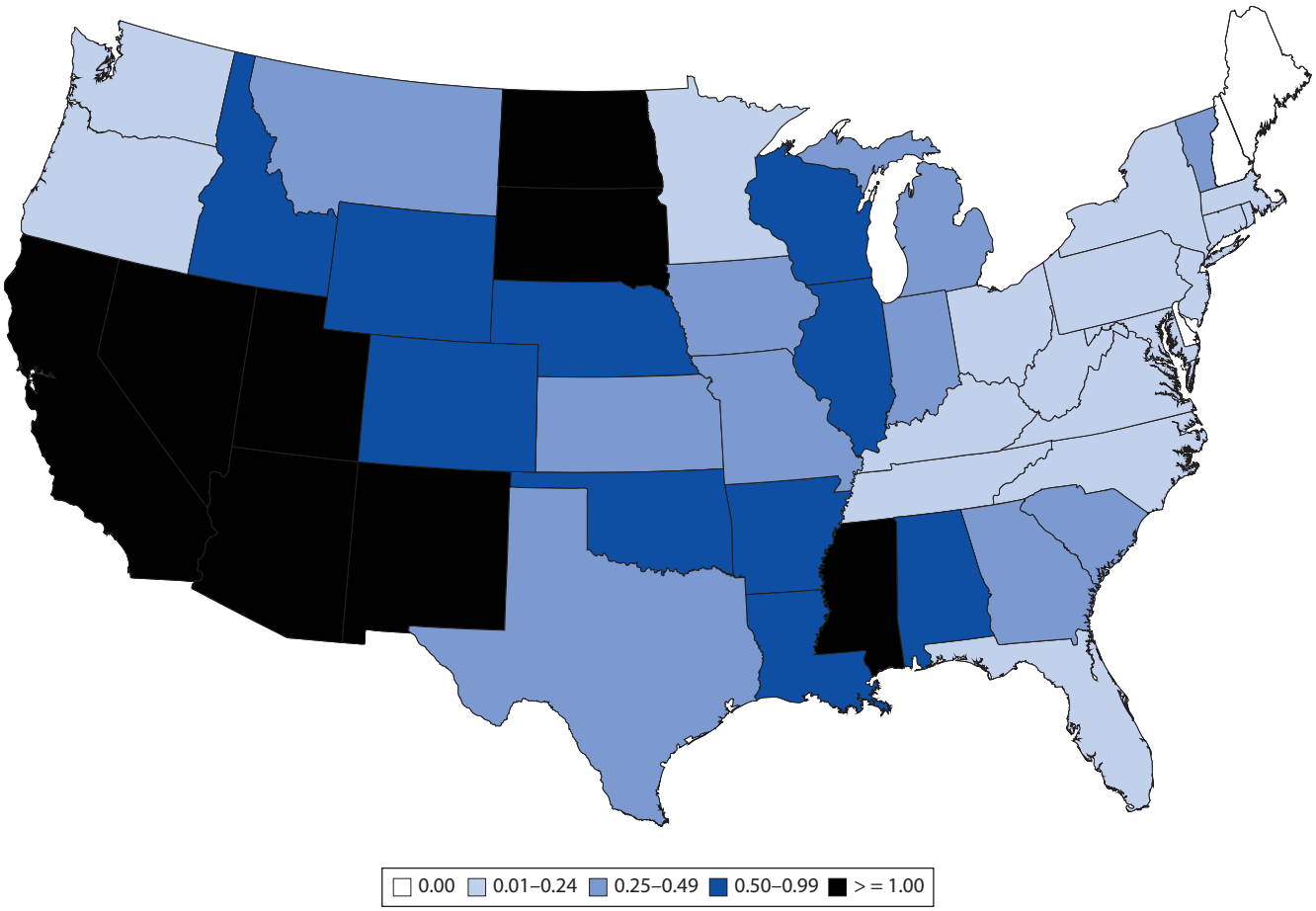

FIGURE 76.1 West Nile virus neuroinvasive disease incidence reported to ArboNET, by state, United States, 2017. West Nile virus neuroinvasive disease incidence maps present data reported by state and local health departments to CDC's ArboNET surveillance system. This map shows the incidence of human neuroinvasive disease (e.g., meningitis, encephalitis, or acute flaccid paralysis) by state for 2017, with shading ranging from 0.01 to 0.24, 0.25 to 0.49, 0.50 to 0.99, and >1.00 per 100,000 population. Neuroinvasive disease cases have been reported to ArboNET from the following states for 2017: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, District of Columbia, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, and Wyoming.
From ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention

1,455 cases of neuroinvasive WNV, with WNV representing 95% of all arboviral disease. Next most common was Lacrosse virus (55 cases), St. Louis encephalitis (23), and Powassan (6). Human rabies cases are reported once every few years.

Immunosuppression—either iatrogenic in transplant recipients or patients treated for immune-mediated disease such as multiple sclerosis, or from HIV infection or other systemic illnesses—is associated with a number of CNS infections. The most prominent viral brain infection in this context is JC virus, the agent responsible for progressive multifocal leukoencephalitis (PML). It is worth emphasizing that viral presence in the nervous system is not synonymous with encephalitis. Herpes viruses commonly take up long-term residence in neurons—typically sensory neurons of the peripheral nervous system—but do not elicit an inflammatory response unless immunosuppression allows their replication to proceed to the point where a response is triggered. Similarly, CNS infection with the JC polyoma virus appears to be highly prevalent—as is infection with the intracellular protozoan *Toxoplasma gondii*—but these infections only result in encephalitis when the immune system's control of the pathogen fails (i.e., perhaps paradoxically, decreased activity of one arm of the immune system leads to increased inflammation).

Epidemiology

While HSV encephalitis is caused by a viral infection, typically HSV-1 (carried by the overwhelming majority of humans) that on rare occasion happens to invade the CNS, most other encephalitogenic viruses are zoonoses—infections involving multiple species. In rabies, transmission is direct, from one mammal to another; for most others, arthropods serve as vectors among reservoir hosts. Diagnosis typically begins with identifying epidemiologically plausible exposure. For rabies this is a matter of "where": Was the patient in

a place where exposure to rabid animals was possible? For vector-borne infections, "when" becomes equally important. In temperate climates mosquitoes and ticks usually start feeding in spring. If a few infected reservoir hosts are present in the ecosystem, infection can be spread to others, leading to steady amplification of the number of infected vectors in the environment; when enough are present, the likelihood of human exposure becomes significant. For equine encephalitis viruses, this becomes apparent over the course of spring, summer, and fall: first, as presence of virus in pooled mosquitoes, then perhaps in sentinel chickens (chickens maintained solely to monitor seroconversion to these viruses), then in a few horses, and finally in a small number of humans. Public health officials monitor and publish information about this cycle throughout the year; being aware of it can be instrumental in early identification of human arboviral encephalitis cases. An extreme example of this occurred when WNV was first introduced into the United States two decades ago. Human disease first occurred in mid to late summer, but only after a massive and initially mysterious die-off of large numbers of crows and other passerine birds, which served as intermediate hosts and provided massive viral—and therefore infected vector—amplification (Table 76.3).

Clinical manifestations

Most viruses that cause encephalitis cause a wide spectrum of symptoms, well exemplified by WNV, in which about 80% of infected individuals are asymptomatic; 20% develop nonspecific viral symptoms, often including gastrointestinal disturbances; and only 1% develop neuroinvasive disease—half of whom develop meningitis and half parenchymal CNS involvement (i.e., encephalomyelitis). At the other end of the spectrum, rabies appears to cause lethal encephalitis in essentially every infected person. Patients with encephalitis typically develop fever and meningeal symptoms: headache, altered mental status, neck stiffness, photophobia, plus more focal findings. Flaviviruses appear to have a particular predilection for anterior horn cells, causing a polio-like flaccid paralysis in some. The basal ganglia are also commonly involved in WNV, Japanese encephalitis, and Powassan. Brainstem and cerebellar involvement are common in WNV and Powassan.

Powassan, a member of the tick-borne encephalitis virus complex, was first identified several decades ago in Ontario. A recent uptick of cases has allowed more detailed study; a separate clade of virus has been identified and termed "deer tick virus." Most cases of

TABLE 76.3 **CLINICAL AND EPIDEMIOLOGIC CHARACTERISTICS OF MAJOR CAUSES OF VIRAL ENCEPHALITIS IN THE UNITED STATES**

Family/virus	Affected hosts	Peak season/pattern	Geography/incidence	Clinical presentation	Epidemiologic clues
Herpesviridae					
HSV	All ages	Year-round; endemic	Ubiquitous (~2,500 cases/yr)	Focal neurologic deficits; seizures; bizarre behavior	
VZV	Healthy and immunocompromised adults; infants	Year-round; endemic	Ubiquitous	Ataxia; stroke-like episodes; can have an accompanying myelitis	Recent primary varicella rash or herpes zoster dermatomal rash
CMV	Immunocompromised adults; infants	Year-round; endemic	Ubiquitous	Periventricular lesions on brain MRI; accompanying lumbosacral polyradiculitis	Known HIV+ individuals; post-transplant recipients (especially bone marrow recipients)
Retroviridae					
HIV	All ages	Year-round; endemic	Ubiquitous (3,000–4,000 cases/y)	Subacute cognitive deficits; psychomotor slowing	High-risk sexual practices; intravenous drug use
Papovaviridae					
JC virus	Immunocompromised adults	Year-round; endemic	Ubiquitous (400–800 cases/y)	Focal neurologic deficits; multifocal MRI lesions	HIV+ individuals; post-transplantion or immunotherapy
Togaviridae					
Eastern equine encephalitis virus	Young and elderly	Summer and fall; endemic/sporadic	East and Gulf Coasts (5–10 cases/y)	Fulminant deficits; seizures; coma	Outdoor occupation or activities; proximity to marshes or standing water

TABLE 76.3 CONTINUED

Family/virus	Affected hosts	Peak season/pattern	Geography/incidence	Clinical presentation	Epidemiologic clues
Western equine encephalitis virus	Young and elderly	Summer and fall; endemic/sporadic	Midwest and Western States (10–15 cases/y)	Nonfocal deficits; headache	Outdoor occupation or activities; travel or habitation in rural areas
Flaviviridae					
West Nile virus	All ages (but most cases in the young and the elderly)	Summer and fall; epidemic	Nationwide (2,000–4,000 cases/y over the past few years)	Nonfocal deficits; headache; ~20% with a poliomyelitis-like illness	Outdoor exposure (urban or rural); most cases are concentrated in a few states each season
St. Louis encephalitis virus	Young and elderly	Summer and fall; epidemic	Nationwide (~100 cases/y; range 2–1,967 cases/y)	Nonfocal deficits; headache	Outdoor exposure; endemic in rural areas in the West; sporadic urban outbreaks in the Eastern States
Bunyaviridae					
La Crosse virus	Young	Summer and fall; endemic and small case clusters	Midwest and Eastern States (75–100 cases/y)	Often asymptomatic; can cause seizures	Outdoor activities; suburban cases occur near wooded areas
Picornaviridae					
Echoviruses Coxsackieviruses Polioviruses Unclassified viruses (EV-68–EV-71)	Young, especially agammaglobulinemic children	Summer and fall; epidemic	Nationwide (~1,000 cases/y)	Accompanying viral exanthem, conjunctivitis, myopericarditis, herpangina, hand-foot-and-mouth disease	Known community epidemic of picornavirus
Rhabdoviridae					
Rabies	All ages	Year-round; endemic	Nationwide (10–15 cases/y)	Prior animal bite or scratch; autonomic symptoms in ~80%; paralysis in ~20%	Animal contact

Abbreviations: CMV = cytomegalovirus, HIV = human immunodeficiency virus, HSV = herpes simplex virus, MRI = magnetic resonance imaging, VZV = varicella-zoster virus.

human encephalitis previously attributed to Powassan are probably attributable to this agent.

The most clinically characteristic is HSV-1 encephalitis, with its predilection for the medial temporal and frontal lobes (Figure 76.2). In addition to nonspecific symptoms, patients may develop olfactory hallucinations, déjà vu, behavioral changes, and temporal lobe seizures. The disease is highly necrotizing so early recognition and treatment is important. If the patient is unconscious at the time of treatment initiation outcome is much more guarded.

The most recent addition to the list of encephalitogenic flaviviruses is Zika.[11] Although best known for its highly destructive impact on the developing nervous system in the fetus, this mosquito-borne agent can involve the CNS in adults as well. Asymptomatic in about three-quarters of patients, in the remainder it causes a viral syndrome often including a maculopapular rash, polyarthralgias, and conjunctivitis. Guillain–Barré syndrome is almost as likely to follow Zika as it is to follow *Campylobacter jejuni*. Encephalitis has been reported infrequently but has been severe and quite diffuse.

Therapy

General supportive care

Specific therapeutic interventions in encephalitis are limited: specific antivirals are available for several herpesviruses, but few such agents have been found effective in other infections. Overall,[10]

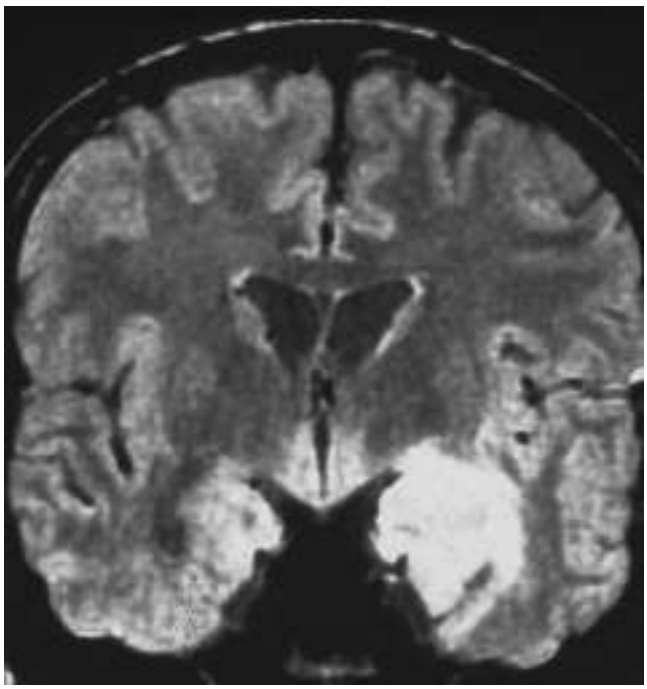

FIGURE 76.2 Coronal fluid-attenuated inversion-recovery MRI from a patient with polymerase chain reaction (PCR)-proven herpes simplex encephalitis (HSE). Hyperintense signal is seen in the medial portion of both temporal lobes as well as in the inferior frontal lobes in a distribution that is highly characteristic of this disease.

about half of all patients with viral encephalitis will have a good outcome, somewhat lower with autoimmune etiologies. Overall mortality in viral encephalitis is >10% with optimal therapy. In HSV-1 in particular, but other etiologies as well, age >65, early coma, immunocompromised state, and delay in treatment for HSV-1 beyond 24 hours are all associated with worse prognosis.

Supportive care is typical of what is needed in neurocritically ill patients: general medical management to prevent complications such as venous thromboembolism, hospital-acquired infections, and nutrition-related complications; and neurospecific issues including early detection and management of seizures—clinical and subclinical—and raised intracranial pressure.

Antiviral therapy

Although there are few effective antiviral regimens for the treatment of patients with acute viral encephalitis, several have demonstrated activity against members of the herpesvirus family (Table 76.4).

Herpesviridae

Acyclovir is the mainstay of treatment for acute HSV encephalitis. In adults, treatment with 10 mg/kg of acyclovir intravenously every 8 hours for 21 days reduces overall mortality from >70% to <20%; importantly, nearly 40% of treated patients recover to the point of returning to normal function. In contrast, clinical trials comparing acyclovir with vidarabine in neonatal HSV-2 encephalitis failed to show significant differences in outcome, and morbidity and mortality remain high. Relapses have occurred after the administration of acyclovir in a few cases outside of large clinical trials; most are associated with persistent fever, perhaps suggesting an inadequate duration of therapy. In some, such treatment failures have been attributed to viral drug resistance or postinfectious encephalomyelitis. Drug-resistant HSV occurs with thymidine kinase alteration or deficiency. Resistant strains have been described in cases of refractory HSE among HIV-infected individuals and should be

TABLE 76.4 **TREATMENT REGIMENS FOR ACUTE VIRAL ENCEPHALITIS CAUSED BY HERPESVIRIDAE**

Virus[a]	Drug of choice	Major toxicities	Alternate regimen[b]	Major toxicities
HSV	Acyclovir, 10 mg/kg IV q8h for 14–21 d	Nephrotoxicity, vomiting, diarrhea, mental status changes	Foscarnet, 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 d	Nephrotoxicity, electrolyte disturbances, nausea, fever
CMV	Induction: ganciclovir, 5 mg/kg IV q12h for 21 d, plus Foscarnet, 60 mg/kg IV q8h or 90 mg/kg IV q12h for 21 d	Bone marrow suppression, rash, fever Nephrotoxicity, electrolyte disturbances, nausea, fever	Cidofovir, 5 mg/kg IV qwk, plus Probenecid, 2 g PO 3 h before cidofovir dose, 1 g 2 h immediately after dose, and 1 g 8 h after dose	Nephrotoxicity, rash, cardiomyopathy
CMV[c]	Maintenance: ganciclovir, 5 mg/kg IV qd, plus Foscarnet, 90 mg/kg IV qd	As above As above	Valganciclovir, 900 mg PO qd	Nephrotoxicity, bone marrow suppression, rash, fever
VZV	Acyclovir, 10 mg/kg IV q8h for 10–14 d	As above	Foscarnet, 60 mg/kg IV q8h for 14–21 d	As above
EBV	Acyclovir, 10 mg/kg IV q8h for 14 d	As above	Ganciclovir, 5 mg/kg IV q12h for 21 d	As above

[a] CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; IV, intravenously; PO, orally; VZV, varicella-zoster virus.
[b] Alternate regimens are indicated in the setting of known drug resistance (rare in immunocompetent hosts, but not uncommon in immunocompromised patients who have received extended prior antiviral therapy).
[c] Continue maintenance therapy in HIV-infected patients until CD4 count >100 cells/mm^3 for >6 months.

considered in the setting of a worsening clinical picture and/or CSF persistence of HSV DNA despite appropriate therapy with acyclovir. Intravenous foscarnet is recommended in these cases. In a few, autoimmune antibodies have been identified, leading to successful treatment with immunosuppression.

CMV encephalitis is not uncommon in patients with AIDS, particularly those inadequately controlled by highly active antiretroviral therapy (HAART). It is invariably preceded by viremia and retinitis; many patients have already received some antiviral therapy and may harbor drug-resistant virus by the time the encephalitis develops. Aggressive anti-retroviral therapy is the optimal way to prolong survival in AIDS-related CMV encephalitis. Ganciclovir, one of the mainstays in the treatment of CMV retinitis, has yielded inconsistent results for brain involvement, and its use is limited by significant myelosuppression. Foscarnet crosses the blood–brain barrier more readily, attaining virustatic concentrations in CSF. It, therefore, is an alternative to ganciclovir despite significant renal and electrolyte effects. Unfortunately, although the combination of ganciclovir and foscarnet may transiently stabilize or improve the condition of most HIV-positive patients with acute CMV encephalitis, the regimen does not have an appreciable effect on survival, which averages only 3 months in this setting.

High-dose parenteral acyclovir has been used in the treatment of varicella-zoster virus (VZV) encephalitis, although the efficacy of antiviral drugs has yet to be proved in this disease. Immunocompetent patients with VZV encephalitis often have an associated granulomatous arteritis of the brain, and a brief course of corticosteroids is often empirically added for its anti-inflammatory effects. Encephalitis is a rare complication of Epstein–Barr virus (EBV) infection. The therapeutic benefit of acyclovir in EBV encephalitis remains unproved as well, but it should be strongly considered given the lack of alternative regimens and the relatively low toxicity of acyclovir.

Papovaviridae

Despite occasional anecdotal reports, efforts to treat PML have generally provided inconsistent results. Reversing immunosuppression, when possible, seems to arrest the process. A recent report of successful treatment with externally expanded virus-specific T cells.[13] may provide a novel approach to this infection. Two of three described patients had clinical and imaging improvement, with clearance of JC virus from the CSF. The third, with HIV infection, had reduction in JC viral load and clinical stabilization but no improvement; she opted for hospice care and succumbed 8 months after treatment.

References

1. Glimaker M, Sjolin J, Akesson S, Naucler P. Lumbar puncture performed promptly or after neuroimaging in acute bacterial meningitis in adults: A prospective national cohort study evaluating different guidelines. *Clin Infect Dis*. 2018;66(3):321–328.
2. Singh TD, Fugate JE, Hocker S, Wijdicks EFM, Aksamit AJ Jr., Rabinstein AA. Predictors of outcome in HSV encephalitis. *J Neurol*. 2016;263(2):277–289.
3. Tunkel AR, Glaser CA, Bloch KC, et al.; Infectious Diseases Society of. The management of encephalitis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;47(3):303–327.
4. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, Whitley RJ. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39(9):1267–1284.
5. Salazar L, Hasbun R. Cranial imaging before lumbar puncture in adults with community-acquired meningitis: Clinical utility and adherence to the Infectious Diseases Society of America Guidelines. *Clin Infect Dis*. 2017;64(12):1657–1662.
6. Hanson KE, Couturier MR. Multiplexed molecular diagnostics for respiratory, gastrointestinal, and central nervous system infections. *Clin Infect Dis* 2016;63(10):1361–1367.
7. Wilson MR, Naccache SN, Samayoa E, et al. Actionable diagnosis of neuroleptospirosis by next-generation sequencing. *N Engl J Med*. 2014;370(25):2408–2417.
8. Wilson MR, Sample HA, Zorn KC, et al. Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis. *N Engl J Med*. 2019;380:2327–2340.
9. Beattie GC, Glaser CA, Sheriff H, Messenger S, Preas CP, Shahkarami M, Venkatesan A. Encephalitis with thalamic and basal ganglia abnormalities: Etiologies, neuroimaging, and potential role of respiratory viruses. *Clin Infect Dis*. 2013;56(6):825–832.
10. Singh TD, Fugate JE, Rabinstein AA. The spectrum of acute encephalitis: Causes, management, and predictors of outcome. *Neurology*. 2015;84(4):359–366.
11. Piantadosi AD, Rubin B, McQuillen DP, et al. Emerging cases of Powassan virus encephalitis in New England: Clinical presentation, imaging, and review of the literature. *Clin Infect Dis*. 2016;62(6):707–713.
12. Krow-Lucal E, Lindsey NP, Lehman J, Fischer M, Staples JE. West Nile Virus and other nationally notifiable arboviral diseases—United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(2):51–55.
13. Muftuoglu M, Olson A, Marin D, et al.(2018). Allogeneic BK virus-specific T Cells for progressive multifocal leukoencephalopathy. *N Engl J Med*. 2018;379(15):1443–1451.

Suggested reading

Gupta RK, Soni N, Kumar S, Khandelwal N. Imaging of central nervous system viral diseases. *J Magn Reson Imaging*. 2012;35:477–491.

Rust RS. Human arboviral encephalitis. *Semin Pediatr Neurol*. 2012;19:130–151.

Whitley RJ. Herpes simplex encephalitis: Adolescents and adults. *Antiviral Res*. 2006;71:141–148.

Wilson MR. Emerging viral infections. *Curr Opin Neurol*. 2013;26:301–306.

77

Intracranial suppuration

Brian Wispelwey and Christopher J. Arnold

Brain abscess

A brain abscess begins as a localized area of cerebritis that develops into a collection of pus surrounded by a well-vascularized capsule. Brain abscesses are uncommon, with occurrence rates of 0.18% to 1.3% in large autopsy series. They most commonly result from contiguous septic foci, but hematogenous spread from a distant source and neurosurgical procedures or trauma represent other risk factors. No predisposing factor can be found in approximately 20% of cases (Box 77.1).

The age distribution of patients with brain abscess varies with its cause. A brain abscess from an otogenic focus typically occurs in patients <30 and shows a male predominance. Brain abscess secondary to sinusitis typically occurs in men in their second to third decade of life.

Pathogenesis

The location of a brain abscess is dependent on its predisposing cause. Abscess from a contiguous focus usually occurs in the cortical area of the brain near its causal site. The most common foci of contiguous infections are otitis or sinusitis. Infection from a contiguous site can spread either directly through intervening tissues, bone, and meninges or indirectly through retrograde thrombophlebitis of the diploic or emissary veins. An abscess may also result from an otogenic infection by spread through preexisting channels such as the internal auditory canal or cochlear and vestibular aqueducts. The majority of otogenic brain abscesses are located in the temporal lobe, followed by the cerebellum. Approximately 90% of cerebellar abscesses are secondary to an otogenic infection. Brain abscesses due to sinusitis are almost always found in the frontal lobe.

Brain abscesses secondary to hematogenous dissemination are often multiple and are located in the territory of the middle cerebral artery at the gray–white junction. They have a distant focus of infection, which is most often within the chest. These abscesses are poorly encapsulated and have a high mortality.

Brain abscesses rarely accompany bacteremia if the blood–brain barrier is intact. For example, despite the presence of persistent bacteremia in bacterial endocarditis, brain abscess is rare (9 brain abscesses reported in 218 cases of infective endocarditis).

Causes

Organisms isolated from brain abscesses are outlined in Table 77.1. Although a single organism is detected in the majority of bacterial brain abscesses, nearly 30% are of mixed infection. Streptococci, Enterobacteriaceae, and anaerobes are most commonly found. In contrast, *Staphylococcus aureus* is commonly isolated in pure culture.

Fungal brain abscesses have increased in incidence due to the prevalent use of immunosuppressive agents, corticosteroids, and broad-spectrum antibiotics. *Candida* spp. are the most common fungi in autopsy series. Risk factors for invasive *Candida* infection include the use of corticosteroids, broad-spectrum antimicrobials, and hyperalimentation. Cerebral aspergillosis occurs in 10% to 20% of all cases of invasive

TABLE 77.1 **PATHOGENS IN BRAIN ABSCESS**

Agent	Frequency (%)
Streptococci (*S. intermedius*, including *S. anginosus*)	60–70
Bacteroides and *Prevotella* spp.	20–40
Enterobacteriaceae	23–33
Staphylococcus aureus	10–15
Fungi[a]	10–15
Streptococcus pneumoniae	<1
Haemophilus influenzae	<1
Protozoa, helminths[b] (vary geographically)	<1

[a] Yeasts, fungi, *Aspergillus*, agents of mucor, *Candida*, cryptococci, coccidiodoides, *Cladosporium trichoides*, *Pseudallescheria boydii*.
[b] Protozoa, helminths, *Entamoeba histolytica*, schistosomes, paragonimus, cysticerci.

aspergillosis, although the brain is rarely the only site of infection. Most cases occur in neutropenic patients with underlying hematologic malignancy. Fungi of the *Zygomycetes* most often cause rhinocerebral mucormycosis, particularly in patients with diabetes mellitus and ketoacidosis, hematologic malignancies, or patients on immunosuppressive therapy. Isolated cerebral mucormycosis is most commonly seen in injection drug users. *Scedosporium apiospermum* is a common mold found in soil. Brain abscess with this organism is often associated with near drowning, trauma, or immunosuppression. While numerous other etiologic agents of fungal brain abscess exist, it is also important to highlight the recent rise in *Cryptococcus gatti* brain abscesses in immunocompetent hosts with epidemiologic exposure in the Pacific Northwest. Patients usually have outdoor exposure and may have a delayed time to diagnosis given that cryptococcal infection is not frequently considered among an otherwise immunocompetent population.

There are several protozoa and helminths that produce brain abscess. The most common is *Toxoplasma gondii*, which typically causes an intracerebral mass or encephalitis in immunosuppressed hosts. While clinically better described as an inflammatory lesion rather than suppuration, the larval form of *Taenia solium*, causative of neurocysticercosis, is of considerable burden in Central and South America. Also found among immunocompetent hosts, cysticercosis is the most common cause of acquired seizure in the developing world.

Infections more often found in patients with defects in cell-mediated immunity include *T. gondii*, *Nocardia asteroides*, *Cryptococcus neoformans*, mycobacteria, and *Listeria monocytogenes*. Neutrophil defects are associated with an increased incidence of infections caused by Enterobacteriaceae, *Pseudomonas*, and fungi. Patients with AIDS may develop focal central nervous system (CNS) lesions as a result of a variety of pathogens (Box 77.2).

BOX 77.1

Clinical settings associated with brain abscess

Spread from a contiguous focus
Otitis media, mastoiditis; 40% of all brain abscesses
Sinusitis, frontal
Dental infections (≤10%), typically with molar infections; abscesses usually frontal but may be temporal
Meningitis; rarely complicated by brain abscess (must be considered in neonates with *Citrobacter diversus* meningitis, of whom 70% develop brain abscess)

Hematogenous spread from a distant focus of infection
Empyema, lung abscess, bronchiectasis, cystic fibrosis, wound infections, pelvic infections, intra-abdominal sepsis

Trauma
After penetrating head trauma, brain abscess develops in about 3%, more commonly after gunshot wounds
Neurosurgical procedures; complicated by brain abscess in only 6–17 per 10 000 clean neurosurgical procedures

Cryptogenic
Asymptomatic pulmonary arteriovenous malformation (AVM), a consideration in cases of cryptogenic brain abscess
Cyanotic congenital heart disease is present in 5–10% of brain abscesses and is the most common predisposing factor in some pediatric series

Clinical manifestations

The clinical course of patients with brain abscess varies dramatically. In approximately 75% of patients, symptoms are present for <2 weeks. Importantly, the prominent symptoms are secondary to mass effect, not infection (Table 77.2). Headache, the most common symptom, may be hemicranial or generalized. Varying degrees of altered mental status are present in most patients. Furthermore, fever may be absent in as many as 50% of all cases.

Brain abscesses in certain anatomic locations may cause additional symptoms. For example, cerebellar abscesses are often associated with nystagmus, ataxia, vomiting, and dysmetria. Frontal lobe abscesses induce headaches, drowsiness, inattention, and decline in mental function. Temporal lobe abscesses are associated with early ipsilateral headaches and, if in the dominant hemisphere, aphasia. Intrasellar abscesses simulate pituitary tumors. Brainstem abscesses often cause facial weakness, headache, fever, hemiparesis, dysphagia, and vomiting.

Laboratory findings

Most laboratory tests are not diagnostic for brain abscess (Box 77.3). Lumbar puncture is contraindicated in patients with known or suspected brain abscess. Not only are cerebrospinal fluid (CSF) findings nonspecific, but patients may herniate after the procedure. In one series, 41 of 140 patients deteriorated within 48 hours after lumbar puncture, and 25 died. Similar results have been reported in other studies.

Imaging studies are most useful in making a diagnosis of brain abscess. CT can be used to evaluate all cranial structures, including the paranasal sinuses, mastoids, and middle ear. It can detect edema,

BOX 77.2

Causes of parenchymal central nervous system lesions in patients with AIDS

Toxoplasma gondii

Most common focal lesion

Occurs in about 10% of all AIDS patients

>1 lesion seen on MRI with surrounding edema, mass effect, and ring enhancement

Most common location is the basal ganglia; most *Toxoplasma* IgG positive

Primary lymphoma

Occurs in about 2% of AIDS patients

Lymphoma is B cell in origin

Lesions are hyperdense or isodense on CT with edema, mass effect, and variable enhancement

Caused by Epstein–Barr virus

Progressive multifocal leukoencephalopathy

Occurs in 2–5% of AIDS patients

Lesions occur at gray–white junction and adjacent white matter; usually hypodense without mass effect

Caused by JC virus (Papovavirus)

Less common

Cryptococcus neoformans[a]

Histoplasma capsulatum[a]

Coccidioides immitis[a]

Other fungi; *Aspergillus*, *Candida*, agents of mucormycosis

Mycobacterium tuberculosis[a]

Mycobacterium *avium* complex

Cytomegalovirus[b]

Metastatic malignancy, notably Kaposi's sarcoma

Acanthamoeba

Bacterial brain abscess of *Listeria*, *Nocardia*, *Salmonella*

Syphilis[a]

Abbreviations: CNS = central nervous system; AIDS = acquired immunodeficiency syndrome; MRI = magnetic resonance imaging; CT = computed tomography; IgG = immunoglobulin G.

[a] More commonly meningitis.

[b] More commonly encephalitis.

hydrocephalus, shift, or imminent ventricular rupture. Contrast enhancement is essential. A brain abscess appears as a hypodense center with an outlying uniform ring of enhancement following the injection of contrast. This is surrounded by a variably hypodense region of brain edema.

MRI is the diagnostic procedure of choice for brain abscess. It appears more sensitive than CT for detecting cerebral edema and is more accurate in differentiating the central necrosis of brain abscess from other fluid accumulations. Gadolinium enhancement can provide further structural detail. On T1-weighted images, enhancement of the abscess capsule occurs, while on T2-weighted images, the surrounding zone of edema has high signal intensity, and the capsule appears as hypointense at the abscess margin. Diffusion-weighted

TABLE 77.2 **CLINICAL MANIFESTATIONS OF BRAIN ABSCESS**[a]

Headache	70%	Nuchal rigidity	≈25%
Fever	50%	Papilledema	≈25%
Altered mental status	>50%	Focal neurologic findings	≈50%
Seizures	25–35%		

[a] Fewer than half have classic triad of fever, headache, and neurologic deficits.

MRI can additionally be used to differentiate neoplasm from abscess as pus leads to restricted diffusion, but false positivity can be observed in cystic or necrotic cerebral metastases. Positron emission tomography (PET) or magnetic resonance spectroscopy may further refine sensitivity and specificity and are routinely available in many settings.

Therapy

Most patients with bacterial brain abscess require surgical management. The two available procedures are aspiration and excision. No prospective randomized trial has been performed to compare these procedures. While aspiration causes less tissue damage than excision, and stereotactic aspiration is particularly valuable for deep-seated abscesses, aspiration during early cerebritis stage may risk hemorrhage and all abscesses >2.5 cm require open excision. In one series, no abscess larger than 2.5 cm resolved without surgical therapy. Ventriculostomy is occasionally required if there is evidence of marked increased intracranial pressure due to obstructive hydrocephalus, ventricular rupture, or other uncontrolled mass effect. Medical therapy alone can be considered in the cerebritis stage prior

BOX 77.3

Laboratory tests and imaging studies

Laboratory tests[a]

WBC: moderate leukocytosis present in about 50% (only 10% WBC >20 000) and normal WBC in 40%

Moderate increase in ESR

Chest x-ray film is useful in detecting the origin of hematogenous brain abscess

EEG abnormal in most patients, lateralizes to side of lesion

Imaging studies

CT scan: useful in evaluating the brain, sinuses, mastoids, and middle ear

MRI: appears more sensitive early in illness and in detecting cerebral edema

^{99m}Tc very sensitive; useful where CT or MRI not available

Abbreviations: WBC = white blood cell count; ESR = erythrocyte sedimentation rate; EEG = electroencephalograph; CT = computed tomography; MRI = magnetic resonance imaging.

[a] Lumbar puncture is contraindicated in patients with known or suspected brain abscess.

to development of the abscess capsule or when the abscess is small or inaccessible.

Approach to the patient with suspected brain abscess

Patients who present with altered consciousness, focal CNS signs, or seizures usually are candidates for contrast-enhanced CT or MRI. Lumbar puncture usually is postponed until a space-occupying CNS lesion is excluded. If rapid clinical progression is occurring, blood cultures for bacteria and fungi may be done and empiric antimicrobial therapy begun before neuroimaging. In every case, management should be done in conjunction with a neurosurgeon. A probable focus in the paranasal sinus or middle ear should prompt consultation also with an otolaryngologist. Empiric treatment depends on the presence or absence of immunosuppression, particularly AIDS.

Antibiotics for the treatment of brain abscess should be administered intravenously, be active against the most likely pathogens, reach adequate concentrations in the abscess fluid, and have bactericidal activity. A third-generation cephalosporin, such as cefotaxime, 3 to 4 g every 8 hours, or ceftriaxone, 2 g every 12 hours, is recommended as first-line empirical therapy of community-acquired brain abscess due to its coverage of streptococci as well as its broad gram-negative spectrum of activity. This antibiotic should be used in conjunction with metronidazole, 7.5 mg/kg (often rounded out to 500 mg) every 6 hours, which attains high concentrations in brain abscess pus and has bactericidal activity against strict anaerobes. A high proportion of deep wound infections after neurosurgical procedures are due to methicillin-resistant *S. aureus* (MRSA), *Staphylococcus epidermidis*, and multiresistant Enterobacteriaceae. Therefore, recommended empiric antibiotics for brain abscess after a neurosurgical procedure include meropenem or cefepime plus vancomycin. Empiric antibiotic therapy should be modified or extended based on culture results, clinical status, and radiologic findings (Table 77.3).

Most patients require surgery. An increasing number of publications advocate the use of stereotactic aspiration as the intervention of choice for many cases. If the patient remains stable and the abscess is accessible and encapsulated, aspiration (CT-guided, if possible) is desirable to make a specific bacteriologic diagnosis and narrow the antimicrobial regimen. If, for any reason, excision or aspiration is delayed or not performed, medical therapy with empiric antibiotic therapy should be instituted immediately. Subsequent management depends on clinical and radiographic (CT) parameters. Later neurologic deterioration, enlargement of an abscess after a 2-week interval, or failure of the abscess to decrease in size after 3 to 4 weeks of antibiotics are indications for further surgery. The duration of microbial therapy remains unsettled. Many authorities treat parenterally for approximately 6 to 8 weeks. Duration cannot be determined by resolution of all CT or MRI abnormalities. A cured brain abscess may continue to appear as nodular contrast enhancement on CT scans for 4 weeks to 6 months after completion of successful therapy.

TABLE 77.3 **ANTIMICROBIAL THERAPY FOR BRAIN ABSCESS**

Antimicrobial agent	Total daily dose
Cefotaxime	8–12 g
Ceftazidime	6–12 g
Ceftriaxone	4 g
Chloramphenicol	4–6 g
Metronidazole	30 mg/kg
Nafcillin	9–12 g
Penicillin G	24 million U
Vancomycin	2 g

See text for discussion of relevant combinations.

AIDS patients and other immunocompromised patients

Patients with advanced HIV infection or AIDS and who have CNS lesions on MRI or contrast-enhanced CT consistent with toxoplasmosis are usually begun on empiric therapy with pyrimethamine and sulfadiazine. Pyrimethamine is given to adults as a single loading dose of 75 to 100 mg followed by 25 to 50 mg daily. Folinic acid is given, 10 mg daily, to decrease bone marrow suppression from pyrimethamine. Sulfadiazine is given, 1 g orally every 6 hours. If sulfadiazine is not available, clindamycin is an acceptable substitute at 600 mg intravenously (IV) every 6 hours. Low-grade fever and a gradual onset also prompt this approach. The limitation of empiric therapy is that radiologic distinction between toxoplasmosis and other lesions is not accurate. Progressive deterioration, an atypical CT or MRI, or failure to show clinical and imaging improvement during 2 weeks of therapy generally warrants biopsy or aspiration. Some physicians also use a negative *Toxoplasma* serology to prompt early neurosurgical intervention. Patients taking trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis for pneumocystosis may be at a lower risk of toxoplasmosis and are therefore more likely to have another diagnosis. Newer diagnostic modalities, such as single-photon emission CT (SPECT), may allow immediate differentiation between *Toxoplasma* and other pathologic processes (see Chapter 101, "Prophylaxis of opportunistic infections in HIV disease").

The range of pathogens for brain abscess is so broad in other immunocompromised patients that empiric therapy has limited value. Early neurosurgical intervention is usually indicated. An exception may be the neutropenic patient in whom fungal abscess is likely, in which case addition of antifungal coverage to antibacterial treatment should be considered. An amphotericin B preparation such as amphotericin B deoxycholate at 0.6 to 1.0 mg/kg/d or liposomal amphotericin B at 5 mg/kg/d will adequately cover brain abscesses from *Candida* species and most endemic fungi. Voriconazole at 4 mg/kg every 12 hours is preferred if an *Aspergillus* species is suspected, and successful combination therapy of voriconazole with an amphotericin B preparation or an echinocandin has been demonstrated.

Corticosteroids

The role of corticosteroids in the treatment of brain abscess remains controversial. They should be restricted to patients who have

progressive neurologic deterioration or impending cerebral herniation and radiologic evidence that the abscess is causing significant cerebral edema and mass effect. The use of corticosteroids may delay the entry of antibiotics into the CNS, impair the clearance of bacteria, inhibit capsule formation, and alter the appearance of follow-up radiologic imaging.

Prognosis

Several factors are associated with a poor prognosis (Box 77.4). In addition, characteristics such as patient's age, abscess diameter, and metastatic lesions also influence outcome. Neurologic sequelae develop in 30% to 55% of patients, and in 17% they are incapacitating. Seizures develop in a variable percentage of patients (12% to >50%).

Subdural empyema

Subdural empyema is the most common sinusitis-associated intracranial infection. The frontal sinus is most frequently implicated, and the most common location of a subdural empyema is the frontal lobe. Other causes of subdural empyema include meningitis, otitis media, prior head trauma, infection of an existing subdural hematoma, or neurosurgical procedure. Subdural empyemas have a male predominance and most often occur in the second decade of life in otherwise healthy individuals. An intracerebral abscess occurs concomitantly in 6% to 22% of cases, and an epidural abscess in 9% to 17%.

Causes

Subdural empyemas are most often monomicrobial; however, polymicrobial infections are common. Organisms found in paranasal sinus cultures often do not correlate with subdural cultures. Aerobic and anaerobic streptococci are the most frequently isolated pathogens. Staphylococci are cultured less often, followed in frequency by aerobic gram-negative bacilli and nonstreptococcal anaerobes (Table 77.4). For example, *Propionibacterium acnes* has been reported following penetrating head trauma and after neurosurgery with the use of dural allograft. Sterile cultures occur in a substantial number of cases, possibly due to the prior administration of antibiotics or difficulties in culturing anaerobic organisms.

TABLE 77.4 **PATHOGENS IN SUBDURAL EMPYEMA**

Aerobic streptococci	32%
Anaerobic streptococci	16%
Staphylococcus aureus	11%
Coagulase-negative staphylococci	5%
Aerobic gram-negative bacilli	8%
Anaerobes	5%
No organism isolated	34%

Clinical presentation

Due to a lack of anatomical constraints to limit the spread of infection in the subdural space, the clinical manifestations can progress rapidly (Table 77.5). Headache and fever are common early symptoms. Altered mental status, focal neurologic deficits, meningismus, papilledema, and vomiting may also result. Seizures are common and occur in 25% to 80% of cases.

Diagnosis

Diagnosis is made by imaging with contrast-enhanced CT or MRI. A subdural empyema appears as a crescent-shaped area of hypodensity adjacent to the falx cerebri or below the cranial vault. With contrast enhancement, an intense line can be seen between the subdural collection and the cerebral cortex. Edema can cause effacement of the basilar cisterns and flattening of the cortical sulci. MRI is more sensitive in detecting subdural empyemas, particularly at the base of the brain, in the posterior fossa, or along the falx cerebri. On MRI, T1-weighted images may reveal mass effect and a hypointense subdural lesion, which in turn is hyperintense on T2-weighted imaging. On diffusion-weighted imaging, subdural empyemas have high signal intensity, in contrast to sterile subdural effusions that have low signal intensity.

Therapy

Surgical intervention using either a burr hole or craniotomy to drain the subdural empyema is an important part of therapy. Drainage is useful to both relieve mass effect and obtain cultures to guide

BOX 77.4

Adverse prognostic factors in brain abscess

Delayed or missed diagnosis
Poor localization, especially in the posterior fossa (before CT)
Multiple, deep, or multiloculated abscesses
Ventricular rupture (80–100% mortality)
Fungal cause
Inappropriate antibiotics

Abbreviation: CT = computed tomography.

TABLE 77.5 **CLINICAL PRESENTATION OF SUBDURAL EMPYEMA**

Headache	
Altered mental status	≈50%
Fever (>39°C [102.2°F])	Majority
Focal neurologic findings Hemiparesis, ocular palsies, dysphagia, cerebellar signs	In all, eventually
Seizures	25–80%
Meningismus	≈80%

antimicrobial therapy. Exploration of a sinus or otologic focus of infection should also be done.

A reasonable empiric antibiotic regimen for a community-acquired subdural empyema would be a third-generation cephalosporin plus metronidazole. Depending on the prevalence of MRSA or the likelihood of coagulase-negative staphylococci, the addition of vancomycin could be considered. Further antimicrobial therapy should be directed against pathogens revealed by Gram stain, culture of aspirated material, and knowledge of the primary site of infection. Parenteral antibiotics are continued for 3 to 6 weeks depending on the clinical response and associated conditions.

Due to the high incidence of seizures, many centers advocate the use of anticonvulsants. Even despite the use of prophylaxis, some small studies have shown a continued high incidence of seizures. Further studies are needed to investigate strategies to decrease this significant complication.

Prognosis

Prognosis is related to the degree of neurologic impairment at presentation. Mortality is approximately 7% in patients who are alert and well-oriented, 21% in patients who are lethargic or comatose but respond purposefully, and 56% in patients who are unresponsive. Neurologic sequelae in the form of hemiparesis and aphasia are common, and up to 40% of patients may have seizures.

Cranial epidural abscess

Cranial epidural abscesses (Figure 77.1) were traditionally the sequelae of sinusitis, mastoiditis, and otitis media. Currently, one of the most common causes of an intracranial epidural abscess is a neurosurgical procedure. The organisms responsible for epidural abscesses are similar to those that cause subdural empyemas.

The dura is essentially adherent to the inner lining of the skull, which constrains the epidural space and limits spread of purulence. Because of this, epidural abscesses are typically slow growing and have an indolent course. Headache may be the only presenting symptom. Over time, complications such as subdural empyema, brain abscess, or meningitis may result. It is the manifestations of these complications that may be the first indication of an intracranial process.

Contrast-enhanced CT or MRI may be used to diagnose an intracranial epidural abscess. Lentiform or crescentic collections overlying a cerebral convexity and/or in the interhemispheric fissure are seen. Treatment is the same as for subdural empyema.

Suppurative intracranial thrombophlebitis

Cavernous sinus thrombosis most commonly results from spread of infection from the sinuses, especially the sphenoid sinus. Infections

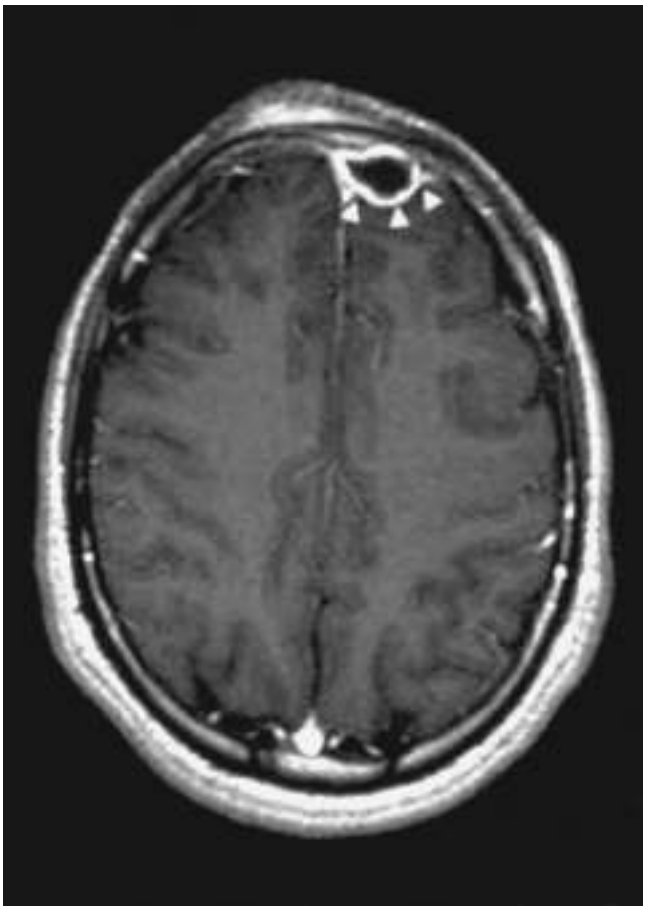

FIGURE 77.1 Epidural abscess associated with frontal sinus disease. Postgadolinium axial T1W MRI showing thick-walled enhancing epidural collection close to the inner table of the frontal bone (*arrowheads*) with adjacent soft tissue swelling.
From Bradley WG. *Neurology in clinical practice*, 4th ed. Oxford: Butterworth-Heinemann, an imprint of Elsevier; 2004.

of the middle third of the face, dental abscesses, otogenic infections, and orbital cellulitis are other sources of cavernous sinus thrombosis (see Chapter 16, "Periocular and retro-orbital infections"). Lateral sinus thrombosis is a serious complication of both acute and chronic otitis media. Infection of the superior and inferior petrosal sinuses may also result from otitis media or mastoiditis. Suppurative thrombophlebitis of the superior sagittal sinus may develop after infection of the face, scalp, or subdural or epidural space or after meningitis.

Pathogenesis

Suppurative thrombophlebitis occurs intracranially because of the close proximity of the dural venous sinuses to other structures in the skull. The transverse sinus receives several important supratentorial veins from the temporal and occipital lobes, as well as many infratentorial veins. The superior petrosal sinus, which receives venous channels from the tympanic structures, also drains into the transverse sinus. The sigmoid sinus, which lies close to mastoid cells, is the inferior continuation of the transverse sinus.

TABLE 77.6 **SUPPURATIVE INTRACRANIAL THROMBOPHLEBITIS: ORGANISM BY SITE OF INFECTION**

Sinusitis	Streptococci
	Staphylococci
	Anaerobes
Soft-tissue infections of the face	*Staphylococcus aureus*
Otitis, mastoiditis	Streptococci
	Haemophilus influenzae
	Gram-negative bacilli
	Staphylococci

The dural venous sinuses and cranial veins are valveless, and blood flow is determined by pressure gradients. Bacteria that enter the facial veins are carried through the cavernous sinuses to the petrosal sinuses and finally the internal jugular vein. Conditions that increase blood viscosity, such as trauma, dehydration, malignancy, and pregnancy, increase the likelihood of developing thrombosis. However, predisposing conditions are not identified in every case.

Causes

The causative pathogen in suppurative intracranial thrombophlebitis depends on the site of the original infection (Table 77.6). *S. aureus* is the most common pathogen in cavernous sinus thrombosis, but other gram-positive cocci such as *Streptococcus* species, gram-negative bacilli, and anaerobes can be seen. The most common bacteria in lateral sinus thrombosis include gram-negative bacilli and anaerobes. Mixed infections are frequent.

Clinical presentation

The clinical presentation depends on the location of disease (Table 77.7). Cavernous sinus thrombosis can present with periorbital edema, chemosis, visual loss, restricted eye movement, and proptosis. Orbital cellulitis and orbital apex syndrome can present similarly. In contrast, preseptal cellulitis is confined to structures anterior to the orbit. Suppurative cavernous sinus thrombosis can spread via intercavernous sinuses to the contralateral cavernous sinus within 24 to 48 hours. The thrombus may also extend to other dural venous sinuses, adjacent vascular structures, or the brain parenchyma. Metastatic spread of septic emboli may occur and most commonly involves the lung.

TABLE 77.7 **SYMPTOMS OF SUPPURATIVE THROMBOPHLEBITIS**

Cavernous sinus thrombosis	Photophobia, ptosis, diplopia, proptosis, chemosis, weak extraocular muscles, papilledema, altered mental status, meningismus, decreased visual acuity, involvement bilaterally; same findings in opposite eye
Septic lateral sinus thrombosis	Headache >80%, earache, vomiting, vertigo associated with otitis, fever and abnormal ear findings, increased facial sensation/pain, sixth-nerve palsy
Superior sagittal sinus	Altered mental status, motor deficits, papilledema, nuchal rigidity, seizures >50%
Inferior petrosal sinus	Gradenigo's syndrome (ipsilateral facial pain and lateral rectus weakness)

Classic symptoms and signs of lateral sinus thrombosis include severe headache, otalgia, spiking fevers, mastoid swelling, and tenderness. However, patient presentations may be highly variable and are influenced by the common occurrence of concurrent intracranial complications and preadmission antibiotics. Symptoms and signs of raised intracranial pressure may result if the thrombosis significantly impairs CSF resorption or cerebral venous outflow. These include headache, nausea, vomiting, sixth nerve palsy, and papilledema. Nuchal rigidity has been reported to occur in 8% to 61% of patients. Unlike meningitis, the nuchal rigidity associated with lateral sinus thrombosis is often unilateral, with negative Kernig and Brudzinski signs.

Diagnosis

On contrast-enhanced CT scan, the most accurate diagnostic finding of sinus thrombosis is the empty delta sign. This consists of a darkened area of thrombus in the vessel lumen, surrounded by the contrast-enhanced sinus wall. The thrombus formed within the lumen of the sinus may present different attenuations according to its developmental stage, and artifacts from adjacent bone structures are factors that may decrease the sensitivity of CT. Contrast-enhanced CT has a sensitivity of approximately 80% for the diagnosis of dural sinus thrombosis. On MRI, an acute thrombus (days 0–3) appears isointense on T1-weighted images and hypointense on T2-weighted images. In the subacute phase (days 3–15), there is increased intensity of the thrombus in both T1- and T2-weighted images. MR venography (MRV) is more sensitive than contrast-enhanced CT or MRI and demonstrates the loss of signal and then absence of flow in the sinus. CT venography may be as accurate as MRV. It is less impaired by motion artifact because of a rapid acquisition time. It more frequently depicts sinuses of smaller cerebral veins with low flow than does MRV. However, its disadvantages include significant exposure to ionizing radiation and the need for intravenous contrast material.

Therapy

Initial IV treatment with antibiotics that have a broad spectrum of activity and good CSF penetration should be used. Surgical removal of the source of infection should also be undertaken. Mortality rates from lateral sinus thrombosis have improved but are still approximately 10%.

Anticoagulation is controversial, and its major risk is intracranial hemorrhage. One study found anticoagulation with antimicrobial therapy may reduce mortality of cavernous sinus thrombosis but only if used early in disease. It has not been proved beneficial in lateral sinus thrombosis.

Suggested reading

Beckham JD, Tyler KL. Neuro-intensive care in patients with acute CNS infections. *Neurotherapeutics*. 2012;9(1):124–138.

Bloch KC, Bailin SS. Update on fungal infections of the central nervous system: Emerging pathogens and emerging diagnostics. *Curr Opin Infect Dis*. 2019;32(3):277–284.

Chen M, Low DCY, Low SYY, Muzumdar D, Seow WT. Management of brain abscesses: Where are we now? *Child's Nerv Sys*. 2018; 34(10):1871–1880.

Chow F. Brain and spinal epidural abscess. *Continuum (Minneap Minn)*. 2018;24(5, Neuroinfect Dis):1327–1348.

French H, Schaefer N, Keijzers G, Barison D, Olson S. Intracranial subdural empyema: A 10-year case series. *Ochsner J*. 2014;14(2): 188–194.

Hakan T. Management of bacterial brain abscess. *Neurosurg Focus*. 2008;24(6):1–7.

Harris JR, Lockhart SR, Debess E, et al. *Cryptococcus gattii* in the United States: clinical aspects of infection with an emerging pathogen. *Clin Infect Dis*. 2011;53(12):1188–1195.

Honda H, Warren DK. Central nervous system infection: meningitis and brain abscess. *Infect Dis Clin North Am*. 2009;23(3):609–623.

Kastenbauer S, Hans-Walter P, Wispelwey B, Scheld WM. Brain abscess. In Scheld WM, Whitley R, Marra CM, eds. *Infections of the Central Nervous System*, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004: 479–507.

Osborn MK, Steinberg JP. Subdural empyema and other suppurative complications of paranasal sinusitis. *Lancet Infect Dis*. 2007;7:62–67.

Prasad KN, Mishra AM, Gupta D, et al. Analysis of microbial etiology and mortality in patients with brain abscess. *J Infect*. 2006;53:221–227.

Pruitt AA. Central nervous system infections complicating immunosuppression and transplantation. *Continuum (Minneap Minn)*. 2018;24(5, Neuroinfect Dis):1370–1396.

Reddy JS, Mishra AM, Behari S, et al. The role of diffusion-weighted imaging in the differential diagnosis of intracranial cystic mass lesions: A report of 147 lesions. *Surg Neurol*. 2006;66:246–250.

Smith SJ, Ughratdar I, MacArthur DC. Never go to sleep on undrained pus: A retrospective review of surgery for intraparenchymal cerebral abscess. *Br J Neurosurg*. 2009;23 (4):412–417.

Sonnevill R, Ruimy R, Benzonana N, et al. An update on bacterial brain abscess in immunocompetent patients. *Clin Microbiol Infect*. 2017;23(9):614–620.

Tunkel AR. Brain abscess. In Mandell GL, Dolin R, Bennett JE, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 7th ed. New York: Churchill Livingstone; 2010: 1265–1278.

78

Spinal epidural abscess

Mark J. DiNubile

Epidural abscess of the spine represents a potentially crippling but treatable cause of back pain. Although relatively infrequent, the incidence appears to be increasing. Early diagnosis and aggressive therapy are essential for optimizing outcomes. Even with an indolent presentation, patients can still suffer seemingly unprovoked catastrophic neurologic deterioration related to delays in recognition and appropriate intervention.

Classification

Epidural abscesses can be separated anatomically into infections involving the spinal or cranial epidural space. Cranial epidural abscesses are discussed in Chapter 77 covering intracranial suppuration.

Spinal epidural infections can have acute and chronic presentations. Categorization by rapidity of onset and progression correlates with certain clinical and laboratory manifestations, bacteriology, anatomic details, pathology, and pathogenesis (Table 78.1). The nontuberculous bacterial spinal epidural abscess constitutes the major focus of this chapter. Tuberculous, fungal, and parasitic abscesses of the spinal epidural space evolve more insidiously than do pyogenic bacterial epidural abscesses. Other than iatrogenic infections, these etiologies are more frequently encountered in tropical and subtropical resource-constrained regions of the world. Metastatic carcinoma and lymphoma represent common alternative diagnoses that can exactly mimic epidural infections.

Another differential feature with therapeutic implications concerns the source of epidural infection. Microbes most commonly access the epidural space by hematogenous dissemination from a distant, sometimes trivial, infectious focus. In contrast, a substantial minority of cases arise from contiguous spread, usually from adjacent vertebral osteomyelitis. Epidural abscesses of hematogenous origin are typically located in the dorsolateral thoracic or lumbar area, where the epidural space is widest. Abscesses that form secondary to adjacent osteomyelitis usually involve the epidural space anteriorly or circumferentially. In some cases, it is hard to determine whether the epidural space represents a primary or secondary site of infection; for example, epidural abscess can be the cause or result of bacteremia or osteomyelitis.

Clinical presentation and course

The classical manifestations of spinal epidural abscess were partitioned by Heusner in 1948 as progressing through four sequential but overlapping stages: (1) spinal ache (or back pain), (2) root (or radicular) pain, (3) weakness, and ultimately (4) paralysis. The actual time between the onset of back pain and development of neurologic deficits can be highly variable. The unpredictable but potentially rapid evolution from backache to neurologic tragedy forces physicians to consider this entity in the differential diagnosis of all patients with new or changing back pain, particularly when fever and localized spinal tenderness coexist. Additional presenting complaints in some patients may include paresthesia

TABLE 78.1 **CHARACTERISTIC FINDINGS IN ACUTE VERSUS CHRONIC SPINAL EPIDURAL ABSCESS**

	Acute	Chronic
Duration of symptoms	<2 wk	>2 wk
Fever	Often present	Low grade or absent
Systemic toxicity	Sometimes	Infrequently
Source	Hematogenous (often from minor skin infection)	Direct extension from vertebral osteomyelitis
Back pain	Always	Always
Localized spinal tenderness	Very common	Nearly universal
Root weakness	Common	Common
Peripheral leukocytosis	Usually present	Often absent
Erythrocyte sedimentation rate/C-reactive protein	Markedly elevated	Markedly elevated
CSF leukocytes[a] (per mm^3)	Usually 50–1,000	Often <50
CSF protein >100 mg/dL	Almost always	Almost always
Anatomic location	Usually posterior to spinal cord	Commonly anterior to spinal cord
Gross pathology	Purulent exudate	Granulation tissue

Abbreviation: CSF = cerebrospinal fluid.
[a] Frank pus may be encountered if a lumbosacral epidural abscess is entered during attempted lumbar puncture. Under such circumstances, the spinal needle must not be further advanced because introducing the needle into the subarachnoid space may precipitate meningitis. The aspirated purulent material should be sent immediately in the airless capped syringe for appropriate studies, including Gram stain and aerobic/anaerobic cultures.

(sometimes described as "electric" in character), paresis, incontinence, constipation, or urinary retention. Atypical presentations include headache or meningismus (with cervical involvement), pleuritic or abdominal pain (with thoracic infection), and hip pain (with lumbar disease).

In patients with epidural abscesses, an inapparent primary source of infection, such as endocarditis, adjacent osteomyelitis, or a distant visceral abscess, may be present. Initially occult infectious foci may ultimately dictate the length of antimicrobial treatment or mandate additional procedures. Not unexpectedly, bacteremia is more often documented in acute hematogenous than chronic locally advancing infections. Especially when *Staphylococcus aureus* is the pathogen, the infection may be multifocal due to seeding of distant sites during a primary or secondary bacteremia.

The dreaded neurologic complications of epidural abscess can arise from either pressure causing compression of the spinal cord or vascular compromise causing ischemic necrosis. Cord compression may be more common, but septic thrombophlebitis is likely responsible for sudden, unforeseen deterioration.

Risk factors

Most, but not all, cases of spinal epidural abscess have recognized local and/or systemic risk factors. Patients with a history of back injury are predisposed to seed the injured area during transient bacteremia and therefore constitute a special risk group for vertebral osteomyelitis and/or epidural abscess. The risk remains long after the initial injury. Penetrating trauma may seed the adjacent bone and epidural space. Suspicion of epidural infection should be raised when a patient with diagnosed osteomyelitis or after recent back surgery, epidural injection, or lumbar puncture reports worsening localized back discomfort.

All patients with bacteremia or candidemia incur some risk of metastatic seeding. Patients with cutaneous infections, infected catheters, dental manipulations, decubitus ulcers, urinary tract infections, or endocarditis can develop a secondary epidural focus through hematogenous spread, even in the absence of previously recognized back injury. The risk appears highest in the aftermath of *S. aureus* bacteremia and is not totally eliminated by the 2 to 4 weeks of antibiotic therapy usually given to such patients. Epidural infection may manifest itself weeks to months later. Under most circumstances, back pain developing or worsening in the year following an episode of *S. aureus* bacteremia should be presumed to represent metastatic infection until proved otherwise. Similar concerns follow candidemia.

Injection drug users may develop infections of the epidural space with or without endovascular seeding. Diabetic patients, patients receiving long-term parenteral nutrition, and patients undergoing hemodialysis also appear to be at increased risk for epidural infection. Infections can arise from epidural injections or catheters due to breach of the anatomic barriers or even contamination of the injected material.

Microbiology

S. aureus remains the predominant pathogen recovered from all types of epidural abscesses, often originating from an unnoticed and otherwise inconsequential primary skin focus. Injection drug use, chronic hemodialysis, and indwelling vascular catheters predispose to *S. aureus* bacteremia associated with metastatic seeding.

A comprehensive clinical history including the epidemiologic circumstances may provide the only clues to otherwise unsuspected pathogens. Gram-negative osteomyelitis, discitis, and epidural infection can complicate injection drug use, where Enterobacteriaceae and *Pseudomonas aeruginosa* need to be considered among the possible pathogens. Gram-negative rods and occasionally enterococci can spread from urinary tract or pelvic infections to the lumbar spine and/or epidural space through vascular anastomoses in Batson's plexus. Less commonly isolated bacterial species include streptococci (especially the *S. milleri* group), coagulase-negative staphylococci (usually postoperatively or after open trauma), and anaerobes (from either the oral or intestinal flora). *Brucella* and *Salmonella* species are considerations under certain circumstances. Rare etiologies like pneumococcus, *Nocardia*, melioidosis, and environmental fungi have been reported.

Tuberculous spondylitis (Pott's disease) is frequently associated with epidural abscess and may be the presenting or sole manifestation of reactivation tuberculosis. Chronic osteomyelitis due to tuberculosis is often clinically and radiologically indistinguishable from disease caused by pyogenic bacteria, although the course is generally more protracted. Histopathology typically reveals fibrous connective tissue studded with caseating granulomata containing multinucleated giant cells. Acid-fast bacilli (AFB) can often be demonstrated by appropriate stains or molecular techniques. Despite paraspinal collections, operative intervention is not routinely required for Pott's disease in the absence of substantial or progressive neurologic involvement.

Nosocomial candidemia can be complicated by osteomyelitis with or without epidural infection and may present as a delayed complication of catheter-related candidemia despite antifungal therapy. Unusual etiologies of epidural abscess have involved *Actinomyces*, *Nocardia*, nontuberculous mycobacteria, *Cryptococcus*, *Blastomyces*, *Aspergillus*, *Exserohilum, Rhizopus*, cysticercosis, and *Echinococcus*.

Diagnosis

Every patient who complains of new or progressive back pain, fever, and local spine tenderness must be quickly assessed for the possibility of spinal epidural abscess. A normal sedimentation rate makes an epidural abscess relatively unlikely.

Not all the symptoms and signs classically attributed to an epidural abscess are present in every patient. With a protracted course, fever and systemic complaints may be diminished. Children especially may exhibit atypical features. In several series, roughly half the reported patients with spinal epidural abscesses were initially given unrelated diagnoses. In oncology and intensive care patients, the symptoms of epidural infection may be obscured by or misattributed to other coexisting problems.

Conventional radiology of the spine is rarely conclusive; early in the process, osseous destruction can be inapparent even in the presence of vertebral osteomyelitis. Although fever is generally unimpressive with chronic epidural abscess, these patients will have abnormal spine radiographs more consistently than patients with acute infection. Findings on bone, gallium, and indium scans and even CT are typically equivocal and thus can delay definitive diagnostic testing and subsequent treatment.

Whether acute or chronic, all patients with suspected epidural space infection require MRI of the spine, CT myelography, or a conventional myelogram on an urgent basis. Gadolinium-enhanced MRI is currently the preferred diagnostic procedure where available. Spinal puncture for myelography when necessary should be performed at a site as far as safely possible from the area of suspected abscess. The needle should be advanced slowly, with frequent aspirations; if pus is encountered, the needle should be withdrawn and the aspirated material sent for appropriate tests. If myelographic contrast material is to be injected into the subarachnoid space, cerebrospinal fluid should be obtained beforehand for stains and cultures, glucose and protein levels, total and differential cell counts, and cytology. Otherwise, lumbar puncture should be avoided unless meningitis is in the differential diagnoses. If nonsurgical management is planned, CT-guided aspiration of the epidural collection may be attempted to obtain specimens for stains and culture (as well as to drain the epidural collection).

Treatment

Traditional management of spinal epidural abscess involves immediate surgical drainage and prolonged antibiotic therapy. Operative evacuation of the abscess allows for decompression as well as procurement of pus and tissue samples for microbiologic processing. Exposure of the entire length of the abscess with adequate drainage, debridement, and irrigation has been standard practice in most situations and can usually be accomplished via a simple laminectomy. Neurologic improvement is often evident soon after decompression. Early surgery improves neurologic outcomes compared with delayed surgical intervention following a failed trial of medical management.

In acute or rapidly progressing cases, antibiotic therapy ought to be initiated promptly and often empirically after blood and other readily accessible sites of infection are sampled for stains and cultures. An antistaphylococcal agent should be routinely included in any empirical antibiotic regimen. With the spread of nosocomial and now community-acquired methicillin-resistant *S. aureus* (MRSA), coverage with antistaphylococcal β-lactam agents has become inadequate for empiric therapy. Antibiotics active against gram-negative and strictly anaerobic bacteria should be added to the regimen when these organisms are suspected based on clinical grounds or epidemiologic context. For example, a patient with a lumbar epidural abscess of suspected urinary tract origin would need broader coverage for gram-negative pathogens. For infections

associated with injection drug use, coverage for *P. aeruginosa* and mouth anaerobes needs to be considered. Many authorities would initiate empiric treatment of all epidural abscesses with broad-spectrum coverage, including vancomycin, metronidazole, and ceftriaxone (or ceftazidime, if *P. aeruginosa* is a suspect). Gram-stained specimens often provide rapid information that can lead to modifications of the planned antibiotic regimen before culture results return.

The initial regimen should be refined once results of stains, cultures, and susceptibility tests from blood, aspirates, or operative samples are available. Aerobic and anaerobic cultures from appropriately processed specimens usually identify the pathogen(s) unless substantial antibiotic treatment has preceded sampling. The dosing guidelines given here are for adults with normal renal and hepatic function. Confirmed methicillin-susceptible *S. aureus* infections have traditionally been treated with nafcillin, 2 g intravenously (IV) every 4 hours (or cefazolin, 1 g IV q8h) in patients not allergic to β-lactam agents. Clindamycin, 600 mg IV every 8 hours, and vancomycin, initially administered as at least 15 mg/kg IV every 12 hours and adjusted to maintain trough levels of 15 to 20 μg/mL, remain the standard alternatives for seriously penicillin-allergic patients. Vancomycin, daptomycin, or linezolid are appropriate when MRSA is recovered or strongly suspected. Community-acquired MRSA may be sensitive to other agents (such as clindamycin, quinolones/rifampin, or trimethoprim–sulfamethoxazole) but susceptibility to these agents should be documented by testing the isolate in the clinical microbiology laboratory before any of these drugs are considered.

Substantial clinical experience supports extended-spectrum quinolones for the treatment of osteomyelitis, discitis, and epidural abscesses. In susceptible staphylococcal infections associated with osteomyelitis, an oral regimen of rifampin 600 mg/d combined with either ciprofloxacin 750 mg twice daily or levofloxacin 750 mg once daily would be a reasonable oral option to complete a prolonged antibiotic course after successful acute management.

For susceptible gram-negative infections, trimethoprim–sulfamethoxazole, an advanced-generation cephalosporin, or a quinolone may be used. Trimethoprim–sulfamethoxazole is not active against *P. aeruginosa*, which mandates treatment with an antipseudomonal β-lactam derivative or ciprofloxacin guided by sensitivity results and sometimes combined with an aminoglycoside antibiotic. Carbapenems or colistin may be necessary for multidrug-resistant gram-negative bacilli. Metronidazole is the drug of choice for most anaerobic infections. Quinolones, trimethoprim–sulfamethoxazole, and metronidazole can be given orally to patients tolerating medication by mouth. The incidence of iatrogenic complications (as well as cost) could be dramatically reduced by discontinuing nonessential intravenous lines and administering antibiotic therapy by mouth when appropriate.

The optimal duration of antibiotic therapy has not been determined in controlled studies. Recommendations range from 4 to 8 weeks. Therapy for at least 6 weeks is typically prescribed, especially when vertebral osteomyelitis coexists or complete surgical drainage was not accomplished.

Selected patients with epidural abscess can be managed conservatively without surgery. Nonsurgical management is more consistently successful in stable patients who present with localized back or radicular pain without objective neurologic signs such as weakness, urinary retention, or incontinence. However, in the majority of cases, a drainage procedure is still considered a critical component of the standard of care under most circumstances, both to establish a microbiologic diagnosis and to decompress the thecal sac.

The optimal procedure requires individualizing the approach for the particular location and extent of the infection. In surgical candidates, decompression and drainage are usually accomplished by posterior laminectomy for dorsal abscesses or by partial or complete anterior or anterolateral corpectomy for ventral abscesses in adults. Complete exposure of the involved segments may be contraindicated in patients with extensive craniocaudal abscesses or spinal instability. Less invasive procedures have been increasingly employed for complicated multilevel infection. Multisegment interlaminar fenestration can replace laminectomy in selected cases with impending anterior instability due to lumbar spondylitis, sometimes accompanied by intraoperative ultrasound to guide decompression in the narrow bony window. Minimally invasive operative procedures or percutaneous CT-guided needle aspiration may be a compromise approach in some patients despite a theoretical concern about inadvertently seeding the subarachnoid space and inducing meningitis during the procedure.

Medical management alone is an appropriate option for neurologically stable patients who exhibit no significant neurologic deficits or have a contraindication to surgery (Box 78.1). Qualifying candidates for medical therapy are not infrequent. Unfortunately, some patients will suffer neurologic progression despite appropriate antibiotics, which can ensue abruptly and unpredictably without warning. The resultant paresis or paralysis may be irreversible, even if surgery is then performed urgently. In addition to mass effect, vascular compromise from septic arterial or venous thrombosis with cord infarction may play a key pathophysiologic role in these tragic cases.

All patients with epidural abscess, whether managed conservatively or not, must be evaluated by careful and repeated physical examinations at least daily for signs of neurologic deterioration. The role for periodic imaging during the course of or after treatment is completed is not well defined.

BOX 78.1

Potential candidates for medical management of spinal epidural abscess without immediate operative intervention

No significant or progressive neurologic dysfunction
Or
Poor surgical candidate
Or
Complete paralysis for >72–96 h
AND
Diagnosis is secure, and causative organism has been identified.

Prognosis

Spinal epidural abscess was often lethal in the pre-antibiotic era. Today, morbidity rates remain disappointingly high. Up to a third of survivors have persistent deficits and unsatisfactory outcomes. In a recent series, 15% of cases had an adverse outcome including paralysis in 8% and a 7% mortality rate.

Presenting symptoms of back pain or radiculopathy are associated with better functional outcomes, regardless of symptom duration, than more severe neurologic findings at presentation. For patients presenting with frank motor deficits, duration of symptoms ("acute" vs. "chronic" presentations) appears to have prognostic implications, with better outcomes when treatment is initiated within 72 hours of onset of weakness. The severity of the neurologic defect at the time of the drainage/decompression procedure is a critical predictor of the ultimate neurologic result. Other prognostic indicators include patient age, the degree of cord impingement on imaging studies, and operative findings of granulation tissue as opposed to purulent fluid.

Conclusion

Epidural abscess is a potentially devastating infection. Early diagnosis and combined aggressive medical–surgical intervention are essential for most patients because neurologic function may deteriorate quickly, leaving irreversible deficits.

Disclosures

The author is employed by BioAegis Therapeutics and owns stock options in the company. The opinions expressed in this report represent the views of the author.

Suggested reading

Alton TB, Patel AR, Bransford RJ, Bellabarba C, Lee MJ, Chapman JR. Is there a difference in neurologic outcome in medical versus early operative management of cervical epidural abscesses? *Spine J*. 2015;15:10–17

Baker AS, Ojemann RG, Swartz MN, et al. Spinal epidural abscess. *N Engl J Med*. 1975;293:463–468.

Connor DE Jr, Chittiboina P, Caldito G, Nanda A. Comparison of operative and nonoperative management of spinal epidural abscess: A retrospective review of clinical and laboratory predictors of neurological outcome. *J Neurosurg Spine*. 2013;19:119–127.

Davis DP, Salazar A, Chan TC, Vilke GM. Prospective evaluation of a clinical decision guideline to diagnose spinal epidural abscess in patients who present to the emergency department with spine pain. *J Neurosurg Spine*. 2011;14:765–770.

Heusner AP. Nontuberculous spinal epidural infections. *N Engl J Med*. 1948;239:845.

Kainer MA, Reagan DR, Nguyen DB, et al. Fungal infections associated with contaminated methylprednisolone in Tennessee. *N Engl J Med*. 2012;367:2194–2203.

Khanna RK, Malik GM, Rock JP, et al. Spinal epidural abscess: evaluation of factors influencing outcome. *Neurosurgery*. 1996;39:958–964.

Patel AR, Alton TB, Bransford RJ, Lee MJ, Bellabarba CB, Chapman JR. Spinal epidural abscesses: risk factors, medical versus surgical management, a retrospective review of 128 cases. *Spine J*. 2014;14(2):326–330.

Pradilla G, Ardila GP, Hsu W, Rigamonti D. Epidural abscesses of the CNS. *Lancet Neurol*. 2009;8:292–300.

Shah NH, Roos KL. Spinal epidural abscess and paralytic mechanisms. *Curr Opin Neurol*. 2013;26:314–317.

Wheeler D, Keiser P, Rigamonti D, et al. Medical management of spinal epidural abscesses: Case report and review. *Clin Infect Dis*. 1992;15:22–27.

Vakili M, Crum-Cianflone NF. Spinal epidural abscess: A series of 101 cases. *Am J Med*. 2017;130:1458–1463.

79

Myelitis and peripheral neuropathy

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Myelitis and peripheral neuropathy complicate many infections. This chapter discusses major infectious etiologies of myelitis (Table 79.1), peripheral neuropathy (Table 79.2), polymorphic syndromes (Table 79.3), and neuropathic syndromes seen in HIV infection (Box 79.1). Furthermore, an algorithm (Figure 79.1) suggests an approach to the clinical and laboratory diagnosis of myelitis and peripheral neuropathy.

Myelitis

Myelitis refers to inflammation of the spinal cord. Myelitis may be infectious or noninfectious and primary—directly attacking cord structures—or secondary—producing adjacent processes altering cord function. Primary myelitis can present as one of three discrete clinical patterns: (1) anterior poliomyelitis, (2) leukomyelitis, or (3) transverse myelitis. Poliomyelitis is inflammation involving gray matter; leukomyelitis is confined to white matter. Transverse myelitis, inflammation of an entire cross-section of the spinal cord, can affect more than one spinal segment. A number of infectious agents are known to cause or to be associated with myelitis. Myelitis can also occur after infection or vaccination, as in the acute disseminated encephalomyelitis (ADEM) syndrome.

There are five cardinal manifestations of spinal cord disease: pain, motor deficits, sensory deficits, abnormalities of reflexes and muscle tone, and bladder dysfunction. The distribution of neurologic deficits depends on the spinal segment(s) affected. Local pain occurs at the site of the lesion and can assume a radicular quality if the nerve roots are involved. Paresthesias have greater localizing value than radicular pain. Weakness is present in virtually all spinal cord disorders and in myelitis may progress over hours, days, or weeks. *Spinal shock* is characterized by absent plantar reflexes and areflexia and atonia below the level of the lesion. More slowly progressive lesions are associated with hyperreflexia and hypertonia. Bladder dysfunction is usually not an early sign of spinal cord disease, although if spinal shock develops, flaccid bladder paralysis ensues with urinary retention and overflow incontinence. Chronic myelopathies cause a spastic bladder and result in urgency, frequency, and incontinence.

Acute primary infectious transverse myelitis must be distinguished from post-infectious secondary myelopathies and other noninfectious causes of myelitis such as multiple sclerosis (MS) or systemic lupus erythematosus. MRI of the spinal cord must be performed early to exclude a compressive lesion.

Tropical spastic paraparesis/HTLV-1–associated myelopathy

Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus associated with adult T-cell leukemia/lymphoma and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Approximately 15 to 20 million people are infected worldwide, with endemic areas in the Caribbean, southern Japan, Africa, and Italy. Among first-time US blood donors, the prevalence in 2009 was 5 per 10,000, half that seen in 2000. In perhaps 4% of those infected, HTLV-1 causes a chronic meningomyelitis with focal destruction of gray

TABLE 79.1 **MYELITIS**

Syndrome/disease	Organism	Symptoms, signs, and neurologic findings	CNS	PNS	Cord	Other findings	Risk factors
Anterior polio myelitis syndrome	Poliovirus 1, 2, 3	*Onset:* Acute *Clinical patterns:* Spinal and bulbar paralysis *Common features:* Asymmetric flaccid paralysis (AFP)	√		√	"Minor illness" (3–4 d) influenza-like syndrome "Major illness" (5–7 d) aseptic meningitis, myeloencephalitis	Absence of protective immunity and travel in endemic areas
	Nonpolio Coxsackie A, B Echovirus Enterovirus West Nile virus (WNV)	*Onset:* Acute *Clinical patterns:* Similar to polio but milder disease *Asymptomatic infection:* Common except at extremes of age and in immunosuppressed	√		√	CNS phase aseptic meningitis, encephalitis, encephalomyelitis	Seasonal incidence in temperate climates (summer), year-round in tropical climates WNV: Vector borne (*mosquito*) and transmitted by breast milk, blood transfusions, and organ transplants
Ascending myelitis syndrome (leukomyelitis)	HIV-1	*Onset:* Acute/subacute *Clinical patterns*:	√	√	√		See below
	HTLV-1	*Onset:* Subacute/chronic *Clinical patterns*: tropical spastic paraparesis (TSP) or HAM			√	"Rosette cells" in CSF lymphocytes Coinfection with HIV in IVDUs	Injecting drug use Prior residence in endemic areas
	Herpesviruses: CMV, EBV HSV, VZV	*Onset:* Acute *Clinical patterns:* Ascending pattern w/initial plexitis Asymmetric commonly		√	√	Primarily seen in immunosuppressed	Related to epidemiology of primary infection
	Herpes B virus (Monkey B)	*Onset:* Subacute (5–30 d) *Clinical pattern:* Aseptic meningitis Ascending encephalomyelitis	√		√	Prodromal illness: Early (*vesicles*); Intermediate (*numbness, weakness, hiccups*)	Macaque monkey bite or exposure to tissues Laboratory workers exposed to contaminated cell cultures
Transverse myelitis syndrome	*Primary* myelitis VZV Dengue Spirochetes[a] Schistosomiasis Post-meningococcal	*Onset:* Acute (after prodrome) *Clinical patterns:* Sensory motor level Initial spinal shock Hyperreflexia below level of lesion			√		Related to epidemiology of primary infection
	Secondary myelitis: Bacteria, fungi, mycobacteria	*Onset:* Acute/subacute *Clinical patterns:* Radicular-spinal cord syndrome Cauda equina syndrome			√	Related to primary infection and organisms	Injecting drug use Hematogenous osteomyelitis Back surgery: Intraoperative contamination
Acute demyelinating encephalomyelitis (ADEM)	*Mycoplasma*, Lyme, Enteroviruses, EBV, CMV, VZV, dengue, measles, hepatitis A, Semple Rabies vaccine	*Onset:* Acute *Clinical patterns:* Pyramidal and extrapyramidal symptoms, hemiplegia, ataxia, cranial neuropathies, myelitis paresthesias, polyradiculopathy, altered mental status	√		√		Related to epidemiology of primary infection

[a] Spirochetes include: *Borrelia* species (*B. burgdorferi*—Lyme, *B. recurrentis*—relapsing fever), *Leptospira* spp, *Treponema pallidum*.
Abbreviations: CMV = cytomegalovirus; CNS = central nervous system; CSF = cerebrospinal fluid; EBV = Epstein–Barr virus; HAM = HTLV-1-associated myelopathy; HIV = human immunodeficiency virus; HSV = herpes simplex virus; HTLV = human T-cell lymphotropic virus; IDUs = injecting drug users; IVDU = intravenous drug use; PNS = parasympathetic nervous system; VZV = varicella-zoster virus; WNV = West Nile virus.

TABLE 79.2 **PERIPHERAL NEUROPATHY**

Syndrome/disease	Organism/antibiotic	Symptoms, signs, and neurologic findings	CNS	PNS	Cord	Other findings	Risk factors
Polyneuritis: Acute (AIDP) Guillain–Barr é Landry Miller-Fisher Chronic (CIDP)	1. Idiopathic 2. Infection-associated	*Onset*: Acute/subacute and chronic *Common features:* Progressive, symmetric weakness Distal→proximal limbs Truncal→cranial muscles Paresthesias, hypotonia, areflexia *Clinical patterns:* Ascending, descending, bulbar	√	√		Variable autonomic dysfunction (ileus, cardiac)	Preceding viral illness or vaccination, prior episode Infection-associated: Viral (EBV, HIV, dengue, hepatitis) Bacterial (*Campylobacter*) Chlamydia (*C. psittaci*) Mycoplasma (*M. pneumoniae*) Spirochetes (Lyme borreliosis)
Neuropathy due to bacterial toxins	*Corynebacterium diphtheriae*	*Onset:* Acute/subacute *Clinical patterns:* Bulbar symptoms Ascending peripheral neuropathy	√	√		Pharyngitis with pseudomembrane Myocarditis Endocarditis	Absence of protective immunity, epidemic respiratory diphtheria, contaminated wound
	Clostridium botulinum	*Onset:* Acute/subacute (dose-related) *Clinical patterns:* Bulbar symptoms Myasthenia-like weakness	√	√		Autonomic dysfunction (dry tongue, ileus, urinary retention) Decreased vital capacity	Food sources Contaminated wounds (IDUs) Sinusitis in cocaine snorters
	Clostridium tetani	*Onset:* Acute/subacute (dose-related) *Clinical patterns:* Localized, cephalic, generalized	√	√	√	Autonomic Dysfunction Hypertensive crises Decreased vital capacity	Absence or loss of protective immunity Puncture/contaminate wounds Infected neonatal cord stumps
Medication *Acute* Antibacterials	Aminoglycosides Polymyxins	*Onset:* Acute (concentration-related) *Clinical patterns:* Neuromuscular blockade	√	√		Decreased vital capacity Generalized paralysis	Excessive or unadjusted dosage for lean body mass
Subacute Anti-TB Antiretrovirals Antibacterials	Isoniazid ddI, ddC, d4T Chloramphenicol Metronidazole Nitrofurantoin	*Onset:* Subacute (dose and duration) *Clinical patterns:* Symmetric Distal paresthesias and weakness Progressive loss of distal DTRs		√			Isoniazid: Lack of pyridoxine Nucleoside antiretrovirals: Pre-existing neuropathy Excessive or unadjusted dosage Antibiotics: Cumulative dosage
Vasculitis	Polyarteritis nodosa (PAN) Wegener's	*Onset*: Subacute *Clinical patterns:* Mononeuritis multiplex *Common features*: Asymmetric weakness, paresthesias, loss of DTRs in affected areas		√		PAN: Asymptomatic micro-aneurysms Wegener's: sinusitis, pulmonary and renal lesions, +/– eosinophilia	PAN: Chronic active hepatitis B Wegener's: Unknown etiology
Leprosy	*Mycobacterium leprae*	*Onset:* Insidious/acute *Clinical patterns:* Mononeuritis multiplex Polyneuropathy *Common features:* Anesthetic lesions, enlarged nerves		√		Deformity Nerves most commonly affected: Median, ulnar, peroneal	General Genetic susceptibility Prior residence in endemic areas Neuropathy Tuberculoid Reversal reaction

Abbreviations: AIDP = acute inflammatory demyelinating polyneuropathy; CIDP = chronic inflammatory demyelinating polyneuropathy; CNS = central nervous system; DTRs = deep tendon reflexes; EBV = Epstein–Barr virus; HIV = human immunodeficiency virus; IDUs = injecting drug users; PNS = peripheral nervous system.

TABLE 79.3 **POLYMORPHIC NEUROLOGIC SYNDROMES ASSOCIATED WITH INFECTIONS**

Syndrome/disease	Organism	Symptoms, signs, and neurologic findings	CNS	PNS	Cord	Other findings	Risk factors
HIV-associated	HIV-1	*Onset:* Acute, subacute, and chronic *Clinical patterns*: Acute*:* GBS, Bell's palsy, mononeuritis multiplex Subacute/chronic: Vacuolar myelopathy: progressive spasticity; Ascending myelitis (leukomyelitis); Sensory peripheral neuropathy (CIDP)	√	√	√	*Acute* infection: aseptic meningitis, infectious mononucleosis syndrome *Late disease:* concurrent HIV encephalopathy	IVDU, sexual transmission, exposure to contaminated blood or body fluids
Dengue-associated	Dengue virus	*Onset:* acute or postinfectious *Clinical patterns:* Myelitis (transverse), Guillain–Barré syndrome, mono- or polyneuropathy, brachial neuritis, ADEM, encephalitis	√	√	√	Fever, headache, myalgia, arthralgia, rash, headache, leukopenia, thrombocytopenia, elevated liver transaminases	Mosquito exposure in endemic region
Mycoplasma-associated	*Mycoplasma pneumoniae*	*Onset:* acute *Clinical patterns:* Ascending myelitis (leukomyelitis), polyradiculitis	√	√	√	Commonly associated with encephalitis	Recent upper respiratory infection in child or young adult
Neurobrucellosis	*Brucella* spp.	*Onset:* Subacute/chronic *Clinical patterns:* Radiculitis, myelitis, CNS palsies	√	√	√	Encephalitis, meningitis, mycotic aneurysm; Leukoclastic vasculitis, thrombocytopenia and splenomegaly in children	Unpasteurized milk products, occupational exposure to livestock and cattle parturition
Neuroborreliosis	*Borrelia burgdorferi*	*Onset:* Acute and chronic *Clinical patterns:* Acute: Bell's palsy, aseptic meningitis, encephalitis, transverse myelitis Chronic: weakness, paresthesias	√	√	√	*Acute*: Erythema chronicum migrans	Tick-bite Travel or residence in endemic areas
Neurosyphilis	*Treponema pallidum*	*Onset:* Acute and chronic *Clinical patterns:* Acute syphilitic meningitis Chronic asymptomatic Chronic symptomatic (meningovascular, behavioral, tabes dorsalis, myelopathy)	√	√	√	Dementia Gumma (cord/meninges) Uveitis, optic atrophy Deafness	Asymptomatic (abnormal CSF) and symptomatic neurosyphilis occurs after early syphilis. Higher risk with HIV infection with or without standard treatment of primary syphilis
Tuberculosis	*Mycobacterium tuberculosis*	*Clinical patterns:* Meningitis, vasculitis, cord infarction, granulomatous myeloradiculitis, intramedullary tuberculoma, cord compression from vertebral collapse	√		√	Pulmonary disease, meningitis, fever	Travel to or residence in high prevalence region, homelessness, incarceration, institutionalization, contacts with known tuberculosis

TABLE 79.3 **CONTINUED**

Syndrome/disease	Organism	Symptoms, signs, and neurologic findings	CNS	PNS	Cord	Other findings	Risk factors
Schistosomiasis	*Schistosoma* spp.	*Clinical patterns:* Transverse myelitis, subacute myeloradiculopathy, encephalitis	√		√	Fever, abdominal pain, hepatosplenomegaly	Travel to or residence in endemic region
VZV-associated	VZV	*Onset:* Acute *Clinical patterns:* Bell's palsy, Ramsey Hunt syndrome Sensory radiculitis (CNS and PNS) Ascending and transverse myelitis	√	√	√	Dermatomal vesicles Encephalitis Uveitis, corneal ulcer	Immunosuppression (with recrudescent VZV)
Herpes simplex-associated	HSV	*Onset:* Acute and recurrent *Clinical patterns:* HSV-1: Bell's palsy; HSV-2: sacral radiculitis (Elsberg syndrome)	√	√	√	Ascending necrotizing myelitis Mollaret's meningitis	AIDS Primary genital HSV

Abbreviations: ADEM = acute demyelinating encephalomyelitis; CNS = central nervous system; CSF = cerebrospinal fluid; HSV = herpes simplex virus; HIV = human immunodeficiency virus; PNS = peripheral nervous system; VZV = varicella-zoster virus; IVDU = intravenous drug use; GBS = Guillain–Barré syndrome; CIDP = chronic inflammatory demyelinating polyneuropathy.

BOX 79.1

Etiology of neuropathic syndromes in HIV infection

Autoimmune/idiopathic
- Acute inflammatory demyelinating polyneuropathy (*AIDP—Guillain–Barré syndrome*)
- Chronic inflammatory demyelinating polyneuropathy (*CIDP*)

Vasculitis
- Bell's palsy
- Ataxic dorsal radiculopathy
- Mononeuritis multiplex from hepatitis B virus (HBV)-associated cryoglobulinemia

Opportunistic infections
- Cryptococcal meningitis: bulbar palsies
- Herpesviruses polyradiculopathy, sacral radiculitis, Bell's palsy
- Epstein–Barr virus
- Cytomegalovirus (CMV)
- *Varicella-zoster virus* (VZV)
- Herpes simplex type 1 (HSV-1) type 2 (HSV-2)
- Neurosyphilis: Polyradiculopathy
- Tuberculous meningitis: Bulbar palsies

Drug toxicity or nutritional
- Antiretroviral nucleoside analogs
- Dideoxycytosine (ddC)
- Dideoxyinosine (ddI)
- Stavudine (d4T)
- Niacin analog: Isoniazid (INH) without B6
- Neurotoxic antibiotics: Aminoglycosides, chloramphenicol, metronidazole, nitrofurantoin, polymyxins
- Vitamin deficiencies: folate, pyridoxine, B_{12}

matter as well as demyelination of white matter primarily within the posterior columns and corticospinal tracts. Neurologic disease usually begins in the fifth decade; women are more commonly affected than men (~2.5–3:1). Patients typically note bilateral lower extremity weakness and stiffness but may also have difficulty walking and back pain. Neurogenic bladder may develop, and neuropathy may be found. Physical examination shows spastic paraparesis, hyperreflexia, extensor plantar reflexes, and reduced vibratory sensation and proprioception. Typically, the disease is slowly progressive and may ultimately leave patients wheelchair dependent; the upper extremities are usually not affected. HAM/TSP may be preceded, more commonly in children, by infective dermatitis, a dermatologic condition associated with HTLV-1 and characterized by recurrent erythematous, scaly, and crusted rash of the scalp, face, neck, axilla, and groin. In one series, 47% of children and adolescents with infective dermatitis went on to develop HAM/TSP.

In patients with HAM/TSP, the cerebrospinal fluid (CSF) may demonstrate a lymphocytic pleocytosis, elevated CSF immunoglobulin G (IgG), and oligoclonal banding, and demonstrable anti-HTLV-1 antibodies. Diagnosis is established clinically in the presence of HTLV-1 seropositivity and characteristic CSF findings. Distinguishing between incidental HTLV-1 infection and patients with true HAM/TSP may be difficult. Recent studies suggest that anti-Gag, anti-Env, and anti-Tax antibodies may help distinguish patients with true HAM/TSP from persons with asymptomatic HTLV-1 infection. No effective antiretroviral or adjunctive therapies have been established to date.

Herpesviruses

All herpesviruses have been implicated in acute transverse myelitis, especially in the setting of immunosuppression. Herpes simplex virus (HSV) types I and II, varicella-zoster virus (VZV), cytomegalovirus

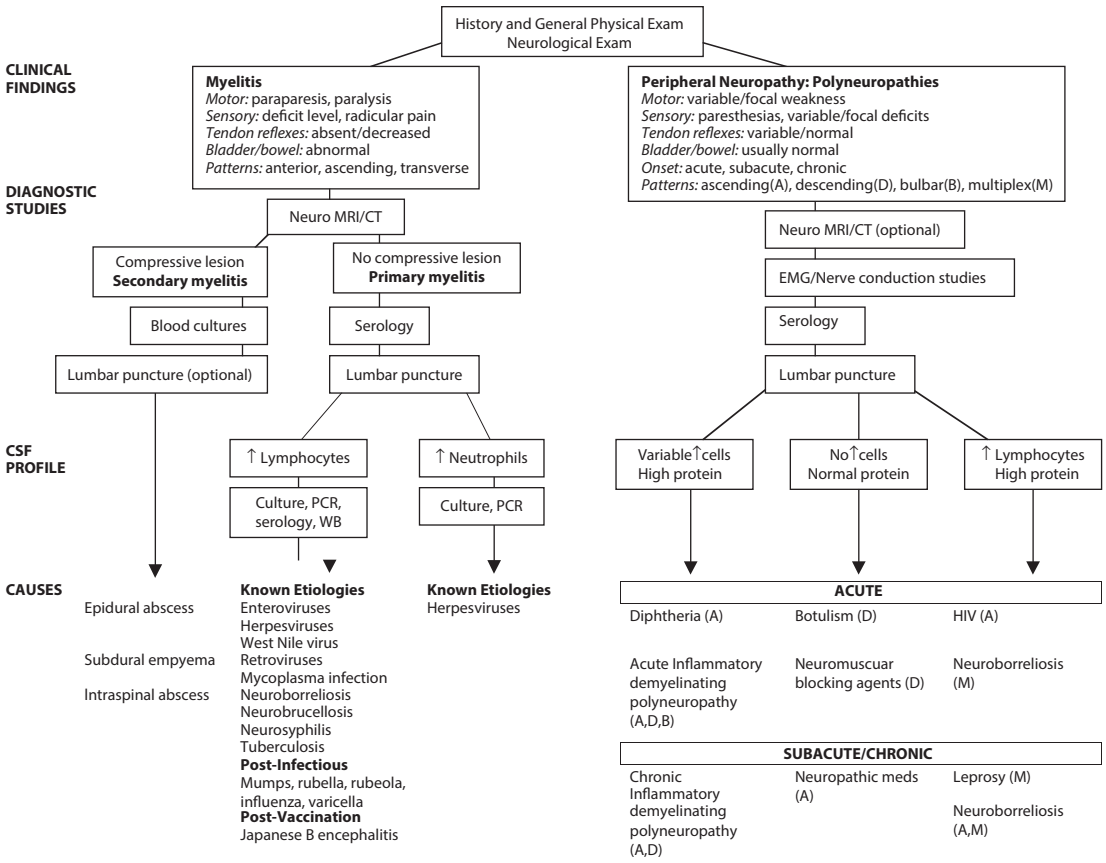

FIGURE 79.1 Algorithm for clinical and laboratory evaluation of acute myelitis and peripheral neuropathy. CSF, cerebrospinal fluid; CT, computed tomography; EMG, electromyogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; WB, Western blot.

(CMV), and Epstein–Barr virus (EBV) have all been associated with a nonspecific myelitis, although ascending necrosis of the cord appears to be most typical. Associated clinical findings of concurrent CMV retinitis, peripheral outer retinal necrosis due to VZV, or vesicular skin lesions characteristic of herpes simplex or VZV are helpful in suggesting the diagnosis.

Patients may have fever and characteristically have rapidly progressive neurologic deficits. CSF with lymphocytic pleocytosis, elevated protein, and normal glucose is typical. Early empiric therapy with intravenous (IV) acyclovir, ganciclovir, or foscarnet may preserve cord function pending definitive diagnosis in immunocompromised patients presenting with acute transverse myelitis of unknown origin. Valacyclovir and valganciclovir are attractive agents in suppressing herpes simplex and CMV myelitis, respectively, in immunosuppressed individuals. Oral ganciclovir is ineffective because of limited bioavailability.

Macacine herpesvirus 1, formerly known as *Cercopithecine herpesvirus* and commonly known as herpes B virus or *Herpesvirus simiae*, is a naturally occurring virus among primates of the genus *Macaca*. It can cause fatal encephalitis in humans with associated ascending myelitis following a bite, cage scratch, or other exposure. Patients may develop vesicular lesions at the site of the bite before developing neurologic manifestations. Human B-virus infections are diagnosed by viral culture and serology, which must be performed in certified laboratories. The US Centers for Disease Control and Prevention (CDC) should be consulted in cases of suspected human B-virus infection. In addition to thorough washing, prophylactic oral acyclovir or valacyclovir should be considered after an at-risk exposure. IV acyclovir or ganciclovir should be considered with evidence of any disease (e.g., vesicles), and IV ganciclovir used in cases with central nervous system (CNS) symptoms.

Enteroviruses

The enteroviruses are well-known causes of infectious myelitis, of which poliovirus has been the most historically significant. Poliovirus infection may present with fever, meningismus, and muscle spasms followed by acute flaccid paralysis from infection of anterior horn cells. Largely due to effective vaccination programs, poliovirus is now unusual, but sporadic cases of myelitis due to other enteroviruses—such as Coxsackie A and B, echovirus, and enteroviruses 70 and 71—still occur. Myelitis due to nonpolio enteroviruses, are generally less severe, and causes weakness rather than paralysis. Enterovirus 71—the causative agent of hand-foot-and-mouth disease—is an important exception and may mimic poliovirus in severity. In some cases of viral myelitis, it may be difficult to distinguish between postinfectious, immune-mediated cord injury and direct viral invasion. Detection of virus in CSF is supportive of direct viral invasion. Enteroviruses can be recovered from CSF as well as from blood, pharynx, and stool. The most

reliable diagnostic test is the CSF enteroviral polymerase chain reaction (PCR).

West Nile virus

Since the appearance of West Nile virus (WNV) in the United States in 1999, >30,000 WNV disease cases have been reported to the CDC. Although most WNV infection is asymptomatic or self-limited, neuroinvasive disease (NID) also occurs. Acute flaccid paralysis occurred in 4% of cases reported to the CDC in 2011; it is one of the most serious presentations of NID and mimics poliomyelitis with injury to spinal cord anterior horn cells. Acute flaccid paralysis commonly accompanies WNV encephalitis, appears abruptly, and often results in asymmetric lower extremity weakness.

Areflexia, loss of bladder and bowel function, and signs of denervation may develop. CSF typically demonstrates pleocytosis; diagnosis is aided by serologic and CSF testing for WNV IgM, or serum or CSF PCR. Although no agents are currently licensed to treat WNV disease, emerging case reports and animal studies suggest a potential benefit of IV immunoglobulins (IVIGs) with high WNV antibody titers; this practice warrants further investigation.

Dengue

Neurologic complications of dengue are increasingly recognized, with recent estimates that neurologic disease may complicate 1% to 5% of infections. An array of neurologic manifestations has been encountered, including meningitis, encephalitis, Guillain–Barré syndrome (GBS), mono- and poly-neuropathies, ADEM, and myelitis. Pathogenesis is likely multifactorial and varies for each clinical syndrome encountered. It seems likely that direct neurologic invasion and autoimmune reactions each play a role in myelitis. CSF may demonstrate pleocytosis and elevated protein. Diagnosis is supported by serologic studies and further aided by CSF antibody testing or PCR, though CSF antibody testing is not very sensitive. Care is supportive. Many patients with neurologic complications of dengue infection recover, though perhaps a quarter of patients may have residual deficits.

HIV

Vacuolar myelopathy is a diagnosis of exclusion. Although of distinctive neuropathology, it often coexists with the AIDS-associated dementia complex, also known as *HIV encephalopathy* or *encephalitis*. Vacuolar myelopathy was found in up to 50% of AIDS patients undergoing autopsy before the highly active antiretroviral therapy (HAART) era. In severe cases patients develop spastic paraparesis of the lower extremities with or without involvement of the arms, mimicking HTLV-1 myelopathy. The weakness, which may be asymmetric, evolves over weeks. Coexisting neuropathy is often present. A discrete sensory level is unusual. Sphincter dysfunction occurs late in the course of the disease.

Other viral causes of myelitis

Other viruses associated with myelitis include Japanese encephalitis virus, tick-borne encephalitis virus, and chikungunya virus. Acute flaccid paralysis may occur in rabies infections before proceeding to fatal encephalitis.

Syphilis

Although there are many manifestations of neurosyphilis, four major types of spinal cord disease are associated with *Treponema pallidum* infection: tabes dorsalis, syphilitic meningomyelitis, spinal vascular syphilis with infarction of the (most commonly anterior) spinal arteries, and gummas of the meninges and cord. Because of its varied presentations, syphilis should be considered in the differential diagnosis of nearly all diseases of the spinal cord. The serum rapid plasma reagin (RPR) titer is usually higher than 1:32 in neurosyphilis, and the CSF usually shows a lymphocytic pleocytosis, elevated protein, and normal glucose; HIV infection with or without HAART may impact these parameters. The CSF Venereal Disease Research Laboratory (VDRL) test is specific but generally insensitive. CSF fluorescent treponemal antibody test and *T. pallidum* PCR may also aid diagnosis. Steroids may be added to IV penicillin to prevent cord edema, ischemia, or Jarisch–Herxheimer reaction associated with treatment.

Mycoplasma pneumoniae

CNS complications of *M. pneumoniae* infection are probably the most frequent extrapulmonary manifestation of infection. Although encephalitis is the most common neurologic complication, meningitis, polyradiculitis, ADEM, and transverse myelitis also occur. The exact pathogenesis of CNS disease is unknown, but it may be secondary to direct invasion, elaboration of neurotoxins, autoimmune complexes, molecular mimicry, or vasculitis. A recent respiratory tract infection, especially in a child or young adult, should suggest the diagnosis. Diagnosis can be confirmed with positive CSF *M. pneumoniae* PCR or by retrospectively observing a fourfold rise in antibody titers. If active infection is present, antibiotic therapy may be effective. Tetracycline penetrates the CNS more effectively than macrolides but is contraindicated in young children. Steroids, plasmapheresis, and IVIG have also been advocated but remain controversial.

Brucellosis

Approximately 2% to 5% of patients with brucellosis have neurologic complications, though a recent study of hospitalized patients in an endemic country with brucellosis confirmed neurobrucellosis in 37.5% of patients with neurologic symptoms. Although meningitis with cranial nerve palsies and vasculitis are the most common neurologic manifestations, direct involvement of the brain or cord can result in encephalitis or myelitis, respectively. Myelopathy typically involves the corticospinal tracts and produces a pure upper motor neuron syndrome without sensory findings. Secondary myelitis can occur from granulomatous spondylitis and epidural abscess.

Radiculopathy due to chronic inflammation of intrathecal nerve roots complicates neurobrucellosis in an eighth of patients. CSF usually reveals a lymphocytic pleocytosis, elevated protein, and hypoglycorrhachia. CSF cultures are positive in <50% of

cases. Cultures of blood and tissue fluids may become positive in 2 to 4 days with modern automated liquid culture systems, particularly when specimens are first processed to release intracellular organisms. PCR methods are reportedly more sensitive than culture. Serum tube agglutination (TA) testing can support a diagnosis of brucellosis. CSF TA testing can help confirm a diagnosis of neurobrucellosis; however, there is no commonly agreed upon titer cut-point for CSF TA titers. Treatment of neurobrucellosis requires multidrug therapy, though there is no consensus for an optimal regimen or duration. Surgical exploration and decompression may be warranted for symptomatic epidural abscess. Adjunctive steroids early in meningitis may reduce complications from vasculitis.

Tuberculosis

While meningitis is the most common neurologic manifestation of tuberculosis, myelopathy may be seen as well. Myelopathy may occur secondary to spinal cord or nerve root compression from Pott's disease, to compression from epidural or intramedullary tuberculomas, to vasculitis with cord infarction, or to granulomatous myeloradiculitis from hematogenous seeding of the CNS. Necrotizing tuberculous granulomas may directly affect spinal arteries. Vasculitis can lead to cord infarction. Most patients with tuberculous myelitis have concurrent meningitis, but coincidental pulmonary tuberculosis is less common. Tuberculosis diagnosis and treatment are addressed in detail elsewhere.

Schistosomiasis

Neuroschistosomiasis should be considered in the differential diagnosis of acute myelopathy in regions where *Schistosoma* species are prevalent. A Brazilian study found that 6% of patients with nontraumatic acute myelopathy had spinal schistosomiasis. Half of patients admitted to a Malawian spinal cord rehabilitation center had spinal schistosomiasis.

Myelitis is most common with *S. mansoni* and *S. haematobium* infection. Schistosoma ova spread hematogenously and invade the CNS where the host inflammatory response, including granuloma formation, can lead to acute myelopathy. The lower thoracic and lumbar cords are most commonly affected. Patients may present with lower extremity weakness, cauda equina syndrome, or lumbar or radicular pain. Spinal artery infarction may be found. Diagnosis is challenging; schistosomal ova are found in stool or urine in fewer than half of cases of neuroschistosomiasis. CSF findings may be nonspecific but may show eosinophils and elevated protein levels. Visualization of schistosomal forms in biopsy specimens provides definitive diagnosis. Treatment is with steroids to reduce inflammatory response, followed by praziquantel, though optimal treatment doses and duration are not established.

Toxocara spp.

Toxocara canis and *T. cati* are round worms and the cause of visceral larva migrans; they have occasionally been reported as a cause of myelitis. Patients present with typical symptoms of myelitis; lower extremity weakness is most common. MRI findings often reveal a single inflammatory lesion. Symptoms generally improve after albendazole therapy.

Other parasitic diseases found to cause spinal cord disease include gnathostomiasis, *Taenia solium*, *Toxoplasma gondii*, and *Echinococcus granulosus*.

Fungal diseases

Fungal infections rarely cause spinal cord disease and present most commonly among immunosuppressed persons. Secondary myelopathy from epidural abscess, granuloma, or vertebral compression fracture is most commonly from *Aspergillus*, *Cryptococcus*, or *Candida* species. *Blastomyces* and *Coccidioides* also causes spinal and paraspinal disease. Fungal myelopathy may result from direct iatrogenic inoculation; cauda equina syndrome was noted in 17% of patients in an outbreak of *Exserohilum rostratum* from contaminated glucocorticoid injections. Iatrogenic paraspinal aspergillus infection has also been described.

Acute flaccid myelitis in pediatrics

Acute flaccid myelitis (AFM) refers to the development of decreased tone and weakness secondary to inflammation in the spinal cord. This is also referred to as a polio-like illness and has a broad differential. Many times the etiology remains unknown. AFM can be seen in adults and children, although more commonly in children and young adults. The characteristic features include preceding febrile or respiratory illness, limb weakness and/or cranial nerve involvement, MRI showing gray matter involvement spanning more than one vertebral segment, and CSF analysis with pleocytosis. Limb weakness in AFM is caused by involvement of the anterior horn cells (gray matter in spinal cord), located at the ventral aspect of the spinal cord, controlling strength and hypertonicity. Damage in this area leads to the flaccid, decreased tone and loss of strength distinctive of this entity.

Diagnosis

AFM should be considered in any individual presenting with focal weakness, decreased tone, and preceding illness. Accompanying features include headache, neck pain, or cranial nerve neuropathies. Evaluation should be expedited to prevent eventual paralysis. Initial evaluation includes MRI of brain and spinal cord, lumbar puncture, and serum evaluation of infectious and other inflammatory causes. Spinal MRI should include cervical, thoracic, and lumbar spine with contrast. Imaging typically shows a non-enhancing hyperintensity of the spinal cord on T2/short tau inversion recovery (STIR) sequences spanning one or more spinal segments in the central and/or ventral gray matter. Lumbar puncture shows pleocytosis (usually lymphocytic), elevated protein, normal glucose, and, if possible, should include evaluation of viral or bacterial entities in CSF. To improve diagnostic yields, multiple sites of potential infection can be obtained.

AFM is a CNS disorder but a common mimicker is GBS, a peripheral nervous system disorder that also presents with flaccid weakness. The latter has a gradual onset, usually starts distally and rises to include proximal muscles with loss of reflexes, with electromyography (EMG) showing prolonged distal latencies as opposed to normal sensory nerve conduction studies with AFM. Another CNS disorder that can mimic AFM is ADEM; it is differentiated by the presence of altered mentation, spastic tone, and involvement of white matter on MRI.

Etiology

Since 2012, several cases of AFM have been cited in the United States, particularly between the months of August and October. Etiology of primary myelitis remains broad, most commonly secondary to a virus, but can also include bacteria and tick-borne diseases. Known viral entities include WNV, Coxsackievirus, adenovirus, poliovirus, and enterovirus. Other entities of concern are included in Box 79.2.

Management

Management of AFM first involves airway protection and monitoring of respiratory status in an intensive care unit. Respiratory precautions are of particular concern in AFM involving the cervical cord as some respiratory control centers are located here. In 2014, the CDC convened a panel of experts to review data and create treatment guidelines for AFM. At the time, there was insufficient evidence to advocate for one standard mode of treatment. Immunotherapy is used empirically, specifically steroids, IVIG, and plasma exchange. Caution should be used with steroids if cord swelling is not seen on imaging as this can worsen symptoms, especially if the AFM is caused by an enterovirus. Assuming that AFM is caused by a viral infection, plasma exchange could worsen the underlying disease process as it filters out antibodies. Anecdotally, IVIG has been used with success in reported clinical cases as well as in mice studies. If infectious entities are identified, treatment for these specific organisms should be initiated and seem to provide the most benefit. Early initiation of physical and occupational therapy is critical to regaining muscle function. Patients can make advances in strength months to years following initial presentation. In addition, use of medications such as fluoxetine has also been anecdotally reported to hasten recovery.

BOX 79.2

Known etiologies of acute flaccid myelitis

Viruses
Enteroviruses
Adenoviruses
Herpesviruses (HSV, VZV, EBV)
West Nile Virus
Retroviruses (HIV, HTLV I/II)
Measles
Rubella
Influenza

Bacteria
Mycoplasma
Mycobacterium tuberculosis
Neurobrucellosis

Spirochetes
Neuroborreliosis
Neurosyphilis

Acute disseminated encephalomyelitis

While the focus of this chapter thus far has been myelitis, discussion of infectious causes of spinal cord disease should include ADEM. ADEM may be considered as one among a spectrum of similar diseases including transverse myelitis, MS, and neuromyelitis optica. At least three-quarters of cases are associated with antecedent infection or vaccination. While the pathogenesis is not definitively established, it appears that infectious antigens may stimulate myelin-reactive T-cell populations by molecular mimicry. A number of infectious agents have been implicated as precipitants of ADEM, including viruses—influenza, enteroviruses, EBV, CMV, varicella, measles, mumps, rubella, hepatitis A—and bacteria including *M. pneumoniae*, *Borrelia burgdorferi*, leptospira, and β-hemolytic streptococci. Semple rabies vaccine is the most definitively associated vaccine-related trigger; other vaccines believed to be associated with ADEM include live measles vaccine (though measles virus-induced encephalitis occurs about 10 times more frequently than vaccine-related ADEM); Japanese encephalitis; tetanus, diphtheria, pertussis, and hepatitis B vaccines; and vaccinia.

Children are affected more commonly than adults. Presentations are acute, evolving over hours, usually peaking around 4 to 5 days, and exhibit a variety of neurologic findings, including pyramidal and extrapyramidal symptoms, hemiplegia, ataxia, cranial neuropathies, optic neuritis, paresthesias, and altered mental status. Spinal cord involvement occurs in about a quarter of patients. Peripheral nerve involvement, such as acute polyradiculopathy, is more common among adults, where it is reported in as many as 40% of cases. Fever and systemic symptoms are typically absent as cases tend to be postinfectious rather than concurrent with infection.

Diagnosis is challenging, in part because of differences in definitions found in the literature. The International Pediatric MS Study Group suggests the following criteria to diagnose (pediatric) ADEM: "a first polyclonal, clinical CNS event with presumed inflammatory demyelinating cause," "encephalopathy that cannot be explained by fever," "no new clinical and MRI findings emerge three months or more after the onset," and "brain MRI is abnormal during the acute (three-month) phase." Spinal cord disease has variable enhancement on MRI but large lesions, most often in the thoracic region, are common. Diagnosis is clinical based on history, symptoms, neuroimaging, and exclusion of other diagnoses; no biomarkers of disease have been found. CSF findings are nonspecific, but a mild lymphocytic pleocytosis and elevated protein may be seen. Though

no prospective, randomized trials have been done, most patients are treated with steroids; IVIG and plasmapheresis are generally reserved for refractory or fulminant cases. These treatments should only be considered after effectively excluding acute infections.

Noninfectious myelitis

Several noninfectious causes for myelitis can look similar to infectious transverse myelitis on initial presentation. Most commonly, demyelinating disorders such as MS or neuromyelitis optica spectrum disorder (NMOSD) should be considered. Demyelination describes the damage caused to myelin sheaths, the protective coverings surrounding nerve fibers.

Multiple sclerosis

MS is one of the most common autoimmune, demyelinating entities, affecting nearly 2.3 million people worldwide and typically seen in individuals between the ages of 20 and 40 years. The disease is multifocal and causes temporally distributed CNS damage that eventually leads to axonal damage. Diagnosis is based on McDonald's Criteria, most recently updated in 2017 to coordinate the clinical manifestations with characteristic MRI and CSF markers. Oligoclonal bands are the spinal fluid biomarker that can also be used as confirmation for early diagnosis in the proper clinical setting. Characteristic lesions are found in the periventricular, juxtacortical, and infratentorial locations in the brain, as well as in the cervical and/or thoracic spinal cord.

Many times, an initial presentation for MS is with a transverse myelitis. These lesions tend to be eccentric, extend one to two spinal levels, and enhance in the acute setting. Chronic MS lesions in the spinal cord will remain hyperintense on T2/STIR sequences and in severe cases can be associated with spinal cord atrophy. Differentiating demyelination between infectious myelitis will include several key aspects of history, obtaining brain imaging, and obtaining oligoclonal bands in CSF if necessary. A history of gradual-onset neurological symptoms (weakness, numbness, vision changes, etc.) lasting >24 hours and resolving spontaneously with characteristic lesions can help differentiate MS from other entities.

Treatment involves glucocorticoids in the acute setting, which can be effective in resolving a relapse of the above-mentioned symptoms. Long-term therapy involves disease-modifying agents to prevent further relapses and subclinical progression and aim to limit cognitive dysfunction at later stages. A diverse group of injectable, oral, and infusion immunosuppressive agents and immunomodulators are available, with many newer agents showing greater reduction in relapse rate.

Neuromyelitis optica

NMOSD is mediated by the aquaporin-4 (AQP4) antibody, leading to secondary demyelination. The antibody is in the CNS and is specifically found along perivascular distribution on astrocytic foot processes around blood vessels and glia. NMOSD, originally called *Devic's disease*, was initially characterized as a longitudinally enhancing lesion in the spinal cord with optic nerve dysfunction. The terminology for longitudinal enhancing transverse myelitis refers to lesions traversing more than three vertebral segments. The clinical characteristics defining NMOSD have now expanded to include area postrema syndrome leading to intractable hiccups or nausea/vomiting, symptomatic narcolepsy, or an acute brainstem syndrome. These clinical syndromes, with an MRI that includes characteristic brainstem lesions in the setting of AQP4 seropositivity, can make the diagnosis even when a longitudinal lesion and optic nerve involvement is not seen. This syndrome can be steroid-responsive, but many times requires the use of plasmapheresis in the acute setting. Presence of AQP4 antibody tends to be related to a relapsing course so long-term therapy with immunomodulation should be considered.

Myelin oligodendrocyte glycoprotein antibody disease

Myelin oligodendrocyte glycoprotein (MOG) antibody disease is a demyelinating syndrome associated with the MOG antibody, expressed on the outer membrane of myelin in the CNS. Clinical symptoms are similar to NMOSD with primary characteristics showing optic nerve and spinal cord involvement. Presentations include paraparesis, sensory loss, and bladder sphincter dysfunction. There is a higher predilection for conus involvement than seen in NMOSD. Longitudinally enhancing lesions are predominantly seen rather than shorter segments of spinal cord inflammation. MOG appears to have a higher frequency of focal myelitis and better clinical outcomes. No clinical criteria exist as of yet but patients who are found to be AQP4-negative in prior cohorts have been ultimately found to be MOG antibody-positive. This group also was found to be younger and have a typically monophasic course. There is a significant response to steroid therapy and a similarly rapid relapse on withdrawal of steroids. A majority of patients have a relapsing course and therefore, after steroid, IVIG, or plasmapheresis treatment in the acute setting, immunosuppression should be considered.

Neuropathy

Because there are many patterns of neuropathy of both infectious and noninfectious etiologies, the approach to the patient with peripheral neuropathy begins with identification of the pattern of illness. The history should focus on the duration of symptoms and their relation to antecedent or comorbid illnesses. An acute onset is highly suggestive of an inflammatory, immunologic, vascular, or toxic cause. Because infectious diseases are known to mediate disease via all of these mechanisms, most neuropathies due to infectious diseases will present acutely or subacutely. Chronic neuropathies of infectious origin, although less common, do occur, particularly Hansen's disease (leprosy) and Lyme borreliosis. In

general, an acute onset suggests a more favorable prognosis and should prompt a timely search for the underlying cause to prevent permanent neurologic sequelae. Etiologic clues may be suggested by recent or current systemic illness, such as pharyngitis in diphtheritic neuropathy, *Campylobacter* gastroenteritis in GBS, or epidemiologic exposures such as tick bites or sexual activity. Travel and residence history is also of diagnostic importance in suggesting an entity such as Lyme borreliosis.

The four major anatomic patterns of neuropathy are *mononeuropathy*, *mononeuropathy multiplex*, *polyneuropathy*, and *plexopathy*. Neuropathies are further classified according to the type of functional nerve involvement: *purely motor*, *sensory*, *autonomic*, or *mixed*. In classifying the neuropathy, the physical exam should address the following questions: Does the involvement include more than one functional nerve type? Is involvement symmetric or asymmetric, distal or generalized, ascending or descending? Is there a sensory level? Do motor and sensory deficits overlap, and do they match subjective complaints? Are deep tendon reflexes and other reflexes (e.g., Babinski, genitoanal) normal? Is sphincter function normal? Is there evidence of denervation (e.g., fasciculation, atrophy)? Are there associated skin lesions? Establishing the pattern of illness and rate of onset lets the neuropathic syndrome be identified and points to specific causes. Discussed next are some of the major infectious causes of peripheral neuropathy.

Hansen's disease (leprosy)

Hansen's disease (leprosy) is a chronic mycobacterial infection in which *Mycobacterium leprae* primarily affects the peripheral nervous system and secondarily involves skin and other tissues. *M. leprae* is shed from skin and mucous membranes, and while the mode of transmission is not definitively established, it appears to be transmitted from person to person by respiratory droplets.

Worldwide, Hansen's disease is one of the most common causes of peripheral neuropathy. Although a rare disease in the United States, new cases are still diagnosed, most frequently in immigrants. Of the approximately 228,000 cases reported globally to the World Health Organization (WHO) in 2010, 95% were reported by 17 countries; more than half were from India.

Clinical Hansen's disease ranges a broad spectrum resulting from complex interactions between the organism and the patient's immune system. The cardinal manifestations of Hansen's disease are anesthetic skin lesions, palpably enlarged peripheral nerves, and, in lepromatous patients only, visible acid-fast bacilli on skin biopsy or slit skin smear that do not grow in conventional mycobacterial cultures.

Although skin lesions vary in appearance, anesthesia of the involved skin is the characteristic feature in typical Hansen's disease. Lepromatous disease can result in symmetric anesthesia of the colder areas of the body (e.g., pinnae, dorsa of hands and feet), whereas nerve involvement in indeterminate and tuberculoid disease is typically asymmetric.

The peripheral nerves most commonly involved are the facial, ulnar, median, common peroneal, and posterior tibial nerves. Superficial nerves, such as the ulnar and posterior auricular nerves, are accessible to palpation and are often enlarged and tender. Neuropathic injury to the hands and feet is a significant cause of disability; a complete motor and sensory exam should be performed before beginning therapy. Proprioceptive deficits are uncommon but have been described. Where the disease is rare, such as in the United States, skin biopsy of the most active margin should be performed. Specific details about therapy and prevention of neuropathy can be found in Chapter 140, "Leprosy."

HIV-associated neuropathies

Neuropathy is the most common neurologic disorder associated with HIV. Many causes of neuropathy have been described in HIV-infected persons (Box 79.1). Predominantly sensory neuropathy is the most common neuropathy seen in AIDS and is one of the most debilitating aspects of advanced HIV infection. Its exact cause is unclear, although pathology studies suggest an immune complex vasculitic etiology. Patients often note painful paresthesias of the distal extremities, primarily of the soles of the feet. On exam, patients with progressive HIV neuropathy will exhibit a generalized decrease in sensation in the affected areas and atrophy of the intrinsic muscles of the feet. Deep tendon reflexes of the ankles are eventually lost, but patellar reflexes may be exaggerated by coexisting myelopathy. When reflexes are affected, nerve conduction studies are consistent with distal axonal degeneration. Reversible causes of neuropathy should be excluded. Treatment of HIV predominantly sensory neuropathy is generally unsatisfactory.

Herpesvirus-associated peripheral neuropathies: CMV, HSV, VZV, EBV, and B-virus

CMV infection of the peripheral nerves, essentially unknown prior to AIDS, is often associated with active CMV infection in other systems, particularly retinitis. The capacity of CMV to invade both endothelial and Schwann cells accounts for its varied clinical manifestations. Polyradiculopathy, the most dramatic of these syndromes, is caused by CMV more often than by other herpesviruses. It is characterized by subacute ascending motor weakness, areflexia, incontinence or urinary retention, paresthesias, and variable sensory dysfunction. Patients often report pain in the back and legs. Inflammation of lumbar nerve roots, dorsal root ganglia, and spinal cord result in characteristic CSF findings mimicking bacterial meningitis: pleocytosis with white blood cell counts from 5 to more than 3,000 with a polymorphonuclear predominance, hypoglycorrhachia, and elevated protein. Enhancement of the cauda equina on MRI has been reported. PCR of CMV viral DNA in the CSF is the diagnostic method of choice.

Herpes simplex type 2 can cause sacral radiculitis (Elsberg syndrome) manifested by urinary retention, constipation, erectile dysfunction, sensory loss in a sacral dermatome, and buttock pain. Lumbar spine MRI may show sacral root edema and enhancement, and the CSF HSV-2 PCR is positive. In AIDS patients, the infection can progress to ascending necrotizing myelitis.

Herpes simplex type 1 causes the majority of Bell's palsy episodes. Steroids combined with antivirals such as acyclovir or valacyclovir improve outcomes. Antivirals should not be given without steroids, as meta-analysis revealed worse outcomes with antivirals alone.

VZV can also cause polyradiculopathy in AIDS patients. VZV classically involves the dorsal root ganglia, but spread of inflammation into the cord can reach anterior horn cells, resulting in pain and paralysis. VZV has also been associated with transverse myelitis and myositis. Zoster-associated disease may occur without a vesicular rash (*Zoster sine herpete*). The diagnosis is established with a positive CSF VZV DNA PCR.

Treponema pallidum-associated neuropathy

CNS syphilis may also present as subacute polyradiculopathy in HIV infection. The CSF contains lymphocytes, and the CSF VDRL test is typically positive.

Mononeuropathy multiplex

Mononeuropathy multiplex is a syndrome of simultaneous or sequential neuropathy of noncontiguous nerve trunks evolving over days to years. Characterized by patchy, asymmetric motor and sensory nerve dysfunction, mononeuropathy multiplex is possibly the result of ischemic injury from viral or other infection of the endothelium of the vasa nervorum and immune complex disease. Mononeuritis multiplex may be seen in HIV infection even before immunosuppression has occurred. Some cases are associated with cryoglobulinemia in persons infected with hepatitis B, in which the course is often benign and may not require specific therapy. Recently, parvovirus B19 has been associated with mononeuritis multiplex; case reports have been described with Q fever as well. Lyme is a common cause of radiculopathy and cranial neuropathies in areas endemic for *B. burgdorferi*. In patients with advanced HIV infection and CD4 counts ≤50 mm^3, CMV is the most likely cause.

Inflammatory demyelinating neuropathies

GBS, a heterogeneous syndrome of demyelinating diseases of peripheral nerves with multiple variants, has well-known association with infectious diseases such as EBV, CMV, VZV, HIV, *M. pneumoniae*, psittacosis, Lyme, dengue, and particularly *Campylobacter jejuni*. In more than half of patients, a mild respiratory or gastrointestinal tract illness precedes the onset of GBS by 1 to 3 weeks. Molecular mimicry and cross-reactive antibodies between infectious agents may play a role in the pathogenesis of some variants.

When an inflammatory demyelinating polyneuropathy persists beyond 8 weeks, or recurs, *chronic inflammatory demyelinating polyneuropathy* (CIDP) is considered. CIDP is associated with multiple predisposing factors and is also seen in patients infected with HIV. Like GBS, CIDP has multiple variants but usually presents as weakness with varying degrees of sensory loss. Physical exam reveals proximal muscle weakness. Weakness of the neck flexors is particularly suggestive. As in GBS, CSF albuminocytologic dissociation is common. The presence of leukocytes should raise suspicion of HIV infection. Electrodiagnostic and neuroimaging studies are also helpful. Multiple diagnostic criteria, including the Koski criteria and criteria from the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS), have been published.

Plasmapheresis is effective short-term, but deterioration after stopping plasmapheresis is common. Glucocorticosteroids are commonly used, although most supporting evidence is from nonrandomized trials. IVIG is superior to placebo in improving disability and comparable to plasmapheresis and steroids. Immunomodulatory drugs such as azathioprine and methotrexate have been used; additional research is needed to determine whether these may provide significant benefit.

Lyme neuroborreliosis

B. burgdorferi infection can result in acute and chronic peripheral neuropathies. Acute disseminated disease is usually characterized by peripheral and/or cranial neuropathies and meningoencephalitis, usually 4 to 12 weeks after a tick bite. Plexitis, mononeuropathy multiplex, and myelitis also occur with acute infection. Facial palsies occurred in 8% of cases reported to the CDC from 2003 to 2005, and radiculopathy in 3%. In endemic areas, facial palsy with a history of tick bite is sufficient to warrant empiric therapy. Peripheral nerve involvement usually presents asymmetrically as motor, sensory, or mixed radiculoneuropathy. Presentation may vary by Borrelia species; meningoradiculitis and radicular pain (Bannwarth's syndrome) is more common in Europe where multiple Borrelia species are found and associated most frequently with *B. garinii*. Long-standing, untreated Lyme borreliosis can cause intermittent distal paresthesias and radicular pain. Physical examination may be normal, but nerve conduction studies demonstrate axonal neuropathy. Diagnosis and specific antibiotic therapy are discussed in Chapter 162, "Lyme disease."

Neuropathies due to bacterial toxins

Diphtheria

Diphtheria is rare in the United States but is still seen in unimmunized children and in adults with waning immunity. All adults are advised to have a diphtheria booster vaccine every 10 years (in combination with tetanus with or without acellular pertussis); travelers to areas with diphtheria outbreaks or endemic diphtheria are advised to either have completed a primary immunization series or received a booster dose within the past 10 years.

Neurological, cardiac, and renal complications of diphtheria are due to its potent toxin, which acts on elongation factor, a protein critical for mammalian protein synthesis. The toxin causes noninflammatory demyelination of cranial and peripheral nerves through its toxic effect on Schwann cells.

In upper respiratory tract diphtheria, locally produced toxin causes paralysis of the pharyngeal and laryngeal muscles. The patient may speak with a nasal voice and report dysphagia and nasal regurgitation. As disease progresses, within days, the trigeminal, facial, vagal, and hypoglossal nerves are affected ("bulbar phase"), and loss of ocular accommodation is followed in 1 to 2 months by a generalized sensorimotor polyneuropathy ("systemic phase") frequently complicated by myocarditis and injury to other organs.

Botulism

Clostridium botulinum is a ubiquitous, spore-forming, anaerobic gram-positive rod that lives in soil and aquatic habitats. It produces a potent neurotoxin, termed BoNT, capable of binding irreversibly and blocking acetylcholine release at the neuromuscular junction.

Manifestations of clinical botulism include (1) *infant botulism* in babies between 1 and 6 months of age occurring after ingestion of *C. botulinum* spores and the most commonly encountered form; (2) *adult infectious botulism* or *adult intestinal toxemic botulism*, also caused by ingestion of spores; (3) *food-borne botulism*, involving ingestion of BoNT and often occurring as small food-borne outbreaks; (4) *wound botulism*, from proliferation of *C. botulinum* in a contaminated anaerobic wound or paranasal sinus in cocaine snorters; (5) *inadvertent botulism*, a complication of therapeutic uses of purified botulinus toxin; and (6) *bioterrorism*, where BoNT is dispersed by aerosol or contaminates food and water supplies.

Neuromuscular symptoms of botulism vary with patient age, by whether exposure is from preformed toxin ingestion or from active toxin production in the gut or a wound, and by toxin type. Infants first develop constipation, then hypotonia ("floppy baby syndrome") and ophthalmoplegia. Clinical features include symmetrical cranial neuropathies, autonomic dysfunction, symmetrical "descending weakness"—eye and facial muscles are most sensitive to neuromuscular blockade—in a proximal to distal pattern, and respiratory dysfunction from respiratory muscle paralysis or airway obstruction. Sensory exam is always normal. Wound botulism has the same clinical pattern as food-borne botulism but may be complicated by concurrent bacterial wound infections. In cases of food-borne exposure, the time to onset of disease is usually 12 to 36 hours. Neurologic effects are dose-dependent; people with a common source exposure exhibit differing degrees of neurologic findings depending on the amount of prototoxin ingested. Toxin type also affects the rate and extent of progression of symptoms. Type E has the shortest incubation period, but type A produces more severe illness and requires intubation more frequently (67%).

Tetanus

Tetanus is caused by the toxic action of tetanospasmin, or tetanus neurotoxin (TeNT), produced by the anaerobic spore-forming rod *Clostridium tetani,* which is widely distributed in nature. *C. tetani* is usually introduced into tissues as a spore. Disease only develops under anaerobic conditions that permit growth of the toxin-producing vegetative form. Tetanus toxin is the next most potent toxin after botulinum toxin. TeNT is a protein with three domains endowed with different functions: neurospecific binding, membrane translocation, and proteolysis for specific components of the neuroexocytosis apparatus. While tetanus neurotoxin acts mainly at CNS synapses, the seven BoNT subtypes act peripherally.

Despite availability of effective and inexpensive tetanus toxoid vaccines, cases of tetanus continue to occur in the United States, with fatality rates up to 25%. Primary prevention of tetanus is accomplished by active immunization with vaccines. All adults should complete a three-dose primary vaccination schedule and a tetanus booster every 10 years thereafter. Pregnant women should receive Tdap between weeks 27 and 36 of each pregnancy. *Secondary prevention* refers to post-wound tetanus prophylaxis and varies with vaccine history and type of wound. All wound patients should receive Td if they have received three or fewer tetanus-containing vaccines, if vaccination history is uncertain, or if more than 10 years has elapsed since the last booster in a patient with a minor wound or more than 5 years since the last booster in a patient with a major wound. Patients should also receive tetanus immunoglobulin if wounds are contaminated with feces, soil, or saliva, or if they have wounds from punctures, avulsions, projectiles, crushing, burns, or frostbite.

The "incubation period" is the time from inoculation to symptom onset and reflects the quantity of toxin released and distance traveled to the CNS. The "period of onset"—the time between the first symptom and start of spasms—reflects rate of progression of neurologic disease and is the most important prognostic factor for generalized tetanus. Diagnosis is clinical and confirmed by characteristic neurophysiologic findings and absence of serum antitetanus antibody. CSF is normal. Gram stain and anaerobic cultures of the wound may or may not reveal the organism.

There are three clinical presentations of tetanus: (1) local tetanus with muscular contraction at the site of injury, which may persist or progress to the generalized form; (2) cephalic tetanus affecting cranial nerves, mostly the seventh pair; and (3) generalized tetanus with lockjaw, reflex spasms provoked by external stimuli, opisthotonos, and risus sardonicus. The patient is conscious during spasms and experiences intense pain. Glottal or laryngeal spasm and urinary retention may occur.

The spastic paralysis induced by tetanus toxin is due to the blockade of neurotransmitter release from spinal inhibitory interneurons. When inhibitory signals to motor neurons are blocked, uninhibited motor nerve transmissions continue, resulting in prolonged muscle spasms that can persist for weeks. Autonomic instability also occurs, including labile hypertension, cardiac tachyarrhythmias, peripheral vasoconstriction, and profuse sweating. Neuronal cell death may occur from unopposed excitation.

Acute treatment has four components: (1) local wound debridement and systemic antibiotics; (2) systemic (intramuscular) administration of human antitoxin; (3) control of spasms, with associated intensive care support, sedation with benzodiazepines, and neuromuscular blockade when necessary; and (4) α- and β-adrenergic blockade to prevent secondary autonomic hyperactivity. Details are provided elsewhere. For tetanus survivors, prevention of future risk requires a primary vaccination series for active immunization after the completion of acute therapy.

Suggested reading

Dargahi N, Katsara M, Tselios T, Androutsou ME, de Courten M, Matsoukas J, Apostolopoulos V. Multiple sclerosis: immunopathology and treatment update. *Brain Sci*. 2017;7(7):78.

Kira R. Acute flaccid myelitis. *Brain Nerve*. 2018 Feb;70(2):99–112.

Messacar K, Schreiner TL, Van Haren K, et al. Acute flaccid myelitis: A clinical review of US cases 2012–2015. *Ann Neurol*. 2016;80(3):326–338.

Narayan R, Simpson A, Fritsche K, et al. MOG antibody disease: A review of MOG antibody seropositive neuromyelitis optica spectrum disorder. *MS Related Dis*. 2018;25:66–72.

Nelson GR, Bonkowsky JL, Doll E, et al. Recognition and management of acute flaccid myelitis in children. *Pediatr Neurol*. 2016 Feb; 55:17–21.

Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Fujihara K. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162–173.

Weinshenker BG, Wingerchuk DM. Neuromyelitis spectrum disorders. *Mayo Clin Proc*. 2017 Apr.;92(4):663–679.

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Reye syndrome

Debra L. Weiner and Amy Kritzer

Background

Reye syndrome is an acute noninflammatory encephalopathy with fatty degenerative liver failure first described by R. D. K. Reye in 1963. Decrease in aspirin use in children, in response to its association with Reye syndrome, and the identification of medications, toxins, and inborn errors of metabolism (IEMs) that present with Reye-like syndrome manifestations have made Reye syndrome exceedingly rare.

While recognizing the rarity of Reye syndrome, the diagnosis should be considered in any child with vomiting, altered mental status, and classic laboratory findings, but it must be a diagnosis of exclusion (Box 80.1). Early recognition and treatment of Reye and Reye-like syndromes, including possible IEMs, is essential to prevent death and optimize the potential for recovery without neurologic impairment.

CDC diagnostic criteria

Pathophysiology

Reye syndrome appears to involve mitochondrial injury resulting in inhibition of oxidative phosphorylation and fatty-acid β-oxidation usually in a virus-infected, sensitized host, most commonly as per 1980–1997 surveillance data from the US Centers of Disease Control and Prevention (CDC) with recent influenza (73%), chickenpox (21%), or diarrheal illness (14%), in association with exposure to mitochondrial toxins, most often salicylates.

Hepatic mitochondrial dysfunction results in hyperammonemia, thought to induce astrocyte edema, which causes cerebral edema and increased intracranial pressure (ICP). Histologic changes include cytoplasmic fatty vacuolization of hepatocytes, astrocyte edema and loss of neurons in the brain, and edema and fatty degeneration of the proximal lobules in the kidneys.

Etiology

Pathogens

Influenza A and B and varicella-zoster are the pathogens most commonly associated with Reye syndrome. Other pathogens include parainfluenza, adenovirus, coxsackie, herpes, rubella, measles, cytomegalovirus, Epstein–Barr, HIV, retrovirus, hepatis A and B, mycoplasma, chlamydia, pertussis, shigella, salmonella, and poliomyelitis. Reye syndrome can occur after vaccination with live viral vaccines.

BOX 80.1

Diagnostic criteria

- Acute noninflammatory encephalopathy with altered level of consciousness
- Hepatic dysfunction, liver biopsy fatty metamorphosis without inflammation or necrosis, or ≥3-fold increase in ALT, AST or ammonia
- No other explanation for cerebral edema or hepatic abnormality
- Cerebrospinal fluid white blood cell count <8/mm3, usually lymphocytes. Opening pressure may be elevated particularly in stages 4, 5 but is usually normal
- Brain biopsy-cerebral edema without inflammation or necrosis

Salicylates

Epidemiologic studies have demonstrated association of Reye syndrome with salicylates, particularly aspirin. While only 0.1% of children who took aspirin developed Reye syndrome, >80% of patients diagnosed with Reye syndrome had taken aspirin in the past 3 weeks. In the United States, a recommendation in 1980 that children not be treated with salicylates led to an immediate and dramatic decrease in the incidence of Reye syndrome. Similar declines were seen in other countries once they issued recommendations against use of aspirin.

Other medications

Nonsteroidal anti-inflammatory drugs, including sodium diclofenac and mephenamic, are thought to produce or worsen Reye syndrome. While data have not substantiated acetaminophen as a single causative agent of Reye syndrome, there is some evidence of possible interaction, synergism, and co-toxicity of aspirin and acetaminophen. Valproate, warfarin, zidovudine, didanosine, tetracycline, some neoplastic drugs, and herbal medications with atractyloside, a diterpenoid glycoside in extracts of the tuber of *Callilepis laureola* (impila poisoning) have been associated with Reye or Reye-like syndrome. Association with antiemetics was postulated but not substantiated.

Toxins

Insecticides, herbicides, aflatoxins, isopropyl alcohol, paint, paint thinner, margosa (neem) oil, hepatotoxic mushrooms, hypoglycin in ackee fruit (Jamaican vomiting sickness), and *Bacillus cereus* cereulide toxin have been reported to cause Reye syndrome.

IEMs

Reye-like syndrome is caused by fatty-acid oxidation defects, particularly medium chain acyl CoA dehydrogenase (MCAD) deficiency and long-chain 3-hydroxyacyl CoA dehydrogenase deficiency (LCHAD); urea-cycle defects; amino and organic acidopathies, such as propionic acidemia and methylmalonic acidemia; primary carnitine deficiency; dihydrolipoamide dehydrogenase deficiency; and disorders of carbohydrate metabolism.

Epidemiology

In the United States, CDC mandatory surveillance reporting began in 1973. From 1979 to 1980, 1,207 cases reported with peak of 555 1979–1980. Between 1987 and 1993, a maximum of 36 cases were reported annually, and since 1994, two cases or fewer annually. Peak age of those diagnosed was 5 to 14 years. Although CDC reporting is no longer mandated, reporting is still required by many local/state health boards

Presentation

Abrupt onset of pernicious vomiting occurs 12 hours to 3 weeks (mean 3 days) after symptoms of viral illness have resolved. Diarrhea and hyperventilation may be the first signs in children <2 years. Neurologic symptoms usually occur 24 to 48 hours after the onset of vomiting, beginning with lethargy and progressing to irritability, agitation, delirium, seizures, and coma.

Exam findings may include dehydration, hepatomegaly, lethargy, encephalopathy, obtundation, coma, seizures, and paralysis. Notably, patients are afebrile with minimal or absent jaundice.

Findings may also include acute respiratory failure, aspiration pneumonia, cardiac arrhythmia, myocardial infarction, cardiovascular collapse, gastrointestinal bleeding, pancreatitis, renal failure, and cerebral herniation.

Clinical staging

Lovejoy described five clinical stages of Reye syndrome 1 to 5. Hurwitz added a nonclinical stage (i.e., stage 0). The CDC added stage 6 for patients who cannot be classified due to treatment. Stage 0 does not meet the CDC case definition because it does not meet the clinical criteria (Box 80.2).

Laboratory abnormalities

Serum bicarbonate is decreased secondary to vomiting. Blood urea nitrogen (BUN) and creatinine are elevated. Venous pH may reveal metabolic acidosis with increased anion gap.

Patients may develop syndrome of inappropriate secretion of antidiuretic hormone, or diabetes insipidus. Glucose, while usually normal, may be low, particularly during stage 5 and in children <1 year.

Ammonia as high as 1.5 times normal (normal ≤80 μmol/L, neonates ≤100 μmol/L) 24 to 48 hours after onset of mental status changes is the most common laboratory abnormality. Ammonia tends to peak 56 to 60 hours after onset of symptoms and may

BOX 80.2

Clinical staging

- Stage 0—Alert, abnormal history and laboratory findings consistent with Reye syndrome, no clinical manifestations
- Stage 1—Vomiting, sleepiness, lethargy
- Stage 2—Restlessness, irritability, combativeness, disorientation, delirium, tachycardia, hyperventilation, dilated pupils with sluggish response, hyperreflexia, +Babinski sign, appropriate response to noxious stimuli
- Stage 3—Obtunded, comatose, decorticate rigidity, inappropriate response to noxious stimuli
- Stage 4—Deep coma, decerebrate rigidity, fixed and dilated pupils, loss of oculovestibular reflexes, and dysconjugate gaze with caloric stimulation
- Stage 5—Seizures, flaccid paralysis, absent deep tendon reflexes, no pupillary response, respiratory arrest
- Stage 6—Patients who cannot be classified due to treatment with medication that alters level of consciousness

return to normal in stages 4 and 5, with clearance from blood more rapid than from brain.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increase to three times normal but may return to normal by stages 4 and 5. Bilirubin is >2 mg/dL, but usually <3 mg/dL, in 10% to 15% of patients. If the direct bilirubin is >15% or total exceeds 3 mg/dL, consider other diagnoses.

Lipase and amylase are elevated.

Lactic dehydrogenase (LDH) may be high or low.

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are prolonged to greater than 1.5-fold in >50% of patients. Levels of factors I (fibrinogen), II, VII, IX, and X may be low because of the disruption of synthetic activities in the liver. Consumption may contribute to low levels of coagulation factors. Platelet counts are usually normal, but mean platelet volumes may be decreased at early stages of disease.

Free fatty acids and amino acids (e.g., glutamine, alanine, and lysine) may be elevated.

Urine specific gravity is increased. Eighty percent have ketonuria.

Cerebral spinal fluid white blood cell count, by disease definition, does not exceed 8/mm^3. Opening pressure is usually normal but may be elevated, particularly in stages 3 to 5.

Brain CT may reveal cerebral edema, but is usually normal.

Electroencephalography (EEG) may reveal slow-wave activity in early stages and flattened waves in advanced stages.

These derangements are not specific for Reye syndrome and may suggest other etiologies that should be considered.

Differential diagnosis

Differential diagnosis includes meningitis, encephalitis, intracranial bleed, sepsis, gastroenteritis, hepatitis, intussusception with obtundation, adverse drug reactions, toxins, and IEM.

IEM is suggested by age <1 year; recurrence of symptoms; precipitating factors, including prolonged fasting and changes in diet; decompensation out of proportion to intercurrent illnesses; failure to thrive; neurologic abnormalities; and family members with similar symptoms and/or unexplained neonatal/infant deaths.

Treatment

Early recognition, careful monitoring, and aggressive management of possible Reye syndrome, as well as possible IEM, are critical. Support of airway, breathing, circulation; minimizing metabolic demands; avoiding catabolism; promoting anabolic state; correcting metabolic derangements and coagulopathy; ammonia detoxification; and prevention/treatment of increased ICP are the mainstays of treatment (Table 80.1). Reye syndrome has been successfully treated with liver transplant.

TABLE 80.1 **TREATMENT**

Airway, breathing	**Oxygen, endotracheal intubation** as required to maintain airway, control ventilation, and prevent increased ICP Intubation using rapid-sequence agents that minimize increasing ICP Nasogastric tube to decompress the abdomen	Continuous cardiorespiratory monitoring of vital signs, oxygen saturation, end-tidal carbon dioxide wave capnography, blood gas
Circulation	Consider restricting fluids to two-thirds maintenance. **Crystalloids** to restore volume **Blood products** to correct hematologic deficiencies	Overhydration may precipitate cerebral edema. Dehydration may compromise cardiovascular volume and reduce cerebral perfusion. Goal is normal urine output. Albumin is controversial.
Electrolyte derangements	**Sodium, potassium** based on specific abnormalities and/or to prevent abnormalities	If sodium bicarbonate given for acidosis and/or sodium phenylacetate, sodium benzoate for hyperammonemia, adjust fluids to account for high sodium loads.

(*continued*)

TABLE 80.1 CONTINUED

Hypoglycemia	**Dextrose** 25%, 1–2 mL/kg IV followed by D10–15 as needed to maintain glucose 100–125 mg/dL	Check glucose, particularly if age <1 year and/or altered mental status. If concern hypoglycemia producing IEM, maintain glucose 100–150 mg/dL to decrease risk of hypoglycemia.
Acidosis	**Sodium bicarbonate** to correct acidosis is controversial due to potential paradoxical CSF acidosis For pH <7.0–7.2, consider 0.5–2 mEq/kg/h to correct pH to 7.25–7.3	Data regarding pH for which bicarbonate should be administered and appropriate dosage are lacking. Avoid rapid correction/overcorrection
Hyperammonemia	**Sodium phenylacetate, sodium benzoate hemodialysis** should be considered for ammonia >500–600 µg/dL and for patients whose condition fails to respond to initial course of sodium phenylacetate, sodium benzoate	FDA approved for treatment of hyperammonemia due to urea-cycle defects. Contraindicated if underlying liver disease. Consultation with a metabolism expert and/or hepatologist is recommended. Follow package insert instructions. Note dose <20 kg is based on weight, >20k is based on meter-squared.
Nausea, vomiting	**Ondansetron** 1–2 mg IV q8h prn vomiting. Give with sodium phenylacetate, sodium benzoate to prevent vomiting. Consider **antacids** for gastrointestinal protection	Prevent vomiting to avoid increasing ICP. Use with caution if prolonged QTc. Avoid in decompensated patients if known or possible IEM, especially organic academia, fatty acid oxidation defect d/t increased incidence QTc.
Increased intracranial pressure	**Head** midline, head of bed 30 degrees **Ventilation** to maintain **PCO_2 normal** range 35–40 mm Hg Avoid overhydration by restoring fluid deficit with **isotonic fluids** rather than hypotonic fluids, **restrict fluid** to volume necessary to maintain normal urine output, administer **furosemide** 1 mg/kg q4–6h prn fluid overload Prevent increased cerebral metabolic demand, blood flow **Antipyretic** for fever to prevent the increased cerebral metabolism and blood flow from hyperpyrexia **Analgesia/sedation** to alleviate agitation and/or perform for painful interventions **Paralytic** to control shivering **Barbiturate coma, hypothermia** controversial For life-threatening ICP, **mannitol** 20% solution, dose 0.25–0.5 g/kg IV infused over 10–20 minutes up to every 6–8 hours or **hypertonic saline** 3%, dose 3–5 mL/kg over 3–30 minutes	Mannitol preferred to hypertonic saline if giving sodium bicarbonate and/or sodium phenylacetate, sodium benzoate.
Seizures	**Phenytoin** 10–20 mg/kg IV loading dose, followed by 5 mg/kg/d IV divided q6h or fosphenytoin as 10–20 mg/kg phenytoin equivalents	Avoid valproate; causes or worsens hyperammonemia.
Coagulopathy	**Fresh frozen plasma** (FFP) 10–15 mL/kg q12–24h, **cryoprecipitate** 10 mL/kg q6h, **platelets, vitamin K** 1–10 mg IV, **and/or exchange transfusion** **Platelets** should be administered to restore count to >50,000/mm^3 prior to invasive procedures	FFP rapid correction, volume expansion if active bleeding or invasive procedures are required. If fibrinogen <100 mg/dL, consider cryoprecipitate instead of FFP because it has a higher concentration of fibrinogen. Consider vitamin K instead of FFP or cryoprecipitate if correction is not emergent. Exchange transfusion is rarely required.

Abbreviations: FFP = fresh frozen plasma, ICP = intracerebral pressure, IEM = inborn errors of metabolism.

Place central venous and/or arterial lines to monitor hemodynamic status, Foley catheter to monitor urine output, and, as indicated, ICP monitoring device. Use electrocardiogram to monitor cardiac function and EEG to monitor seizure activity.

Prognosis

Mortality has decreased from 50% to less than 20% as a result of early diagnosis, recognition of mild cases, and aggressive therapy, as well as appropriate diagnosis and disease-specific treatment of Reye-like syndromes, including IEMs. Death is usually due to cerebral edema or increased ICP, but may be due to myocardial dysfunction, cardiovascular collapse, respiratory failure, gastrointestinal bleeding, renal failure, and/or sepsis.

Patients who survive may recover completely. US data from peak years 1981–1997 show that 62% of patients with known outcome had full recovery. Poor prognosis was associated with

- Age <5 years (death 42.8% vs. 24.2%; relative risk 1.8, 95% confidence interval [CI] 1.5, 2.1)
- Rapid progression from stage 1 to 3 and/or presentation stage 4 or 5. Meaningful survival beyond stage 3 unlikely. Full recovery possible stages 0–2
- Central venous pressure (CVP) <6 mm Hg
- Elevated ammonia (death 28.6% vs. 8.4%; relative risk 3.4, 95% CI 1.9, 6.2). In survivors, higher levels of ammonia and prolonged hyperammonemia were associated with increased likelihood of neurologic sequelae.
- Serum glucose <60 mg/dL
- Hypoproteinemia
- Muscle involvement
- Antecedent diarrheal illness

Prevention

Salicylates and salicylate-containing medications should be avoided in children. Children with a condition for which salicylates are a mainstay of therapy (e.g., Kawasaki disease) should discontinue salicylate at first signs/symptoms of Reye syndrome and should possibly avoid acetaminophen until salicylates taken have been completely metabolized.

Influenza vaccine is recommended by the CDC for all children >6 months of age.

Suggested reading

Belay ED, Bresee JS, Holman RC, et al. Reye's syndrome in the United States from 1981 through 1997. *N Engl J Med*. 1999;340(18):1377–1382.

Brassier A, Ottolenghi C, Boutron A, et al. Dihydrolipoamide dehydrogenase deficiency: A still overlooked cause of recurrent acute liver failure and Reye-like syndrome. *Mol Genet Metab*. 2013;109(1):28–32.

Cag M, Saouli AC, Audet M, Wolf P, Cinqualbre J. Reye syndrome and liver transplantation. *Turk J Pediatr*. 2010;52(6):662–664.

Centers for Disease Control (CDC). Reye syndrome surveillance–United States, 1982 and 1983. *MMWR Morb Mortal Wkly Rep*. 1984;33:41–42.

Chornomydz I, Boyarchuk O, Chornomydz A. Reye (Ray's) syndrome: A problem everyone should remember. *Georgian Med. News* 2017;272:110–118.

Diagnosis and treatment of Reye's syndrome. *JAMA*. 1981;246(21):2441–2444.

Dinakaran D, Sergi CM. Co-ingestion of aspirin and acetaminophen promoting fulminant liver failure: A critical review of Reye syndrome in the current perspective at the dawn of the 21st century. *Clin Exp Pharmacol Physiol*. 2018;45:117–121.

Glasgow JF, Middleton B. Reye syndrome-insights on causation and prognosis. *Arch Dis Child*. 2001;85(5):351–353.

Gosalakkal JA, Kamoji V. Reye syndrome and Reye-like syndrome. *Pediatr Neurol*. 2008;39:198–2008.

Johnson GM, Scurletis TD, Carroll NB. A study of sixteen fatal cases of encephalitis-like disease in North Carolina children. *N C Med J*. 1963;24:464–473.

Lovejoy FH Jr, Smith AL, Bresnan MJ, et al. Clinical staging in Reye syndrome. *Am J Dis Child*. 1974;128(1):36–41.

Pugliese A, Beltramo T, Torre D. Reye's and Reye's-like syndromes. *Cell Biochem Funct*. 2008;26(7):741–746.

Reye RDK, Morgan G, Barel J. Encephalopathy and fatty degeneration of the viscera: A disease entity in childhood. *Lancet*. 1963;2:749–752.

Sert A, Kilicaslan C, Solak ES, Arslan S. Mean platelet volume in children with Reye-like syndrome. *Platelets*. 2015;26:212–215.

Sullivan KM, Belay ED, Durbin RE, Foster DA, Nordenberg DF. Epidemiology of Reye's syndrome, United States, 1991–1994: Comparison of CDC surveillance and hospital admission data. *Neuroepidemiology*. 2000 Nov-Dec;19(6):338–344.

Weiner DL. Metabolic emergencies. In KN Shaw, RG Bachur, eds. *Fleisher & Ludwig's textbook of pediatric emergency medicine*, 7th ed. Philadelphia: Wolters Kluwer; 2016: 894–913.

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Progressive multifocal leukoencephalopathy

Christopher M. Perrone and Joseph R. Berger

Introduction

In their seminal report in 1958, Astrom, Mancall, and Richardson described a progressive neurologic syndrome with a characteristic triad of neuropathologic findings: namely, demyelination, giant astrocytes, and oligodendrocytes with abnormal nuclei. They named the disorder *progressive multifocal leukoencephalopathy* (PML). The viral etiology of this neurologic disease was not determined until later. Until the advent of the AIDS pandemic, PML remained a vanishingly rare disorder seen almost exclusively in individuals with underlying immunosuppressive disorders. Prior to the advent of highly active antiretroviral therapy (HAART), PML occurred in approximately 1 in 20 of all HIV-infected persons in developed countries. While the introduction of HAART led to a decline in AIDS-associated PML, AIDS is currently estimated to be the predisposing disorder for about 80% of all PML cases. Hematologic malignancies account for another 10%. However, development of immunosuppressive and immunomodulating therapies has led to a growing incidence of PML in patients with autoimmune disorders. To date, at least 50 drugs have been associated with PML; however, the risk of PML with them varies widely. Three factors can be used to determine whether a drug has a unique risk for PML, namely: (1) whether the underlying disorder being treated is associated with PML in the absence of the drug, (2) whether there is a latency from the initiation of the drug to the onset of PML, and (3) the frequency with which PML is observed with the drug. Used in the treatment of rheumatologic disorders such as rheumatoid arthritis (RA) and lupus, immunosuppressive therapies such as methotrexate, azathioprine, and mycophenolate mofetil have been linked with a number of PML cases. Regarding immunomodulating therapies, the monoclonal antibody natalizumab, an $\alpha 4\,\beta 1$ integrin inhibitor, approved for the treatment of multiple sclerosis (MS) and inflammatory bowel disorders, has been associated with >800 cases of PML since its reintroduction to the market in 2006. Because MS does not predispose to PML, natalizumab seems to be the therapeutic agent with the greatest risk of inducing PML.

JC virus and the pathogenesis of PML

In 1965, Zu Rhein and Chou identified viral particles in glial nuclei resembling papovavirus. Subsequently, Padgett isolated polyomavirus from PML brain in glial cell cultures. The virus has a simple DNA genome of 5.1 kilobases in a double-stranded, supercoiled form, encapsidated in an icosahedral protein structure measuring 40 to 50 nm in diameter. The virus was named the JC virus (JCV) after the initials of the person from whom it was first isolated. JCV DNA encodes for three capsid proteins (VP1, VP2, and VP3) and five regulatory proteins (agnoprotein, t, T, T′135, T′136, and T′165); the latter three are derived by alternative splicing of early viral mRNA. To date, all cases of PML have been associated with JCV, although there are rare reports of other polyomaviruses, in particular BK virus, being associated with a PML-like disorder in immunosuppressed individuals.

JCV uses serotonin receptor 5-HT2A linked to sialic acid for binding to the cell surface. It is likely that other receptors remain to be identified that also permit JCV binding. Following binding, the virus enters the cell through clathrin- and eps15-dependent pathways, following which it is transported to the endoplasmic reticulum through caveosomes. From there, it enters the nucleus. Nuclear DNA binding proteins that selectively interact with the regulatory region of the genome are critical to the tropism of the virus. JCV is most likely carried into the brain by white blood cells. Pathologically, the gray–white junction is the most common location for typical PML. Whether the virus enters the brain by itself or in a cell-associated fashion remains unknown. Some investigators have suggested that the B cell plays a fundamental role in genetically modifying JCV as well as assisting the virus in central nervous system (CNS) entry. T lymphocytes, especially JCV-specific cytotoxic CD8+ T lymphocytes, play an important role in controlling CNS infection with JCV. These cytotoxic T lymphocytes (CTLs) correlate with survival and in the appearance of the immune reconstitution inflammatory syndrome (IRIS). Seroepidemiologic studies demonstrate that the virus is ubiquitous. By the age of 20 years, approximately 50% to 70% of the population or more has been exposed to JCV. The mechanism of spread of JCV remains uncertain. The detection of JCV in tonsillar tissue suggests the possibility of a respiratory or oropharyngeal route, but studies of the expression of reactivated JCV in saliva and oropharyngeal secretions by polymerase chain reaction (PCR) have not demonstrated its presence in immunologically normal individuals. No acute illness has been consistently identified with primary JCV infection. Following infection, latent virus can be demonstrated in many extraneural sites, including kidneys, lymph nodes, tonsils, intestines, and lungs. Urinary excretion of JCV is detected in as many as one-third of all adults. Differences in the virus isolated from the kidney and that from the brain of patients with PML have led to the designation of the former as "archetypal" virus. It has been proposed that the archetype virus is genetically modified in cells of B-cell lineage to a neurotropic form of the virus that subsequently migrates into the brain as cell-associated virus. A number of lines of evidence support the contention that PML is the result of a reactivated latent or persistent non-CNS infection including the demonstration of immunoglobulin G (IgG) directed to JCV in all patients, the demonstration of a neurotropic JCV from blood and tissue months to years before the development of PML in a small group of patients, the presence of JCV-specific antibody within 6 months of the development of PML in a large number of natalizumab-associated PML cases, and the rarity of the illness in children. It is possible that, in rare instances, the disease develops after primary infection. Many controversies surround the pathogenesis of PML. The current proposed hypothesis regarding the development of PML is that it is a stochastic event in which several hurdles must be overcome, including (1) initial infection, (2) establishment of viral latency, (3) mutation of the archetype strain to one that is neurotropic, perhaps within B cells, (4) re-expression of the virus, (5) entry into the brain with establishment of productive infection of oligodendrocytes, and (6) failure of normal immune mechanisms to suppress and/or clear the virus from the brain.

The numbers of AIDS patients developing PML greatly exceed those of patients developing other illnesses having similar degrees of impaired cell-mediated immunity, suggesting that factors related to HIV infection may be amplifying the frequency of the disease. This unique association may be related to the degree and duration of the immunosuppression, alteration of the blood–brain barrier by HIV infection, the upregulation of endothelial adhesion molecules for JCV-infected B lymphocytes due to cytokines elaborated by HIV-infected macrophages and microglial cells in the brain, the B-cell activation associated with HIV, and transactivation of JCV by the HIV tat protein and HIV-induced chemokines.

There appears to be a vastly increased risk of developing PML in patients who receive natalizumab for the treatment of MS or inflammatory bowel disease as well as efalizumab, a lymphocyte function-associated (LFA) antagonist once used in the treatment of psoriasis. It has been proposed that these monoclonal antibodies predispose to PML by preventing the surveillance of the CNS by JCV-specific CTLs and by the release of premature B cells, which hypothetically may increase the likelihood of genetic modification of the archetype JCV to the neurotropic form as well as amplifying JCV replication within these cells. The risk of PML with these pharmacologic agents greatly exceeds that of others reported to date which have been associated with PML.

Pathology

As its name implies, the disease is characterized by multiple sites of demyelination with a distinctive microscopic triad of multifocal myelin and oligodendroglial cell loss with minimal inflammatory infiltrate, hyperchromatic enlarged oligodendroglial nuclei (Figure 81.1), and enlarged and bizarre-appearing astrocytes with irregularly lobulated nuclei. The enlarged oligodendroglia are found

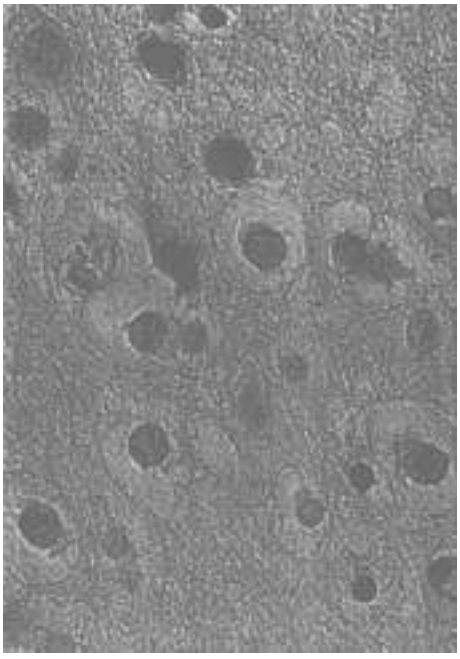

FIGURE 81.1 An abnormal infected oligodendrocyte with enlarged nuclei.

mostly at the periphery of the lesion, whereas the atypical astrocytes are generally more centrally located. Ultrastructurally, the viral particles may be detected by electron microscopy. Alternatively, the virus can be detected by immunohistochemical staining or by PCR. The virus appears in three forms: a filamentous form in nuclei of infected cells and in spherical or paracrystalline forms in either the nucleus or cytoplasm. Virions are visualized mostly in oligodendrocytes and rarely in astrocytes. Infection of oligodendrocyte is productive, whereas the astrocyte is nonpermissive for viral replication. JCV has also been associated with other forms of CNS disease including granular cell degeneration of the cerebellum and encephalitis, and, on occasion, these pathologies may be observed in association with PML.

Epidemiology

The epidemiology of PML may be divided into several epochs characterized by the growth of certain at-risk populations. These include the pre-AIDS era (1958–1981), the AIDS era (1981–1995), the HAART era (1995–2006), and the monoclonal antibody era (2006 to present). Prior to 1982, 200 cases of PML had been recorded by the National Center for Health Statistics and an extensive review of the literature published in 1984 was able to find 230 cases. The overwhelming majority of these cases were the consequence of lymphoid (predominantly B cell) malignancies.

The first reported case of PML as a complication of AIDS came in 1982. Subsequently, the prevalence in the HIV population rose sharply to 5%, accounting for nearly 20% of fatal CNS disease in AIDS patients. Until the mid-1990s, patients with HIV accounted for nearly 90% of PML cases. However, the introduction and refinement of HAART led to a gradual decline in the incidence of PML in HIV patients, as 14.8 cases per 1,000 patient-years in 1996 was lowered to 2.6 in 2005.

The decreased incidence in the HIV population during the HAART era led to increased recognition of PML in patients with rheumatologic conditions. In a review of 35 published cases, there were 22 cases reported between 1995 and 2006. Many of the patients suffered from systemic lupus erythematosus, but other conditions included RA, polymyositis and dermatomyositis, granulomatosis with polyangiitis (GPA), and scleroderma. While underlying autoimmunity may contribute to risk for development of PML, each case was linked to a form of immunosuppressive therapy such as azathioprine, methotrexate, mycophenolate mofetil, chlorambucil, cyclophosphamide, or chronic steroids.

The emergence of monoclonal antibodies has ushered in a new risk of PML in specific patient populations. In 2006, rituximab, an anti-CD20 monoclonal antibody, was approved for the treatment of RA and has subsequently expanded to treatment of GPA and microscopic polyangiitis. As of 2015, PML in the setting of rituximab has been noted in nine patients with RA and two patients with GPA. However, the risk with rituximab pales in comparison to natalizumab, an $\alpha 4\,\beta 1$ integrin inhibitor, which blocks cell adhesion at the blood–brain barrier for treatment of patients with MS and has been linked to >800 cases of PML since 2006.

As newer immunomodulating therapies for MS such as fingolimod and dimethyl fumarate have been linked to PML, patients with MS represent a growing population at-risk for PML. While HIV still represents the greatest risk as a predisposing factor in approximately 80% of PML cases and 10% are attributable to hematologic malignancies, patients with MS and other autoimmune conditions constitute a greater part of the remaining 10%. As reflected over time, the incidence and at-risk populations will continue to evolve with therapeutic advances.

Clinical manifestations

The clinical manifestations of PML are varied and depend on the area of the brain involved as well as the predisposing condition (Table 81.1). In natalizumab-associated PML, the most common abnormalities were behavioral and cognitive abnormalities followed by weakness, whereas, in the HIV-associated PML cases, the most common manifestations have been weakness (generally, hemiparesis), gait disturbance, speech and language disorders, cognitive dysfunction, and visual loss. Ataxia, dysarthria, numbness, headaches, aphasia, seizures, and vertigo are occasionally noted. Rarely, focal cognitive deficits, such as prosopagnosia, apraxia, left-sided neglect, and Gerstmann's syndrome, are observed; however, global deficits such as memory disturbances and personality changes are more common. There may be some differences in clinical presentation of PML based on the predisposing cause. On rare occasion, MRI abnormalities due to PML may be detected in advance of any clinical features; however, symptoms typically intervene within weeks of this observation.

TABLE 81.1 **PRESENTING SYMPTOMS FOR PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) IN THE SETTING OF HIV OR NATALIZUMAB**

Symptoms	HIV-associated PML	Natalizumab-associated PML
Weakness	42%	25%
Speech/language impairment	40%	25%
Cognitive abnormalities	36%	50%
Gait abnormalities	29%	14%
Sensory loss	19%	4%
Visual impairment	19%	29%
Seizures	9%	21%
Diplopia	9%	4%
Limb incoordination	6%	14%

Adapted from Clifford et al., 2010; and Berger, 1998.

Radiology

The diagnosis of PML is strongly suggested by the typical appearance on imaging studies. On CT, multiple white matter hypodensities are revealed (Figure 81.2), but MRI is more sensitive. The lesions of PML appear hyperintense on T2 (Figure 81.3) and hypointense on T1. No mass effect is observed in the absence of PML-IRIS, and, with PML-IRIS, brain edema remains rare. The scalloped appearance of these areas is due to subcortical "U" fiber involvement. Although any area can be affected, there is a predilection for the frontal and parieto-occipital regions, perhaps due to the large volume of white matter in these areas. About one-third of patients have posterior fossa involvement, and 5% have only cerebellar and brainstem lesions. Most patients have bilateral abnormal areas, and the basal ganglia may be affected, chiefly due to involvement of myelinated fibers that course through this region. Enhancement had not been considered typical, but in a pre-HAART AIDS PML population, 10% of patients had contrast enhancement on CT scan and 15% had gadolinium enhancement on MRI. In natalizumab-associated PML, 40% to 50% have gadolinium enhancement on MRI. On gradient-recalled echo (GRE) and susceptibility-weighted imaging (SWI) MRI, a thin dark rim may surround PML lesions, which is thought to be the consequence of iron-laden macrophages. Occasionally, the first MRI abnormalities will be multiple punctuate lesions that slowly grow and coalesce. Wallerian degeneration may be observed if survival is long enough.

When PML occurs in association with HIV infection, it must be differentiated from HIV leukoencephalopathy, although this can be difficult on a radiologic basis. The MRI of HIV encephalopathy often shows atrophy, and the white matter lesions do not enhance and are typically isointense on T1-weighted imaging. Clinical distinguishing HIV PML characteristics are its rapid course, subcortical involvement, and focal features. In contrast, HIV encephalopathy or dementia has a more protracted course, is of a cortical nature, and rarely has focal features.

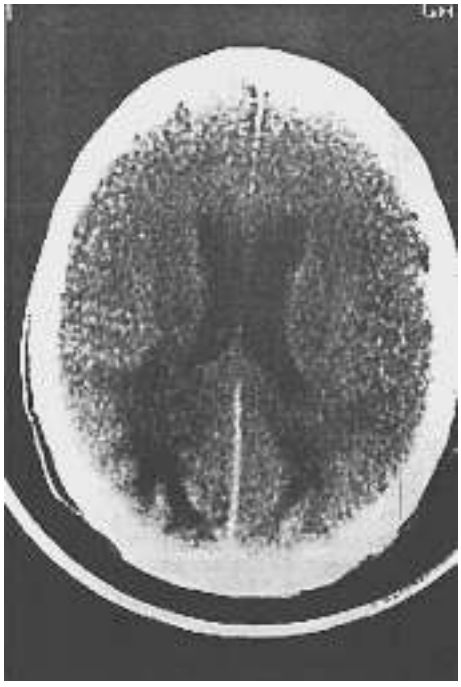

FIGURE 81.2 CT scan shows hypodense abnormalities in bilateral occipital lobes.

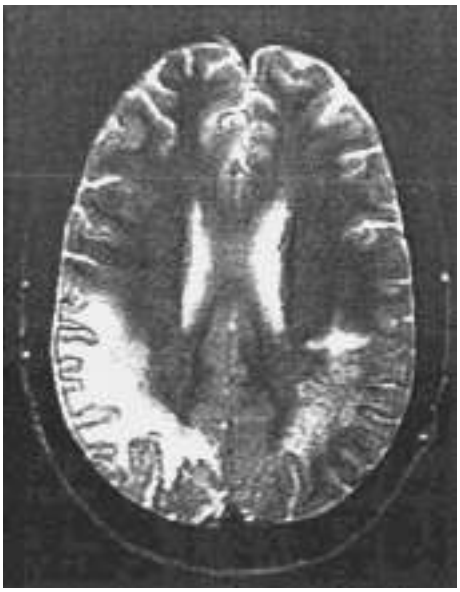

FIGURE 81.3 This T2-weighted MRI shows extensive hyperintense signal abnormalities in the right hemisphere white matter and smaller subcortical lesions on the left.

In patients developing PML while under treatment for MS with natalizumab, distinguishing the white matter lesions of MS from those of PML can be difficult. Lesions of MS are often periventricular or have Dawson's finger appearance, and the enhancement typically appears as an incomplete ring or is homogeneous throughout. In contrast, a subcortical location, faint or irregular contrast enhancement, a sharp border toward the gray matter and an ill-defined border toward the white matter on T2-weighted images, as well as T1-hypointensity and diffusion-hyperintense lesions, are suggestive of PML.

Cerebrospinal fluid

Routine studies on cerebrospinal fluid (CSF) are not particularly helpful for diagnosing PML. A mild increase in protein as well as an increase in myelin basic protein may be detected in the CSF. In HIV-infected individuals, the presence of oligoclonal bands and increased IgG synthesis (elevated CSF index) is not infrequently observed but occurs as a consequence of HIV rather than JCV. PCR for JCV is an indispensable test for diagnosing PML in persons with the appropriate clinical and radiographic features. Ultrasensitive quantitative CSF PCR has a specificity that approaches 100% and a sensitivity of 95%. In qualified laboratories, the level of viral detection is on the order of 10 copies/mL.

Diagnosing PML

The 2013 consensus statement for diagnosing PML established two primary approaches. The appropriate clinical presentation and radiologic features combined with the demonstration of JCV in the CSF is sufficient for establishing the diagnosis of PML. The second option, when the clinical picture is more obscure or if the CSF PCR is negative, is confirmation by brain biopsy with immunohistochemistry and classical pathologic features. Tissue diagnosis with brain biopsy is not without error. Brain biopsy for focal lesions in AIDS patients was associated with 93% to 96% sensitivity along with a 12% postoperative morbidity and 2% postoperative mortality. The 2013 American Academy of Neurology guidelines for PML diagnosis segregate PML into definite, probable, and possible categories based on the evidence for diagnosis. A diagnosis can be made comfortably in patients presenting with clinical features and MRI pattern consistent with PML coupled with the detection of JCV DNA by PCR in the CSF. In some patients a definitive diagnosis rests on demonstrating the characteristic histopathologic triad at brain biopsy and detecting the virus.

Prognosis

In the absence of a reversible immunosuppressive disorder, the prognosis of PML is typically grim, with death occurring in most patients between 1 and 18 months (mean 4 months) after disease onset. However, there is a significant difference in prognosis depending on the predisposing factors for disease. For instance, PML associated with AIDS pre-HAART was fatal in about 90% to 95% of cases. After the institution of optimized HAART therapy, 1-year survival increased to close to 50%. Natalizumab-associated PML has a much higher survival rate, approximately 80%, although the vast majority of these patients are debilitated by significant neurologic deficits. Certain features seem to be associated with a greater likelihood of long survival (in excess of 12 months), including PML as the heralding illness of AIDS, lesser degree of immunosuppression (CD4 counts >300 cells/mm^3), enhancement on radiographic imaging, and any evidence of clinical recovery. Low CSF JC viral loads have also correlated with longer survival. The cellular immune response against JCV appears to tightly correlate with a favorable clinical outcome in PML. The presence of JCV-specific CTLs in these patients is likely related to the presence of inflammatory infiltrates in the PML lesions and contrast enhancement seen on imaging studies.

Treatment

To date there are no unequivocally successful therapeutic modalities for preventing or treating PML. The best means to decrease the risk of developing PML for those who are HIV-positive is the institution of HAART therapy. For those who are HIV-negative, there is no form of prophylaxis as their risk for developing PML often stems from a treatment needed for another condition. Once PML is diagnosed, an initial approach to treatment is contingent on the predisposing condition, as reversal will lead to recovered immune function with the aim to contain JCV. In the setting of HIV, HAART should be initiated with a goal of normalizing CD4 counts. The advent of HAART therapy has led to nearly 50% of HIV patients demonstrating long-term survival (>12 months) with PML. Removing an immunosuppressive or immunomodulating medication can have similar benefit. It is recommended that patients who develop PML on natalizumab should undergo plasmapheresis, as nearly 80% will survive.

Following the reversal of the predisposing condition, there is a significant risk that reconstitution of the immune system will lead to an aggressive response to JCV and result in PML-IRIS. In this setting, there may be new or worsening neurologic deficits, new or enlarged lesions, contrast enhancement of lesions, and mass effect that can be fatal, especially in the posterior fossa. If PML-IRIS is evident, administration of corticosteroids is recommended to prevent excessive damage to the infected tissue. However, even if the inflammatory response is contained, the reconstitution of the immune system is not effective long-term strategy for many, such as those with autoimmune disease or organ transplant recipients.

With this understanding, a targeted anti-JCV treatment has been sought. Treatment strategies have focused on antivirals, immune response modulators, and immunization. However, with no reliable animal model of PML and the challenge of timely recruitment for human studies, there have been only five clinical trials of PML treatment to date. In an attempt to inhibit viral replication, cytosine arabinoside, topotecan, cidofovir, enfuvirtide, and mefloquine have been tested. The largest of these trials was the ARA-C trial in AIDS-related PML which compared ARA-C administered intravenously or intrathecally with antiretroviral therapy to antiretroviral therapy alone. It had only 57 patients; all the other trials had smaller numbers of study subjects. None demonstrated any benefit.

The remainder of the literature consists of case reports. There are anecdotal benefits of therapies aimed at preventing JCV cell entry (mirtazapine, risperidone, ziprasidone) and inhibiting JCV DNA replication (leflunomide, ganciclovir). Improvements have occasionally been noted when stimulating the host immune response (interferon-α, interleukin-2, and interleukin-7) and decreasing inflammation (maraviroc, glucocorticoids). With a goal of boosting a JCV-specific T-cell response, immunization with a JCV capsid protein and recombinant IL-7 was beneficial in two cases. However, none of these therapies has been consistently successful.

Identification of an effective treatment strategy for PML remains an active research area. Due to homology of the JC virus and the BK virus, T cells specifically targeting the BK virus have been recently explored in the treatment of PML. Three patients with PML, one with HIV and two with immunosuppression secondary to treatment for myeloproliferative neoplasms, were treated with partially human leukocyte antigen (HLA)-matched, BK virus–specific T cells from healthy donors. In two cases (HIV and non-HIV patients), T-cell infusion was followed by clinical and radiographic improvement in PML as well as clearance of JCV from the CSF. In the third case, there was clinical and radiographic stabilization and reduced JCV in the CSF. As this therapy was well-tolerated, larger studies are needed to adequately measure efficacy.

The development of programmed cell death-1 (PD-1) inhibitors represents another intriguing therapeutic approach. Expression of PD-1, a marker of cellular immune exhaustion, appears to be higher on CD8+ T-lymphocytes in patients with PML compared to healthy controls. With evidence of being able to boost the JCV-specific T-cell immune response, PD-1 inhibition may help to control JCV infection.

Perhaps most alluring in the treatment of PML is the therapeutic potential of antisense oligonucleotides that are designed with a specific complementary base sequence that binds selectively to a targeted region of messenger RNA (mRNA) to prevent the translation of the mRNA into protein. Antisense oligonucleotide directed to JCV T antigen may reduce viral expression by 80%. Antisense oligonucleotides that target other sites of the viral genome, such as transcription sites, may prove to be effective therapeutic strategies. As strong JCV-specific cellular immunity has been associated with a favorable clinical outcome of PML, the enrichment of an autologous population of JCV-specific CTLs using tetrameric MHC class-I/JCV peptide complexes may be demonstrated to be a therapeutic option.

Conclusion

Increasing reports of stabilization or remission of PML and the growing understanding of the pathophysiology of the JC virus provide hope for the future development of curative strategies. The growing number of persons affected with PML permit the organization of carefully designed therapeutic trials to address this issue.

Suggested reading

Antinori A, Cingolani A, Lorenzini P, et al. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: Data from the Italian Registry Investigative Neuro AIDS (IRINA). *J Neurovirol*. 2003;9 Suppl 1:47.

Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: Consensus statement from the AAN Neuroinfectious Disease Section. *Neurology*. 2013;80:1430–1438.

Berger JR, Khalili K. The pathogenesis of progressive multifocal leukoencephalopathy. *Discov Med*. 2011;12:495–503.

Berger JR, Malik V, Lacey S, Brunetta P, Lehane PB. Progressive multifocal leukoencephalopathy in rituximab-treated rheumatic diseases: A rare event. *J Neurovirol*. 2018;24(3):323–331.

Berger JR, Pall LM, Lanska DJ, Whiteman MS. Progressive multifocal leukoencephalopathy in patients with HIV infection. *J Neurovirol.* 1998;4(1):59–68.

Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med*. 2012;366:1870–1880.

Calabrese LH, Molloy ES, Huang D, Ransohoff RM. Progressive multifocal leukoencephalopathy in rheumatic diseases: Evolving clinical and pathologic patterns of disease. *Arthritis Rheum*. 2007;56(7):2116–2128.

Casado JL, Corral I, Garcia J, et al. Continued declining incidence and improved survival of progressive multifocal leukoencephalopathy in HIV/AIDS patients in the current era. *Eur J Clin Microbiol Infect Dis*. 2014;33(2):179–187.

Chahin S, Berger JR. A risk classification for immunosuppressive treatment-associated progressive multifocal leukoencephalopathy. *J Neurovirol*. 2015;21(6):623–631.

Clifford DB, De Luca A, Simpson DM, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol*. 2010;9:438–446.

Gheuens S, Wuthrich C, Koralnik IJ. Progressive multifocal leukoencephalopathy: Why gray and white matter. *Annu Rev Pathol*. 2013;8:189–215.

Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurolo*. 2010;68:295–303.

Hodel J, Outteryck O, Verclytte S, et al. Brain magnetic susceptibility changes in patients with natalizumab-associated progressive multifocal leukoencephalopathy. *Am J Neuroradiol*. 2015;36(12):2296–2302.

Muftuoglu M, Olson A, Marin D, et al. Allogeneic BK virus-specific T cells for progressive multifocal leukoencephalopathy. *N Engl J Med*. 2018;379:1443–1451.

Palazzo E, Yahia SA. Progressive multifocal leukoencephalopathy in autoimmune diseases. *Joint Bone Spine*. 2012;79(4):351–355.

Pavlovic D, Patera AC, Nyberg F, Gerber M, Liu M. Progressive multifocal leukoencephalopathy: Current treatment options and future perspectives. *Ther Adv Neurol Disord*. 2015;8(6):255–273.

Sacktor N. The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. *J Neurovirol*. 2002;8 Suppl–2:115–121.

Tan CS, Bord E, Broge TA Jr, et al. Increased program cell death-1 (PD-1) expression on T lymphocytes of patients with progressive multifocal leukoencephalopathy (PML). *J Acquir Immune Defic Syndr*. 2012;60(3):244–248.

White MK, Khalili K. Pathogenesis of progressive multifocal leukoencephalopathy–revisited. *J Infect Dis*. 2011;203:578–586.

Yousry TA, Pelletier D, Cadavid D, et al. Magnetic resonance imaging pattern in natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol*. 2012;72:779–787.

Zaheer F, Berger JR. Treatment-related progressive multifocal leukoencephalopathy: Current understanding and future steps. *Drug Safety*. 2012;3:227–239.

Zhai S, Brew BJ (2018). Progressive multifocal leukoencephalopathy. In BJ Brew, ed., *Handbook of clinical neurology: The neurology of HIV infection*, *Vol. 152*. Cambridge, MA: Elsevier; 2018: 123–125.

82

Cerebrospinal fluid shunt infections

Elisabeth E. Adderson and Patricia M. Flynn

Cerebrospinal fluid (CSF) shunts are critical for many patients surviving congenital central nervous system (CNS) anomalies, infection, or intracranial hemorrhage. Infection is a common complication of these devices and a leading cause of morbidity and hospitalization. Clinical studies performed over the past half-decade have more clearly defined the optimal means to prevent and treat these infections.

Pathogenesis

Most CSF shunts are silastic tubes inserted into the cerebral ventricles or subarachnoid space and connected to a pressure-regulating valve on the external skull. The proximal shunt is connected to tubing tunneled under the skin to the peritoneal cavity (ventriculoperitoneal shunt), the right atrium (ventriculoatrial shunt), or pleural cavity (ventriculopleural shunt). Lumboperitoneal shunts drain from the lumbar spinal canal subarachnoid space to the peritoneal cavity.

The reported incidence of CSF shunt infections ranges from 1% to 30%, with an average of approximately 10% in recent studies. Risk factors for infection include previous shunt infection, recent shunt placement or revision, younger age (particularly premature neonates), a less-experienced surgeon, endoscopic surgery, and the presence of a postoperative CSF leak. Prior cardiac surgery and any surgical procedure within 30 days of shunt insertion are risk factors for shunt infection in infants ≤1 year of age. Shunt valve design does not appear to influence infection rates.

The majority (40–75%) of CSF shunt infections are caused by coagulase-negative *Staphylococcus* spp. *Staphylococcus aureus* and gram-negative bacilli are each responsible for between 6% and 35% of infections. *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa* are the most commonly reported gram-negative pathogens. Anaerobic bacteria, especially *Cutibacterium acnes* (formerly *Propionibacterium acnes*), and fungi are occasionally reported.

Most (50–70%) CSF shunt infections occur within 60 days of shunt insertion, and 90% occur in the first 6 months after placement. This timing, and the prominent role of bacteria that normally colonize the skin in causation, suggests that most infections result from the intraoperative contamination of shunt devices. One small prospective study found that contamination of surgeons' gloves by normal skin flora such as coagulase-negative *Staphylococcus* and *C. acnes* was universal and occurred within a short time after surgery was commenced. Less commonly, shunt infections may result from direct extension of surgical wound infections. Infections with delayed onset (after 2–3 months) and those caused by gram-negative bacilli may originate from an intra-abdominal focus (appendicitis, bowel perforation or surgery, trauma) by retrograde spread or bacteremia. Organisms such as coagulase-negative *Staphylococcus* and *S. aureus* adhere to medical devices or to the host proteins that are rapidly deposited on these foreign bodies. Adherent bacteria are enveloped in biofilm, a complex mixture of carbohydrate and proteins that both augments adherence and protects the organism from host immune defenses. Bacteria in biofilm are less susceptible to antimicrobial killing than planktonic organisms. In some cases, biofilm acts as a mechanical barrier to reduce

the penetrance of drugs. Sessile organisms also have reduced growth rates and metabolic changes that may affect the expression and function of drug targets.

Clinical presentation

The clinical presentation of shunt infections may range from almost asymptomatic colonization of the shunt device to fulminant ventriculitis depending on the infecting organism and the patient's underlying medical condition. Illness is frequently nonspecific. It is imperative to exclude CSF shunt infections in patients with unexplained febrile illness or symptoms of shunt malfunction since these infections cannot reliably be distinguished from systemic illnesses or noninfectious causes of shunt malfunction. The most common symptoms include fever, vomiting, lethargy, new or worsening altered consciousness, and irritability. Fever may be absent initially in up to 40% of patients. Some patients have more obvious presentations, with evidence of wound infection, inflammation along the subcutaneous shunt tract, or signs of meningeal irritation or elevated intracranial pressure. Approximately 10% have symptoms and signs of distal infection, including abdominal pain, guarding, gastrointestinal obstruction, or a palpable peritoneal pseudocyst. Patients with infected ventriculoatrial shunts are generally bacteremic and have more prominent fever and other constitutional symptoms. Ventriculoatrial shunt infections are occasionally complicated by an immune complex–mediated glomerulonephritis characterized by hypocomplementemia, hematuria, proteinuria, and renal dysfunction. Symptoms and signs of pleural inflammation are strongly suggestive of shunt infection in patients with ventriculopleural shunts.

Diagnosis

CSF shunt infections are diagnosed by examination and culture of CSF obtained from the shunt reservoir or cerebral ventricles (Table 82.1). Examination of CSF from the lumbar spine is indicated in patients with lumboperitoneal shunts or if ventricular CSF is unremarkable but patients have signs and symptoms consistent with a CNS infection. CSF abnormalities, however, are often subtle, and normal findings do not reliably exclude CSF shunt infections, especially in patients who have received antimicrobial therapy and in immunocompromised patients. CSF abnormalities caused by infection may also be difficult to distinguish from changes related to recent surgery or medical devices. A mild pleocytosis, for example, may accompany mechanical shunt malfunction and hypersensitivity reactions to shunt material. The CSF white blood cell count is usually elevated. A neutrophilic predominance is typical; mild eosinophilia is also relatively common. The CSF protein is generally elevated; low CSF glucose concentrations are less commonly observed. Elevated CSF lactate concentrations may support the diagnosis of CSF shunt infections, and elevated serum C-reactive protein may help distinguish bacterial shunt infections from noninfectious etiologies.

TABLE 82.1 **DIAGNOSTIC TESTS FOR CEREBROSPINAL FLUID (CSF) SHUNT INFECTIONS**

Test	Typical findings
CSF Gram stain	Positive in 70–90%
CSF cultures	Positive in 85%
CSF β-D-glucan and galactomannan detection	May be elevated in fungal infections
CSF cell count	Elevated WBC (usually 100–2,500 cells/mm^3, range 0–18,000 cells/mm^3)
CSF WBC differential	Neutrophil predominance (range 0–93%) Eosinophilia (>5% of WBC) in 15–25%
CSF protein	Elevated (usually 150–400 mg/dL)
CSF glucose	Normal or low (usually 30–60 mg/dL)
CSF lactate	Elevated in 80%
Serum C-reactive protein	Elevated in 80%
Diagnostic imaging	Debris within ventricles, gadolinium enhancement of ventricular ependymal lining, restricted diffusion, periventricular hyperintensities, brain abscess Distal complications of VP shunts: intra-abdominal fluid collections, ascites, fat stranding, bowel wall edema, catheter migration

Abbreviations: CSF, cerebrospinal fluid; VP, ventriculoperitoneal; WBC, white blood cell.

Gram stain examination of CSF permits a rapid diagnosis in 70% to 90% of patients. CSF cultures are positive in about 85% of patients, but less commonly in those who have received antimicrobial therapy prior to CSF sampling and in infections caused by unusual pathogens (e.g., anaerobic bacteria and fungi). Cultures should be obtained prior to administration of antimicrobials if possible. The addition of anaerobic cultures of CSF may increase the yield of *C. acnes*. Bacterial cultures should be held for at least 10 days and fungal cultures for 30 days to detect slowly growing pathogens. Cultures of CSF shunts or drains are recommended if these are removed because of concern for infection. It may be difficult to interpret growth from CSF of bacteria that are commonly considered culture contaminants, such as coagulase negative *Staphylococcus* spp. Growth of such organisms in enrichment broth only, or from only one of multiple cultures obtained from patients who are afebrile and have unremarkable CSF findings, may not reflect a true infection. In contrast, isolation of more virulent organisms, such as *Staphylococcus aureus*, aerobic gram-negative bacilli, and fungi is likely to reflect ventriculitis or meningitis.

Polymerase chain reaction amplification of microbial DNA may be more sensitive than culture, but the specificity of these tests has not been established and they are expensive and may not be readily available. Blood cultures are commonly positive in ventriculoatrial shunt infections but rarely in ventriculoperitoneal and ventriculopleural shunt infections.

Neuroimaging is recommended in patients suspected of having CSF shunt infections to evaluate infection and shunt function. MRI is more sensitive than CT for detecting abnormalities. Abdominal ultrasound or computed tomography are recommended to evaluate suspected complications of distal ventriculoperitoneal shunts.

Therapy

Initial approach to management

In patients with suspected CSF shunt infections, initial management includes obtaining CSF from the shunt reservoir or ventricle for diagnostic studies. Patients with presentations suggestive of ventriculitis or meningitis should begin antimicrobial therapy while awaiting these results. Patients who have mild illness, no evidence of shunt malfunction, a mild pleocytosis, and negative CSF stains may be observed without empirical therapy. Contamination of diagnostic CSF samples is possible. It is prudent, therefore, to obtain a second CSF sample before instituting therapy in cases where antimicrobials have not been administered and the patient's course is not consistent with infection.

Surgical therapy

Management that includes complete removal of the infected shunt, placement of an extraventricular drain (EVD) if required, intravenous (IV) antimicrobials, and shunt replacement once the CSF is sterile has a success rate of >85% and is recommended for most patients with infected CSF shunts. Shunt removal and local debridement is also indicated for wound or shunt tract infections, and other infected hardware, including drains and infusion pumps, should also be removed. A one-stage procedure combining IV and intraventricular antibiotic therapy with immediate replacement of the infected shunt is effective in about 65%. Treatment with antibiotics alone without shunt removal is effective in only a third of patients, likely because of the combination of persistent viable bacteria in biofilms and the limited achievable CSF concentrations of many antimicrobial agents. This treatment may be appropriate, however, for patients with a short life expectancy, an Ommaya reservoir, and those with infections caused by coagulase-negative *Staphylococcus* spp. that respond promptly to aggressive medical therapy. These patients should receive IV and intraventricular antimicrobial agents (administered via an EVD or the shunt) for a minimum of 14 days after CSF sterilization, with meticulous attention to ensuring CSF antimicrobial concentrations are adequate. Patients with isolated infection of an abdominal pseudocyst who do not have positive CSF cultures may be treated by shunt externalization, drainage of the fluid collection, and systemic antimicrobials appropriate for intra-abdominal infections.

Antimicrobial therapy

Empirical antibiotic therapy should be based on the likely pathogen, clinical findings, the severity of illness, and known colonization or infection with antimicrobial-resistant pathogens. Vancomycin plus an anti-pseudomonal β-lactam agent (based on local susceptibility data) is recommended for initial treatment of adults, children with moderate to severe clinical illness, patients with findings suggestive of intra-abdominal infection, and those with gram-negative bacilli seen on CSF stain (Table 82.2). Children with uncomplicated infections may be treated with vancomycin alone, in doses appropriate for intracranial infections. Definitive antimicrobial therapy should be based on culture results and in vitro susceptibility testing and taking the ability of the antimicrobial agent to cross the blood–brain barrier into consideration.

Achieving good CSF penetration is a significant problem with some antimicrobial agents, most notably vancomycin. Serum vancomycin levels should be monitored, aiming for trough concentrations of 15 to 20 μg/mL in those receiving intermittent administration. Patients should be monitored clinically and have CSF cultures monitored every 1 to 3 days to ensure they become sterile. Intraventricular antimicrobial therapy should be considered for patients with suboptimal microbiological or clinical responses to systemic antibiotics, especially those for whom shunt removal is not feasible, although no prospective randomized trials have compared combined parenteral and intraventricular administration with parenteral therapy alone. Other indications include infections cause by microorganisms that are susceptible only to antibiotics with poor CSF penetration and in infections when shunt devices cannot be practicably removed, including infections of Ommaya reservoirs. No antimicrobial agents are currently licensed for intraventricular use, but intraventricular vancomycin and aminoglycosides have few reported adverse affects when used at appropriate concentrations (Table 82.3). Preservative-free formulations of these drugs should be reconstituted in sterile normal saline for administration, and, when an EVD is used for administration, it should be clamped for 15 to 60 minutes to permit diffusion throughout the ventricular system. An alternative "flush" procedure has been described in which a more dilute antimicrobial solution is infused slowly through one EVD and allowed to drain through a second EVD placed in the contralateral ventricle. Antimicrobial CSF concentrations achieved by intraventricular administration are highly variable and should be monitored periodically to both ensure adequate levels and avoid toxicity. A reasonable approach is to obtain CSF for determination of the antimicrobial inhibitory quotient 24 hours after administration of the first dose. Subsequent doses and dosing schedules should be adjusted to maintain a CSF antimicrobial trough concentration that exceeds the pathogen's minimum inhibitory concentration by 10- to 20-fold. Combination therapy with rifampin, which has excellent CSF and biofilm penetration, may be helpful in treating infections caused by susceptible gram-positive bacteria. The possibility that the EVD has become colonized, which occurs in 5% to 10% of cases, should also be considered if CSF cultures are persistently positive. Routine changes of EVDs, however, have not been proved to reduce the risk of colonization or secondary infection.

Continuing management

The optimal duration of therapy for CSF shunt infections has not been systematically studied. Most infections can be treated

TABLE 82.2 **RECOMMENDED DOSES OF INTRAVENOUS ANTIMICROBIAL AGENTS**

Agent	Age[a]	Total daily dose	No. daily doses
Amphotericin B	Neonate <7 days	1 mg/kg	1
	Neonate 8–28 days	1 mg/kg	1
	Children	1 mg/kg	1
	Adults	0.7–1 mg/kg	1
Amphotericin B liposome	Neonate <7 days	–	
	Neonate 8–28 days	–	
	Children	3–5 mg/kg	1
	Adults	5 mg/kg	1
Ampicillin	Neonate <7 days	150–300 mg/kg	3
	Neonate 8–28 days	200–300 mg/kg	4
	Children	300 mg/kg	4
	Adults	12 g	6
Cefepime	Neonate <7 days	–	
	Neonate 8–28 days	–	
	Children	150 mg/kg	3
	Adults	6 g	3
Cefotaxime	Neonate <7 days	100–150 mg/kg[a]	2–3
	Neonate 8–28 days	150–200 mg/kg	3–4
	Children	300 mg/kg	4–6
	Adults	8–12 g	4–6
Ceftazidime	Neonate <7 days	100–150 mg/kg[a]	2–3
	Neonate 8–28 days	150 mg/kg	3
	Children	150 mg/kg	3
	Adults	6 g	3
Ceftriaxone	Neonate <7 days	–	
	Neonate 8–28 days	–	
	Children	100 mg/kg	2
	Adults	4 g	2
Flucytosine	Neonate <7 days	–	
	Neonate 8–28 days	–	
	Children	100 mg/kg	4
	Adults	100 mg/kg	4
Linezolid	Neonate <7 days	20 mg/kg	2
	Neonate 8–28 days	30 mg/kg	2
	Children	30 mg/kg	2
	Adults	1,200 mg	2
Meropenem	Neonate <7 days	–	
	Neonate 8–28 days	–	
	Children	120 mg/mL	3
	Adults	6 g	3

(*continued*)

TABLE 82.2 CONTINUED

Agent	Age[a]	Total daily dose	No. daily doses
Metronidazole	Neonate <7 days	–	
	Neonate 8–28 days	–	
	Children	30–40 mg/kg	3
	Adults	30 mg/mL, maximum 4 g/d	4
Nafcillin	Neonate <7 days	75 mg/kg	2–3
	Neonate 8–28 days	100–150 mg/kg[a]	3–4
	Children	200 mg/kg	4–6
	Adults	9–12 g	6
Oxacillin	Neonate <7 days	75 mg/kg	2–3
	Neonate 8–28 days	150–200 mg/kg[a]	3–4
	Children	200 mg/kg	4
	Adults	9–12 g	6
Penicillin G	Neonate <7 days	150.000 units/kg	2–3
	Neonate 8–28 days	200,000 units/kg	3–4
	Children	300,000 units/kg	4–6
	Adults	24,000,000 units	6
Rifampin	Neonate <7 days	–	
	Neonate 8–28 days	10–20 mg/kg	2
	Children	10–20 mg/kg	1–2
	Adults	600 mg	1
Vancomycin	Neonate <7 days	20–30 mg/kg	2–3
	Neonate 8–28 days	30–45 mg/kg	3–4
	Children	60 mg/kg (maximum 4 g/d)	4
	Adults	30–60 mg/kg (maximum 2 g/dose)	2–3

[a] Lower doses and increased intervals are advisable for infants weighing <2,000 g.

for 10 to 14 days after CSF is sterile. Some experts recommend that infections caused by gram-negative pathogens should be treated for 21 days after CSF sterilization. Published studies have described a variety of criteria for the timing of shunt replacement, but most practitioners consider this after the CSF is sterile for 7 to 10 days and CSF protein concentrations fall below 200 mg/dL. Some experts suggest that shunt replacement may be considered as early as 3 days after the CSF is sterile for patients with good clinical responses, infections caused by coagulase-negative *Staphylococcus* spp. or *C. acnes,* and who have no CSF abnormalities.

Outcomes

CSF shunt infections are an uncommon direct cause of death. These infections, however, may be a risk factor for mortality related to underlying medical conditions. Some studies in children have noted an increased incidence of intellectual impairment and learning disabilities in patients with CSF shunt infections compared to those with shunts and no history of infection.

Prevention

Strict attention to disinfection of skin and surgical technique at the time of shunt or EVD placement may prevent many shunt infections. In one study, initial double-gloving with interoperative removal of the outer pair of gloves before handling the shunt catheter reduced infection rates relative to continuous double-gloving and studies evaluating the implementation of a standardized perioperative care bundle have consistently demonstrated reduced shunt infection rates. EVDs should be removed at the earliest feasible time.

TABLE 82.3 **RECOMMENDED INITIAL DOSES AND CEREBROSPINAL FLUID (CSF) CONCENTRATIONS OF INTRAVENTRICULARLY ADMINISTERED ANTIMICROBIALS**

Agent/age	Initial dose	Peak concentration[a] (MG/L)	Trough concentration[b] (MG/L)
Amikacin			
Infants and children	2–50 mg/kg/d	25–30	<5
Adults	5–50 mg/d, usual dose 30 mg/d		
Amphotericin B			
Infants and children	0.01–0.6 mg q1–3 days	NE[c]	NE[c]
Adults	0.01–0.5 mg q2–3d		
Colistimethate			
Infants and children	3.75 mg base activity/d	NE[c]	NE[c]
Adults	3.75–4.2 mg base activity/d		
Gentamicin			
Infants and children	1–4 mg/d	5–20	<2
Adults	4–8 mg/d		
Polymyxin B			
Infants and children	20,000 units/d or 25,000 units q2d	NE[c]	NE[c]
Adults	50,000 units/d		
Tobramycin			
Infants and children	1–20 mg/d	5–20	<2
Adults	4–20 mg/d		
Vancomycin			
Infants and children	2–20 mg/d	50–80	<10
Adults	5–20 mg/d		

[a] Peak concentrations measured 15 to 30 minutes after administration.
[b] Initial trough concentration measured 24 hours after administration of the first dose.
[c] Not established.

Periprocedural prophylactic antimicrobials are recommended for patients undergoing placement of CSF shunts or EVDs. Most studies have used cefazolin, with the first dose of 1 g IV for adults and 20 mg/kg for children within 60 minutes before surgical incision, followed by two additional doses at 8-hour intervals. Vancomycin (adults, 15 mg/kg within 120 minutes before surgical incision and 12 hours later; children, 10–15 mg/kg IV within 120 minutes before surgical incision and q6h for a total of four doses) is an alternative for patients with allergies to β-lactams and in institutions with a high incidence of infections caused by methicillin-resistant *S. aureus*.

The use of shunts and drains impregnated with antimicrobial agents (clindamycin, minocycline, and/or rifampin) significantly reduces infection rates. Antibacterial activity gradually decays over a period of months, in some cases persisting for >90 days after shunt insertion.

Meningitis in patients with CSF shunt infections

Rarely, patients with CSF shunts may develop hematogenous bacterial meningitis caused by common pathogens such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b. These infections can generally be treated by systemic antimicrobial agents alone, without removal of the shunt.

Suggested reading

Klimo P, Van Poppel M, Thompson CJ, et al. Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 6: Preoperative antibiotics for shunt surgery in children with

hydrocephalus: a systematic review and meta-analysis. *J Neurosurg Pediatrics*. 2014;14:44–52.

Parker SL, McGirt MJ, Murphy JA, et al. Comparative effectiveness of antibiotic-impregnated shunt catheters in the treatment of adult and pediatric hydrocephalus: Analysis of 12,589 consecutive cases from 287 US hospital systems. *J Neurosurg*. 2015;122: 443–448.

Pelegrin I, Lora-Tamayo J, Gomez-Junyent J, et al. Management of ventriculoperitoneal shunt infections in adults: Analysis of risk factors associated with treatment failure. *Clin Infect Dis*. 2017; 64:989-997.

Schaffzin JK, Simon K, Connelly BL, et al. Standardizing preoperative preparation to reduce surgical site infections among pediatric neurosurgical patients. *J Neurosurg Pediatr*. 2017;1:399–406.

Seidelman J, Lewis SS. Neurosurgical device-related infections. *Infect Dis Clin N Am*. 2018;32:861–876.

Simon TD, Schaffzin JK, Stevenson CB, et al. Cerebrospinal fluid shunt infection: Emerging paradigms in pathogenesis that affect prevention and treatment. *J Pediatr*. 2018. doi.org10.1016/j.jpeds.2018.11.026.

Tunkel AR, Hasbun R, Bimrah A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis*. 2017;64:701–706.

Section 11

The susceptible host

83

Evaluation of suspected immunodeficiency

Thomas A. Fleisher and Sergio D. Rosenzweig

The need to evaluate immunologic function has become a part of the standard practice of clinical medicine, resulting at least in part from the secondary immunodeficiency produced by HIV infection. In addition, since the early 1990s, the molecular basis of primary immunodeficiency disorders (PIDD) has evolved, with now >350 genetic defects identified impacting host defense with an expanded range of clinical phenotypes associated with the genetic defects. This chapter presents the general methods available to assess immune function, linking these to the clinical infectious history that is suggestive of specific types of PIDDs.

The primary clinical problem that sets the stage for initiating an immunologic evaluation is a history of increased susceptibility to infection. In general, the specific characteristics of the recurrent and/or chronic infections, including organism(s), site(s), frequency, and response to therapy provide critical insights into the most likely type or category of immunodeficiency. Moreover, it has been observed that, in a number genetic defects of immune function, immune dysregulation, autoimmunity, and cancer susceptibility are part of the clinical phenotype in addition to increased susceptibility to infection. These observations clearly expand the spectrum of clinical findings associated with PIDD.

Defects in adaptive immunity involving decreased immunoglobulin levels and abnormal antibody production (humoral immunity) most typically lead to recurrent infections with high-grade encapsulated extracellular bacteria such as *Haemophilus influenzae* (often untypable) and *Streptococcus pneumoniae,* usually affecting the sinopulmonary tract. The protective immune response to these infectious agents depends on the production of antibodies against the capsular carbohydrate antigens present on the surface of the microorganisms. These patients may also have increased susceptibility to selected viruses (i.e., enterovirus). In contrast, the clinical picture of patients with defective T-cell (cellular) immunity typically involves recurrent infections with opportunistic organisms, examples of which include *Pneumocystis jirovecii*, *Candida* spp., cytomegalovirus and others. This demonstrates that functional T cells are required to prevent or clear infection with these opportunistic intracellular microorganisms. A more recent focus of study has been directed at the interface between the adaptive and innate immune systems associated with defects in the interferon (IFN)-γ/interleukin (IL)-12 circuit identified in certain patients with persistent tuberculous or nontuberculous mycobacterial (NTM) infection as well as infections with other intracellular pathogens. The critical role of the lymphoid arm of the innate immune system (natural killer cells) in host defense has been clarified based on defects affecting these cells and resulting in clinical presentations that include increased susceptibility to the herpesvirus family including Epstein–Barr virus (EBV) and herpes simplex virus (HSV) infections, as well as in some cases uncontrolled inflammation. Recently, genetic defects associated with increased susceptibility to cutaneous infections involving both virus and fungi have been defined such that significant, persistent cutaneous infections justify consideration of specific immunologic defects. Abnormalities in the phagocytic arm of innate immunity primarily affecting neutrophils include either decreased cell numbers (infections associated with neutropenia are discussed in Chapter 84, "Infection in the neutropenic patient") or genetically defined neutrophil disorders. These include congenital neutropenias and inherited disorders impacting neutrophil function that result in cutaneous and deep-seated abscesses, pneumonia, periodontitis, and osteomyelitis. This clinical picture of the latter is demonstrated in patients with chronic granulomatous disease (CGD) associated with a set of different genetic disorders that affect the nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase machinery and impair reactive

oxygen species (ROS) generation. Typically, the infections in CGD involve bacteria such as *Staphylococcus aureus*, *Serratia marcescens*, and *Nocardia* spp. as well as fungi such as *Aspergillus* spp. The clinical findings point to the critical role of mobile phagocytic cells in normal host defense. Congenital defects in specific complement components that form another arm of the innate immunity can be associated with recurrent infections. Those impacting the earlier components of the complement cascade also are also linked to the development of autoimmune disease, while those affecting the terminal components of complement result in increased susceptibility to neisserial infections.

Clinical suspicion of a defect in immune function is primarily generated by the medical history, and any patient with a history of increased susceptibility to infection should be evaluated for secondary forms of immunodeficiency due to other comorbidities or HIV infection. The family history has also proved important with the increasing number of immune deficiencies that have been characterized at the molecular level, each with its particular inheritance pattern. The physical examination can provide clues in the case of specific primary immunodeficiencies (e.g., typical facies in the hyperimmunoglobulin E [IgE] [Job] syndrome, scars from abscess drainage sites in CGD, petechiae in Wiskott-Aldrich syndrome, chronic cutaneous viral infections in DOCK8 deficiency, chronic mucocutaneous candidiasis [CMC] in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED] syndrome). This may also provide clues to the evaluation of secondary immune disorders (e.g., oral hairy leukoplakia or Kaposi's sarcoma in HIV infection).

BOX 83.1

Evaluation of suspected antibody (B-cell) immunodeficiency

Screening tests

- Quantitative immunoglobulins
- Natural antibody (e.g., isohemagglutinins)
- Circulating specific antibodies
- Post-immunization antibodies
  - Protein antigens
  - Carbohydrate antigens
- IgG subclasses (+/−utility)
- Human immunodeficiency virus testing

Secondary tests

- B-cell immunophenotyping (e.g., CD19+, CD20+, IgM-switched/IgM+ nonswitched, CD27-naïve/CD27+ memory B cells)
- In vitro B-cell function tests (primarily research)

Evaluating B-cell function

Clinical findings that suggest an abnormality in antibody production are recurrent or chronic infections with encapsulated bacteria involving the sinopulmonary tract. Gastrointestinal, hematologic, liver, and autoimmune disorders as well as arthritis (infectious and noninfectious) may also be associated with antibody deficiencies.

The clinical screening of antibody-mediated immune function (Box 83.1) can be accomplished by measuring the levels of the major immunoglobulin classes, IgG, IgA, IgM, and IgE. The results must be compared with age-matched reference intervals (normal ranges) as these levels change significantly during childhood, with the results typically expressed as 95% confidence intervals. The serum immunoglobulin levels are the net of protein production, utilization, catabolism, and loss.

There are no rigid standards regarding the diagnosis of immunoglobulin deficiency, although an IgG value below 4 g/L (400mg/dL) in an adolescent or adult generally suggests an increased risk for infection. Agammaglobulinemia associated with significant recurrent bacterial infection is a definitive indication for intravenous or subcutaneous immunoglobulin replacement therapy after completing the immunologic evaluation to establish a diagnosis.

Measurement of a functional antibody response is often required before immunoglobulin replacement therapy reimbursement is approved and is particularly useful when the total immunoglobulin levels are only modestly depressed (or possibly normal) in the face of a strong history of recurrent infection. The simplest means to accomplish this is evaluation for natural antibodies (e.g., anti–blood group antibodies [isohemagglutinins] and specific antibodies to well-documented prior immunizations). The definitive method is immunizing and assessing preimmunization versus 3- to 4-week post-immunization antibody levels using both protein antigens (e.g., tetanus toxoid) and polysaccharide antigens (e.g., Pneumovax). Guidelines for normal responses, which are usually provided by the testing laboratory, typically consist of at least a fourfold increase in antibody and/or protective antibody levels following immunization. Protective titers to particular antigens or infectious diseases must be individually established and cannot be predicted based on the total levels of immunoglobulins.

An additional and readily available test is quantitation of IgG subclass levels; these are most useful in evaluating the IgA-deficient patient with a history of significant recurrent bacterial infections. However, in many clinical settings the detection of an IgG subclass deficiency still requires the demonstration of an abnormality in specific antibody production before immunoglobulin replacement therapy is indicated. IgG subclass levels acquire a more robust clinical reference range when tested in children >4 years. Moreover, low IgG subclass levels not accompanied by abnormal antibody functional testing are rarely an explanation for underlying recurrent upper respiratory infections.

Despite the preponderance of recurrent opportunistic infections resulting from HIV infection, appropriate testing to rule this out should be considered even in the face of recurrent bacterial infection. This type of clinical presentation may be seen more often in children infected with HIV. Testing focused on viral load may be needed to rule out HIV infection in the face of absent or diminished antibody production because the screening tests depends on an adequate humoral immune response measured by the presence of anti-HIV antibodies (tested by either enzyme-linked immunosorbent assay [ELISA] or Western blot assays).

Additional tests focused on humoral immune function are generally performed in specialized centers and fall into two general categories: evaluation of the number and characteristics of B cells and testing the function of B cells in vitro. The former determines the number of B cells as well as specific surface characteristics of B cells associated with B-cell development and function (e.g., immature B cells, memory B cells, switched B cells, transitional B cells, etc.) and is generally performed by flow cytometry (immunophenotyping). This is evolving as a useful approach to subcategorize certain patients with PIDD involving the humoral arm of adaptive immunity. The latter involves studies that test in vitro B-cell signaling and immunoglobulin biosynthesis but these approaches are generally confined to research centers.

Evaluating T-cell function

A clinical history of recurrent opportunistic infections strongly suggests an abnormality in T-cell function. Immunodeficiency involving T cells has the highest prevalence as a secondary defect associated with HIV infection. Thus, initial screening assays (Box 83.2) should always include testing for HIV infection. In addition, the absolute lymphocyte count (generated from the white blood cell count and differential) and cutaneous delayed-type hypersensitivity (DTH) response to recall antigens have served as standard T-cell function screening tests. The significance of the former relates to the fact that T cells constitute approximately two-third to three-quarters of circulating lymphocytes, with lymphocytes present in higher number than neutrophils in pediatric patients. Therefore, conditions that inhibit T-cell development or increase T-cell destruction will typically result in lymphopenia. The DTH response provides an in vivo window of T-cell function in response to a previously encountered (recall) antigen. However, failure to respond can either reflect T-cell dysfunction (T-cell anergy), lack of prior exposure to the antigen, particular dermatologic problems, or even immaturity of the immune system as seen in very young infants. Consequently, it is prudent to use more than one antigen for testing, and increasing issues with availability of recall antigens have resulted in decreasing availability of DTH testing. Clinical correlates in the medical history linked to a DTH response include the cutaneous response to poison ivy and/or other contact hypersensitivity reactions.

The screening tests for T-cell function are often followed by additional testing to complete the assessment of cellular immunity (Box 83.2). This parallels that of B cells, with quantitation and characterization (immunophenotyping) of T cells and T-cell subsets by flow cytometry (e.g., naïve and memory cells, recent thymic emigrants, etc.) together with in vitro functional testing (e.g., proliferation assays [mitogens, recall antigens, alloantigens], cytokine production, cytotoxicity testing). Both of these approaches are generally available in large medical centers as well as via commercial laboratories.

BOX 83.2

Evaluation of suspected T-cell immunodeficiency

Screening tests

- Human immunodeficiency virus testing
- Lymphocyte count
- Delayed-type hypersensitivity skin tests

Secondary tests

- T-cell enumeration (e.g., CD3+, CD4+, CD8+, naïve/memory T cells)
- T-cell proliferation (mitogen, alloantigen, antigen)
- T-cell cytokine production
- T-cell cytotoxicity

Evaluating defects in the IL-12/23 and interferon-γ pathways

Abnormalities in specific components of a cytokine-linked pathway involving T cells and monocytes/macrophages associated with recurrent infections to a limited range of opportunistic organisms, particularly mycobacteria and *Salmonella* spp., are well-documented. The infections are typically invasive and can fail to respond to long-term multiple-agent antimicrobial therapy. These findings led to a study demonstrating that IFN-γ can be an effective adjunct to antimicrobials in treating certain of these patients. Specific defects involving various components of this pathway have been identified in more than one-half of these patients, with the current research focus being clarification of the molecular basis of the remaining patients. The laboratory evaluation of patients with persistent mycobacterial infection is generally performed in specialized centers and focused on evaluating for defects in the cellular signaling pathways involving IL-12/23 and IFN-γ. More recently, a secondary defect associated with high-titer autoantibodies to IFN-γ has been characterized in association with later onset NTM infection in previously healthy hosts.

Evaluating defects in natural killer cell function

The third arm of the lymphoid system consists of circulating cells distinct from B and T cells, the natural killer (NK) cells. Deficiency in NK cell numbers and/or function has been described in patients with recurrent herpes and human papillomavirus infections, as reported in patients with transcription factor GATA2 haploinsufficiency. The actual GATA2 clinical disorder is far more complex, with infections including organisms other than viruses as well as a significant risk for malignancy together with other findings. This autosomal dominant disorder continues to be characterized as more patients are identified. Additional genetic defects have been characterized associated with increased susceptibility to generalized herpes virus infection (particularly EBV). Another category of NK cell (and cytotoxic T cell) defects is found in disorders with uncontrolled

inflammatory response initiated by specific infections that can lead to multiple organ damage (hemophagocytic lymphohistiocytosis [HLH]). An example of this is the X-linked lymphoproliferative syndrome (XLP) associated with defective NK- and NKT-cell function resulting in increased susceptibility to overwhelming EBV infection, often during childhood, that can initiate HLH. In addition, experimental models point to a role for the NK cell in allograft and tumor rejection. These various disorders point out that discovering the role of NK cells in host defense is an emerging field. Testing of NK-cell function includes immunophenotyping NK cells by flow cytometry using a variety of monoclonal reagents and assessing NK-cell cytotoxicity using standard in vitro assays; these assays are now available via selected commercial labs and medical centers.

Evaluating defects in innate immune signaling

An area of intense current investigation involves the identification of disorders associated with defective signaling by Toll-like receptors (TLR). This is a family of 13 receptors, 10 of which are expressed in humans, and these represent a phylogenetically more primitive arm of the immune system signaling via pattern recognition of unique bacterial, fungal, and viral products. An example of such a process is the activation of monocytes and macrophages by bacterial lipopolysaccharide (LPS) binding to TLR4 (complexed with CD14). This pathway of activating the immune system appears to be one of the first lines in host defense as it does not require prior exposure to the pathogenic microorganism. Two different clinical phenotypes have been identified with genetic defects involving TLR signaling. In one, there is a genetic susceptibility to serious bacterial infections that present in childhood and appear to have decreased lethality starting in adolescence. One of the hallmark features of these patients is the very limited inflammatory response to overwhelming infection (i.e., limited fever and C-reactive protein [CRP] response). The other described defect is associated with the development of herpes simplex encephalitis linked to defects in TLR3 function. Additional alterations in TLR function are likely to be identified, and this represents an evolving field in clinical immunology. Currently, the evaluation of TLR function is confined to a limited number of centers that usually screen by evaluating TLR-induced cytokine production associated with stimulation by a variety of ligands that are specific for one or more of the TLRs.

Evaluating neutrophil function

The clinical features of neutrophil dysfunction usually include recurrent bacterial and fungal infections of the skin, lymph node, lung, liver, bone, and, in some cases, the periodontal tissue. This clinical presentation is most commonly observed with neutropenia as a result of decreased production, altered localization, or increased destruction of neutrophils (see Chapter 84, "Infection in the Neutropenic Patient"). In addition, some primary and secondary abnormalities of neutrophil function also demonstrate patterns of increased susceptibility to infections (Box 83.3).

The clinical pattern of infection often can help to discriminate the underlying problem. Patients with neutropenia and those with the leukocyte adhesion deficiency Type 1 (LAD-1) tend to present with recurrent cellulitis, periodontal disease, otitis media, pneumonia, and rectal or gastrointestinal abscesses. Although LAD-1 is accompanied by a persistent circulating granulocytosis, there is effectively a tissue neutropenia. This is due to the underlying adhesion defect that prevents the directed movement of phagocytic cells, including neutrophils, to sites of infection; other rarer forms of LAD have been subsequently reported (e.g., LAD-2 and LAD-3). In contrast, patients with CGD have significant problems with liver and bone abscesses as well as pneumonias involving certain organisms, including *S. aureus*, *S. marcescens*, *Burkholderia cepacia*, *Nocardia* spp., and *Aspergillus* spp. In addition, CGD patients have exuberant inflammation that may be associated with gastrointestinal and genitourinary complications. More recently CGD patients have been reported infected with the unusual human pathogens *Chromobacterium violaceum* and *Francisella philomiragia*, organisms associated with exposure to brackish water. Finally, these patients tend to have a lower frequency of β-strep and *Escherichia coli* infections than do patients with neutropenia.

Screening studies directed at the evaluation of neutrophil function (Box 83.3) should start with the leukocyte count, differential, and morphologic review. If neutropenia (determining cyclic neutropenia requires a sequential and systematic evaluation over time) and morphologic abnormalities are ruled out, the evaluation then should be directed at assays that provide functional information about neutrophils. Included are the flow cytometric assessment of neutrophil adhesion molecules to assess for the expression of CD11a,b,c and CD18 surface antigens (the β 2-integrins that are absent or depressed in LAD-1 patients) as well as CD15s (absent in LAD-2 patients). The neutrophil oxidative burst pathway can be screened using a flow cytometric assay (dihydrorhodamine [DHR] test) or the simpler but less commonly used nitroblue

BOX 83.3

Evaluation of suspected neutrophil deficiency

Screening tests

- Multiple sequential neutrophil counts
- Review of neutrophil morphology

Secondary tests

- CD11, CD18 assessment
- Respiratory burst assessment
- Nitroblue tetrazolium test
- Flow cytometric test
- Specific enzyme activity testing
- Chemotaxis testing
- In vivo (Rebuck skin window)
- In vitro (Boyden chamber, soft agar assay)

tetrazolium (NBT) test, both of which are abnormal in patients with CGD as well as in X-linked CGD carriers. Finally, evaluation of neutrophil-directed movement (chemotaxis) can be performed in vitro with a Boyden chamber or a soft agar system as well as in vivo using the Rebuck skin window technique. Abnormalities of chemotaxis have been observed secondary to certain pharmacologic agents as well as the leukocyte adhesion deficiency, Chédiak–Higashi syndrome, Pelger–Huet anomaly, and juvenile periodontitis. A hallmark clinical feature of significantly abnormal chemotaxis is diminished neutrophil infiltration and decreased inflammation at sites of infection.

Functional testing of neutrophils has its greatest yield when evaluating patients with recurrent infections associated with a genetic neutrophil abnormality. Many patients with histories of recurrent cutaneous abscesses fail to demonstrate abnormalities in the preceding tests. This likely is related to the relative insensitivity of the available tests in discerning more subtle functional abnormalities.

Evaluating the complement system

The clinical setting in which complement defects should be suspected varies depending on the type of defect. Abnormalities in the early components of the complement pathway may result in recurrent bacterial sinopulmonary infections but typically also have a history of autoimmunity. Defects in the later components of complement affecting the membrane attack complex (MAC, C5–C9) result in increased susceptibility to infections with *Neisseria* organisms, usually presenting with meningitis and/or sepsis. There are rare defects in components of a second complement pathway, the *alternative pathway*, that may also present with recurrent infections.

The best screening test (Box 83.4) for the classical complement pathway is the total hemolytic complement activity (CH50) assay, which is often ordered together with the alternative pathway (AP) 50 test used to screen for defects in the alternative complement pathway. Assuming correct handling of the serum sample (complement components are very labile so any abnormal test result should be repeated to rule out mishandling of the sample), a markedly depressed or absent CH50 result strongly suggests a classical complement component deficiency. If the CH50 and AP50 are both abnormal, it suggests that the common components to both pathways (i.e., late components) are defective. Selected component immunoassays are available in larger laboratories, and component functional testing may be available in very specialized complement laboratories.

BOX 83.4

Evaluation of suspected complement abnormality

Screening tests
- CH50 assay
- AP50 assay

Secondary tests
- Component immunoassays
- Component functional assays

Genetic testing

The availability of nonbiased genetic testing depending on next-generation sequencing (NGS) has revolutionized the capacity to identify patients with inherited defects in immune function. This has resulted in an expanding number of genetic defects linked to PIDD and has also defined a widening spectrum of the clinical phenotypes associated with specific genetic variants. It is now reasonable to introduce genetic testing in the setting of a patient with a laboratory-established defect in immune function. Presently, this involves either targeted NGS using prescribed gene panels linked to PIDD or whole-exome sequencing (WES), with the likelihood that, in the near future, whole-genome sequencing (WGS) will become more readily available. Defining a specific genetic defect can help in better choosing the most appropriate therapy and, with some of the more recently defined immune defects, can lead to a personalized approach to therapy.

Recommendations

The clinical pattern of recurrent infections remains the single most useful clue in determining the likelihood of immune deficiency and identifying the best approach for evaluation. HIV infection remains one of the most likely cause of immune deficiency, and appropriate diagnostic testing for HIV is critical, particularly in the setting of recurrent opportunistic infection. When the history identifies repeated bacterial infections involving the sinopulmonary tract, abnormalities in antibody production, and very rarely complement component deficiency, should be considered. Opportunistic infections suggest T-cell dysfunction, while bacterial and fungal infections of the skin, lungs, and bone strongly suggest defective neutrophil function. The current area of intense investigation is focused on recurrent/chronic infections involving a more limited range of microorganisms or particular organs or organ systems, with much of this focused on the innate immune system or the interface between the innate and adaptive immune systems. It is important to keep in mind that the frequency of infections between affected individuals can vary significantly, and the line distinguishing normal from abnormal is not always clear. However, infections that are recurrent and difficult to treat or those that involve unusual organisms should definitely raise suspicion of an underlying immunodeficiency.

Laboratory studies are essential for evaluating the status of immune function. However, the prudent use of these tests requires that they be applied in an orderly fashion, starting with simpler screening tests selected according to the clinical clues provided from the patient history and examination. The results of these tests are relatively easy to interpret when either clearly normal or absolutely abnormal.

The difficulty arises in determining the actual degree of immune dysfunction when the test results fall in an indeterminant region. To address this, combinations of tests often help to clarify the status of immune function or dysfunction, and involvement of a specialist with extensive knowledge of the clinical presentation and evaluation of PIDD can be crucial.

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Suggested reading

Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiencies. *J Allergy Clin Immunol*. 2015;136:11861205.

Camargo JF, Lobo SA, Hsu AP, et al. MonoMAC syndrome in a patient with a GATA2 mutation: Case report and review of the literature. *Clin Infect Dis*. 2013;57(5):697–699.

Casanove JL, Abel L, Quitana-Murci L. Human TLRs and IL-1Rs in host defense: Natural insights from evolutionary, epidemiological, and clinical genetics. *Annu Rev Immunol*. 2011;29:447–491.

Delmonte OM, Fleisher TA. Flow cytometry: Surface makers and beyond. *J Allergy Clin Immunol*. 2019;143:528–537.

Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev*. 1991;4:359–395.

Heimall JR, Hagan D, Hajjar J, et al. Use of genetic testing for primary immunodeficiency patients. *J Clin Immunol*. 2018;38:320–329.

Holland SM. Chronic granulomatous disease. *Hematol Oncol Clin North Am*. 2012;27:89–99.

Leiding JW, Holland SM. Warts and all: Human papilloma virus in human immunodeficiencies. *J Allergy Clin Immunol*. 2012;130:1030–1048.

Mace EM, Orange JS. Emerging insights in human health and NK cell biology from the study of NK cell deficiencies. *Immunol Rev*. 2019;287:202–225.

Notarangelo KD, Fleisher TA. Targeted strategies directed at the molecular defect: Toward precision medicine for select primary immunodeficiencies. *J Allergy Clin Immunol*. 2017;139:715–723.

Orange JS, Ballow M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2012;130 (Suppl 3):S1–S24.

Picard C, Gaspar BH, Al-Herz W, et al. International Union of Immunologic Societies: 2017 Primary Immunodeficiency Diseases Committee report on inborn errors of immunity. *J Clin Immunol*. 2018;38:96–128.

Puel A, Cypowyj S, Maródi L, et al. Inborn errors of IL-17 immunity underlie chronic mucocutaneous candidiasis. *Curr Opin Allergy Clin Immunol*. 2012;12:616–622.

Rosain J, Kong XF, Martinez-Barricarte R, et al. Mendelian susceptibility to mycobacterial disease. *Immunol Cell Biol*. 2018; doi:10.1111/imcb.12210.

Rosenzweig SD, Holland SM. Recent insights into the pathobiology of innate immune defects. *Curr Allergy Asthma Rep*. 2011;11:369–377.

Stray-Pedersen A, Sorte HS, Samarakoon P, et al. Primary immunodeficiency diseases: Genomic approaches delineate heterogeneous Mendelian disorders. *J Allergy Clin Immunol*. 2017 Jan;139(1):232–245.

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Infection in the neutropenic patient

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Patients receiving chemotherapy are at high risk for developing neutropenia and severe infections when their neutrophil count is depressed. The American Society of Clinical Oncology (ASCO) and Infectious Diseases Society of America (IDSA) define neutropenia as an absolute neutrophil count (ANC) of ≤1,000 cells/μL. Severe neutropenia is considered <500 cells/μL, and the term "profound neutropenia" is used for an ANC <100 cells/μL. Fever in the neutropenic patient is defined as a single temperature of >38.3°C/101°F or a temperature of >38.0°C/100°F lasting more than an hour. Given the lack of inflammatory cells associated with neutropenia, signs of infection may be subtle. Skin and soft tissue infections may lack the typical induration, erythema, and warmth often seen in patients with an intact immune system. A pulmonary infection may have only a subtle infiltrate on chest radiography, and cerebrospinal fluid pleocytosis may be modest or absent despite ongoing meningitis. Some patients may not mount a fever at all, and the presence of hypotension, tachycardia, or delirium may be the only presenting features of infection.

By its very nature, neutropenic fever occurs in those who are immunologically vulnerable and often carry significant infectious comorbidities, such as central venous access, breakdown of the body's physical barriers to infection, and nutritional deficiencies. Therefore, it is not surprising that febrile neutropenia carries significant morbidity and mortality. Researchers have been investigating modalities to help prevent febrile neutropenia, such as the use of colony-stimulating factors (CSF), dietary changes, and infection control measures. In this chapter, we focus on the main causes of infections in febrile neutropenia and selection of antimicrobial therapies.

Causes of infection in the neutropenic patient

Gram-negative organisms

Gram-negative organisms cause a variety of infectious processes ranging from primary bacteremia to infections of the gastrointestinal, genitourinary, and respiratory tracts. Enteric gram-negative organisms such as *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp. play a significant role in the morbidity and mortality due to infection in neutropenic patients. The mechanism of infection is related to chemotherapy-induced mucositis facilitating translocation of these organisms into the bloodstream, which in turn aids their dissemination. Another important organism that can lead to significant disease is *Pseudomonas aeruginosa*, which colonizes patients and may then gain entry through the respiratory tract, disruption of skin and mucosa, and indwelling catheters.

Because infections due to gram-negative organisms, especially *P. aeruginosa*, can be life-threatening, patients with neutropenic fever should be started on an agent with gram-negative and anti-pseudomonal activity. Another concern is increased incidence of plasmid-mediated extended-spectrum β-lactamases in the Enterobacteriaceae family, which inactivate most penicillins and cephalosporins. Carbapenemases can render Enterobacteriaceae and pseudomonas resistant to all β-lactams including carbapenems. Resistance patterns vary significantly among institutions, persons, and over time, and sensitivity testing of bacterial

isolates is important to ensure adequacy of therapy. Appropriate antimicrobial therapy, coupled with source control such as abscess drainage or catheter removal, provides the best chances of treatment success.

One particular infection unique to neutropenic patients is *neutropenic enterocolitis* or "typhlitis," an inflammatory process of the cecum and ascending colon. While the exact etiology of this process is unclear, it is believed to be caused by mucosal injury from cytotoxic agents and impaired host defenses leading to invasion by microorganisms. Patients develop fever and right-sided abdominal pain and are at increased risk for perforation. CT demonstrates right-sided colitis and, in severe cases, can show pneumatosis coli or evidence of bowel perforation. In cases where perforation has not occurred, treatment consists of broad-spectrum antibiotics that cover enteric gram-negative rods, anaerobes, and *Enterococcus* spp. Surgery is technically difficult in these patients and not usually needed as studies have demonstrated that antibiotics are usually able to control the infection until the neutrophils recover.

Gram-positive organisms

Among patients with neutropenia, there has been an increase in severity and numbers of gram-positive infections due to indwelling catheters and damage to mucosal surfaces from cytotoxic chemotherapy. The bloodstream is the most common site of gram-positive infections. The three most common organisms causing bacteremia from indwelling catheters are coagulase-negative staphylococci, *Staphylococcus aureus*, and *Enterococcus* spp. (see Table 84.1). When cellulitis occurs, it is most commonly due to β-hemolytic streptococci and *S. aureus*. Most of these organisms have the potential for antimicrobial resistance, such as methicillin-resistant *S. aureus* (MRSA), and require targeted antimicrobial therapy. Infections due to viridans streptococci resulting in severe sepsis have been noted in patients with severe mucositis, ceftazidime use, or prophylaxis with ciprofloxacin or levofloxacin.

In patients with possible gram-positive infections, vancomycin is an appropriate empiric treatment. It provides adequate coverage for the most common organisms such as staphylococci, streptococci, and most enterococci; however, *Enterococcus faecium* is often resistant to vancomycin. The rates of this resistance are variable among institutions, but may be as high as 90%. *E. faecalis* is less likely to have vancomycin resistance. For patients with vancomycin-resistant organisms or vancomycin allergy, alternative agents include daptomycin or linezolid. Daptomycin is effective in staphylococcal bacteremia and severe skin and soft tissue infection. It is inactivated by pulmonary surfactant and is therefore not recommended for disease affecting the airways. Linezolid is approved for skin and soft tissue infections but should not be used for bloodstream infections.

Duration of treatment for gram-positive organisms varies based on the type of infection. Infections with these organisms do not lead to sepsis syndrome and early mortality as quickly as gram-negative bacteria but may cause significant complications if not treated appropriately. Infections of the skin and soft tissue require at least 7 days of therapy with adequate debridement when indicated. Bacteremia due to *S. aureus* often necessitates 4 weeks of therapy if the source is not located or if the bacteremia does not resolve quickly, whereas enterococcal and coagulase-negative staphylococcal infections can be treated for shorter durations, especially in central line–associated bacteremia with prompt removal of infected catheters.

Anaerobes

Anaerobes are often commensal flora of the gastrointestinal tract but can cause infections in neutropenic patients as a result of mucosal damage. Anaerobic coverage is considered in patients with significant abdominal complaints while awaiting cultures. This includes coverage for *Bacteroides* spp. and *Prevotella* spp. Acceptable antibiotics include ampicillin/sulbactam, piperacillin/tazobactam, carbapenems, or addition of metronidazole to other regimens.

Clostridioides (formerly clostridium) difficile (C. diff) colitis is a concern in those whom develop diarrhea while on antibiotics. Numerous chemotherapies and conditioning regimens cause diarrhea, and chemotherapeutics have antimicrobial activity. When a patient develops significant diarrhea and abdominal pain while receiving antibiotics, consider initiating oral vancomycin while awaiting C. diff testing. An important part of C. diff treatment includes stopping the causative agent; unfortunately, that can be impractical in febrile neutropenia because of the concern for other

TABLE 84.1 **COMMON GRAM-POSITIVE BACTERIA CAUSING INFECTION IN THE NEUTROPENIC PATIENT**

Bacteria	Form of infection	Empiric antibiotic of choice
Staphylococcus aureus	Bacteremia, skin, and skin structure infection	Vancomycin[a]
Coagulase-negative staphylococci	Bacteremia	Vancomycin
Enterococcus spp.	Bacteremia	Daptomycin[b]
β-hemolytic streptococci	Skin and skin structure infection	Penicillin
α-hemolytic streptococci	Bacteremia, endovascular infection	Ceftriaxone[c]
Streptococcus pneumoniae	Respiratory	Ceftriaxone

[a] Variable resistance to β-lactams, and clindamycin.
[b] Incidence of vancomycin resistance is increased in individuals with previous antibiotic exposure.
[c] Penicillin resistance varies; local resistance rates should be reviewed.

infections. Definitive therapy consists of oral vancomycin, however, the presence of ileus may interfere with drug delivery to the site of infection and therefore intravenous (IV) metronidazole or vancomycin enemas are often added as adjuvant therapies. In addition, close monitoring for complications is necessary, as severe or refractory cases may require surgical intervention.

Fungi

Fungal infections are increasingly common among patients with neutropenia, especially those with profound and prolonged neutropenia, such as patients with acute leukemia or lymphoma or those awaiting engraftment post stem cell transplant. Other factors that increase the risk of infection include chronic indwelling catheters, mucosal breakdown, parenteral nutrition, and prolonged antimicrobial therapy.

Candida spp. are the most common cause of fungal infections in these patients and one of the leading causes of catheter-associated bloodstream infections. Therapy for *Candida* bloodstream infection includes initiation of antifungals, preferably an echinocandin, as well as removal of any indwelling catheter to help clear the organism from the bloodstream. In addition, ophthalmologic exam is recommended to rule out endophthalmitis, preferably after white cell counts have recovered. *Candida* may also cause disseminated disease involving organs such as the liver and spleen. In invasive candidiasis, blood cultures are <70% sensitive; therefore, in patients with a high clinical suspicion for candidiasis, imaging of the abdomen with attention to the liver and spleen is necessary. Yeast and mold infections are seldom the initial cause of fever in neutropenic patients but instead present as persistent or recurrent fevers in patients receiving antibiotics. Empiric antifungal therapy and investigation for fungal infection should be considered for patients who remain febrile after 4 to 7 days of appropriate antibacterial therapy or those who received antimicrobial prophylaxis.

With the commonplace usage of yeast-active antifungals, the emergence of molds in a susceptible patient may occur. The most common pathogen in this setting is *Aspergillus*; however, other molds such as the Zygomycetes are increasing in incidence and have a similar presentation. Molds are ubiquitous in the environment and may cause pulmonary or sinus disease in neutropenic patients. Zygomycetes infection should be considered if rhinosinusitis or pulmonary disease occurs while the patient is on voriconazole or an echinocandin.

Pulmonary fungal infections have variable presentations including nodules, infiltrates, infarction, or cavities. A biopsy demonstrating the organism on pathology in addition to a positive culture proves the diagnosis; however, due to procedural risks and patient comorbidities, the diagnosis is often made clinically. Because many filamentous fungi resemble *Aspergillus* on histology, cultures are important to distinguish it from the other molds. Duration of therapy should be prolonged, with radiologic evaluation to demonstrate improvement or cure.

Any patient with neutropenia and fever who complains of sinus congestion, pain, or epistaxis should be evaluated for possible fungal sinusitis. Typical findings include mucosal thickening on radiography and necrosis or eschar on direct visualization. Definitive diagnosis is made by culture and histopathology of biopsy specimens. The treatment course is often protracted but consists of immediate therapy with an appropriate antifungal agent along with rapid surgical debridement.

Pneumocystis jirovecii (*carinii*) is seen in patients with leukemia or lymphoma—especially those who have been on long-term steroids. *Pneumocystis* pneumonia typically presents insidiously with progressive dyspnea, dry cough, and fever, but may also present with a more rapid onset of symptoms resembling a bacterial pneumonia. When this infection is suspected, bronchoscopy with a Gomori-methenamine silver stain (GMS), direct fluorescent antibody staining, or detection of DNA using polymerase chain reaction (PCR) can also aid in diagnosis. The yield of bronchoscopy for the diagnosis of *Pneumocystis* is lower in cancer patients than in HIV-1-infected patients due to lower fungal burden. Therapy including high-dose trimethoprim-sulfamethoxazole (TMP-SMX) and steroids if significant hypoxia is present) should be adequate for a duration of up to 3 weeks.

Because the diagnosis of many fungal infections requires invasive procedures, two serum diagnostic tests can be used to help in the detection of common fungal infections. The β-(1–3)-D glucan test is used to detect a cell wall component of many pathogenic fungi, including *Candida, Aspergillus, Pneumocystis,* and *Fusarium* spp. One significant limitation of the β-(1–3)-D glucan test is that it is not specific for any single fungal species. The galactomannan assay is more specific for *Aspergillus* spp. as it detects the galactomannan in the *Aspergillus* cell wall. False-positive results are seen in both assays with the use of β-lactam antibiotics, while false-negative results are seen in patients who are receiving antifungal therapy. Despite these limitations the β-(1–3)-D glucan and the galactomannan tests can assist in determining the need for empiric treatment.

Other organisms

Respiratory viral infections can cause fever as well as significant morbidity in the neutropenic patient. Expanded availability of quantitative real-time multiplex PCR has assisted in identifying the associated pathogen in patients with respiratory symptoms. Respiratory viral infections are often seasonal, and their identification can help implement infection control practices to halt their spread as well as identify those who would benefit from treatment. While no guidelines exist for the treatment of respiratory viral infections in the neutropenic patient, individuals diagnosed with influenza are generally offered a course of medication even if their symptoms commenced >72 hours prior. The treatment of respiratory syncytial virus with ribavirin and/or intravenous immunoglobulins can be considered. Some centers will additionally offer treatment for parainfluenza or human metapneumovirus although there is great variability in practice. Other common respiratory viruses are treated with supportive care.

Atypical bacteria such as *Legionella*, *Mycoplasma*, or *Chlamydia* can cause pneumonia similarly to those without neutropenia. Mycobacterial infections are not very common in the neutropenic patient but adequate cultures with acid-fast stains can usually establish the diagnosis. Appropriate therapy is determined by the organism and the site of infection but is similar to what is given to

the non-neutropenic patient. Finally, parasites should be considered where the epidemiology is appropriate and the symptoms are consistent with their diseases.

Approaches to the neutropenic patient with fever

Antibiotic therapy in the neutropenic patient with fever

Some patients who present in the outpatient setting do not require admission for neutropenic fever. The cause of the fever should be assumed to be bacterial until proved otherwise. Patients should have pretreatment labs drawn including blood cultures, started immediately on antimicrobial therapy, and observed for several hours before being sent home with close follow-up. The preferred regimen for these patients is a fluoroquinolone plus amoxicillin/clavulanate.

There are numerous sets of criteria for inpatient versus outpatient treatment but ultimately a clinician's judgment is paramount. Characteristics of patients appropriate for outpatient therapy are listed in Box 84.1. If a patient fails to improve on outpatient therapy, there should be a low threshold to admit them for further treatment and workup.

Despite advances in diagnostic imaging and testing, >50% of patients with neutropenia and fever have no identifiable cause. Due to their complexity, comorbidities, and high risk of complications, many patients with neutropenic fever require hospital admission and empiric treatment with IV antibiotics. Antibiotics should include broad gram-negative coverage, including *P. aeruginosa* (Box 84.2).

The role of extended-spectrum gram-positive coverage has been well studied. Despite the preponderance of these organisms as a cause of bacteremia in patients with febrile neutropenia, routine addition of expanded gram-positive coverage does not alter mortality and therefore is not required as empiric therapy. Patients with additional risk for gram-positive infections should, however, receive vancomycin when febrile (Box 84.3).

After patients have been started on empiric agents, reassessment of antibiotics at 2 to 5 days is necessary. By this time, results of initial cultures are available. If an infectious agent is identified, antibiotics can be tailored to that organism. In those who are already on vancomycin, it should be stopped if there is no clinical evidence of an infection secondary to a gram-positive organism. In patients with continued fever at 4 days or in high-risk patients, an antifungal agent can be added to prevent or treat an indolent fungal infection, as discussed later.

BOX 84.1

Characteristics of patients appropriate for outpatient treatment of neutropenic fever

Presents in outpatient setting
Good functional status and low comorbidities
Age <60
Solid tumor or no history of prior fungal infections
Absence of kidney injury, hypotension, or other end organ damage
No severe symptoms

BOX 84.2

Antimicrobial agents for empiric therapy in the hospitalized febrile neutropenic patient

Antibiotic
Cefepime
Imipenem
Meropenem
Piperacillin/tazobactam

Antifungal therapy in the neutropenic patient with fever

There is currently no consensus recommendation on the best agent for empiric antifungal treatment. Candidemia is the most common fungal infection in the neutropenic patient and is rarely considered a contaminant. Multiple agents are available for treatment of *Candida* spp. including the azoles, echinocandins, and polyenes; however, *Candida* spp. have variable resistance to available agents. The triazole fluconazole has activity against many *Candida* spp., including *C. albicans*, *C. tropicalis*, and *C. parapsilosis*, but its activity is limited against *C. glabrata* and *C. krusei*. Therefore, an echinocandin such as micafungin, caspofungin, or anidulafungin is the preferred empiric therapy for candidemia. Echinocandins target the β-1,3-synthase enzyme in the cell wall of *Candida* spp. and are active against nearly all *Candida* spp. Amphotericin, in either its lipid or liposomal form, is an effective alternative but possesses a less desirable toxicity profile including nephrotoxicity and electrolyte wasting. Due to concerns of resistance, azoles are best used in candidemia as step-down therapies in stable patients whose isolates have demonstrated

BOX 84.3

Indications for addition of gram-positive coverage

Hemodynamic instability or severe sepsis
Radiographic evidence of pneumonia
Positive blood culture with gram-positive organism
Clinical suspicion of central line-associated infection
Skin or soft-tissue infection
Colonization with methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci, or penicillin-resistant *Streptococcus pneumoniae*
Severe mucositis
Prior fluoroquinolone prophylaxis
Use of ceftazidime as empiric gram-negative coverage

susceptibility. Many azoles also have interactions with other agents that are hepatically metabolized.

For the treatment of invasive aspergillosis, the triazoles with mold activity, such as isavuconazole, voriconazole, and posaconazole, are preferred to the various formulations of amphotericin. This is due to their improved side-effect profile and oral availability. Monitoring of steady-state drug levels is recommended for the triazoles as they are metabolized by the liver and can be affected by drug–drug interactions. Isavuconazole is the newest triazole, with high oral bioavailability in its prodrug form, known as isavuconazonium. Echinocandins are not recommended first-line for treatment of *Aspergillus* spp., and their role is limited to salvage therapy or in combination therapy for refractory disease.

For treatment of Zygomycetes, amphotericin and isavuconazole are recommended as first-line therapies. Posaconazole shows acceptable in vitro response and remains an option for step-down or salvage therapy. The oral suspension of posaconazole has variable bioavailability, and therefore the tablet or IV formulation is highly preferred. Combination therapy of amphotericin plus either an appropriate triazole or echinocandin has been utilized, most often in refractory disease, but the data supporting the efficacy of these regimens are limited.

Prophylaxis

Antibacterial prophylaxis is recommended for patients at high risk for febrile neutropenia or a neutropenia lasting >7 days. High-risk patients are those whom have received a stem cell transplant or treatment for acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS). Prophylaxis in these patients is associated with a significant reduction in all-cause mortality. The benefits of prophylaxis in lower risk patient are outweighed by adverse effects (the emergence of resistance, C. diff infection, as well as side effects). Fluoroquinolones remain the antibacterial of choice for prophylaxis due to coverage and tolerability and are recommended over TMP-SMX and cefpodoxime.

Antifungal prophylaxis is recommended for patients at high risk of profound or prolonged neutropenia and severe mucositis for the duration of the neutropenia. These factors increase the risk of *Candida* infections, and therefore the recommended prophylaxis consists of an oral triazole or parenteral echinocandin. For those with elevated risk of invasive mold infection, such as those with AML, MDS, graft-versus-host disease (GVHD), or an allogeneic-stem cell transplant, an azole active against molds, such as voriconazole, posaconazole, or isavuconazole should be utilized instead.

Prophylaxis against herpes simplex virus (HSV) and varicella zoster virus (VZV) are recommended during periods of active treatment or neutropenia. Patients who have received alemtuzumab or an allogeneic stem cell transplant should additionally receive prophylaxis against cytomegalovirus (CMV) with valganciclovir, ganciclovir, foscarnet, or letermovir.

Screening practices for hepatitis B prior to therapy vary widely between international guideline producing bodies. ASCO and IDSA recommend screening those planned to receive an anti-CD20 monoclonal antibody such as rituximab or a stem cell transplant with a hepatitis B surface antigen (HBsAg) test and hepatitis B core antibody (anti-HBc). Those who are HBsAg positive and anti-HBc positive should receive prophylaxis, and those who are HBsAg negative but anti-HBc positive should be closely monitored for hepatitis B reactivation.

Adjunctive agents

Granulocyte and granulocyte/monocyte G-CSFs have been used in patients receiving chemotherapy to shorten the duration and depth of neutropenia. The major complications of G-CSF are bone pain and flu-like symptoms. In controlled trials, human CSFs have been shown to decrease the risk of developing febrile neutropenia and infection associated with intensive chemotherapy.

TABLE 84.2 **COMMON FUNGI CAUSING INFECTION IN THE NEUTROPENIC PATIENT**

Organism	Azole of choice	Echinocandin activity	Amphotericin activity
Candida albicans	Fluconazole	Yes	Yes
Candida tropicalis	Fluconazole	Yes	Yes
Candida parapsilosis	Fluconazole	Yes[a]	Yes
Candida glabrata	Voriconazole[b]	Yes	Yes
Candida krusei	Voriconazole	Yes	Yes
Cryptococcus neoformans	Fluconazole	No	Yes
Aspergillus spp.	Voriconazole	Yes	Yes
Zygomycetes	Isavuconazole	No	Yes
Histoplasma capsulatum	Itraconazole	No	Yes
Coccidioides immitis	Fluconazole	No	Yes
Blastomyces dermatitidis	Itraconazole	No	Yes

[a] *C. parapsilosis* tends to have a higher minimal inhibitory concentration (MIC) to echinocandins, but is usually susceptible.
[b] *C. glabrata* tends to have a higher MIC to voriconazole, but is usually susceptible.

CSFs have also been studied in neutropenic patients who develop fevers. CSFs decrease days of neutropenia, but they have not been shown to decrease duration of fever, use of anti-infective agents, or cost. Importantly, there has been no decrease in mortality. Therefore, the routine use of CSFs is not recommended in neutropenic patients who develop fever.

White blood cell (WBC) transfusions are not currently recommended as an adjunctive therapy for patients with neutropenic fever. Transfusions have significant risk and toxicity including transmission of viral infections such as CMV, graft-versus-host reactions, and fever associated with transfusion reactions. Despite these risks, some centers give WBC transfusions to patients with refractory neutropenia and severe uncontrollable infections. At this point in time, this approach should be considered only experimental.

Suggested reading

Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med*. 2005;353:977–987.

Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Disease Society of America. *Clin Infect Dis*. 2011;52:e56–e93.

National Comprehensive Cancer Network. Prevention and treatment of cancer related infections (version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf

Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1–e60.

Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol*. 2018;36(30):3043–3054.

Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice clinical guideline update. *J Clin Oncol*. 2018;36(14):1443–1453.

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Infections in patients with neoplastic disease

Amar Safdar and Donald Armstrong

Patients with neoplastic disease and suspected infection require the following main factors to be considered in their evaluation: (1) geographic predisposition for exposure to and to acquire infection including prior colonization with drug-resistant organisms and alteration in hosts' micro-biota; (2) known and unrecognized immune defect or defects due to underlying malignancy or antineoplastic therapy, or both (Table 85.1); (3) breakthrough infections due to drug-resistant pathogens in patients receiving antimicrobial chemoprophylaxis, and (4) familial/genetic predisposition to certain infections in the immunocompromised host. The febrile cancer patient may also have fever from noninfectious conditions such as tumor fever or drug fever. After evaluation, the next question is whether to treat empirically.

Epidemiology

People may be exposed to a variety of organisms through travel, work, habits, or hobbies; in the home; or in other hospitals, outpatient clinics, and infusion centers. A person with children at home is likely to be exposed to a number of infectious agents such as influenza, parainfluenza, respiratory syncytial virus, varicella-zoster virus (VZV), human herpesvirus 6 (HHV-6), and cytomegalovirus (CMV). Hospitals are a rich source of antibiotic-resistant microorganisms, including multidrug-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant and/or vancomycin-tolerant *Enterococcus* species, multidrug-resistant *Pseudomonas* and *Stenotrophomonas*, and extended-spectrum β-lactamase-producing Enterobacteriaceae such as *Escherichia coli* and *Klebsiella* species. The recent global spread of carbapenem-resistant Enterobacteriaceae (CRE) has underscored the limitations of antibiotic regimens.

A recent review of 27 reports published since 2008 showed gram-negative bacteria continued to be the most prominent cause of bacteremia in cancer patients, especially patients not receiving broad-spectrum antimicrobial prophylaxis. Furthermore, high prevalence of invasive bacterial disease due to multidrug-resistant gram-negative bacteria has had substantial impact on prolonged hospitalization, higher morbidity, and death. It is important to know where an individual has been hospitalized and what resistance patterns are known to inhabit organisms in that hospital. Furthermore, as the spectrum of infection continues to change, it is imperative to follow these trends; just as community-acquired MRSA has recently surpassed hospitalization as a more common source of these resistant bacteria, other traditional risk factors for acquiring an infection may also change. In this regard, potentially life-threatening *Stenotrophomonas maltophilia* lung infections have been observed in cancer patients even in the absence of known risk factors for such infections including (1) severe, prolonged neutropenia, (2) prolonged hospitalization, and (3) stay in critical care units or mechanical ventilation.

Systemic infections due to multiple organisms have been largely underrecognized, probably reflecting underreporting due to the lack of well-established disease definition and guidelines. Polymicrobial infections, including bloodstream, pulmonary, gastrointestinal, and urinary tract, account for 15% to 20% of all infections in cancer patients. It is not uncommon to have gram-positive and gram-negative bacteremia

TABLE 85.1 **INFECTIONS CAUSING PNEUMONIA IN CANCER PATIENTS BASED ON THE UNDERLYING IMMUNE DEFECT**

Immune defect (associated neoplastic diseases)	Bacteria	Fungi	Parasites	Viruses
Granulocytopenia	*Staphylococcus aureus* *Streptococcus pneumoniae* *Streptococcus* spp. *Pseudomonas aeruginosa* Enterobacteriaceae *Escherichia coli Klebsiella* spp. *Stenotrophomonas maltophilia Acinetobacter* spp.	*Aspergillus fumigatus*; non-*fumigatus Aspergillus* Non-*Aspergillus* species hyalohyphomycosis such as *Pseudallescheria boydii*, *Fusarium solani Mucorales* (zygomycoses) Dematiaceous (Black) fungi such as *Alternaria*, *Bipolaris, Curvularia, Scedosporium apiospermum Scedosporium prolificans*		Herpes simplex virus I and II VZV
Cellular immune dysfunction	*Nocardia asteroides* complex *Salmonella typhimurium Salmonella enteritidis Rhodococcus equi Rhodococcus bronchialis Listeria monocytogenes Mycobacterium tuberculosis* Nontuberculous mycobacteria *Legionella* spp.	*Aspergillus* and non-*Aspergillus* filamentous molds *Pneumocystis jirovecii (P. carinii) Cryptococcus neoformans* Endemic mycoses due to *Histoplasma capsulatum*, *Coccidioides immitis, Blastomyces dermatitidis*	*Toxoplasma gondii* *Microsporidium* spp. *Leishmania donovani* *Leishmania infantum* *Strongyloides stercoralis* Cryptosporidium *Cyclospora* spp.	Human cytomegalovirus Respiratory viruses Influenza A and influenza B Parainfluenza type-3 Respiratory syncytial virus Adenovirus VZV HHV-6 SARS-associated coronavirus? Parvovirus B19 Paramyxovirus? Hantavirus?
Humoral immune dysfunction and splenectomy	*S. pneumoniae Haemophilus influenzae Neisseria meningitidis Capnocytophaga canimorsus Campylobacter*	*P.jirovecii (P. carinii)?*	*Giardia lamblia Babesia microti*	VZV Echovirus Enterovirus
Mixed defects	*S. pneumoniae S. aureus* *H. influenzae Klebsiella pneumonia* *P. aeruginosa Acinetobacter* spp. *Enterobacter* spp. *S. maltophilia Nocardia asteroides* complex *L. monocytogenes Legionella* spp.	*P. jirovecii (P. carinii)* *Aspergillus spp. Candida* spp. *C. neoformans Mucorales* (zygomycoses) Endemic mycoses (severe systemic dissemination)	*T. gondii* *S. stercoralis*	Respiratory viruses Influenza Parainfluenza Respiratory syncytial virus Adenovirus VZV

Abbreviation: HHV-6 = human herpesvirus 6; SARS = severe acute respiratory syndrome; VZV = varicella-zoster virus.
Note: Patients with mixed immune defects include recipients of allogeneic hematopoietic stem cell transplant; acute or chronic graft-versus-host disease; myelodysplastic syndrome; adult T-cell leukemia lymphoma. Antineoplastic agents such as cyclophosphamide, fludarabine, *L. donovani*, and *L. infantum* may lead to serious visceral leishmaniasis. *L. donovani* is seen in Africa and Asia, *L. infantum* is seen in Africa, Europe, Mediterranean, Central and South America. VZV is rarely associated with systemic dissemination in patients with humoral immune defects, or even those with mixed immune dysfunctions. *S. stercoralis* may lead to serious, life-threatening hyperinfection syndrome in patients with marked cellular immune defects.

along with *Candida* spp. bloodstream infection in severely immunosuppressed patients with orointestinal tract ulcers resulting from chemotherapy and/or radiation therapy.

With a thorough knowledge of the epidemiologic background of the patient the physician can direct investigation or start empiric antimicrobial therapy accordingly.

The next step is to consider the patient's underlying immune defect. The immune dysfunction may result from the underlying cancer, or antineoplastic therapy, including monoclonal antibodies. The organisms that must be considered in empiric therapy with reference to the host's immune dysfunction are listed in Table 85.1. In hospitalized patients, the organisms may be specific to the hospital

and, therefore, an empiric regimen appropriate for one hospital may not be appropriate for another. The infectious complication also depends on the nature of the underlying neoplasm. In patients with a hematologic malignancy such as acute myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma, and lymphoma, the overall frequency of infections may be as high as 75% to 80%, whereas patients with solid tumors such as breast or colon cancer have lower frequency of infection (≤30%) during the course of their disease.

Neutrophil defects

The most common neutrophil defect encountered in patients with malignancy is an absolute neutropenia following cytotoxic chemotherapy. Patients with acute myelogenous leukemia, aplastic anemia, or myelodysplastic syndrome may present with severe neutropenia (≤500 cells/mm^3) due to the underlying disease. It should be remembered that neutropenic patients do not make pus. Physical signs may be absent or altered, as may x-ray findings. After careful evaluation, if there is no obvious site of infection, such as cellulitis or pneumonia, the source of infection is often translocation of bacteria from the gastrointestinal tract, and empiric therapy should be directed against the organisms anticipated to be in that patient's intestinal microbiota at that time. The microbiota may vary according to the hospital the patient is in or has been in, previous courses of antibiotics, and other epidemiologic factors (see Chapter 85, Infections in the neutropenic patient). Recently, despite an overall increase in bloodstream infections due to gram-positive bacteria such as *Staphylococcus* spp., gram-negative bacteria including *E. coli* and *Pseudomonas* spp. have remained an important cause of serious systemic infection in patients with febrile neutropenia. Cather-related bacteremia is often a concern as most patients have indwelling intravascular access devices for chemotherapy and supportive care (see Chapter 107, Intravascular catheter-related infections).

Viridans streptococci can lead to rapidly fulminant sepsis, disseminated intravascular coagulation, multiorgan failure, and shock in neutropenic patients with treatment-induced disruption of orointestinal mucosa.

Patients with prolonged neutropenia (>2 to 3 weeks) are at increased risk of invasive fungal infections (IFI). With the frequent use of fluconazole prophylaxis in high-risk neutropenic patients, a decline in systemic candidiasis has been encouraging, although this has led to a rise in infections due to drug-resistant *Candida* spp. such as *Candida glabrata* and *Candida krusei*. During the past decade, introduction of echinocandin drugs such as caspofungin, micafungin, and anidulafungin has provided a safe and effective alternative for treatment of invasive candidiasis or empiric therapy in patients with persistent febrile neutropenia. In patients with profound neutropenia extending beyond 2 weeks, *Aspergillus* spp. account for most invasive mold disease. During the past two decades, a risk in nonamphotericin B-susceptible mold infections such as *Scedosporium* and *Pseudallescheria* spp. has been noted. Furthermore, increased use of *Aspergillus* active azole-based drugs such as voriconazole has resulted in a higher number of cases of sinopulmonary zygomycosis. Response to invasive mold disease continues to remain a challenge in patients with persistent neutropenia, those receiving high-dose systemic corticosteroids, and patients with graft-versus-host disease (GVHD) following hematopoietic stem cell transplantation (HSCT).

Helper T-lymphocyte defects

CD4$^+$ lymphocyte–mononuclear phagocyte defects are seen regularly in patients with underlying lymphomas, such as Hodgkin's disease, peripheral T-cell lymphoma, cutaneous T-cell lymphoma/mycoses fungoides, and those with leukemia, such as acute lymphoblastic, hairy cell leukemia, human T-lymphotropic virus 1-associated adult T-cell leukemia/lymphoma, recipients of allogeneic HSCT, and patients receiving treatment for post-HSCT GVHD. Antineoplastic therapy that disrupts the adaptive cellular immune response includes high-dose systemic corticosteroids given for extended duration; irradiation therapy; treatment with fludarabine and other purine analogs; and cyclosporine, tacrolimus, and antithymocyte globulins used in the treatment of GVHD. The antineoplastic biologics such as antibodies that inhibit interleukin-2, tumor necrosis factor, and T-cell surface receptors such as CD52 can lead to prolonged and severe defects in the cellular immune function. These patients are prey to an entirely different group of opportunistic pathogens than are patients with neutrophil defects as shown in Table 85.1. Some of these, such as *Mycobacterium tuberculosis*, nontuberculous mycobacteriosis due to *Mycobacterium avium* complex, *Nocardia asteroides* complex, and CMV, produce subacute as well as acute disease, and immediate empiric therapy may not be necessary. In other instances, however, optimal specimens should be collected and empiric therapy instituted for a subacute infection that can become acute and produce rapidly fatal disease in the severely immunosuppressed individual. Examples are tuberculosis, histoplasmosis, and pneumocystosis. If a patient with a severe T-cell defect does have fever and looks toxic without specific signs or symptoms and if there is any question about a B-lymphocyte defect, empiric therapy that covers pneumocystosis (even with negative chest radiographic findings), salmonellosis, and pneumococcus should be initiated. A reasonable regimen for this is ceftriaxone plus trimethoprim–sulfamethoxazole. *Listeria monocytogenes* can lead to serious systemic infection and due to neurotropism, empiric therapy in such patients with suspected bacterial meningitis should include coverage for listeriosis.

In patients with complex cellular immune defects such as those with GVHD receiving corticosteroids, infections due to filamentous fungi such as *Aspergillus* species and nonamphotericin B-susceptible *Pseudallescheria boydii*, *Scedosporium* species, and other black (dematiaceous) fungi may present with asymptomatic pulmonary, sinus, and/or skin lesions. If appropriate therapy with an effective antifungal agent such as voriconazole is delayed, the progressive invasive fungal disease may extend locally and disseminate to the brain. These infections at that stage are often refractory to therapy. However, immune enhancement strategies with recombinant growth factors such as granulocyte–macrophage colony-stimulating

factor and a proinflammatory cytokine such as interferon-γ may be beneficial in select groups of cancer patients with difficult-to-treat invasive fungal infections. Because voriconazole is often preferred to amphotericin B as the drug of choice for the treatment of systemic aspergillosis, a rise in invasive zygomycosis is concerning. Patients who are at a higher risk include patients with refractory leukemia, prolonged neutropenia, corticosteroid therapy, diabetes mellitus, and involvement of paranasal sinuses. In these patients treatment should include lipid formulations of amphotericin B (Am Bisome or Abelcet), although recent experience with posaconazole has led to favorable outcomes in select cancer and HSCT recipients with life-threatening zygomycosis. Because the outcome is so poor in these patients when treated with conventional therapy, other modalities have been tried, including combination antifungals (Abelcet plus caspofungin), hyperbaric oxygen therapy, granulocyte colony-stimulating factor–mobilized donor granulocyte transfusions, recombinant cytokine therapy, and prompt surgical debridement of the devitalized infected tissue.

Splenic and B-cell defects

Patients without a spleen may develop extraordinarily severe infections caused by *Streptococcus pneumoniae* (see Chapter 97, CT overwhelming postsplenectomy infection). They are also at risk for severe infections caused by *Haemophilus influenzae* and *Neisseria meningitidis*. The risk for severe disease due to *Babesia* species in such patients in the Northeastern United States has also been infrequently reported. With the emergence of penicillin-resistant pneumococci, an empiric regimen should contain ceftriaxone and vancomycin. Newer antipneumococcal agents such as linezolid may also be used. Infections with these same organisms are seen in patients with B-cell defects, especially those caused by multiple myeloma and chronic lymphocytic leukemia, in whom hypogammaglobulinemia may be severe and prolonged. In all of these patients, the disease resulting from these encapsulated organisms can be especially severe, with accompanying bacteremia, often with no obvious source. The defect may last for years, and, because of humoral immune dysfunction, these patients may respond poorly to conventional vaccines. Therefore, at present, antibiotic prophylaxis is recommended in cancer patients who are at increased risk of serious pneumococcal disease.

Summary

Evaluation of infections in the patient with neoplastic disease depends on multiple factors, including (1) epidemiologic background, (2) immune defects, (3) resident organisms in a given hospital, and (4) clinical judgment. The first three can be estimated easily. The last requires considerable bedside experience, and, in general, it is prudent to err on the side of treatment rather than observation.

Suggested reading

Montassier E, Batard E, Gastinne T, Potel G, de La Cochetière MF. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. *Eur J Clin Microbiol Infect Dis*. 2013;32:841–850.

Safdar A. Immunotherapy for invasive mold disease in severely immunosuppressed patients. *Clin Infect Dis*. 2013;57:94–100.

Safdar A. Stenotrophomonas maltophilia and Burkholderia cepacia complex. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 8th edn. Philadelphia, PA: Elsevier Churchill Livingstone; 2014 pp. in press.

Safdar A, Armstrong D. Infections in patients with hematologic neoplasms and hematopoietic stem cell transplantation: neutropenia, humoral, and splenic defects. *Clin Infect Dis*. 2011;53:798–806.

Yusuf SW, Ali SS, Swafford J, et al. Culture-positive and culture-negative endocarditis in patients with cancer: a retrospective observational study, 1994–2004. *Medicine (Baltimore)*. 2006;85:86–94.

86

Corticosteroids, cytotoxic agents

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Iatrogenic alteration of the immune system occurs with use of corticosteroids or noncorticosteroid immunosuppressants. Although there is overlap, noncorticosteroid immunosuppressants can be broadly divided into cytotoxic antineoplastic drugs and immunosuppressants used in transplantation. Because some of the cells or biologic pathways targeted by therapeutic immunosuppressive agents are essential for the body's defenses against pathogenic microorganisms, the use of immunosuppressants involves walking a fine line between therapy and iatrogenic harm.

The mechanism of action of the immunosuppressant, the dosage used, the length of therapy, and underlying disease(s) all affect the type and severity of subsequent infections. These factors also inform decisions on immunization, prophylaxis, or empirical therapy in high-risk patients.

Corticosteroids

Mechanisms of immune suppression

Corticosteroids exert a broad suppressive effect on the immune system. They achieve this in part by inhibiting transcription factors involved in activating pro-inflammatory genes, and also inhibiting lymphocyte activation, proliferation, and migration. Further, corticosteroids impair cytotoxic T-cell response and delayed-type hypersensitivity reaction. By reducing the production of interleukin-2 (IL-2), interferon-γ, leukotrienes, and tumor necrosis factor (TNF), corticosteroids dysregulate the cytokine response to antigens. Adhesion molecules on endothelial cells are reduced, and the migration of granulocytes to sites of infection is inhibited. Indirectly, corticosteroids impair phagocytosis due to their effect on glucose homeostasis. Antibody formation and turnover are also affected especially at high corticosteroid dosages and with prolonged use, and there may be reversible lymphopenia and monocytopenia. Collectively, these effects blunt cellular immunity and antigen-specific responses. Thus, while corticosteroids can be beneficial to some patients, they increase susceptibility to pathogens, particularly those that are controlled by cellular immune responses. Corticosteroids can also induce anergy and block the normal febrile response to infection. There is essentially no bone marrow suppression.

Corticosteroids as therapeutic agents in infectious diseases

The immunologic and/or inflammatory response to a pathogen may be excessive and deleterious to the host. Because the inflammatory mediators of tissue damage such as TNF, IL-1, and interferon-γ can also cause significant injury at sites distant from the initiating infection, the systemic anti-inflammatory properties of corticosteroids may provide clinical benefit. Glucocorticoids have demonstrated a beneficial role in infections such as severe *Pneumocystis jirovecii* (previously *carinii*) pneumonia (PCP) in HIV-infected individuals, tuberculosis affecting the central nervous system, and some forms of bacterial meningitis. Table 86.1 outlines disease processes for which there is moderate to good evidence that corticosteroids confer clinical benefit.

TABLE 86.1 **INFECTIONS/COMPLICATIONS OF INFECTIONS WITH MODERATE TO GOOD EVIDENCE THAT ADJUVANT CORTICOSTEROID USE HAS BENEFIT**

Infection	Corticosteroid therapy
Acute bacterial meningitis caused by *Haemophilus influenzae* type B in children or *Streptococcus pneumoniae* in adults	Dexamethasone 0.15 mg/kg q6h × 4 d
Pneumocystis jirovecii pneumonia, $P0_2$ ≤70 mm Hg in HIV-infected patients	Prednisone 40 mg BID × 5 d, then 40 mg qd × 5 d, then 20 mg qd for 11 d
Acute severe laryngotracheobronchitis (croup)	Dexamethasone >0.3 mg/kg qd × 3–4 d
Allergic bronchopulmonary aspergillosis	Prednisone 45–60 mg qd until infiltrate clears then taper
Typhoid fever, critically ill with mental status changes or shock	High-dose dexamethasone × 2–3 d
Tuberculous pericarditis, peritonitis and meningitis	Prednisone 60–80 mg qd for several weeks followed by taper
Eosinophilic meningitis caused by helminths (*Angiostrongylus cantonensis, Gnathostoma spinigerum*)	Prednisone 60 mg/d divided into three doses for 2 weeks
Severe histoplasmosis (including cases with obstruction or compression of contiguous structures)	Prednisone 0.5–1.0 mg/kg daily (maximum 80 mg/d) in taper over 1–2 weeks

Abbreviations: HIV = human immunodeficiency virus.

BOX 86.1

Pathogens associated with corticosteroid use or other causes of cellular immunodeficiency

Bacteria
- *Legionella pneumophila*
- *Listeria monocytogenes*
- *Mycobacterium tuberculosis*
- *Nocardia* spp.
- *Salmonella* spp.
- *Rhodococcus equi*

Fungi
- *Blastomyces dermatitidis*
- *Candida* spp.
- *Coccidioides immitis*
- *Histoplasma capsulatum*
- *Cryptococcus neoformans*
- *Aspergillus* spp.

Helminths
- *Strongyloides stercoralis*

Protozoa
- *Cryptosporidium parvum*
- *Pneumocystis jirovecii*
- *Toxoplasma gondii*
- *Plasmodium* spp.

Viruses
- Cytomegalovirus
- Epstein–Barr
- Herpes simplex
- Varicella-zoster
- Influenza
- Hepatitis B

Corticosteroids and risk of infection

Myriad pathogens are associated with impaired cellular immunity and corticosteroid use (Box 86.1). Most of the organisms listed rarely cause significant or life-threatening infections in the immunocompetent patient. Some, such as *P. jirovecii*, cause disease only in immunocompromised individuals.

Patients with severe opportunistic infections often have concurrent underlying impairment of cellular immunity separate from the iatrogenic impairment secondary to steroid use. Thus, the risk of infection varies by underlying disease process. For instance, patients with AIDS or childhood acute lymphocytic leukemia have higher rates of PCP than do patients without these diseases but receiving chronic corticosteroid therapy. For patients requiring chronic corticosteroid therapy, the infection rate for many of the pathogens listed in Box 86.1 is actually quite low. Infectious complications are not shown to be increased in those receiving a daily dose of <10 mg or a cumulative dose of <700 mg of prednisone. Overall, the risk increases with the dose and duration of use and may be increased by concomitant administration of other immunosuppressants. Patients who require ≥20 mg of prednisone or an equivalent dose of other corticosteroids for >1 month in combination with a second immunosuppressive drug should receive prophylaxis against PCP and other infections with trimethoprim-sulfamethoxazole (TMP-SMX). Alternative agents include dapsone, atovaquone, and inhaled pentamidine. Of note, aerosolized pentamidine is less effective than the other regimens and does not provide protection against other opportunistic infections covered by TMP-SMX. Skin induration of ≥5 mm after a tuberculin skin test is indicative of latent tuberculosis in the immune-suppressed population.

Cytotoxic antineoplastic agents

Mechanisms of action

Cancer itself is associated with immune suppression, such as neutropenia in acute leukemia or numerical/functional lymphocyte impairment in lymphoma patients. However, clinically significant infections in cancer patients are often related to the effects of cytotoxic antineoplastic agents.

The oldest class of cytotoxic drugs comprises alkylating agents, such as cyclophosphamide, busulfan, melphalan, and chlorambucil.

The purine analogs fludarabine and cytarabine constitute another important class. Although cytotoxic agents are primarily cancer chemotherapeutic drugs, they are also used in hematopoietic stem cell transplantation and severe autoimmune disorders. Antineoplastic agents are a fast-developing area, and data on infectious diseases related to these new agents are still sparse. Immunotherapy approaches are also in early phases of development, including monoclonal antibodies, bispecific antibodies, and chimeric antigen receptor (CAR) T cells, and checkpoint inhibitors such as programmed cell death protein (PD)-1 inhibitors. Recent developments in monoclonal antibodies include cluster of differentiation (CD)33 antibodies such as gemtuzumab ozogamicin or cytotoxic T-lymphocyte associated antigen (CTLA)-4 antibodies such as ipilimumab.

Clinicians must carefully consider the risks when cytotoxic agents are used in patients without cancer, recognizing that these agents, in general, inhibit DNA and/or RNA synthesis and are bone marrow suppressive with a range of effects on B and/or T lymphocytes.

Cytotoxic antineoplastic agents and risk of infection

Inhibition of proliferative cell types by cytotoxic antineoplastic agents is important for their therapeutic effects. However, all replicating cells are affected. Mucositis occurs during cytotoxic chemotherapy due to the effects on proliferative cells of the gastrointestinal and genitourinary systems, as well as on epithelial cells of the skin. Accordingly, cytotoxic chemotherapy predisposes to translocation of normal microflora (e.g., viridans streptococci from the oropharynx and intestinal gram-negative bacteria and *Candida* species) into blood and other sterile spaces, as well as superinfection (e.g., *Herpes simplex virus)* provoking severe illness.

The most common infectious complications of cytotoxic antineoplastic agents arise from therapy-induced neutropenia. Bacterial infections with gram-positive organisms are most common during periods of neutropenia, although gram-negative organisms such as *Pseudomonas aeruginosa* cause the most serious bacterial infections. *Candida* is a common fungal pathogen, likely related to disruption of mucosal integrity by cytotoxic chemotherapy. Because neutrophils are terminally differentiated cells that are continuously replenished through hematopoiesis, the effect of cytotoxic agents is typically reversible within a few weeks of stopping cytotoxic therapy. However, patients with hematologic malignancies and bone marrow transplant recipients are at risk for prolonged neutropenia. When neutropenia is prolonged, patients become at increased risk for fungal pathogens such as *Aspergillus* and *Mucorales.* American Society of Clinical Oncology/Infectious Diseases Society of America (ASCO/IDSA) guidelines (2018) recommend prophylaxis for bacterial and fungal infections when the patient is at risk for prolonged neutropenia.

Cytotoxic agents can also alter T-cell–mediated immune competence. They cause variable numerical reduction in lymphocytes, changes in the ratio of B lymphocytes to T lymphocytes, or changes in ratio of CD4+ T lymphocytes to CD8+ T lymphocytes. In contrast to neutrophils, T-cell populations are heterogeneous, including quiescent long-lived cells and short-lived cells that are sustained by variable levels of antigen-mediated differentiation. Hence, restoration of T-cell populations and immunity after cytotoxic chemotherapy may be incomplete for prolonged periods (even up to 1 year) depending on the affected T-cell populations. These effects predispose patients to viral, fungal, and parasitic infections, some of which are listed in Box 86.1. The immunosuppressive effects of cytotoxic antineoplastic agents on T-cell–mediated immune response are compounded in hematopoietic stem cell transplant recipients by the underlying disease and need for further immunosuppression due to graft-versus-host disease.

Dysfunctional cellular immunity during cytotoxic chemotherapy is associated with reactivation of quiescent infections such as herpesviruses and hepatitis B virus (HBV). Reactivation hepatitis may be fulminant and fatal, and therefore guidelines from the American Society of Clinical Oncology (2015) advise clinicians to consider HBV screening (with hepatitis B surface antigen with or without hepatitis B core antibody) in patients from high epidemiologic risk groups. In addition, screening is recommended if highly immunosuppressive treatment such as hematopoietic transplantation or a regimen containing rituximab is planned. HBV treatment before and during cytotoxic therapy should be considered in those with concerns for chronic HBV (including HBsAg negative/anti-HBc positive), but this should not delay initiation of chemotherapy. Preemptive HBV treatment should continue for at least 12 months after cessation of rituximab-based chemotherapy.

Reactivation of latent tuberculosis can occur during cytotoxic chemotherapy, and the risk varies between patient groups. For example, the risk of reactivation tuberculosis in foreign-born persons with hematologic malignancies was estimated to be 50 to 100 times that of US-born patients, while the risk of tuberculosis in US-born individuals with solid tumors was estimated to be similar to the risk in US-born individuals without cancer. Skin induration of ≥10 mm after a tuberculin skin test is considered indicative of latent tuberculosis in patients with some hematologic malignancies or some solid tumors (e.g., carcinoma of the head and neck).

Importantly, antineoplastic agents differ in their propensity for immunosuppression. Illustratively, vincristine appears less likely to cause infectious complications compared to more toxic agents. The infectious complications of purine analogs deserve special mention because these agents cause profound lymphopenia plus selective suppression (delayed recovery) of CD4+ T lymphocytes that may last several years after administration. Thus, patients have infection risks similar to what occurs in patients with AIDS. Infections caused by cytomegalovirus, *P. jirovecii*, and *Listeria monocytogenes* are particular risks when corticosteroids are used concomitantly.

Recent agents such as immune checkpoint inhibitors targeting CTLA-4, PD-1, and PD-1 ligand (PD-L1) display immune-related adverse events that differ from conventional cytotoxic chemotherapy. While overall risk for infection is relatively low, patients receiving concomitant corticosteroids or TNF- α inhibitors are at risk for developing serious bacterial infections including pneumonia and intra-abdominal infections.

Transplant immunosuppressants

Iatrogenic immune suppression is indispensable to prevent organ rejection posttransplantation. The degree of immune suppression

is the net effect of the underlying condition and treatments that the patient has received over time. This is because the immunesuppressive effects of some drugs can be prolonged and become additive with subsequent treatment. The net immune suppression, hence risk of opportunistic infections, is particularly high in patients who have received multiple treatments for rejection or hematologic malignancies. Overall, due to the growing population of immunosuppressed patients with improved survival and improved diagnostic tools, an increased incidence and spectrum of opportunistic infections has been observed.

Transplant immunosuppressants and risk of infection

For details about immunosuppressant risk in transplanted patients, see Chapter 88. The infectious disease complication is dictated by the synergy between two factors: the epidemiological exposure and the net state of immunosuppression. When the immune defect involves T cells, intracellular pathogens (Box 86.1) can be seen commonly. Thus, calcineurin inhibitors such as cyclosporine or tacrolimus block T-lymphocyte activation and inhibit cell-mediated immunity and are likely to predispose to infection with intracellular pathogens. Treatment antilymphocyte globulin (ALG) and azathioprine are also likely to inhibit cell-mediated immunity and increase the risk of infection with intracellular pathogens. Special vigilance for *Mycobacterium tuberculosis*, endemic fungi, *Cryptococcus*, PCP, and Herpesviridae is warranted in patients receiving these drugs.

In situations where the defect involves B lymphocytes and primary antibody responses, such as is the case with rituximab, infections with extracellular bacteria (Box 86.2) are more likely. Treatment with alemtuzumab can cause profound panlymphocytic effects, leading to overwhelming opportunistic infections from bacterial, viral, fungal, and parasitic causes. Finally, plasmapheresis is associated with increased risk for encapsulated bacterial infections.

Other factors that are predictive of the infectious complication posttransplant include the time elapsed since transplantation, underlying disease, and the presence of active or latent infections in the transplant recipient or donor. In general, infections in the first month posttransplant are caused by bacteria or *Candida* and often are related to the hospitalization and the surgical procedure. With the exception of herpes simplex virus reactivation, opportunistic infections due to transplant immunosuppressants occur after 1-month posttransplant. Epstein–Barr virus is unique in that it can cause posttransplant lymphoproliferative disorder (PTLD), typically after 6 months posttransplant. Belatacept in particular is associated with higher incidence of PTLD when compared to cyclosporine. Appropriate prophylaxis or empiric therapy is necessary to minimize the infectious complications of transplant immunosuppression.

BOX 86.2

Some of the pathogens encountered in patients with deficiencies in humoral immunity and/or granulocytopenia

Gram-negative bacilli
- *Escherichia coli*
- *Klebsiella* spp.
- *Pseudomonas aeruginosa*
- *Enterobacter cloacae*
- *Haemophilus influenzae*
- *Serratia* spp.
- *Proteus* spp.
- *Salmonella* spp.

Gram-positive cocci
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Enterococcus* spp.

Anaerobes
- *Bacteroides* spp.
- *Clostridium* spp.
- *Fusobacterium* spp.

Parasites
- *Giardia lamblia*

Fungi
- *Candida* spp.
- *Aspergillus* spp.

Suggested reading

Castagnola E, Mikulska M, Viscoli C. Prophylaxis and empirical treatment of infections in cancer patients. In Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 8th ed. Philadelphia, PA: Churchill Livingstone; 2015: 3395–3413.

Donnelly JP, Blijlevens NMA, van der Velden WJFM. Infections in the immunocompromised host: general principles. In Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 8th ed. Philadelphia, PA: Churchill Livingstone; 2015: 3384–3394.

Fishman JA. Infection in organ transplantation. *Am J Transplant*. 2017;17:856–879.

Lake DF, Briggs AD. Immunopharmacology. In Katzung BG, ed. *Basic and clinical pharmacology*, 14th ed. New York: McGraw-Hill; 2017: 977–1002.

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Biologics

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Introduction

Biologic therapies have revolutionized nearly every discipline of medicine. As our understanding of the relevant immunologic pathways of cancer, rheumatologic disease, and hematopoietic and solid organ transplantation has evolved, so has the discovery of new monoclonal antibodies for targeted therapy. Currently, >100 monoclonal antibodies have been approved for clinical use. This chapter highlights two major categories of commonly used monoclonal antibodies and their associated infectious complications. We outline the immunologic mechanism of action and indications of use of these important biologic therapies. We also examine the commonly reported infectious complications and summarize the role for pre-implementation diagnostics, post-implementation surveillance, and antimicrobial prophylaxis.

Lymphocyte-depleting therapies

Monoclonal antibodies that target surface proteins found on lymphocytes including alemtuzumab (humanized chimeric monoclonal antibody that recognizes CD52) and rituximab (chimeric murine/human monoclonal antibody directed against the CD20) have been used successfully in the management of lymphoproliferative disorders and autoimmune diseases. We focus on rituximab because of the propensity of available data. Rituximab is constructed with human immunoglobulin G (IgG1) and κ-chain constant regions and heavy and light chain variable regions from a murine antibody to the CD20 antigen, a hydrophobic transmembrane protein which is present on mature B lymphocytes but absent from the surface of normal plasma cells. Rituximab eliminates mature B cells. Although the CD20 antigen is absent from the surface of mature plasma cells, rituximab can be complicated by hypogammaglobulinemia; the precise mechanism is incompletely understood. Rituximab is currently approved for the treatment of non-Hodgkin's lymphoma (NHL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, and pemphigus vulgaris (PV). In addition, rituximab is approved as second-line therapy for rheumatoid arthritis (RA) not responsive to tumor necrosis factor (TNF)-blocking agents. This anti-CD20 monoclonal antibody has also been widely used off-label for lupus, autoimmune hematologic diseases (including primary idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia), multiple sclerosis, bullous dermatologic disorders, immune-mediated glomerular disease, cryoglobulinemia, and desensitization therapy prior to kidney transplantation. The recent ability to administer this drug subcutaneously provides for greater ease in administration at home.

With the expiration of the rituximab patent in the European Union and United States in 2013 and 2016, respectively, an emergence of rituximab biosimilars have surged. In a randomized trial with the biosimilar CT-P10 compared to rituximab plus cyclophosphamide, vincristine, and prednisone (CVP), treatment of advanced FL was efficacious in 97% and 93% of the patients, respectively, with comparable safety parameters.

Similarly, the biosimilar GP2013 resulted in an overall response in 87% of patients (compared to 88% in the rituximab-CVP treatment group). While these results are promising, further studies are warranted to evaluate the robust endpoints previously used to evaluate treatment of follicular lymphoma (i.e., tumor burden, maintenance, long-term effects, etc.) and potential risk of infections.

The B-cell immunomodulatory effects of rituximab can be long-lasting. Rituximab persists in the serum for many months after the drug is initially administered and can cause sustained depletion of B cells for 6 to 9 months after completion of therapy. One year after completion of rituximab, even when the quantitative number of B cells has recovered, these populations of B cells are often functionally nonequivalent to pre-rituximab B cells, with decreased expression of CD27, suggesting a relative deficiency in memory B-cell populations. In a retrospective study, marked differences were noted between different types of vasculitides. Within 9 months, patients with RA or connective tissue disease showed recovered B-cell numbers. On the contrary, patients with microscopic polyangiitis, granulomatosis with polyangiitis, or eosinophilic granulomatosis with polyangiitis showed little to no B-cell repopulation within 9 months. Additionally, late-onset neutropenia can complicate rituximab therapy, with the median time to onset of neutropenia around 102 days, often coinciding with B-lymphocyte depletion.

It is important to note the potential impact on newborns of rituximab treatment in pregnant women. Rituximab can freely pass through the placenta during the third trimester, and reductions in the B-cell populations have been noted during the first weeks of life in these newborns. Additionally, low expression of κ-deleting recombination excision circles may result in B-cell immunodeficiencies testing to be erroneously positive in these infants.

The nature and duration of these immunomodulatory effects of rituximab have implications for infectious complications. The risk of infection is elevated with increased number of rituximab courses, low serum IgG lasting as least 6 months, comorbid conditions (e.g., chronic lung disease, cardiac disease, extra-articular condition in RA patients), and the use of granulocyte colony-stimulating factor. In a study evaluating the preemptive use of rituximab in treating Epstein–Barr virus (EBV)-related posttransplantation lymphoproliferative disorder (PTLD), individuals receiving rituximab had a significantly higher incidence of bacterial infections, predominantly from gram-negative bacilli (including *Pseudomonas* and *Haemophilus*), gram-positive cocci, and atypical mycobacteria, as compared to controls. Increased rates of post-rituximab viral infections have also been reported, with hepatitis B virus (HBV) reactivation, cytomegalovirus (CMV) infection, and varicella-zoster virus (VZV) all well documented and with the median time from initiation of rituximab treatment to diagnosis of viral infection approximately 5 months. HBV reactivation occurring in the context of rituximab therapy has been specifically associated with significant morbidity and mortality. The median duration of time from rituximab administration to HBV reactivation is approximately 3 months, with 29% of cases occurring >6 months after the last dose of rituximab. While the control of HBV infection is mediated by HBV-specific cytotoxic T lymphocytes, the profound and durable depletion of circulating B lymphocytes prevents adequate antigen presentation and is thought to be a major contributing factor involved in HBV viral replication and reactivation complicating rituximab therapy. Although the risk of HBV reactivation is greatest in hepatitis B surface antigen positive (HBsAg (+)) individuals, HBV core antibody positive patients (HBcAb (+)) are also at risk for serious complications. Moreover, in a meta-analysis of patients with NHL treated with rituximab therapy where 387 individuals were found to have HBV reactivation, 304 were HBcAb (+)/HBsAg (−) individuals while only 83 individuals were HBsAg (+). Thus, early identification of patients at risk for HBV reactivation—before they receive rituximab therapy—is critical for avoiding morbidity and mortality from HBV-related disease. In patients who will receive rituximab therapy, screening for chronic HBV infection with HBsAg, HBcAb, HBsAb, and serum HBV DNA testing is indicated. HBsAg (+) individuals—regardless of whether HBV DNA is detectable in the serum—should be initiated on antiviral therapy immediately to block viral replication and disease progression prior to administration of rituximab. While there have been differing opinions as to whether HBcAb (+)/HBsAg (−) individuals should be monitored by serial HBV DNA and liver function tests (LFTs) versus immediately placed on preemptive antiviral therapy, more recent recommendations are to use prophylactic antiviral therapy in these individuals as well. While the nucleoside analog lamivudine has been most extensively studied for antiviral prophylaxis of chronic HBV, high rates of lamivudine resistance have been reported. Therefore, newer nucleoside analogs including entecavir and tenofovir—either alone or in combination—are the preferred prophylactic therapy for chronic HBV infection in the setting of rituximab administration. Current guidelines suggest initiation of anti-HBV viral therapy 1 to 2 weeks prior to rituximab therapy with continuation of antiviral therapy for a minimum of 6 months after this biologic therapy is discontinued and recommend concomitant close monitoring of HBV DNA and LFTs during the course of rituximab therapy.

Progressive multifocal leukoencephalopathy (PML), a severe and fatal central nervous system (CNS) demyelinating disease caused by reactivation of the polyomavirus John Cunningham (JC) virus, has also been reported in individuals with lymphoproliferative disorders treated with rituximab. For example, HIV-negative individuals with CLL treated with fludarabine and rituximab have been described to have clinical syndromes compatible with PML, with JC virus detectable by PCR in the cerebrospinal fluid; these patients survived only months after the diagnosis of PML was made. It is not clear if PML from reactivated JC virus was a direct result of mature B-lymphocyte depletion caused by rituximab or a consequence of concurrent T-cell–depleting therapies. Many patients with lymphoproliferative disorders who developed PML received multiple other chemotherapeutic agents, including purine analogs, corticosteroids, and alkylating agents in addition to rituximab, thus making it difficult to ascribe the presentation of PML to rituximab-related immunomodulatory effects alone. Nevertheless, given that PML has been described in individuals receiving rituximab therapy, it remains important for clinicians to remain vigilant about any neuropsychiatric decline that may be attributable to JC virus-related disease.

While no firm guidelines exist regarding prophylaxis against *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP) in non–HIV infected patients who are immunosuppressed, there is evolving

evidence that PCP prophylaxis is warranted in individuals who receive rituximab as either mono- or combination therapy, particularly in the setting of use in individuals for hematologic malignancies or underlying renal disease.

It is important to ensure that vaccinations against polio (inactivated), influenza (inactivated), *Haemophilus influenzae*, pneumococcus, tetanus, diphtheria, pertussis, hepatitis A and B, and meningococcus (when indicated) are up to date in individuals who may receive lymphocyte-depleting biologic therapies. Administration of live viral vaccines during the course of or in the peri-administration period of rituximab is contraindicated. The UK Department of Health does provide some guidance on the timing of live vaccine administration in patients who receive biologic agents, suggesting that live vaccines should not be given 4 weeks before first administration of any biologic agent or 12 months after rituximab.

Tumor necrosis factor-α inhibiting therapies

TNF-α–blocking therapy has revolutionized the care of individuals with rheumatologic disorders and inflammatory bowel disease (IBD). Four monoclonal antibodies to TNF-α—infliximab, adalimumab, golimumab, and certolizumab—are clinically used routinely. Infliximab is a chimeric monoclonal antibody comprising human immunoglobulin constant regions with murine variable regions, while adalimumab and golimumab have both human constant and variable immunoglobulin regions. These monoclonal antibodies against TNF-α are approved for the treatment of RA, psoriasis, psoriatic arthritis, and ankylosing spondylitis. Infliximab, adalimumab, and certolizumab (a pegylated humanized Fab fragment) are all approved for use in Crohn's disease. Infliximab, adalimumab, and golimumab are additionally approved for use in ulcerative colitis. Adalimumab is further indicated for juvenile idiopathic arthritis, hidradenitis suppurative, and uveitis. Furthermore, certolizumab is indicated for non-radiographical axial spondylarthrosis. Etanercept has a different mechanism of action from the anti–TNF-α monoclonal antibodies and is a soluble TNF-α receptor that binds both TNF-α and lymphotoxin. Etanercept is used to treat RA, psoriatic arthritis, plaque psoriasis, juvenile idiopathic arthritis, and ankylosing spondylitis. A systematic review revealed greater patient retention over 2 years from the initiation of treatment with golimumab when compared to other TNF-α inhibitors, specifically in the treatment of axial spondyloarthritis. Furthermore, this persistence may be lower in biologics-experienced compared to the naïve patients.

Similar to the lymphocyte-depleting therapies, there is an emergence of novel biosimilars to TNF-α inhibitors. Results from the 52-week NOR-SWITCH study demonstrated that changing from the originator (infliximab) to the biosimilar CT-P13 does not impact disease severity of all indicated diseases, safety, or immunogenicity. On the contrary, another study reported 24% of patients discontinued CT-P13 due to adverse events during a 6-month period. In a randomized, double-blind, phase 3 transition study, patients with RA had similar efficacy, immunogenicity, and safety when transitioned to the biosimilar SB2 compared to infliximab or ABP501 compared to adalimumab. Switching between the biosimilar, GP2015, and the originator etanercept product in patients with psoriasis has comparable efficacy, safety, and immunogenicity in the EGALITY phase III confirmatory efficacy and safety study. Little is known regarding the risk for infection in these biosimilars and whether the risk is comparable to TNF-α inhibitors.

TNF-α is released by activated macrophages and is essential in the control and containment of intracellular pathogens. TNF-α production recruits inflammatory cells to an area of infection and stimulates the formation and maintenance of granulomas that physically contain infection. In addition, TNF-α directly activates macrophages, which phagocytose and kill mycobacteria and other pathogens. Thus, inhibition of TNF-α significantly increases the risk of infection. Indeed, adverse effects of TNF-α inhibition includes infections, malignancies, reaction at injection site, heart failure, and demyelinating disease. In a meta-analysis of nine randomized control trials to assess the harmful effects of infliximab and adalimumab versus methotrexate or other disease-modifying antirheumatic drugs (DMARDs), the odds ratio of risk of serious infection associated with anti–TNF-α therapy was 2.0. The rate of risk of serious infection in patients with rheumatologic diseases treated with anti–TNF-α agents ranged from 3 to 6 infections per 100 patient-years, with approximately a 2.2 increase in relative risk of infection with use of these biologic agents. Anti–TNF-α therapy has also been shown to double the risk of opportunistic infections (OIs) in individuals with IBD. Similar risks were reported in a 2018 study comparing all of the TNF-α inhibitors, which may be higher with the interleukin-6 receptor inhibitor tocilizumab.

Anti–TNF-α therapies are not equivalent in their risk of infectious complications; in fact, the infectious risks associated with infliximab and adalimumab therapies are higher than that associated with etanercept. This observation is particularly relevant for mycobacterial and fungal OIs, where, compared to etanercept, infliximab has been associated with a two- to sevenfold increased risk of coccidioidomycosis, histoplasmosis, and tuberculosis (TB), with a shorter time to TB onset (17 vs. 48 weeks) and a higher proportion of TB cases with disseminated or extrapulmonary disease (25% vs. 10%). Other studies demonstrate a 12-fold greater risk of latent TB infection (LTBI) reactivation with infliximab compared to etanercept. Interestingly, the risk of acquiring nontuberculous mycobacterial infections (including *M. avium*, *M. chelonae*, *M. abscessus*, *M. marinum*) appears to be equal whether TNF-α antibodies or soluble receptors are used for therapy. Although the exact immunologic differences portending the infectious risks associated with anti–TNF-α monoclonal antibodies and the soluble TNF-α receptor inhibitor are not known, multiple mechanisms have been postulated. Unlike etanercept, monoclonal antibodies to TNF-α may have the ability to cross-link transmembrane TNF-α and induce apoptosis of TNF-producing cells. The anti–TNF-α monoclonal antibodies also bind TNF-α with greater avidity and for longer duration than etanercept; the half-life of infliximab is approximately 11 days and its biologic effect can persist up to 2 months, whereas etanercept has a half-life of 3 days and its effect on TNF-α is much more short-lived. Etanercept binds strongly to soluble TNF-α alone, whereas infliximab binds TNF-α irreversibly and has high avidity for both

soluble and transmembrane TNF-α, thus prolonging inhibition of TNF-α more than etanercept.

The most common types of infection in RA patients treated with anti–TNF-α therapy are upper and lower respiratory tract infections, urinary tract infections, and skin infections. In the Research Axed on Tolerance of bIOtherapies (RATIO) registry, where all cases of OI in patients receiving anti–TNF-α therapy for rheumatologic indications over a 3-year period were documented, multiple OIs were found in individuals receiving infliximab, adalimumab, or etanercept. The median time to occurrence of an OI from the initiation of anti–TNF-α therapy was found to be approximately 16 months. Twenty-six percent of infected individuals required hospitalization in an ICU and 10% ultimately died from OI-related complications. In almost all cases, infections were due to intracellular organisms. One-third of infections were bacterial (including *Listeria*, *Nocardia*, nontyphoidal *Salmonella, Legionella*, atypical mycobacterial spp.), 40% viral (primary and reactivation varicella, herpes simplex virus [HSV], CMV), 22% fungal (*Pneumocystis*, *Aspergillus* spp., *Cryptococcus*), 4% *Mycobacterium tuberculosis*, and 4% parasitic (*Leishmania*). Listeriosis and legionella infections ultimately became black box warnings for anti–TNF-α therapies on US packing inserts. Interestingly, the anatomic sites of infection in anti–TNF-α therapies were often unusual (i.e., TB cases were predominantly extrapulmonary, and there were several cases of *Listeria* and *Salmonella* causing septic arthritis). At OI diagnosis, anti–TNF-α therapy was discontinued in all but one patient; anti–TNF-α therapy was resumed in 40% of patients after a median duration of 1.7 months of therapy for the OI. Postoperative *Staphylococcus aureus* infection has also been observed in individuals on anti–TNF-α therapy, with increased wound dehiscence and postoperative bleeding noted in individuals who had continued anti–TNF-α therapy close to the perioperative time period.

In a meta-analysis of 22 randomized controlled trials of adults with either Crohn's disease or ulcerative colitis receiving biologic therapy, anti–TNF-α therapy was found to double the risk of OI. In IBD patients receiving anti–TNF-α therapy, infection with *Streptococcus pneumoniae*, *Legionella pneumophila*, *Salmonella* spp., *Listeria monocytogenes*, *Nocardia*, and *Clostridium difficile* species have all been observed. Infection with *M. tuberculosis*, herpes simplex, primary varicella, herpes zoster, CMV, EBV, and oral/esophageal candidiasis was also reported.

M. tuberculosis infection is a well-documented risk in the early phase of anti–TNF-α treatment and often manifests as extrapulmonary and disseminated *M. tuberculosis* infection rather than isolated pulmonary infection. The majority of TB infection observed in the context of anti–TNF-α therapy is due to reactivation of LTBI rather than newly acquired TB infection. For these reasons, screening for LTBI is recommended prior to initiation of anti–TNF-α therapy, and repeated screening is recommended for individuals who may have acquired TB since their first screening. Diagnostics options for evaluating LTBI prior to or during anti–TNF-α therapy include regular tuberculin skin test (TST), boosted TST, and interferon-γ release assay (IGRA) using *M. tuberculosis*-specific antigens. For individuals found to have LTBI, there are limited data on the time interval during which patients should be on LTBI therapy before initiation of anti–TNF-α therapy, although there is some evidence that suggests concurrent LTBI and anti–TNF-α therapy is acceptable. If an active TB infection is diagnosed while an individual is on anti–TNF-α therapy, guidelines suggest discontinuation of anti–TNF-α therapy. Patients with Crohn's disease treated with a TNF-α inhibitor and an existing *M. paratuberculosis* infection induces survival of the bacteria, which may contribute to elevated risk of infections. However, there are reported cases of clinical worsening with discontinuation of anti–TNF-α therapy in the setting of disseminated or extrapulmonary TB. The hallmark of this clinical scenario—termed *paradoxical reaction*—is the presence of worsening inflammation despite evidence for microbiologic response and improvement. In this specific clinical situation, the optimal timing of reinitiation of anti–TNF-α therapy is not clear.

Endemic fungal infection is also a well-described complication in patients on anti–TNF-α therapy. Histoplasmosis, which can present as asymptomatic infection, severe pneumonitis, mediastinal lymphadenopathy, chronic pulmonary cavitary disease, pericarditis, and arthritis, is the most commonly reported invasive fungal infection in patients treated with TNF-α inhibitors and is actually reported more frequently in these immunocompromised hosts than TB. Even in the United States, individuals on anti–TNF-α therapy had significantly increased risk of histoplasmosis infection with mortality as high as 20%. Similar to *M. tuberculosis*, there is an increased risk of histoplasmosis with the anti–TNF-α monoclonal antibody therapies as compared to etanercept; the incidence of histoplasmosis is estimated at 18.8/100,000 persons treated with infliximab, compared to 2.7/100,000 persons treated with etanercept. Like histoplasmosis, blastomycosis infection (presenting as CNS involvement or severe pulmonary infection in the immunocompromised host) and coccidioidomycosis infection (presenting as acute or subacute pneumonia) are typically acquired as a new infection rather than reactivation in individuals on anti–TNF-α therapy. Since coccidioidomycosis often is asymptomatic, in individuals who reside in endemic areas (southwestern United States, Central America, South America) without prior history of fungal infection, a chest radiograph and *Coccidioides immitis* serology are recommended prior to initiation of anti–TNF-α therapy. Interestingly, a retrospective study suggested screening preceding anti–TNF-α therapy may reduce risk of symptomatic coccidioidomycosis. Other fungal infections such as invasive pulmonary aspergillosis, cryptococcal cavitating pneumonia, reactivation of pulmonary paracoccidioidomycosis, meningitis and disseminated disease, oral/genital candidal infection, and PCP have been less commonly described in the setting of anti–TNF-α therapies.

The impact of anti–TNF-α therapy on the incidence of viral infections is less clear. CMV infection is known to complicate therapy with TNF-α antagonists; while CMV reactivation is common, disseminated life-threatening end-organ disease is less common. Primary varicella and reactivation HSV and herpes zoster have been identified in individuals with IBD treated with anti–TNF-α therapy. While there is limited literature on hepatitis B (HBV) reactivation in the setting of TNF-α blockade, animal models do suggest that TNF-α promotes clearance of HBV and that TNF-α is secreted by HBV-specific cytotoxic T lymphocytes (CTL) and synergizes with interferons to suppress HBV viral activity. There have been case reports of individuals with chronic HBV who

developed fulminant hepatitis after being treated with infliximab. For this reason, prophylactic anti-HBV therapy is recommended during the duration of anti–TNF-α therapy and for 3 to 6 months post completion of anti–TNF-α therapy in HBsAg(+) individuals and can be considered in HBcAb(+) individuals. Hepatitis C infection does not appear to progress in the setting of TNF-α blockade. The limited data on HIV infection in the setting of anti–TNF-α therapy suggest that HIV infection does not progress in individuals where anti–TNF-α therapy is used. However, there are limited data on HIV outcomes and risk for OI in the setting of anti–TNF-α therapy, and, consequently, HIV infection is still considered a relative contraindication to initiation of anti–TNF-α therapy. Human papillomavirus (HPV) infection is not a contraindication for use of anti–TNF-α therapy, though individuals with extensive cutaneous and/or anogenital HPV-related disease are at high risk for progressive skin disease. Individual case reports of EBV-related PTLD in the setting of anti–TNF-α therapy have also been reported. PML from JC virus reactivation is not a common complication of anti–TNF-α therapy.

In addition to identifying epidemiologic risk factors that place an individual on anti–TNF-α therapy at risk for reactivation of LTBI, endemic fungal infection, and/or reactivation of latent herpesvirus or chronic HBV infection, ensuring that vaccinations are up to date prior to initiation of anti–TNF-α therapy is critical in preventative care. All patients receiving anti–TNF-α therapy should be vaccinated against pneumococcus and should receive inactivated influenza vaccination annually. Hepatitis B vaccination is also prudent. Other non-live vaccines can be given according to established US Centers for Disease Control and Prevention (CDC) guidelines/schedules. Live attenuated vaccines including intranasal influenza, oral polio, measles/mumps/rubella, yellow fever, and zoster should not be administered in individuals who have been recently treated with anti–TNF-α therapy, and guidelines suggest waiting a minimum of 6 months after infliximab and 4 weeks after etanercept is completed before any live vaccine is considered for administration.

Suggested reading

Atzeni F, Sarzi-Puttini P, Botsios C, et al. Long-term anti–TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: Comparison of adalimumab, etanercept and infliximab in the GISEA registry. *Autoimmun Rev*. 2012;12(2):225–229.

Bae SC, Lee YH. Comparative efficacy and safety of biosimilar-infliximab and originator-infliximab in combination with methotrexate of randomized controlled trials. *Int J Rheum Dis*. 2018;21(5):922–929.

Campbell L, Chen C, Bhagat SS, Parker RA, Östör AJ. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: A systematic literature review and meta-analysis of randomized controlled trials. *Rheumatology (Oxford)*. 2011;50(3):552–562.

Christou EAA, Giordino G, Worth A, Ladomenou F. Risk factors predisposing to the development of hypogammaglobulinemia and infections post-rituximab. *Int Rev Immunol*. 2017;36(6):352–359.

Downey C. Serious infection during etanercept, infliximab and adalimumab therapy for rheumatoid arthritis: A literature review. *Int J Rheum Dis*. 2016;19(6):536–550.

Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: Meta-analysis of randomized controlled trials. *Am J Gastroenterol*. 2013;108(8):1268–1276.

Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. *Semin Arthritis Rheum*. 2010;39(5):327–346.

Linda H, von Heijne A, Major EO, et al. Progressive multifocal leukoencephalopathy after natalizumab monotherapy. *N Engl J Med*. 2009;361(11):1081–1087.

Makita S, Tobinai K. Rituximab biosimilars: introduction into clinical practice. *Lancet Haematol*. 2017;4(8):e342–e343.

Martin SI, Marty FM, Fiumara K, et al. Infectious complications associated with alemtuzumab use for lymphoproliferative disorders. *Clin Infect Dis*. 2006;43(1):16–24.

Peleg AY, Husain S, Kwak EJ, et al. Opportunistic infections in 547 organ transplant recipients receiving alemtuzumab, a humanized monoclonal CD-52 antibody. *Clin Infect Dis*. 2007;44(2):204–212.

Ruderman EM. Overview of safety of non-biologic and biologic DMARDs. *Rheumatology (Oxford)*. 2012;51(Suppl 6):vi37–43.

Salles G, Barrett M, Foà R, Maurer J, O'Brien S, Valente N, Wenger M, Maloney DG. Rituximab in B-cell hematologic malignancies: A review of 20 years of clinical experience. *Adv Ther*. 2017;34(10):2232–2273.

Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: Meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis*. 2009;68(1):25–32.

Svedbom A, Storck C, Kachroo S, Govoni M, Khalifa A. Persistence with golimumab in immune-mediated rheumatic diseases: A systematic review of real-world evidence in rheumatoid arthritis, axial spondyloarthritis, and psoriatic arthritis. *Patient Prefer Adherence*. 2017; 11:719–729.

Wallis RS. Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. *Lancet Infect Dis*. 2008;8(10):601–611.

Wallis RS, Schluger NW. Pulmonary infectious complications of tumor necrosis factor blockade. *Infect Dis Clin North Am*. 2010;24(3):681–692.

Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. *Nat Clin Pract Rheumatol*. 2006;2(11):602–610.

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Infection in transplant patients

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Introduction

Infections are common complications of organ, tissue, and stem cell transplantation. Whether it is due to a bacterium, virus, fungus or parasite, the clinical disease caused by any of these pathogens is often severe, leading to increased morbidity and potential mortality. Several factors inherent to the transplant recipient or related to the donor, the environment, and circumstances surrounding the transplant procedure (such as surgical techniques and immunosuppressive drugs) increase the risk of infectious complications. Depending on risk profiles of transplant recipients, some infections are predictable and preventable, while others remain unexpected. Generally, the overall risk of infection after transplantation is determined by (1) epidemiologic exposures of the donor and recipient and (2) the overall net state of immunosuppression.

Risk factors of infection after transplantation

Epidemiologic exposures

The major sources of pathogens are (1) the transplant recipient who may harbor latent, active, or subclinical infection prior to transplantation; (2) the donor who may harbor latent, active, or subclinical infection that could be transmitted through the allograft (donor-transmitted infections); and (3) the environment (including the healthcare setting and the community). Table 88.1 lists some of the common risk factors for acquiring infection after transplantation.

The transplant candidate and recipient

The epidemiologic exposures of transplant candidates should be assessed to determine the risk of infection after transplantation and guide preventive measures. A detailed medical and exposure history should be elicited during their evaluation for transplantation. Box 88.1 lists the tests that are recommended in the evaluation of transplant candidates (and their donors) prior to organ transplantation. During the process of their evaluation, some transplant candidates will be found to have active infection (such as subacute bacterial peritonitis in liver candidates with ascites; or pneumonia in lung transplant candidates; or line-associated bloodstream infection among stem cell, heart, and kidney transplant candidates with indwelling vascular catheters); in general, these infections do not absolutely preclude organ and tissue transplantation, but these infections should be adequately controlled and treated prior to and after the transplant procedure. Often, serologic evidence of past infection would suggest the presence of latent viruses, such as cytomegalovirus (CMV), varicella-zoster virus (VZV), and Epstein–Barr virus (EBV), or parasites, such as *Toxoplasma gondii* (especially for heart recipients) and *Strongyloides stercoralis*.

TABLE 88.1 **RISK FACTORS FOR ACQUIRING INFECTION FOLLOWING SOLID ORGAN TRANSPLANTATION**

Preoperative period	Intraoperative period	Postoperative period
Lack of pathogen-specific immunity (e.g., CMV-seronegativity)	Presence of pathogens in the transplant allograft (donor-transmitted infections)	Prolonged hospitalization
Severity of underlying clinical illnesses and comorbidity (e.g., high MELD score)	Prolonged operative time Complicated surgical procedure (e.g., break in intestinal compartment)	Prolonged stay in intensive care unit (and need for indwelling vascular and urinary catheters, endotracheal tubes)
Fulminant hepatic failure	Profound blood loss and infusion of large volume of blood products	Prolonged antibiotic use (invasive fungal infections and *Clostridium difficile*)
Renal failure (especially need for renal replacement therapy)	Choledochojejunostomy (for liver recipients)	Renal insufficiency (especially need for renal replacement therapy)
Active infection (e.g., peritonitis, bacteremia, viral hepatitis)	Indwelling vascular and urinary catheters Endotracheal intubation	Gastrointestinal and biliary complications (e.g., biliary leaks)
Prior fungal infection (i.e., coccidioidomycosis and aspergillosis)		Vascular complications (e.g., thrombosis and surgical site hematoma)
		Anastomotic leaks (e.g., biliary leak, ureteral leak, bronchial dehiscence) Wound dehiscence
		Allograft rejection Lymphocyte-depleting drugs (e.g., anti-thymocyte globulins, alemtuzumab) Immunosuppressive drugs
		CMV and HHV-6 reactivation
		Reoperation within 1 month after transplantation
		Retransplantation

Abbreviations: HHV = human herpesvirus; CMV = cytomegalovirus.

Knowledge of the presence of latent and subclinical infections will guide implementation of prevention efforts prior to, or after, organ and tissue transplantation. For example, seronegativity to VZV suggests the need to vaccinate the transplant candidate at least 28 days prior to organ transplantation and immunosuppression. Likewise, latent tuberculous infection, as detected either by tuberculin skin testing or interferon-γ release assay, should be treated preferably prior to organ and tissue transplantation.

The transplant donor

The epidemiologic exposures of transplant donors should be determined so that the potential for donor-transmitted infections is reduced. Screening for CMV, EBV, VZV, *T. gondii* (especially for heart transplant donors), hepatitis B and C viruses, and HIV are routinely performed in transplant donors (Box 88.1). Risk for tuberculosis in the donor should also be elicited based on history, while living donors should undergo tuberculin skin testing or interferon-γ release assay. Transplant donors often have prolonged stay in the hospital prior to organ harvest, and they may have acquired nosocomial infections which could be transmitted to the transplant recipient through transplantation (Table 88.2). Clinical suspicion or documentation of potential donor-transmitted infection should be reported to the national database so that recipients of all organs from the infected donor can be screened and managed accordingly.

The environment

The healthcare environment is a major source of pathogens that may cause infectious disease in transplant recipients. Moreover, surgical and other invasive procedures, such as the insertion of indwelling urinary catheters, intravascular catheters, and endotracheal tubes, could serve as portals of entry for infectious pathogens.

Many infections are acquired by the transplant recipients in the community setting where natural transmission of pathogens continually occurs. Classic examples are respiratory viral and bacterial pathogens which can cause potentially severe pneumonia or other respiratory illness in transplant recipients. Table 88.2 lists the epidemiologic exposures and the pathogens associated with specific exposures.

BOX 88.1

Selected infectious disease screening tools in the evaluation of donors and recipients prior to transplantation

Human immunodeficiency virus (HIV) antibody (HIV RNA in selected cases)
Herpes simplex virus (HSV) 1 and 2 IgG antibody
Cytomegalovirus (CMV-IgG) antibody
Epstein–Barr virus (EBV) antibody panel
Varicella-zoster virus (VZV) antibody
Toxoplasma antibody (in heart recipients)
Rapid plasma reagin test and treponemal tests for syphilis
Human T-cell lymphotropic virus (HTLV) I and II antibody (selected cases only, based on epidemiologic risk)
Hepatitis C virus (anti-HCV) antibody (HCV RNA in selected cases)
Hepatitis B virus (HBV) surface antigen, surface antibody, and core antibody
PPD skin testing or interferon-gamma release assay (e.g., QuantiFERON TB test) (for living donors and all recipients)
Strongyloides stercoralis serology (with stool ova and parasites for candidates from endemic areas)
Coccidioides immitis serology (for candidates and donors from endemic areas)
Trypanosoma cruzi serology (for donors and recipients from endemic areas)

TABLE 88.2 **EPIDEMIOLOGIC EXPOSURES AND SELECTED PATHOGENS THAT CAUSE INFECTIOUS DISEASES IN TRANSPLANT PATIENTS**

Community-acquired infections	
Residence or travel to endemic areas	*Mycobacterium tuberculosis, Strongyloides stercoralis, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Trypanosoma cruzi*, human herpesvirus 8, *Plasmodium* species, dengue virus, Zika virus
Exposure to index cases	*Mycobacterium tuberculosis*, respiratory viruses (influenza, parainfluenza, respiratory syncytial virus, adenoviruses)
Contaminated food and water	*Salmonella* spp., *Campylobacter jejuni, Listeria monocytogenes, Giardia lamblia, Cryptosporidium parvum*
Environmental source	*Aspergillus fumigatus, Nocardia* sp., *Sporothrix schenckii*, norovirus, *Legionella pneumophila*
Vector-borne	West Nile virus, tick-borne diseases, *Plasmodium* species, Zika virus
Nosocomial infections	
Contaminated air	*Aspergillus fumigatus*
Contaminated water	*Legionella pneumophila*
Hand contact	Methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant enterococci, drug-resistant gram-negative bacilli, influenza virus
Hospital environment	*Clostridium difficile,* multidrug-resistant bacteria including methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant enterococci, drug-resistant *Pseudomonas aeruginosa*

Net state of immunosuppression

The major factors that influence the overall net state of immunosuppression are (1) the intensity of drug-induced immunosuppression (dose, frequency, duration, and magnitude of effect on the T-cell compartment), (2) the presence of inherent immunodeficiency, and (3) other factors such as the reactivation of immunomodulating viruses, increasing age, and presence of other comorbidity (e.g., diabetes mellitus).

Immunosuppressive drugs are essential to maintain allograft survival (by preventing and treating acute and chronic graft cellular rejection and humoral rejection among the solid organ transplant [SOT] recipients) and to prevent and treat acute or chronic graft-versus-host disease (in allogeneic hematopoietic stem cell transplant [HSCT] recipients). The use of induction immunosuppression, often with T-lymphocyte–depleting drugs such as anti-thymocyte globulins and alemtuzumab, markedly impair cell-mediated immune function. The degree of drug-induced immunosuppression is especially intense during the first 3 months after organ and stem cell transplantation and is characterized by severe impairment of cellular and humoral immunity. Although defect in cell-mediated immunity is a well-recognized effect of the immunosuppressive drugs, impairment in humoral immunity, as indicated by severe hypogammaglobulinemia, may also occur. The individual and collective suppressive effects of these drugs on the immune system places the patients at high risk of opportunistic infections. In particular, lymphocyte-depleting agents increase the risk of CMV disease, human herpesvirus 6 (HHV-6), *Aspergillus* spp., and *Pneumocystis jirovecii*. Severe hypogammaglobulinemia may also increase the risk of infections with encapsulated organisms such as *Streptococcus pneumonia*.

There is increasing evidence that inherent defects in innate and adaptive immunity may augment the net state of immune deficiency, further increasing the risk of infections after transplantation. Increasing age, diabetes, and other comorbidity (such as

renal failure) augment the risk. Reactivation of latent viruses with immunomodulating properties, such as CMV and HHV-6, during periods of intense drug-induced immunosuppression may paradoxically further enhance the overall state of immunosuppression, leading to increased risk of bacterial and fungal opportunistic infections.

Time course of infections after transplantation

Infections after SOT and HSCT follow a temporal pattern that is predicted by risk factors related to time since transplantation. Figures 88.1 and 88.2 depict the timing of infections after SOT (Figure 88.1) and allogeneic HSCT (Figure 88.2). However, this traditional timeline is evolving, influenced by various factors, most notably the use of antimicrobial prophylaxis. For example, CMV infection and disease traditionally occurs during the first 3 months after SOT, but this has been delayed among high-risk CMV donor-positive/recipient-negative SOT patients to the first 3 months after completion of antiviral prophylaxis. In addition, widespread use of antimicrobial prophylaxis has modified the drug susceptibilities of various pathogens, as exemplified by the emergence of fluconazole-resistant *Candida* spp. infections in centers utilizing fluconazole prophylaxis. There is also increasing incidence of drug resistance among bacterial pathogens, which complicates empiric antimicrobial prophylaxis and treatment approaches.

Timetable of infections after solid organ transplantation

Infections after SOT follow a characteristic time frame that reflects epidemiologic and clinical factors and the net state of immunosuppression. These time frames are important to remember during the clinical evaluation of SOT patients presenting with various clinical syndromes after transplantation. In this regard, clinical syndromes such as pneumonia and cellulitis may occur at any time, but the offending pathogen may vary depending on its onset after transplantation.

The first month after solid organ transplantation

The three major sources of infections during this period are (1) infection that is present in the recipient prior to transplantation (i.e., bacterial peritonitis in liver recipients, catheter-related bloodstream infection in kidney recipients, bacterial pneumonia in lung recipients, and infected cardiac device in heart transplant recipients), (2) infection transmitted in the allograft (e.g., unrecognized or undiagnosed bacterial, viral, parasitic, and fungal infection prior to organ harvest), and (3) infections related to surgery and hospitalization.

The majority of infections that occur during the first month after SOT are related to surgical procedures and hospitalization (Figure 88.1): surgical site infections due to *Staphylococcus* spp. and *Streptococcus* spp. or other nosocomially acquired pathogens; catheter-associated urinary tract infections with gram-negative bacteria such as *Escherichia coli*, gram-positive bacteria such as

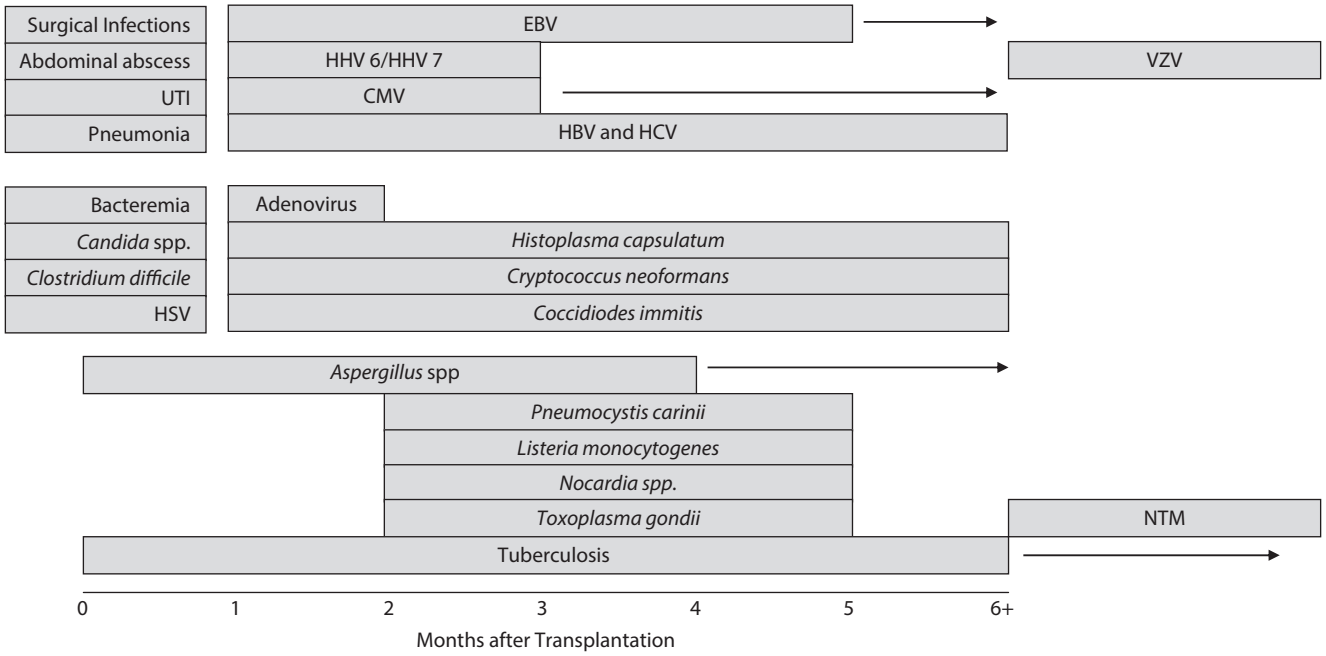

FIGURE 88.1 Natural history timeline of infections following solid organ transplantation in the absence of antimicrobial prophylaxis.

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; HSV, herpes simplex virus; NTM, nontuberculous mycobacteria; UTI, urinary tract infection; VZV, varicella-zoster virus.

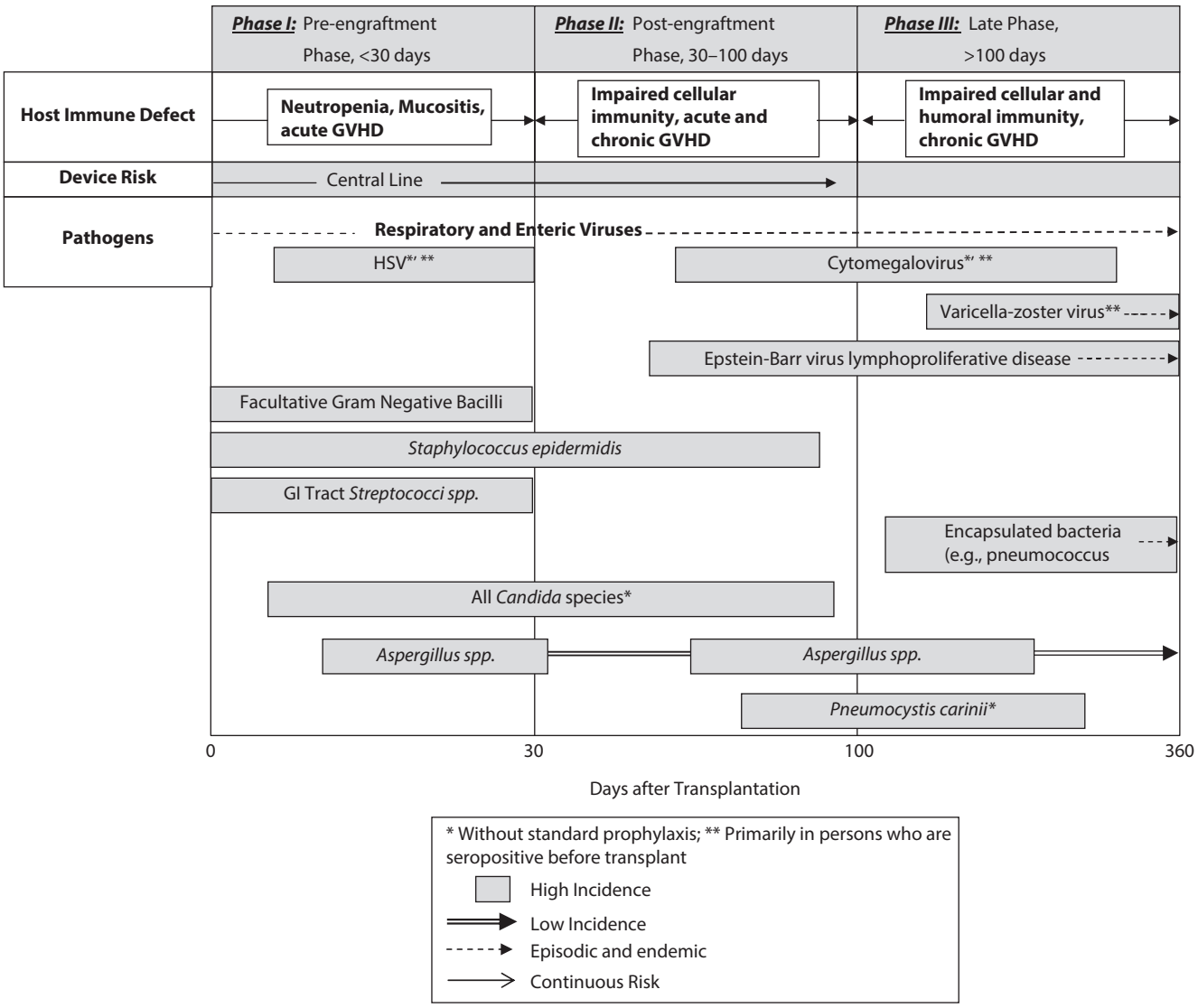

FIGURE 88.2 Natural history timeline of infections following allogeneic hematopoietic stem cell transplantation in the absence of antimicrobial prophylaxis. GI, gastrointestinal; GVHD, graft-versus-host disease; HSV, herpes simplex virus.

enterococcus, and fungi such as *Candida albicans*; nosocomial and ventilator-associated pneumonia due to drug-resistant *Pseudomonas aeruginosa, Acinetobacter* spp., *Staphylococcus aureus*, and others; and catheter-associated bloodstream infection with gram-positive bacteria such as *S. aureus*, enterococcus, and coagulase-negative staphylococcus are seen. Polymicrobial intra-abdominal infections are especially common among liver recipients who require abdominal re-exploration (for hepatic artery thrombosis, bleeding, biliary leakage, or retransplantation). Prolonged hospitalization increases the risk of nosocomial pneumonia, urinary infections, and antibiotic-related *Clostridium difficile* diarrhea. The widespread use of antibacterial agents for prophylaxis and treatment of defined infections has led to the rising incidence of *C. difficile* infection during this early posttransplant period.

During this time period, herpes simplex virus (HSV) types 1 and 2 commonly reactivate and may cause localized ulcerative or disseminated disease in the HSV-seropositive SOT recipients; antiviral prophylaxis has significantly decreased its incidence. Donor-transmitted infections such as an unrecognized fungal infection (due to *Histoplasma capsulatum* or *Cryptococcus neoformans*) and other unusual infections such as West Nile virus (WNV), rabies virus, or lymphocytic choriomeningitis virus may be manifested clinically during this period, often with poor outcomes. One clue to the possible donor-transmitted infection is the occurrence of similar clinical syndromes among multiple recipients of organs from the same organ donor.

Second to the sixth month after solid organ transplantation

The impact of intense immunosuppression resulting from the use of lymphocyte-depleting induction therapy and the immune-paralyzing effect of a combination of immunosuppressive drugs becomes evident during this second period after SOT. Accordingly, this is the period when most opportunistic infections classically

occur. During this period, infections due to CMV, EBV, HHV-6, *Aspergillus fumigatus*, and *Pneumocystis jirovecii* occur. In the absence of antiviral prophylaxis, CMV reactivates and cause fever and end-organ disease during this period. Invasive aspergillosis, most commonly due to *A. fumigatus*, may occur during this time, especially among patients transplanted for fulminant hepatic failure, those on renal replacement therapy, and those with epidemiologic exposure (i.e., exposure to areas of construction or previous colonization among lung transplant recipients) and profound immunosuppression. Pneumonia is the most common clinical presentation of aspergillosis, but the clinical illness may disseminate to any body organ system, possibly due to the vasculotropic nature of *Aspergillus* spp. and cause abscesses in many organs, including the liver and the brain. Infections with endemic fungi (e.g., *H. capsulatum* and *Coccidioides immitis*) may occur during this period to cause pneumonia or disseminated disease. *P. jirovecii* pneumonia traditionally occurs during this opportunistic period but prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) has made this infection and those due to *Nocardia* spp. uncommon during this early period.

Beyond the sixth month after solid organ transplantation

There are generally two types of SOT patients with varying risk of infection during this period: (1) those with good allograft function and minimal immunosuppression and (2) those with poor allograft function as a result of recurrent rejection or chronic allograft dysfunction. In addition, liver transplant recipients with underlying chronic viral hepatitis (due to hepatitis B or C) may develop an accelerated clinical course characterized by graft failure if not prevented or treated and, subsequently, the need for retransplantation. These patients may benefit from prophylaxis with hepatitis B immunoglobulin and nucleoside or nucleotide analogs (for hepatitis B patients), or targeted therapy with direct-acting antivirals (for hepatitis C patients).

The vast majority of transplant patients will have good allograft function, and their level of immunosuppression has already been reduced to minimal levels. These patients are primarily at risk of infections similar to those observed in nonimmunocompromised populations. However, a small group of SOT patients will have poor graft function as a result of recurrent rejection or chronic dysfunction; these patients are generally considered to be over-immunosuppressed and remain at high risk of opportunistic infections, including *P. jirovecii, L. monocytogenes, C. neoformans, Nocardia asteroides*, CMV, and *Aspergillus* spp. infections. Patients with a persistent hypogammaglobulinemia are particularly at risk of pneumonia and bacteremia due to encapsulated organisms.

Infection with endemic mycoses, such as *C. immitis* in patients living in the Southwest United States, may occur in patients with epidemiologic exposures such as residence in certain geographic regions. One of the most common opportunistic infections during this time is the reactivation of VZV causing dermatomal zoster, with potential for dissemination. In endemic areas, HHV-8 may reactivate to cause Kaposi's sarcoma (KS) and, less commonly, Castleman's disease and primary effusion lymphoma; in these endemic regions, KS is one of the most common malignancies in transplant recipients. CMV disease is increasingly observed during the late period (i.e., beyond the sixth month after SOT, especially among high-risk CMV D+/R− SOT recipients who receive 6 months of antiviral prophylaxis; termed *post-prophylaxis delayed onset CMV disease*). Late-onset CMV disease may also sporadically occur years after transplantation, and these patients may present with atypical clinical presentations that could lead to severe morbidity and potential mortality if diagnosis and treatment is delayed.

EBV may occur at any time after SOT and cause posttransplant lymphoproliferative disorder. Infections due to respiratory pathogens such as *S. pneumoniae*, and seasonal viruses such as influenza virus and respiratory syncytial virus may occur with increased severity at any time after transplantation.

Timetable of infections after hematopoietic stem cell transplantation

Infections after HSCT follow a traditional pattern (Figure 88.2) that reflects the severity of immune dysfunction and the different phases of immune recovery after transplantation.

The pre-engraftment period (0 to 30 days after HSCT)

The two major factors that influence the risk of infection during this period are (1) severity and duration of neutropenia and (2) disruption of mucocutaneous barrier, such as mucositis and use of vascular access catheters. *Candida* spp. is traditionally a prevalent fungal infection during this period, and, hence, antifungal prophylaxis with an azole (choice of azole depends on the risk) is commonly used. As the duration of neutropenia is prolonged, the risk for *Aspergillus* spp. is increased, and, in these high-risk patients, prophylaxis with voriconazole or voriconazole is preferred. HSV reactivation commonly occurs to cause mucosal ulcerations that complicate chemotherapy-induced mucositis. Breaks in mucocutaneous barrier, such as severe mucositis, may cause translocation of oral and gastrointestinal flora. For example, this predisposes to severe systemic infection and septic shock due to viridans group streptococcus. Gram-positive bacteria such as *S. aureus* and coagulase-negative staphylococci and vancomycin-resistant enterococcus, gram-negative bacteria such as *E. coli* and *P. aeruginosa*, and fungi such as *C. albicans* may gain entry into the bloodstream through indwelling vascular catheters. HSCT patients are commonly febrile during this period, especially during periods of severe neutropenia, and receive empiric broad-spectrum antimicrobial therapy. However, this may predispose them to develop *C. difficile* diarrhea.

Post-engraftment period (days 30–100 after HSCT)

This period is highlighted by an impaired cell-mediated immunity and is characterized by the occurrence of classic opportunistic infections. Following engraftment, the risk of acute and chronic graft-versus-host disease is increased and immunosuppressive drugs are given to prevent this complication, thereby increasing the risk of opportunistic infections. This period is classically associated with the occurrence of CMV infection, which could manifest as severe and potentially fatal pneumonia if not detected and treated early.

Allogeneic HSCT recipients undergo serial (at least once weekly) CMV surveillance using CMV nucleic acid testing (or alternatively, pp65 antigenemia) so that CMV reactivation is detected early and treated promptly. Alternatively, patients may receive anti-CMV prophylaxis, preferably with letermovir (since valganciclovir is associated with leukopenia and may delay or impair engraftment), but this may only delay the onset of CMV disease to beyond 100 days after HSCT (post-prophylaxis delayed onset CMV infection), particularly among those with severe immunosuppression. HHV-6 and adenovirus infections may occur during this period and cause febrile illness, rash, and hepatitis. Posttransplant acute limbic encephalitis is a classic clinical presentation of HHV-6 disease after allogeneic HSCT. *Aspergillus* spp., *Fusarium* spp., *Mucor* and *Rhizopus* spp. may cause invasive disease. Risk of *P. jirovecii* pneumonia is reduced by prophylaxis with TMP-SMX or inhaled pentamidine.

Late phase (beyond 100 days after HSCT)

In some HSCT patients, such as those with chronic graft-versus-host disease, the period beyond 100 days after transplantation is characterized by persistent impairment in cell-mediated and humoral immunity as a result of the administration of augmented immunosuppression. In these patients, infections with CMV, VZV, EBV, *Aspergillus* spp., and *P. jirovecii* may continue to occur, and they may benefit from prolonged administration of antimicrobial prophylaxis.

The majority of HSCT patients will have adequate immune reconstitution during this period, and the risk of infections will be lower although still at a relatively higher rate compared to healthy hosts. Once fully engrafted and immune reconstitution is achieved, allogeneic HSCT recipients may benefit from vaccination program to reestablish immunity against vaccine-preventable diseases. Infections with community-acquired respiratory viruses such as influenza, parainfluenza, and respiratory syncytial viruses may occur and so do infections with encapsulated bacteria such as *S. pneumoniae* and *Haemophilus influenzae*. These infections with encapsulated bacteria are particularly more common among patients with persistent low levels of immunoglobulins.

Selected pathogens and syndromes

Bacterial infections

Any bacterial pathogen can cause clinical disease, often with increased severity and morbidity, in transplant patients. Surgical site infection is often due to *S. aureus* and other gram-positive bacteria. Bloodstream infection due to gram-positive and gram-negative bacteria may occur among HSCT recipients, especially during the period of mucositis and neutropenia. In many of these cases, bloodstream infection is related to indwelling vascular catheters. One of the causes of septic shock in HSCT recipients with severe mucositis is bloodstream infection due to viridans group streptococci. Kidney transplant recipients are particularly at high risk of developing urinary tract infection, most often due to *E. coli,* other members of the *Enterobacteriaceae*, and enterococcus, especially during the first 6 to 12 months after transplantation. Bacterial pneumonia and tracheobronchitis may occur among lung recipients, potentially due to impaired mucociliary clearance. Intra-abdominal bacterial infections, such as cholangitis, peritonitis, and abscesses, may occur during the early period after liver transplantation; many of these intra-abdominal abscesses are polymicrobial in etiology and include members of the *Enterobacteriaceae*, enterococcus, anaerobes, and *Candida* spp. Table 88.3 lists the most common strategies for the prevention of bacterial and other infections after transplantation.

In HSCT patients, it is standard practice to provide antibacterial prophylaxis during the high-risk period of neutropenia, primarily to prevent sepsis due to *P. aeruginosa*. Antibacterial prophylaxis with fluoroquinolones is a standard practice, but this is associated with a risk of sepsis due to viridans group streptococci, especially during the period of mucositis. The addition of penicillin to quinolones, to reduce the risk of viridans group streptococcal sepsis, has been associated with emergence of resistance in enterococcus. Empiric treatment of HSCT patients with fever during the period of neutropenia should include broad-spectrum anti-Pseudomonal cephalosporins (cefepime or ceftazidime), piperacillin-tazobactam, or carbapenems; vancomycin may be added empirically for severe sepsis and if there is concern for pneumonia and line-related sepsis. Some experts have advocated the use of intravenous immunoglobulins (IVIG) to prevent bacterial infections, such as sinopulmonary infections with *S. pneumoniae*, in patients with hypogammaglobulinemia.

Mycobacterium species

Transplant candidates should be screened for latent tuberculosis (TB) infection (LTBI) by history, tuberculin skin test (TST), or interferon-γ release assays (IGRA) and treated preferably prior to transplantation. Some cases of donor-transmitted TB have been reported, and hence all living donors are also screened for the infection by history, TST, or IGRA. Deceased donors should be screened for possible TB through detailed history.

Pulmonary TB is the most common clinical presentation, although dissemination and extra-pulmonary disease may occur. Involvement of the transplanted organ allograft raises concern for donor-transmitted TB, and should alert for screening of all organ recipients from the same organ donor. The diagnosis of TB is confirmed by mycobacterial culture, acid-fast smear, and molecular testing such as polymerase chain reaction (PCR) assays. Treatment of *M. tuberculosis* in transplant recipients is similar to that in the non-transplant population, initially with use of isoniazid, rifamycin, ethambutol, and pyrazinamide. However, it is important to remember that rifampin has strong interaction with tacrolimus and cyclosporine, and their systemic drug levels should be monitored closely.

In the transplant patient, atypical mycobacteria, such as *Mycobacterium avium* complex may be a cause of pulmonary infection after lung transplantation. *Mycobacterium abscessus*, *M. chelonae*, *M. fortuitum*, and *M. marinum*, among others, should be considered potential causes of skin lesions, tenosynovitis, or joint infection. Non-tuberculous mycobacteria may colonize and

TABLE 88.3 **SUGGESTED PROPHYLACTIC STRATEGIES IN TRANSPLANTATION**

Indication	Prophylaxis	Dose and duration	Comments
Perioperative prophylaxis (SOT)	Cefotaxime	1–2 g q8h IV for 24 h	Should be adjusted based on resistance patterns; alternative agents (vancomycin plus quinolone) may be used if resistance risk is high
Perioperative prophylaxis (SOT)	Cefazolin	1–2 g q8h IV for 24 h	Should be adjusted based on resistance patterns; alternative agents (vancomycin plus quinolone) may be used if resistance risk is high
Neutropenia prophylaxis (HSCT)	Quinolone (e.g., levofloxacin)	500 mg PO once daily (for the duration of neutropenia)	Reduce risk of gram-negative sepsis, particularly *Pseudomonas aeruginosa*; risk of viridans streptococcal sepsis is not completely prevented
Pneumocystis jirovecii	Trimethoprim-sulfamethoxazole	80 or 160 mg of trimethoprim component PO once daily	Trimethoprim-sulfamethoxazole may protect against *Nocardia* spp., *Listeria* spp., and other bacteria Alternatives: pentamidine, atovaquone, dapsone
Herpes simplex virus	Acyclovir	200–400 mg PO BID–TID for 28 d	Should be withheld when ganciclovir or valganciclovir is used; valacyclovir may be used if available
Cytomegalovirus	Valganciclovir	900 mg once daily; duration variable (3–12 months depending on the organ and risk profile)	Used as prophylaxis; dose should be increased to 900 mg BID for preemptive therapy; may protect against HHV-6, HSV, VZV
Cytomegalovirus (HSCT only)	Letermovir	480 mg PO once daily (240 mg PO once daily if with cyclosporine)	Used as prophylaxis; does not have activity against HHV-6, HSV, VZV
Hepatitis B virus	Hepatitis B immunoglobulin with nucleotide/nucleoside analogs	10,000 IU daily for first week then q4wk (the dose of nucleotide and nucleoside analog varies depending on the drug)	Maintain serum HBIg level >100 IU; may be used in combination with nucleotide analogs such as lamivudine and entecavir
Candida spp.	Fluconazole	200–400 mg PO daily (duration varies depending on the transplant type)	Targeted to patients with risk factors for Candida infections, such as complicated and prolonged surgery or profound blood loss
Coccidioides spp.	Fluconazole	200–400 mg PO once daily (duration varies depending on risk profile)	At-risk transplant recipients in endemic regions
Aspergillus spp. and other invasive mycelial infection	Itraconazole Voriconazole Posaconazole Echinocandin Amphotericin B	Variable drug dose and duration depending on the fungi of interest	Administered to patients with risk factors such as prolonged neutropenia, and fulminant hepatic failure

Abbreviations: HBIg = hepatitis B immunoglobulin; PO = orally; IV = intravenous; tid = 3 times daily; HHV = human herpesvirus; HSV = herpes simplex virus; VZV = varicella-zoster virus
Role of oral bowel decontamination solution is highly debated, and not routinely recommended.

contaminate central venous catheters, especially among allogeneic HSCT recipients, and lead to bloodstream infection. Antimicrobial treatment will depend on the mycobacterial species and surgical debridement (if abscesses, arthritis, and tenosynovitis) or catheter removal (for line-related bloodstream infections).

Nocardia species

Nocardia spp. typically cause pneumonia but can disseminate to involve the joints, skin, and especially the brain. Imaging of the brain is recommended to rule out central nervous system involvement in patients with *Nocardia* infection. Risk factors for nocardiosis include the severity of immunosuppression as influenced by immunosuppressive drugs, graft rejection, and neutropenia. The routine use of TMP-SMX prophylaxis during the first 3 to 6 months after transplantation, while intended to prevent *P. jirovecii* pneumonia, may also prevent some cases of nocardiosis and has lowered its incidence. However, breakthrough nocardia infections may still occur even in patients receiving TMP-SMX prophylaxis. The diagnosis is established using a modified acid-fast stain and culture. Antimicrobial resistance has been reported; antimicrobial susceptibility testing of the isolate is recommended. Depending on the severity of the disease, empiric therapy may include 2 or 3 agents active against *Nocardia* species.

Viral infections

Cytomegalovirus

CMV is the most common infection that causes significant morbidity and preventable mortality after transplantation. CMV infection occurs traditionally (in patients not receiving antiviral prophylaxis) during the first 3 months after SOT and HSCT. In CMV D+/R− SOT recipients who receive antiviral prophylaxis, the onset of CMV infection and disease has been delayed to the first 3 to 6 months after completion of antiviral prophylaxis, a condition termed post-prophylaxis delayed onset CMV infection.

CMV causes direct and indirect effects that negatively affect the outcome of organ and tissue transplantation. The direct effects, otherwise known as *CMV disease*, can be manifested as CMV syndrome (febrile illness, flu-like illness, myalgias, and bone marrow suppression) or end-organ disease (CMV pneumonitis, gastrointestinal disease, hepatitis, retinitis, encephalitis, allograft infection, and others). The indirect effects of CMV infection include its association with increased risk of acute and chronic allograft rejection, higher risk of other opportunistic infections such as invasive fungal disease and EBV posttransplant lymphoproliferative disorder, and higher rate of chronic allograft dysfunction, such as accelerated vasculopathy in heart recipients, bronchiolitis obliterans in lung recipients, and tubulointerstitial fibrosis in kidney transplant recipients. Increase risks of graft versus host disease and mortality have been reported in allogenic HSCT recipients with CMV reactivation. Risk factors for CMV disease include a CMV mismatch status; a CMV-seronegative SOT patient who receives solid organ allograft from a CMV-seropositive donor (CMV D+/R− mismatch) is at highest risk of CMV infection and disease after SOT. In contrast, a CMV-seropositive HSCT patient who receives hematopoietic stem cells from a CMV-seronegative donor (reverse CMV D−/R+ mismatch) represents a high risk after allogeneic HSCT. Immunosuppressive regimens such as antithymocyte globulins, antilymphocyte globulins, alemtuzumab, and mycophenolate mofetil increase the risk of CMV. The diagnostic tests for CMV after transplantation include molecular tests such as quantitative PCR to detect and quantify CMV nucleic acid (currently considered the most sensitive assay for CMV detection), while pp65 antigenemia (which detects pp65 expressed in neutrophils during active CMV infection) is considered the alternative test. Viral culture is highly specific but with poor to modest sensitivity, and it is no longer widely available. Histopathology remains as the gold standard for the diagnosis of end-organ CMV disease. Serology is not useful for diagnosis of acute CMV disease because transplant patients have delayed and impaired ability to develop antibodies during infection.

Prevention of CMV disease is an integral component in the management of transplant recipients. There are two major methods of prevention: (1) antiviral prophylaxis through the administration of antiviral drugs, most commonly with valganciclovir (or letermovir for CMV-seropositive allogeneic HSCT recipients) to all patients at risk of CMV disease and (2) preemptive therapy through the administration of antiviral drugs, most commonly with IV ganciclovir or oral valganciclovir, to transplant patients with asymptomatic CMV infection as indicated by a positive pp65 antigenemia or CMV PCR test. Treatment of CMV disease is with IV ganciclovir or oral valganciclovir. Oral valganciclovir has been used for treatment of mild to moderate CMV disease, while IV ganciclovir is preferred for severe disease. Because of adverse effects such as nephrotoxicity and electrolyte imbalances, cidofovir and foscarnet are reserved only for the treatment of ganciclovir-resistant CMV disease. Letermovir is not clinically approved for treatment of clinical disease. CMV viral load monitoring to detect the response to antiviral treatment is recommended once weekly; antiviral treatment is continued until clearance of the virus is demonstrated and clinical symptoms have resolved.

Herpes simplex virus

The vast majority of HSV infections after transplantation represent reactivation of endogenous latent virus. Most commonly, the clinical presentation is orolabial and genital ulcers, although disseminated disease may occur in the form of hepatitis, pneumonitis, and esophageal disease. Most of the HSV infections occur during the first month after SOT and HSCT but antiviral prophylaxis with acyclovir (or valganciclovir, which is intended primarily against CMV) has reduced its incidence. The diagnosis of mucocutaneous HSV disease is based mainly on clinical findings of typical herpetic lesions. PCR testing to demonstrate the viral DNA may confirm the diagnosis. Treatment is with oral acyclovir, valacyclovir, and famciclovir for a duration guided by clinical response.

Varicella-zoster virus

Because >90% of the adult population has antibodies against VZV, almost all cases of VZV disease after SOT and HSCT represent reactivation disease. Most commonly, this is manifested clinically in the form of mono- or multidermatomal zoster. Disseminated VZV disease, with possible visceral involvement, may occur in severely immunocompromised transplant recipients. The incidence of VZV disease is approximately 10% of all transplant patients. The median onset of disease is 9 to 14 months after transplantation. The diagnosis is based on clinical grounds, with typical vesicular lesions in a dermatomal distribution (for typical localized disease) or in a widespread distribution (for disseminated disease). Treatment is with IV acyclovir for serious disease and with oral valacyclovir for limited or localized disease. Duration of treatment should be guided by clinical response. Vaccination with adjuvant herpes zoster subunit vaccine for VZV-immune transplant candidates >50 years is strongly recommended. In allogeneic HSCT recipients, acyclovir prophylaxis for up to 1 year is given to prevent zoster. The use of live attenuated zoster vaccine is contraindicated after transplantation since there is potential for activation and dissemination of the attenuated vaccine strain. The role of adjuvant herpes zoster subunit vaccine for transplant recipients is currently under investigation.

Epstein–Barr virus and posttransplant lymphoproliferative disorder

EBV posttransplant lymphoproliferative disorder (PTLD) consists of all clinical syndromes associated with EBV-driven

lymphoproliferation, whether this is nodal or extranodal, symptomatic or subclinical, localized or disseminated, monoclonal or polyclonal, benign hyperplasia or true malignancies containing chromosomal aberrations. Primary EBV infection is the most significant risk factor for EBV PTLD especially among severely immune compromised transplant recipients, particularly those who have received lymphocyte-depleting antibodies. CMV disease also further increases the risk of PTLD potentially due to its immunesuppressive effects. The incidence of PTLD varies among organ transplant types; it is highest in small bowel and lowest in kidney transplant recipients. The diagnosis of EBV PTLD is confirmed by histopathology of specimens obtained by excisional biopsy. Surveillance measures such as PCR assays to quantitate EBV viral load are commonly utilized to assess the risk of PTLD in high-risk EBV D+/R− patients. Detection of EBV by PCR in high-risk patients should trigger evaluation for PTLD and reduction in the degree of immunosuppression. The clinical utility of EBV PCR for diagnosis of PTLD is debatable. Although low or absent EBV viral load has a very good negative predictive value, the specificity of higher EBV load is only modest. The first-line treatment of EBV PTLD is reduction in immunosuppression. Since EBV PTLD is predominantly through B-cell proliferation, rituximab alone or in combination with chemotherapeutic agents is the treatment of choice. Prophylaxis with acyclovir and valganciclovir is of theoretical value but has not been proved to be effective for prevention. Antiviral therapy has no role in the treatment of established PTLD.

Human herpesviruses 6 and 7

HHV-6 (A and B) and HHV-7 infect >95% of humans. Primary infection with HHV-6 and HHV-7 is uncommon in adult transplant recipients. However, secondary reactivation from latency is very common in adult transplant recipients, but the vast majority is subclinical and transient. In the minority of cases, HHV-6 can cause a febrile illness, bone marrow suppression, hepatitis, pneumonitis, and encephalitis. In allogeneic HSCT recipients, a condition known as *posttransplant acute limbic encephalitis* is attributed to HHV-6 infection. The most common diagnostic test for HHV-6 and HHV-7 is nucleic acid amplification by PCR using blood and other body fluid such as cerebrospinal fluid. Serology is rarely helpful and not widely available. Viral culture is also not readily available and it has slow turnaround time. Histopathology and immunohistochemistry may be used to confirm the diagnosis of tissue-invasive disease. There are no solid clinical trial data to guide antiviral treatment of HHV-6 and HHV-7, although HHV-6 appears to be susceptible to ganciclovir, cidofovir, and foscarnet, whereas HHV-7 may be resistant to ganciclovir.

Human herpesvirus 8

Infections with HHV-8 cause KS and, less commonly, Castleman's disease; primary effusion lymphoma; and other nonmalignant myelosuppressive disease. HHV-8 may occur as primary infection or reactivation of latent virus. The incidence of posttransplant HHV-8 infection and disease parallels the geographic seroprevalence of HHV-8, so that it occurs at a rate of <1% in the United States to as high as 5% in HHV-8 endemic regions of the world such as Saudi Arabia, South Africa, and the Mediterranean region. KS is considered the most common malignancy in kidney recipients in some parts of the Middle East. The median time to the onset of KS is 22 months after transplantation. Skin involvement is the most common manifestation, and visceral lesions such as gastrointestinal and pulmonary KS may also be observed. Reduction (or withdrawal) of immunosuppression is the mainstay of treatment. Surgery and chemotherapy with doxorubicin, vincristine, and bleomycin has been used for treatment.

Polyomaviruses BK and JC

Infection with the BK polyomavirus is mainly reported in kidney transplant recipients, where it causes tubulointerstitial nephritis; this is often manifested clinically as an unexplained rise in serum creatinine and impairment in renal function. Ureteral stenosis and strictures may also be observed. In HSCT recipients, BK virus may manifest as hemorrhagic cystitis. The definitive diagnosis of BK virus–associated nephropathy is made by histopathologic examination of kidney biopsy specimens. Routine screening for BK virus infection in blood or urine is recommended after kidney transplantation, and the detection of BK viremia above the threshold 10,000 copies is treated with reduction in immunosuppressive therapy. High BK viral load in the plasma has been directly correlated with BK virus–associated nephropathy. In HSCT recipients, the role of BK virus in hemorrhagic cystitis is indicated by very high BK viral load in the urine. Infection with the JC virus causes a highly fatal syndrome of progressive multifocal leukoencephalopathy (PML). Diagnosis of PML is suggested by typical MRI findings and the demonstration of JC virus in the cerebrospinal fluid by PCR. Reduction in immunosuppression is the mainstay of treatment for both BK virus infection and PML. Cidofovir (and investigational brincidofovir) and leflunomide are used as experimental therapies but are of no proven benefit. Surveillance testing, with the use of blood or urine PCR or urinary decoy cell testing, is used to identify BK infection early, which is treated preemptively with reduction in immunosuppression in efforts to prevent its progression into allograft failure.

Parvovirus B19

Parvovirus B19 primarily infects and lyses erythroid cells and clinically manifests mainly as recurrent and refractory anemia. Almost all transplant patients with parvovirus B19 infection have anemia, and some also have low platelet count and leukocyte counts. It should be considered a potential cause of failure of engraftment in HSCT recipients. Organ-invasive manifestations may occur in the form of pneumonitis, hepatitis, and myocarditis, although these are not common. The definitive diagnosis is bone marrow examination to demonstrate pure red cell aplasia and giant pronormoblasts. Serology may be used as a noninvasive test, but this may be falsely negative in some patients due to delayed and impaired ability of transplant patients to mount an antibody response. Nucleic acid testing by PCR to demonstrate the presence of parvovirus B19 DNA in clinical specimens is preferred. PCR is considered the most sensitive method

for diagnosis, while bone marrow examination is highly specific for the disease. The treatment is with IVIG, although the dose and duration are not defined. Reduction in the degree of immunosuppression should be considered, and red cell blood transfusion should be given for symptomatic patients and those with severe anemia.

Hepatitis C virus

Chronic hepatitis C is a common indication for liver transplantation. Persistence of infection is the hallmark, and, with immunosuppression, the clinical course of HCV may be accelerated after transplantation. In the past, this was treated with interferon and ribavirin, with modest response. More recently, there has been rapid expansion of direct-acting antiviral drugs for the cure of hepatitis C. With cure rates exceeding 95%, the outcome of liver transplantation for chronic hepatitis C has remarkably improved. Moreover, the directly acting antivirals have allowed for HCV-infected organs to be transplanted to HCV-negative candidates. This has increased the availability of organs, as some HCV-uninfected transplant candidates are accepting offers of HCV-infected organs as long as they can be treated with highly effective direct-acting antivirals in the posttransplant period.

Fungal infections

Fungi may cause opportunistic infection in transplant recipients. However, it is essential to differentiate whether the isolation of fungi in clinical samples represents colonization or true infection. Factors that could indicate true fungal infection include (1) the presence of compatible clinical symptoms, (2) radiographic signs, and (3) isolation of the fungus in more than one clinical sample. Confirmation of true invasive fungal infection is made by the demonstration of the fungal pathogen on biopsy specimens. The diagnosis may be considered probable or definitive based on the strength of evidence. The use of PCR assays to demonstrate fungal nucleic acid (such as *P. jirovecii*) and detection of antigens such as galactomannan and β-D-glucan in clinical samples offer non- or less-invasive methods for diagnosis.

The most common fungal infections in transplant patients are caused by *Candida* spp., *Aspergillus* spp., and *C. neoformans*. The majority of invasive fungal infections during the early posttransplant period are due to *Candida* spp., and these are often related to surgical procedures, indwelling urinary and intravascular catheters, and prolonged antibiotic use. *Aspergillus* spp. may also occur during the early period after transplantation, especially among patients with prior colonization, fulminant hepatitis (for liver recipients), prolonged neutropenia (for HSCT recipients), and severe immunocompromise. *Mucorales* spp. and *Fusarium* spp. infections may be seen in hematopoietic stem cell recipients with prolonged neutropenia. Zygomycosis due to *Mucor* spp., *Rhizopus* spp., and others is a highly fatal invasive fungal disease. *C. neoformans*, endemic mycoses such as *Histoplasma capsulatum*, dermatophytes, hyalohyphomycoses, and phaeohyphomycosis may also occur, often during the later period after transplantation. *Coccidioides* spp. infections are especially common in endemic regions, causing potentially fatal disseminated disease.

Liver transplant patients are at especially high risk of fungal infection with *Candida* spp. and *Aspergillus* spp. Antifungal prophylaxis, usually with low-dose amphotericin B, azoles, or an echinocandin, is given to liver transplant patients with certain risk factors such as fulminant hepatitis, those who require renal replacement therapy, those who undergo abdominal re-exploration, those who have high blood transfusion requirement, and those who require retransplantation. Lung transplant recipients with certain risk factors (hyperacute rejection, ischemic bronchial segments, *Aspergillus* spp. colonization, CMV disease, anastomotic dehiscence, and retransplantation) are at higher risk of developing invasive fungal disease, especially with *Aspergillus* spp. Heart transplant patients may infrequently develop invasive fungal infection, most often with *Candida* spp. causing mediastinitis. Kidney transplant patients are at risk of fungal infection, most commonly presenting as catheter-associated candida urinary tract infection. Pancreas and intestinal patients are also at high risk of invasive *Candida* spp. infections, often as part of a polymicrobial intra-abdominal abscess. Allogeneic HSCT recipients are at high risk of *Candida* spp. infection related to indwelling vascular and urinary catheters and mucositis, while prolonged neutropenia increases their risk for mycelial fungal infection, especially *Aspergillus* spp. and zygomyces.

Treatment of opportunistic invasive fungal diseases entails reduction in immunosuppression, surgery (debridement, debulking, or resection in some cases), and antifungal drug therapy. Depending on the fungal pathogen and the severity of disease, three classes of antifungal drugs are available—amphotericin B (deoxycholate and lipid formulations), echinocandins (caspofungin, micafungin, and anidulafungin), or azoles (fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole). There are three different antifungal strategies: (1) therapeutic, which is the treatment of established fungal infection; (2) preemptive, which is the administration of antifungal drug to transplant patients at high risk of invasive fungal disease as suggested by clinical and laboratory features; and (3) prophylactic, which is the administration of antifungal drug to all at-risk patients to prevent infection.

Pneumocystis jirovecii

P. jirovecii is one of the most important opportunistic fungal pathogen that causes pneumonia in SOT and HSCT patients. The clinical presentation is often subacute with low-grade fever, progressive dyspnea, hypoxemia, and nonproductive cough. This is accompanied by typical radiographic finding of diffuse pulmonary infiltrates. Extrapulmonary disease may occur rarely. Coinfection with CMV and *Aspergillus* spp. is not uncommon. The overall incidence has decreased with the use of prophylaxis, most commonly TMP-SMX, and alternatively with dapsone or aerosolized pentamidine. The current guidelines recommend the use of *P. jirovecii* prophylaxis during the periods of immunocompromise in all allogeneic HSCT and SOT recipients. The duration of prophylaxis is at least 6 months after transplantation; the duration should be prolonged in patients who remain highly immune compromised from augmented use of drugs to treat recurrent rejection or graft-versus-host disease. The diagnosis of *P. jirovecii* pneumonia requires the demonstration of the organism in lung tissue and respiratory secretions with the use of calcofluor staining or methenamine silver stain or by molecular tests such as PCR. The treatment of choice is TMP-SMX with or without

corticosteroids in patients with significant hypoxemia. Alternative therapies include pentamidine, atovaquone-dapsone-trimethoprim, primaquine-clindamycin, and pyrimethamine-sulfadiazine.

Parasitic infections

Parasitic infections are increasing becoming more common after transplantation as a result of international travel, immigration, and transplant tourism. An increasing number of transplant procedures are performed in parasite-endemic regions. In the transplant recipient, parasitic infections may occur as a result of primary infection, reactivation of latent endogenous infection, or "activation" of an active but subclinical infection. Allograft-transmitted parasitic disease may also occur, as illustrated by the occurrence of donor-derived primary toxoplasma infection after heart and liver transplantation. A detailed exposure and travel history is essential in defining parasitic infections that may cause an opportunistic infectious disease syndrome in transplant recipients.

Toxoplasma gondii

T. gondii infection after transplantation may manifest with fever and lymphadenopathy and could progress to cause tissue-invasive infection, including myocarditis and cardiomyopathy, pneumonia, and neurologic manifestations. Parasitism is often extensive in the brain, heart, lungs, and lymphoid organs. Infection is especially more common in heart transplant recipients since the parasite may be harbored in cardiac muscles and thus could be transmitted through the heart allograft. The diagnosis is suspected based on exposures and may be confirmed by serology and the demonstration of the organism in biopsy specimens. Molecular testing using PCR may also be utilized. The prevention of toxoplasmosis is recommended mainly in heart transplant recipients, especially when there is a *Toxoplasma* D+/R− serologic mismatch. The suggested prophylaxis is pyrimethamine and sulfadiazine or TMP-SMX. Many centers provide lifelong TMP-SMX prophylaxis for heart transplant recipients at high risk of toxoplasmosis. Alternative regimens include dapsone with pyrimethamine and atovaquone. The treatment of toxoplasmosis after transplantation includes the synergistic combination of pyrimethamine and sulfonamide or clindamycin.

Trypanosoma cruzi

Trypanosoma cruzi is a vector-borne parasite that causes Chagas disease (or American trypanosomiasis) and may be manifested as fever, myocarditis, and heart failure in transplant recipients. Skin nodules, panniculitis, and brain abscesses may also occur in transplant recipients. Infection should be suspected in patients residing in endemic regions, such as Latin America, where the triatome vector may transmit the parasite through bites. Reactivation of latent infection may occur. Donor-derived infection has also been observed in transplant recipients of organs from donors from endemic regions. Diagnosis and monitoring is through the PCR or the detection of trypomastigote in the buffy coat layer. Skin lesions may be biopsied to demonstrate the presence of the parasite. Treatment of Chagas disease is with benznidazole and nifurtimox in addition to reduction of immunosuppression.

Strongyloides stercoralis

Strongyloides stercoralis is a nematode whose larval stage has the tendency to disseminate in the setting of immune compromise, with larval accumulation in the lungs causing Loeffler's syndrome or eosinophilic pneumonia. Peripheral eosinophilia is often present. Gut penetration by the larva may also cause the translocation of bacteria and fungi and leads to systemic bacterial and fungal hyperinfections. This hyperinfection syndrome may be associated with pneumonitis, abdominal crisis, eosinophilic meningitis, and septic shock. Polymicrobial bloodstream infection, including *Candida* spp., gram-negative organisms such as *E. coli*, and other gut-derived bacteria, may occur and clue in for the diagnosis. Death is often due to gram-negative bacterial septic shock. The treatment options for *S. stercoralis* infection are thiabendazole, ivermectin, and albendazole. Treatment of other superimposed infections should complement parasite-directed therapy.

Conclusion

Infections cause significant morbidity and preventable mortality after transplantation. Infections in transplant recipients are generally more severe, and, at times, the classic clinical manifestations of these infections may be atypical. Hence, a high degree of suspicion is necessary for prompt and proper diagnosis of these infections.

Infections portend a worse allograft and patient survival outcome after transplantation. Hence, the major goal is prevention, prompt diagnosis, and aggressive treatment. To the extent possible, reduction of the degree of pharmacologic immunosuppression should complement antimicrobial therapy.

Suggested reading

Blumberg E, Dazinger L, Kumar D, Michaels M, Razonable RR, eds. American Society of Transplantation Infectious Diseases Guidelines, 3rd edition. *Am J Transplant*. 2013;13 Suppl. (currently updated for 2019 Guidelines, to be published in *Clinical Transplantation*).

Cesaro S, Dalianis T, Hanssen Rinaldo C, et al. ECIL guidelines for the prevention, diagnosis and treatment of BK polyoma virus-associated hemorrhagic cystitis in hematopoietic stem-cell transplant patients. *J Antimicrob Chemother*. 2018;73:12–21.

Martens JA, Girmenia C, Bruggemann RJ, et al. European guidelines for primary antifungal prophylaxis in adult hematology patients: Summary of the updated recommendations from the European conference on infections in leukemia. *J Antimicrob Chemother*. 2018;73:3221–3230.

Tissot F, Agrawal S, Pagano L, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem-cell transplant patients. *Hematologica*. 2017;102(3):433–444.

Tomblyn M, Chiller T, Einsele H, et al. Guidelines for the prevention of infectious disease complications among hematopoietic stem cell transplant recipients: A global perspective. *Biol Blood Marrow Transplant*. 2009;15(10):1143–1238.

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Diabetes and infection

Sylvia J. Shaw and Raza Iqbal

Diabetes mellitus (DM) affects >30.3 million people in United States; 84.1 million are known to have prediabetes. Worldwide, the prevalence of diabetes will increase 366 million by 2030. More than 90% of diabetic patients have type 2 diabetes. Diabetes is a metabolic and vascular disease; both microvascular and macrovascular complications are related to blood glucose control and disease duration and are more commonly seen in the elderly. The annual cost of diabetes is tremendously expensive; according to American Diabetes Association, it was $245 billion in 2012. While nearly $70 billion of this figure was associated with reduced workforce productivity, the remaining $176 billion occurred as healthcare expenditures. Annual increments of healthcare costs ranged from $11,710 to $16,883 per patient with diabetic foot ulcer, or as high as $13 billion nationally, in addition to the cost associated with diabetes itself.

Diabetic patients have increased risk for infections (Table 89.1) and are accountable for 50% of hospital admission or outpatient visits. Respiratory and foot infections are overrepresented and have increased risk of infection-related mortality.

Predisposing factors to infection

Uncontrolled diabetes alters host immune response and has been implicated in disorders of immune function by alteration of polymorphonuclear leukocyte (PML) chemotaxis, phagocytosis, and decreased intracellular bactericidal activities. The effect of hyperglycemia on phagocytic activity is associated with an increase in cytosolic calcium and is reversible with the improvement of blood glucose level. There are other metabolic imbalances that impair the immune system, such as presence of acidemia. In addition, presence of chronic inflammatory changes may contribute to the metabolic imbalances. Tumor necrosis factor (TNF-α), interleukin (IL)-1β, IL-6, and IL-18 are known to activate the stress hormones, creating hyperglycemia and insulin resistance.

Hyperglycemia was reported to impair complement receptor-3 and Fcy receptor–mediated phagocytosis. Defective cellular immunity includes decreased opsonization and response to phytohemagglutinins and poor skin test reactivity. Diabetics also have poor granuloma formation. All these changes are aggravated by microcirculatory failure, which alters the diffusion of both cellular and humoral factors to the affected site. The risk of infection also is enhanced by the presence of peripheral and autonomic neuropathy and peripheral arterial disease (PAD). Obesity is also a risk factor for moderate or severe infection-related morbidity.

Respiratory infections

Respiratory infections in the diabetic population are associated with increased mortality. Diabetic patients are four times more likely to die from pneumonia or influenza compared to nondiabetics. The risk of

TABLE 89.1 **COMMON INFECTIONS ASSOCIATED WITH DIABETES MELLITUS**

Organ system	Type of infections
Respiratory	Pneumonia
	Aspiration pneumonia
	Pulmonary tuberculosis
Head and neck	Mucormycosis
	Invasive otitis externa
Gastrointestinal	Periodontal infections
	Candida esophagitis
	Emphysematous cholecystitis
Genitourinary	Upper and lower urinary tract infections
	Emphysematous cystitis
	Emphysematous pyelonephritis
	Papillary necrosis
	Perinephric abscess
	Fungal urinary tract infection (UTI)
Skin and soft tissue	Superficial infections
	Superficial necrotizing infections
	Deep necrotizing infections
	Diabetic foot infections (mild/moderate/severe)
Nosocomial	Soft tissue
	UTI
	Respiratory tract infections

developing staphylococcal pneumonia is increased since 30% of diabetics are nasal carriers of *Staphylococcus aureus.* Patients with DM have a higher risk of developing pneumonia (*Streptococci*, *Klebsiella, Legionella*) following influenza, so immunization against pneumococcus and influenza is recommended. Patients not vaccinated for pneumococci should be vaccinated with both polysaccharide and conjugated vaccine according to Advisory Committee on Immunization Practices (ACIP) guidelines. The incidence of acute bronchitis, pneumonia, or exacerbation of chronic obstructive pulmonary disease (COPD) is similar in type 1 and type 2 diabetics. Diabetic patients are also prone to aspiration pneumonia, especially in the presence of gastroparesis (occurs in 40–60% of patients with DM). The risk of aspiration also increases with impairment of consciousness (i.e., hypoglycemia, hyperosmolar state).

The incidence of tuberculosis is 16 times higher in the diabetic population than in the nondiabetic population, and atypical locations are common. For this reason, a positive purified protein derivative (PPD) skin test with 10 mm induration is considered positive even with a normal chest radiograph and requires isoniazid (INH) or rifapentine and INH according to current guidelines. Diabetes also predisposes to cavitary lung disease with coccidioidomycosis, and disseminated and extrapulmonary coccidioidomycosis is more common in diabetics. Pulmonary mucormycosis is complicated by fungal vascular invasion and high mortality. These infections require cultures, serology, imaging study, and biopsy for confirmatory diagnosis. Antifungal agents (voriconazole, posaconazole, or amphotericin B) should be initiated early pending the laboratory results.

Mucormycosis

More than three-fourths of cases of rhinocerebral mucormycosis occur in diabetics, particularly in the presence of diabetic ketoacidosis. It is a medical emergency with high mortality if early diagnosis is not made. Mucormycosis is caused by a group of fungi known as *Mucorales*, the most common genera being *Rhizopus, Absidia*, and *Rhizomucor*. These fungi invade nasal and paranasal membranes as well as blood vessels, resulting in thrombosis and tissue infarction. Local spread of infection results in ophthalmoplegia, blindness, cavernous sinus thrombosis, meningoencephalitis, and brain abscesses, leading to rapid death in untreated cases. Patients with mucormycosis may present with facial or ocular pain, nasal stuffiness, generalized malaise, and fever. Periorbital edema, chemosis, and nasal black eschars or necrotic turbinates are common presentation. Diagnosis is made by biopsy of the necrotic eschars and demonstration of nonseptate thick-walled hyphae with special staining. CT scan or MRI can be helpful in assessing the extent of disease and can aid the surgeon in debridement. Treatment with intravenous (IV) amphotericin B, 1 mg/kg/d, or liposomal amphotericin B, 5 mg/kg/d, should be started as soon as possible with surgical consultation for debridement. Posaconazole (800 mg in divided doses) is the oral agent that can be effective in 60% to 70% of patients with zygomycosis. Hyperbaric oxygen therapy also is reported to be beneficial. Those who survive may require reconstructive surgery and long-term psychological counseling due to facial disfiguration. Even with early diagnosis and treatment, mortality with mucormycosis can be as high 50%, but 100% if untreated.

Invasive otitis externa

Invasive otitis externa is an aggressive infection usually caused by *Pseudomonas aeruginosa*. Rarely, the etiologic agent is *Aspergillus, Klebsiella pneumoniae*, or other organisms. More than 90% of patients have diabetes, often with poor metabolic control. Patient usually presents with severe ear pain. Clinically, the disease begins with periauricular cellulitis and granulation tissue at the junction of the cartilaginous and osseous portions of the external auditory canal. When infection spreads, it results in parotitis, mastoiditis, septic thrombophlebitis, cranial nerve palsy, and meningitis. Osteomyelitis of the temporomandibular joint, skull base, and cervical vertebrae can also occur. Facial nerve VII palsy occurs in 30% to 40% of cases and does not necessarily carry a poor prognosis. However, development of palsies of cranial nerves IX and XII implies deep infection. This can be complicated by sinus thrombosis and central nervous system (CNS) infection, which results in death in 30% of patients. The use of MRI or CT scan can help to assess the extent of infection and needed debridement. CT scan is ideal for assessment of bone erosion; MRI was slightly better at demonstrating medial skull base disease due to its ability to delineate changes in the fat content of the marrow. Since bone erosion distinguishes malignant external otitis from external otitis, CT scan is better test for

initial diagnosis, while MRI is better for establishing the extent of disease and monitoring response to therapy.

Parenteral antipseudomonal antibiotic therapy is generally recommended. Combination therapy of β-lactam agents (piperacillin, ceftazidime, cefepime, imipenem, or aztreonam) with or without an aminoglycoside can be used. Oral quinolones can be used if susceptibilities are available. If *Aspergillus* is the causative organism, liposomal amphotericin B needs to be used. Hyperbaric oxygen therapy may have an adjuvant effect.

Widespread use of topical and oral fluoroquinolones for treatment of otitis externa may make the isolation of *Pseudomonas* difficult and has contributed to emergence of *P. aeruginosa* resistant to ciprofloxacin.

Gastrointestinal infections

Periodontal infections are considered the sixth complication of diabetes since 1993 and affect 17.3% of the diabetic population and 9% of the general public. The risk factors for periodontal disease are increase salivary glucose, decrease salivary pH, small-vessel disease, changes in collagen metabolism, and immune changes (i.e., inflammatory cytokines). *Porphyromonas gingivalis* is the most common pathogen. Professional cleaning and local treatment of periodontal infections may be adequate. However, antibiotic treatment is needed if patients develop dental symptoms. *Candida* esophagitis has been reported to occur with increased frequency in diabetic patients and more often in those who receive broad-spectrum antibiotics. The most common presentation is retrosternal pain or dysphagia after the ingestion of cold or hot drinks. Oral thrush can be absent. Endoscopic examination and biopsy are the preferred diagnostic procedures. Treatment with oral fluconazole if no dysphagia (400 mg initial dose, followed by 200 mg/d) is necessary for a minimum of 3 weeks or at least for 2 weeks after resolution of symptoms. An alternative therapy is itraconazole, 100 mg swished in mouth daily for 3 weeks. Oropharyngeal infection can be treated with itraconazole, 200 mg swished in mouth daily for 1 to 2 weeks. Infections with resistant *Candida* spp. also respond to voriconazole intravenously or orally or caspofungin intravenously. Success of treatment may depend on strict diabetic control.

Emphysematous cholecystitis is a surgical emergency, characterized by gas production in or around the gallbladder. The infection is highly virulent and often induced by multiple pathogens; among the most common are *Clostridia* (50–70%) and gram-negative bacilli such as *Escherichia coli* and *Klebsiella*. Other common organisms reported are *Salmonella enteritidis, Campylobacter*, and *Bacteroides fragilis.* This infection is predominantly seen in diabetic male patients (70%) and is associated with gallbladder gangrene (74%) and perforation (21%). Gallstones are present in half of these patients. Diagnosis requires serial x-ray examinations or CT scan. Treatment requires high-dose parenteral broad-spectrum antibiotics aimed at both anaerobic and gram-negative bacteria (imipenem or piperacillin-tazobactam), together with prompt surgical intervention. There is high mortality even with early diagnosis (15–25%).

Urinary tract infections

Diabetic female patients have a two- to fourfold higher incidence of bacteriuria. Diabetic women are at risk to develop recurrent asymptomatic bacteriuria, which in general is benign and seldom permanently eradicable. Treatment of asymptomatic bacteriuria is not recommended since the outcome does not change and chances of a patient colonized with resistant organism is increased. Diabetic patients have a higher prevalence of developing nosocomial urinary tract infection (UTI) and a higher risk of developing pyelonephritis. Predisposing factors are the presence of neurogenic bladder, uncontrolled diabetes and glycosuria, recurrent vaginitis, renal disease, and urologic instrumentation.

Emphysematous cystitis is often the result of infection with *E. coli* or other Enterobacteriaceae. More than 80% of DM patients present with pneumaturia. Gas in the urinary bladder wall and the collection system may be seen on either plain x-ray or CT scan studies. The disease usually responds to antibiotics targeting the Enterobacteriaceae.

Emphysematous pyelonephritis is a life-threatening suppurative infection of the renal and perirenal tissue. It occurs predominantly in diabetic patients (70–90%), more often in women. The disease is usually unilateral, more often affecting the left kidney. More than 40% of cases have underlying urinary tract obstruction; *E. coli* is the predominant isolated organism (70%). Patients present with fever, chills, flank pain, confusion, and often sepsis. Thrombocytopenia, cognitive changes, and proteinuria are independent risk factors for poor outcome. Patients present with fever of unknown origin, and the diagnosis is made by demonstration of gas on plain x-ray film or CT scan of the abdomen. Treatment usually requires a combination of surgical intervention, removal of urologic obstruction when present, and frequently unilateral nephrectomy and antibiotic therapy. Rarely the emphysematous cystitis can coexist with emphysematous pyelonephritis, and this condition has a mortality rate as high as 50%. Survival rate is >90% in patients who have both surgical and antibiotic treatment versus 25% in cases treated with antibiotics alone.

Papillary necrosis can occur as a complication of emphysematous pyelonephritis or as an isolated entity. More than 50% of cases are described in diabetic patients. Other cases are analgesic abuse, sickle cell disease, and urinary tract obstruction. Many patients present acutely with fever, ureteral colic, microscopic or macroscopic hematuria, and pyuria, with renal failure developing in 50% of cases. Some patients have an indolent presentation and may pass sloughed papillary tissue in the urine. Diagnosis can be made by renal ultrasound. However, the test of choice is retrograde pyelography. For patients who present with obstruction and do not pass the detached papilla spontaneously, surgical removal is indicated through cystoscopy with ureteral instrumentation.

Perinephric abscess should be suspected in patients who present with "pyelonephritis" but who have a poor response to 4 or 5 days of IV antibiotic therapy. One-third of cases are described in diabetic patients who present with pyuria, moderate fever, and a mass over the affected kidney (50% of cases). Among the gram-negative organisms, *E. coli* is the most common isolate, and ascending

infection is the usual route of spread. The diagnosis requires use of renal ultrasound, CT, or MRI studies, which also can help exclude ureteral obstruction. Surgical drainage is mandatory (open surgery or percutaneous catheter placement) in combination with IV antibiotics.

Fungal UTIs occur with increased frequency in the diabetic population, especially after long-term broad-spectrum antibiotics or Foley catheter placement. Most of the patients have asymptomatic candiduria and are afebrile. Elderly females with candiduria and UTI symptoms should be evaluated for yeast or atrophic vaginitis. However, severe infections complicated with fungus ball formation, obstruction, and sepsis have been reported. For this reason, all asymptomatic (presumably colonized) patients should be carefully observed for any signs of deterioration. Development of fever or azotemia must be investigated for possible ureteral obstruction, renal involvement, or disseminated fungal disease. Quantitative colony counts of only 10,000/mL of yeast in the urine may be sufficient to cause disease. Among the most common isolates are *Candida albicans, C. tropicalis*, and *C. glabrata*. Antifungal agents according to susceptibilities should be used. Patients who have evidence of obstruction will require urological intervention.

Skin and soft tissue infections

Superficial infections are often caused by *S. aureus*, which commonly colonizes the nasal mucosa and skin of diabetic patients. The most common soft tissue infections reported in the diabetic population are impetigo, carbuncles, cellulitis, folliculitis furuncles, necrotizing fasciitis, septic bursitis, and subcutaneous abscesses. Elimination of *S. aureus* carrier state require use of bacitracin ointment to the nares and oral administration of rifampin, Bactrim, or minocycline (two drugs in combination). Recurrent abscesses require drainage and antibiotic therapy.

Superficial necrotizing infections

Crepitant (anaerobic) cellulitis is a superficial process produced by multiple organisms, most often anaerobes. Infection is seen more frequently in diabetic patients with chronic, nonhealing, lower extremity ulcers. Crepitus is present on palpation because of subdermal and subcutaneous gas dissection. Treatment of this infection requires appropriate parenteral antibiotics and surgical debridement. Necrotizing fasciitis occurs when infection spreads along the superficial fascial planes without muscle involvement. This is a mixed infection (type I variant) that is present in 90% of cases caused by aerobes and anaerobes (e.g., *Streptococcus pyogenes*, *Bacteroides species*, *Enterococcus* species, *Peptostreptococcus, E. coli, Proteus*). Group A streptococci either alone or in combination with *S. aureus* (type II variant) is present in 10% of cases. Group B streptococci–induced necrotizing fasciitis has also been reported. This potentially lethal infection frequently presents with cutaneous necrosis, suppurative fasciitis, vascular thrombosis, and extreme systemic toxicity. In the later stages of the infection, destruction of the small nerve fibers results in patchy area of skin anesthesia. Necrotizing fasciitis early in its evolution is clinically indistinguishable from other soft tissue infections. The most affected sites are upper and lower extremities, perineum, groin, and thorax. Mortality rate is 30% to 70% if diagnosis is delayed. Management requires thorough debridement and drainage, using the "filleting procedure," and broad-spectrum antibiotics (i.e., Zosyn, imipenem). The subcutaneous tissue is left open, and irrigation with normal saline or Ringer's lactate solution is performed. Many patients require repeated debridement followed later by reconstructive surgery. Infection produced by *S. pyogenes* is often complicated by toxic shock syndrome. It should be treated with penicillin and clindamycin in combination with debridement. IV immunoglobulin (IVIG) is used in severe cases.

Deep necrotizing infections

Necrotizing cellulitis (nonclostridial myonecrosis) is produced by the same bacteria responsible for necrotizing fasciitis. This form of infection occurs most commonly in diabetic patients (75%) and involves the muscle, skin, fat, and fascia. Necrotizing fasciitis of the male genitalia (Fournier's gangrene) is associated with diabetes in 40% to 60% of cases. Infection can also affect the abdominal wall or perineum, especially after surgery, penetrating trauma, or instrumentation. Treatment requires coverage of both aerobic and anaerobic pathogens and should cover *S. aureus*, gram-negative enteric organisms, *E. coli, Proteus, Bacteroides fragilis*, and *Enterococcus* species. All patients need to have aggressive debridement, resection of the necrotic muscle, hyperbaric oxygen, and supportive therapy.

Clostridial myonecrosis, if present, requires aggressive surgical debridement and appropriate antimicrobial therapy.

Diabetic foot infection is responsible for 20% of hospital admissions and a frequent precursor of amputations. Predisposing factors are peripheral neuropathy, PAD, immunopathy, and history of a previous ulcer. The severity of diabetic foot infection can vary from mild and superficial (often monobacterial, caused by *S. aureus* or *Staphylococcus epidermidis*) to severe deep infection. Tissue gangrene is usually induced by polymicrobial (mixed aerobic and anaerobic) infections. The MRI study is used to make the diagnosis of bone involvement and also to delineate the extent of bone resection necessary to treat osteomyelitis. Clinically, a probe to bone can be suggestive of osteomyelitis. If any patient has diminished or absent peripheral pulses, arterial Doppler (with both pressure and wave form studies) and/or transcutaneous oxygen tension (TcPo2) are needed. An ankle brachial index of <0.80 mm Hg or a $TcPO_2$ of <40 mm requires vascular consultation.

Mild infections without systemic symptoms can be treated with oral antibiotics (Augmentin, quinolones, or first-generation cephalosporins) and require close follow-up at 48 to 72 hours. If parenteral therapy is considered, cefazolin or vancomycin (methicillin-resistant *S. aureus* [MRSA] suspected or colonized) may be used for presumed monobacterial infection. Moderate nonlimb–threatening infections require local debridement and parenteral antibiotic therapy with a broader coverage. The empiric therapy

can be altered based on culture results of biopsy, ulcer curettage, or aspiration (Table 89.2). No systemic treatment should be done unless a wound is infected. For soft tissue infection, duration of therapy should be based on the clinical outcome. Limb-threatening infections (extensive cellulitis, deep ulcer, plus lymphangitis and/or osteomyelitis) may require broad coverage (piperacillin-tazobactam, imipenem, or meropenem). Surgical debridement should be done promptly. Bone infection may require extirpation of the affected bone or amputation. Preservation of the ambulatory capacity should be considered. The intraoperative culture should be used to guide the choice of antibiotic therapy. Following surgery, duration of treatment should be guided by an estimate of residual infection. Long-term (6 weeks) of treatment is recommended for residual osteomyelitis. Therapeutic goals are achievable by IV followed by oral antibiotics. Oral antibiotics are available that achieve therapeutic levels in bone. Studies support the use of oral antibiotics to achieve similar therapeutic results when compared to parenteral therapy for chronic osteomyelitis. Therefore, the risks and cost of parenteral antibiotics can be avoided. There is no evidence that antibiotic therapy of longer than 4 to 6 weeks improves the outcomes compared to shorter regimens.

Nosocomial infections affecting skin/soft tissue, the urinary tract, and the respiratory system are common in diabetic population, and 50% of organisms isolated from diabetic foot ulcers are MRSA. Vancomycin-resistant enterococci (VRE), diphtheroids (group JK), and *Pseudomonas* are also common pathogens. Culture-guided antibiotics selection is recommended. Management of these infections may require use of newer antibiotics such as linezolid

TABLE 89.2 **SUGGESTED EMPIRICAL ANTIBIOTIC REGIMENS, BASED ON CLINICAL SEVERITY, FOR DIABETIC FOOT INFECTIONS**

Route and agent(s)	Mild	Moderate	Severe
Advised route	Oral for most	Oral or parenteral, based on clinical situation and agent(s) selected	Intravenous, at least initially
Dicloxacillin	Yes	–	–
Clindamycin	Yes	–	–
Cephalexin	Yes	–	–
Trimethoprim–sulfamethoxazole	Yes	Yes	–
Amoxicillin/clavulanate	Yes	Yes	–
Levofloxacin	Yes	Yes	–
Cefoxitin	–	Yes	–
Ceftriaxone	–	Yes	–
Ampicillin/sulbactam	–	Yes	–
Linezolid[a] (with or without aztreonam)	–	Yes	–
Daptomycin[a] (with or without aztreonam)	–	Yes	–
Ertapenem	–,	Yes	–
Cefuroxime with or without metronidazole	–	Yes	–
Ticarcillin/clavulanate	–	Yes	–
Piperacillin/tazobactam	–	Yes	Yes
Levofloxacin or ciprofloxacin with clindamycin	–	Yes	Yes
Imipenem–cilastatin	–	–	Yes
Vancomycin[a] and ceftazidime (with or without metronidazole)	–	–	Yes

Definitive regimens should consider results of culture and susceptibility tests as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have US Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid is currently specifically approved for diabetic foot infections.

[a] For patients in whom methicillin-resistant *Staphylococcus aureus* infection is proved or likely.

From Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. *Plastic Reconstruct Surg*. 2006;117: 212S–238S. Reprinted with permission.

(MRSA, VRE), daptomycin (MRSA, VRE), oritavancin, telavancin, and others.

Overall, because patients with DM have a high incidence of chronic kidney disease, adjustment of the antibiotic dose based on renal function is imperative. Drug interaction and toxicity should be always considered prior to therapy since these patients are frequently on multiple medications.

Suggested reading

Bertoni AG, Saydah S, Brancati FI. Diabetes and the risk of infection-related mortality in the US *Diabetes Care*. 2001;24(6):1044–1049.

Casqueiro J, Casqueiro J, Alves C. Infections in patient with diabetes mellitus: A review of pathogenesis. *Indian J Endocrinol Metab*.2012;16:S27–S36.

Chin-Hong PV. Infections in patients with diabetes mellitus: Importance of early recognition, treatment, and prevention. *Johns Hopkins Adv Stud Med*. 2006;6(2):71–81.

Gardner SE, Hillis SL, Frantz RA. Clinical signs of infection in diabetic foot ulcers with high microbial load. *Biol Res Nurs*. 2009;11(2):1–14.

Gupta S, Koirala J, Khardori R, Khardori N. Infections in diabetes mellitus and hyperglycemia. *Infect Dis Clin N Am*. 2007;21:617–638.

Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. *Plast Reconstr Surg*. 2006:117:212S–238S.

Muller LAMJ, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AIM. Increase risk of common infections in patients with type1 and type 2 diabetes mellitus. *Clin Infect Dis*. 2005;41:281–288.

NIDDK Diabetes Statistics. www.niddk.nih.gov/health-informatikon/health-statistics/diabetes-statistics, 2019.

Oral versus IV antibiotics (OVIVA) for bone and joint infections. *N Engl J Med*. 2019, Jan 31;380:5.

Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis*. 2011;54(3):393.

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Infectious complications in the injection and non-injection drug user

Carlo Contoreggi

Drug abuse is a widespread public health problem and many of its medical complications are infectious due to the transmission of blood-borne, environmental, and respiratory infectious agents. The ongoing opioid epidemic has changed the face of addiction in the United States and Canada; this has resulted in more published data characterizing the medical complications associated with substance abuse in both non-injection and injecting drug users (DUs/IDUs). According to the US Centers for Disease Control and Prevention (CDC) *Morbidity and Mortality Weekly* (2016), there has been a five-fold increase in opiate-related deaths (from both prescription and street opiates, such as heroin and fentanyl) from 1999 to 2014. This reflects the catastrophic nature of the epidemic and its expanding effects on society as a whole.
As before, DUs/IDUs are less likely to access care and maintain adherence for optimal benefit of treatments. Recent studies find that social and access factors related to criminalization and economic status are major barriers to care, including highly active retroviral therapy (HAART) for HIV-positive individuals. Increasing treatment options and societal acceptance of harm reduction efforts have been demonstrated to improve outcomes in countries that have undertaken them.

Endocarditis

The most serious infectious complication in the injection user is endocarditis. This is a life-threatening infection of the heart valves and/or endocardium associated with septic parenteral injections. Right-sided valvular infections are very frequent in IDUs due to septic inoculations. Intravenous (IV) injections increase the susceptibility of right-sided valvular and other structures to infection. Concurrent pulmonary hypertension from drug adulterants, such as talc, may also predispose to right-sided disease.

Despite the high prevalence of endocarditis, the offending pathogens are not specific to injectors. *Staphylococcus aureus*, often methicillin-resistant (MRSA), is the most commonly identified organism, but other pathogens are seen. These include *Pseudomonas*, *Serratia*, *Enterococci*, *Streptococcus* groups A and B, and *Streptococcus viridans*. Increasingly, fungal pathogens are seen with and without immunodeficiency.

Clinical diagnosis of endocarditis in the drug abuser can be difficult. The hallmark symptom is fever. Other constitutional symptoms such as chills, sweats, and arthralgia are less specific as they are commonly observed in opiate withdrawal. The physical signs associated with left-sided endocarditis are seldom present. Coexistent HIV-1 immunodeficiency (non- or poor adherence with HAART) appears to predispose to more severe systemic infections.

Because clinical diagnosis alone presents challenges, echocardiography is the primary method by which to diagnose and monitor endocarditis treatment. Blood cultures and other routine tests are used to identify pathogens and antimicrobial sensitivities. Transthoracic and transesophageal echocardiography are used to evaluate suspected endocarditis (e.g., high clinical suspicion but negative blood cultures). Detection of

valvular vegetations, valve disease with hemodynamic compromise, associated intraventricular shunts, or abscesses, or the presentation of patients with persistent fever, continued bacteremia, or clinical deterioration may mandate serial testing.

Therapy should be multidisciplinary as patients may be unwilling to comply with adequate treatment regimens especially if inpatient hospital stays and serial testing are required. Combination short-course IV followed by oral therapy may be considered. Left-sided disease, large vegetations, or presence of cardiovascular compromise mandates more intensive therapy. Medication selection is an evolving science, and isolation of pathogen and discovering drug sensitivities are critical in this respect. Mortality with right-sided disease is low; the presence of left-sided valvular and/or chordae tendineae involvement, fungal pathogens, congestive heart failure, other cardiovascular compromise, vegetations of >20 mm, and HIV-1 (ineffective treatment w/HAART) with immune compromise all greatly increase morbidity and mortality. Inflammatory myocarditis can be seen independently of and with endocarditis. Causation is multifactorial; cocaine, HIV-1 infection, and inflammatory responses from adulterants in drugs are common causes.

Pulmonary infections

Complications due to IV drug use include pneumonia, aspiration pneumonitis, lung abscess, and septic pulmonary emboli. Talc contamination of the injected drugs enters the bloodstream and lodges in the pulmonary capillary bed, causing foreign-body granulomatosis that results in pulmonary fibrosis, acute inflammatory pneumonitis, and pulmonary hypertension. Septic pulmonary emboli may result in clinically evident ventilatory and perfusion mismatch on scintigraphic imaging.

Chronic inhalation of drugs and their adulterants will accelerate alveolar destruction and result in early-onset chronic obstructive pulmonary disease (COPD) and emphysema. Chronic immunosuppression from HIV increases likelihood of pneumonitis, community and immunocompromised pneumonia, and other respiratory disorders. Chronic smoking of opiates and cocaine is often associated with COPD. Smoking (nicotine/marijuana) may result in decreased vital capacity, a decrease in diffusion capacity, and small airway disease. IDUs also have a 10-fold increased risk of community-acquired pneumonia compared to the general population due to failure to vaccinate, the destructive action of marijuana/tobacco abuse, and increased susceptibility to viral and bacterial exposures.

Neurologic complications

Multiple serious neurologic complications are associated with drug abuse, most commonly with injection use. Neurologic disease often compounds underlying drug use–related pathology. Endocarditis is associated with ischemic stroke, encephalitis, cerebral hemorrhage, and brain abscess. A non-IDU/DU population with endocarditis was found to have about a 15% chance of a neurologic complication of stroke, encephalitis, and hemorrhage often with long-lasting residual deficits, and one would expect frequency and severity of complications to be higher in more medically compromised groups.

Bone and joint infections

According to Jicha et al., osteomyelitis and associated septic arthritis from disseminated cutaneous infection are the second most common drug use infections. Direct injection at or near the affected area as well as systemic bacterial seeding is common. Gram-positive organisms and *Pseudomonas aeruginosa* are the most commonly implicated organisms. Osteomyelitis most commonly affects the fibrocartilaginous joints such as the vertebral, sternoarticular, and sacroiliac joints. In addition to bacterial infections, fungal infections are increasingly described in both immunocompetent and immunodeficient hosts (i.e., diabetics, end-stage renal disease, HIV, and cancer). Treatment protocols do not differ from other immunosuppressed hosts; bone or joint cultures are necessary for accurate diagnosis. Compliance with long-term therapies poses additional problems with adherence in the DUs/IDUs.

Skin and soft tissue infections

Septic parenteral injections frequently lead to skin and soft tissue infections. Infectious and chemical thrombophlebitis, abscesses, and cellulitis are common venous insults. Life-threatening cutaneous infections include fasciitis, myonecrosis, and gangrene. Tissue crepitans, extensive cellulitis, evidence of systemic toxicity, severe pain, and sepsis suggest serious and life-threatening infections. Plain radiographs may be helpful, although MRI is optimal to determine the extent of soft tissue, bone, and marrow involvement.

Injected drugs and their adulterants often damage veins. Progressive venous sclerosis is common. With loss of peripheral access, deeper and more dangerous sites (i.e., femoral, axillary, jugular, penile, and mammary veins) may be used. More serious infections, thrombosis, and gangrene can result from injections at these sites.

Once IV access is less accessible, many substance abusers will administer drugs subcutaneously. Staphylococci and streptococci are frequent pathogens. However, with immunosuppression, other bacterial pathogens are encountered. *Escherichia coli, Klebsiella, Bacteroides*, *Clostridia*, and mixed flora consisting of both aerobic and anaerobic organisms as well as fungal organisms such as *Candida* are seen.

Small localized infections can be treated locally with or without systemic antibiotics. Severe infections should be managed with surgical debridement and inpatient antibiotic therapy.

Viral hepatitis

The opiate crisis of the past decade has markedly changed the epidemiology of hepatitis infections. Hepatitis A, B, C, and D (HBV, HCV, and HDV), respectively are associated with fecal–oral (HAV), parenteral, and sexual transmission (HBV, HCV, and HDV). The incidence of HBV and HCV in IDU populations is very high worldwide, with a significant proportion showing coinfection with both HBV and HCV.

Chronic HBV infection is associated with persistent hepatitis B surface antigen (HBsAg) and hepatitis Be antigen (HBeAg), although presence of hepatic inflammation varies widely. Positive HBeAg is associated with increased infectivity, more severe disease, and eventual cirrhosis. The HBV virion itself is not cytotoxic but mediates a host cytotoxic T-cell response that causes hepatocellular inflammation and necrosis. Coinfection with HIV-1, with its associated cellular immune deficiency, reduces the severity of the host immune response. Progressive HIV-1–associated cellular immunodeficiency can reduce hepatic inflammation and lowers serum transaminase concentrations. Other serologic measures of HBV infection in HIV-1 are not diminished.

HDV, or delta particle infection, is also common. This infection, which requires coinfection with HBV, imparts a more severe course than HBV alone. Coinfection with HBV and HDV is associated with increased incidence of fulminant hepatic failure. Vaccination with HBV vaccine also prevents HDV infection.

Therapeutic interventions for HCV have markedly improved over the past 5 years with the advent of multimodal antiviral therapies. Greater than 95% of patients w/HCV can be cured with a single course of therapy. Failure to treat DUs and IDUs increases morbidity and lethality in mid to later adulthood. In addition there is increasing evidence that IDU patients who have been successfully treated with antiviral medications may become reinfected with continued injection behaviors. Statistics are now emerging that, although reinfection appears infrequent, this may increase.

Interventional dynamic modeling of HCV infections in Switzerland found that aggressive treatment with antiviral therapy of ≥10% of the IDU HCV-infected pool per year would result in a >99% reduction in total cases by 2030. Discontinuation of injection use removes these individuals from the HCV dissemination pool. As with most other medical conditions that affect the DUs/IDUs, integration of medical treatment with effective substance abuse and psychiatric care improves efficacy while improving the overall quality of life. Individuals stabilized with opiate substitution therapy (i.e., methadone or buprenorphine) can show sustained clinical responses/disease eradication comparable to non–drug-abusing populations. This presents a rational public health direction to alleviate HCV in drug users in North America.

Despite improvements in therapy of patients with hepatitis C, substance abuse, alcohol abuse, and comorbid psychiatric disorders are major barriers to achieving improvement and disease remission. There remains considerable debate on the ethics of performing liver transplants in patients with alcohol and drug abuse. When organ recipients significantly outnumber available cadaver organs, many transplant groups routinely disqualify patients with substance abuse from consideration. However, the increasing the number of living donor transplants has increased availability and reduced the morbidity and mortality of chronic liver disease and liver failure; it is unclear how these procedures will impact drug users.

Immunologic abnormalities

Opiate receptors (μ-, κ-, δ-, and ζ-opioid receptors) are found in the central nervous system (CNS), spinal cord, and immune elements. Widely distributed in CNS glial/immune cells, they are also widely found in peripheral immune tissues and the digestive tract. A main function of ζ-receptors, also called *opioid growth factor receptors*, is modulating immune cellular growth, development, and immune regulation. Opiate ligands (endogenous or pharmacologic) have affinity to the ζ-receptor and the μ-receptor, as well as affinity to other immune regulatory receptors (Toll-like receptor 4 [TLR-4], nitric oxide [iNOS], and glutamate receptors). All of these regulate inflammation, apoptosis, and neoplastic proliferation. Exogenous opiate concentrations can activate or deactivate these receptors as full agonists, antagonists, or inverse agonists. Immune modulation on a molecular level by opiates has been studied for decades. In vitro, in vivo, and, increasingly, limited clinical studies have shown that low doses of the μ-, and ζ-opioid receptor antagonist naltrexone may have important albeit limited beneficial effects in immune disorders (inflammatory bowel disease, multiple sclerosis, and fibromyalgia). The molecular actions of opioids in these immune regulatory pathways in opiate abusers are largely unknown and will require further investigation.

Opiate abusers show subtle abnormalities in serum immune marker activation/immune responsivity independent of HIV and other retroviral/systemic infections. In vitro measures of cellular immunity can show diminished cellular cytotoxic/killer cell action and decreased cytokine and immune cell signaling. Natural killer (NK) cell and cytotoxic T-cell (CTL) functions are impaired. Drug users can also show abnormalities in circulating immune factors including elevated plasma immunoglobulins, especially the immunoglobulins M (IgM) and G (IgG); false-positive rheumatoid factor and syphilis serology; febrile agglutinins; acute phase reactants; and complement fixation tests. Cellular immunity abnormalities are evident in both the DU/IDU, with the IDU often more severely affected. HIV-1 antibody-negative parenteral opiate abusers may have elevated total T-lymphocyte counts as well as increases in both T-helper and T-suppressor cells. Injection behaviors increase HIV susceptibility. Measures of cellular immunity show diminished function. Cellular immune functions are essential for host recognition of pathogens and for immune stimulants such as those in vaccines. Without intact cellular immunity, future HIV-1 vaccine efficacy may be decreased in active DUs/IDUs.

Effective substance abuse treatment with discontinuation of septic injections may restore immunocompetence. Immune studies of patients maintained on methadone show some reversal of immune dysfunction after discontinuation of IV injections. The durability of these improvements especially with aging is unknown.

Tuberculosis

Tuberculosis remains a significant global health problem. Mycobacterium tuberculosis (TB) remains endemic in vulnerable, chronically ill, and marginalized populations (i.e., IDUs, the HIV-1 infected, prisoners, the homeless, and alcoholics). Other important risk factors for TB infection include diabetes, malnutrition, and smoking; these risk factors are supra-additive. TB is a highly virulent pathogen that infects both immunocompetent and immunodeficient individuals. Coinfection of TB and HIV-1 is present in a significant number of new TB cases. In those infected with HIV-1, TB primarily shows pulmonary involvement early, whereas with progressive immunosuppression, disseminated extrapulmonary TB is not uncommon.

Immune deficiency is due to both impaired humoral and cellular immunity. Antigen presentation from monocytes, NK, CTL, macrophages, and Th-1 to Th-2 cells is impaired, resulting in defective antibody production. Critically, suppression of immune competence due to heightened anti-inflammatory cytokine production (IL-10) can suppress the immunity in the infectious microenvironment. Other cytokines (interferon [IFN]-γ, interleukin [IL]-12, tumor necrosis factor [TNF-α]) can either enhance or partially negate localized immunosuppression action(s). Susceptibility to TB can also be increased by direct pharmacologic actions of drugs of abuse; opiates, as noted previously, can have immune-suppressive effects as can nicotine. Persistent localized (bronchoalveolar) and systemic inflammation can also render a host more susceptible to infection. It is likely that more frequent parenteral injections and exposure to immunosuppressive opiates/other drugs of abuse and adulterants increases an injector's risk to active TB.

All HIV-1–infected IDU patients should be tested for TB as early in the course of their disease as possible because the first several years post seroconversion show peak infection rates. Patients should be tested for TB every 6 months or if clinical symptoms dictate. Previously untreated individuals with past exposure to TB as evidenced by positive tuberculin skin test (TST) with positive purified protein derivative are at high risk for recurrence of latent infection with progressive immunodeficiency. Positive results for the TST in immunocompetent individuals is induration of at least 15 mm, 10 mm for the IDU, and 5 mm for HIV-positive patients. Anergic responses are common in these populations, though there is no clear consensus for additional testing. Immunocompromised hosts who are TST positive and recently exposed to TB should receive prophylaxis, as should anergic individuals with known environmental exposure or patients who are at high risk. If compliance with TST is poor, chest radiography of high-risk individuals has been demonstrated to increase disease detection.

Fungal infections

Fungal pathogens infect in the setting of moderate to severe immunosuppression, with CD4 counts in the 250/mm^3 to 100/mm^3 range. Invasive *Candida* infections are commonly seen as vaginitis in mild to moderate immunosuppression; oropharyngeal and invasive esophageal candidiasis is seen in moderate disease. Systemic colonization and CNS infection is seen with profound immunodeficiency. Fungal endocarditis requires more intensive pharmacotherapy and carries higher morbidity and mortality in the general population and in the DU/IDU.

Opportunistic viral infections

Herpes simplex virus, varicella-zoster virus, cytomegalovirus, and Epstein–Barr virus are common viral pathogens seen with immunosuppression. Varicella-zoster vaccination should be considered especially in patients in their sixth decade, although an incomplete/anergic response should be considered.

Conclusion

The integration of substance abuse treatment with primary and specialized care for infectious diseases, immunodeficiency, psychiatric, and other medical conditions is most effective for clinical outcome and cost of care. Addiction is a brain disease with neurochemical underpinnings disrupting decision-making, cognition, emotional control, motivation, drug abuse, sexual drive, and impulsivity. Impaired executive functioning limits adherence with therapy. A provider's acceptance of these patients is critical for successful management; many providers have difficulty with these patients, thus a team approach may be most effective for care delivery.

Buprenorphine is a μ, κ mixed agonist/antagonist opiate and a more acceptable alternative to methadone. It is widely available and can be administered in more convenient settings (i.e., doctors' offices). Buprenorphine has achieved increased financial coverage through private insurance, Medicaid, and other social services, which improves treatment availability and adherence. Therapeutic constraints can influence treatment options for comorbid medical conditions, such as prescribing oral instead of IV antibiotics, diagnostic testing, and duration of therapy. The incidence of comorbid psychiatric conditions such as affective disorders, thought disorders such as schizophrenia, schizo-affective disorders, and posttraumatic stress disorder is high and can limit treatment efficacy. Access to social workers, mental health professionals, and specialized providers who can coordinate complex services improves outcomes.

Societal realization and acceptance of harm reduction strategies have made additional treatment options more accessible to more substance users. These programs have been effective in Europe and Canada. However proposed changes in US federal government policies are inconsistent; there are potential reversals on treatment availability and harm reduction which seriously endanger efforts to reduce drug use and its associated morbidity and mortality. That said, prison and sentencing reforms for nonviolent drug offenders have been enacted. Political policies can undermine public health concerns; the experience in Indiana in 2015 exemplifies this. Over the course of months, the incidence of HIV infection spiked in IDUs. Attempts to introduce and expand harm reduction efforts,

especially needle exchange, were politically blocked by the governor and the legislature. The failure to implement a timely response resulted in hundreds of unnecessary HIV infections with the consequence being increased morbidity and eventually medical costs.

The demographics of opiate epidemic have changed; previously DUs/IDUs were older, often people of color, from the inner city, and of lower socioeconomic status (SES). Now a broader spectrum of individuals is affected. Rural outstrips urban areas in some geographic regions. The majority of injection users are no longer from minority groups. Younger individuals from higher SES backgrounds are nearly as likely as more disadvantaged groups to begin to abuse opiates and inject drugs. Injection heroin use is increasing along with prescription opiate abuse in younger addicts. Adulterated drugs are common, with exceptionally high-potency opiates such as fentanyl contributing to climbing numbers of overdose deaths.

There is a serious deficiency of gender-specific data, which are critical in delivering effective therapies and treatment interventions. Male IDUs outnumber females by approximately 4 to 1 but research relevant to harm reduction, transmitted blood-borne viral and sexually transmitted infections, endocrine dysfunction, injection-related complications, mental health, and physical and sexual violence has rarely been addressed in women. Gender equity and basic human rights are in question, with the need to refine approaches to address the high morbidity associated with gender disparities. Recognition of the special vulnerabilities of women is critical to effectively address harm reduction and disease complications and progression.

The Affordable Care Act of 2010 ("Obamacare") along with Medicaid expansion made access to treatment greater, but with increasing opiate abuse in both urban and rural areas, the availability of care is often limited. These changes are now in political danger with reversals to the policies of the 1980s and 1990s becoming more likely. Healthcare is a basic human right, and it is critical for successful drug abuse treatment and associated acute and chronic comorbid medical conditions. The challenges in treating this population are changing but are no less important for overall public health. Integrating treatment and care with a more diverse population offers new challenges. Clinicians must better tailor care and treatment to alleviate this ongoing crisis.

Suggested reading

Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: Diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association; endorsed by the Infectious Diseases Society of America. *Circulation*. 2005;111(23):394–434.

Bennett CL, Pascal A, Cvitanic M, et al. Medical care costs of intravenous drug users with AIDS in Brooklyn. *J Acquir Immune Defic Syndr*. 1992;5:1–6.

Brown SM, Stimmel B, Taub RN, et al. Immunologic dysfunction in heroin addicts. *Arch Intern Med*. 1974;134:1001–1006.

Bruce RD, Kresina TF, McCance-Katz EF. Medication-assisted treatment and HIV/AIDS: Aspects in treating HIV-infected drug users. *AIDS*. 2010;24(3):331–340. doi:10.1097/QAD.0b013e32833407d3.

Bruggmann P, Blach S, Deltenre P, et al. Hepatitis C virus dynamics among intravenous drug users suggest that an annual treatment uptake above 10% would eliminate the disease by 2030. *Swiss Med Wkly*. 2017 Nov 8;147:w14543. doi:10.4414/smw.2017.14543. eCollection 2017

Campbell EM, Jia H, Shankar A, Hanson D, et al. Detailed transmission network analysis of a large opiate-driven outbreak of HIV infection in the United States. *J Infect Dis*. 2017 Nov 27;216(9):1053–1062. doi:10.1093/infdis/jix307.

Chambers HE, Morris DL, Tauber MG, et al. Cocaine use and the risk for endocarditis in intravenous drug users. *Ann Intern Med*. 1987;104:833–836.

Darke S, Ward J, Zador D, Swift G. A scale for estimating the health status of opioid users. *Br J Addict*. 1991;86:1317–1322.

Dupont B, Drouhet E. Cutaneous, ocular and osteoarticular candidiasis in heroin addicts: New clinical and therapeutic aspects in 38 patients. *J Infect Dis*. 1985;152:577–591.

Foster M, Ramachandran S, Myatt K. Hepatitis A virus outbreaks associated with drug use and homelessness—California, Kentucky, Michigan, and Utah, 2017. *MMWR Morb Mortal Wkly Rep*. 2018 Nov 2;67(43):1208–1210. doi:10.15585/mmwr.mm6743a3.

Golub JE, Astemborski J, Ahmed M, et al. Long-term effectiveness of diagnosing and treating latent tuberculosis infection in a cohort of HIV-infected and at-risk injection drug users. *J Acquir Immune Defic Syndr*. 2008;49(5):532–537. doi:10.1097/QAI.0b013e31818d5c1c.

Grady BP Schinkel J, Thomas XV, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. *Clin Infect Dis*. 2013 Aug;57 Suppl 2:S105–10. doi:10.1093/cid/cit301.

Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. *J Infect Dis*. 2011 Jul 1;204(1):74–83. doi:10.1093/infdis/jir196

Hind CR. Pulmonary complications of intravenous drug misuse. 1. Epidemiology and non-infective complications. *Thorax*. 1990;45(11):891–898.

Hu DJ, Jiles R, Holmberg SD. Evolving epidemiology of hepatitis C virus in the United States. *Clin Infect Dis*. 2012;55(Suppl 1):S3–S9. doi:10.1093/cid/cis393.

Iversen J, Page K, Madden A, Maher L. HIV, HCV, and health-related harms among women who inject drugs: Implications for prevention and treatment. *J Acquir Immune Defic Syndr*. 2015 Jun 1;69(Suppl 2):S176–81. doi:10.1097/QAI.0000000000000659.

Janowicz DM. HIV Transmission and injection drug use: Lessons from the Indiana outbreak. *Top Antivir Med*. 2016 Jul/Aug;24(2):90–92.

Jicha C, Saxon D, Lofwall MR, Fanucchi LC. Substance use disorder assessment, diagnosis, and management for patients hospitalized with severe infections due to injection drug use. *J Addict Med*. 2018 Sep 24. doi:10.1097/ADM.0000000000000454. [Epub ahead of print]

Kamath GR, Shah DP, Hwang LY. Immune response to hepatitis B vaccination in drug using populations: A systematic review and meta-regression analysis. *Vaccine*. 2014 Apr 25;32(20):2265–74. doi:10.1016/j.vaccine.2014.02.072. Epub 2014 Mar 12.

Kumari P1, Meena LS. Factors affecting susceptibility to Mycobacterium tuberculosis: A close view of immunological defence mechanism. *Appl Biochem Biotechnol*. 2014 Dec;174(8):2663-73. doi:10.1007/s12010-014-1217-3. Epub 2014 Oct 9.

Kwiatkowska W, Knysz B, Gąsiorowski J, Witkiewicz W. Deep vein thrombosis of the lower limbs in intravenous drug users. *Postepy*

Hig Med Dosw (Online). 2015 Apr 22;69:510–20. doi:10.5604/17322693.1150215.

Lee HH, Weiss SH, Brown LS, et al. Patterns of HIV-1 and HTLV-I/II in intravenous drug abusers from the middle Atlantic and central regions of the USA. *J Infect Dis*. 1990;162:347–352.

Li Z, You Y, Griffin N, Feng J, Shan F. Low-dose naltrexone (LDN): A promising treatment in immune-related diseases and cancer therapy. *Int Immunopharmacol*. 2018 Aug;61:178–184. doi:10.1016/j.intimp.2018.05.020. Epub 2018 Jun 7.

Loftis JM, Matthews AM, Hauser P. Psychiatric and substance use disorders in individuals with hepatitis C: Epidemiology and management. *Drugs*. 2006;66(2):155–174.

Merck Manual of Diagnosis and Therapy. Drug Use and Dependence. Section 15. Chapter 195.

Miller WC, Hoffman IF, Hanscom BS, et al. A scalable, integrated intervention to engage people who inject drugs in HIV care and medication-assisted treatment (HPTN 074): A randomised, controlled phase 3 feasibility and efficacy study. *Lancet*. 2018 Sep 1;392(10149):747–759. doi:10.1016/S0140-6736(18)31487-9.

Milloy MJ, Montaner J, Wood E. Barriers to HIV treatment among people who use injection drugs: Implications for "treatment as prevention." *Curr Opin HIV AIDS*. 2012;7(4):332–338. doi:10.1097/COH.0b013e328354bcc8.

Moorman JP, Krolikowski MR, Mathis SM, Pack RP. HIV/HCV co-infection: Burden of disease and care strategies in Appalachia. *Curr HIV/AIDS Rep*. 2018 Jun 21. doi:10.1007/s11904-018-0404-1. [Epub ahead of print]

Nunes D, Saitz R, Libman H, et al. Barriers to treatment of hepatitis C in HIV/HCV-coinfected adults with alcohol problems. *Alcohol Clin Exp Res*. 2006;30(9):1520–1526.

Paquette CE, Pollini RA. Injection drug use, HIV/HCV, and related services in nonurban areas of the United States: A systematic review. *Drug Alcohol Depend*. 2018 Jul 1;188:239–250. doi:10.1016/j.drugalcdep.2018.03.049. Epub 2018 May 8.

Platt L, Minozzi S, Reed J, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. *Cochrane Database Syst Rev*. 2017 Sep 18;9:CD012021. doi:10.1002/14651858.CD012021.pub2.

Rosenthal ES, Karchmer AW, Theisen-Toupal J, Castillo RA, Rowley CF. Suboptimal addiction interventions for patients hospitalized with injection drug use-associated infective endocarditis. *Am J Med*. 2016 May;129(5):481–485. doi:10.1016/j.amjmed.2015.09.024. Epub 2015 Nov 18.

Rudd RA, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose deaths: United States, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2016 Dec 30;65(50–51):1445–1452. doi:10.15585/mmwr.mm655051e1.

Selwyn PA, Hand D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med*. 1989;320:545–550.

Starakis I, Mazokopakis EE. Injecting illicit substances epidemic and infective endocarditis. *Infect Disord Drug Targets*. 2010;10(1):22–26.

Suzuki J, Johnson J, Montgomery M, Hayden M, Price C. Outpatient parenteral antimicrobial therapy among people who inject drugs: A review of the literature. *Open Forum Infect Dis*. 2018 Aug 7;5(9):ofy194. doi:10.1093/ofid/ofy194. eCollection 2018 Sep.

Tai B, Volkow ND. Treatment for substance use disorder: Opportunities and challenges under the affordable care act. *Soc Work Public Health*. 2013;28(3–4):165–174. doi:10.1080/19371918.2013.758975.

Wolff AJ, O'Donnell AE. Pulmonary effects of illicit drug use. *Clin Chest Med*. 2004;25(1):203–216.

Wood E, Kerr T, Tyndall MW, Montaner JS. A review of barriers and facilitators of HIV treatment among injection drug users. *AIDS*. 2008;22(11):1247–1256.

Wu LT, Blazer DG. Illicit and nonmedical drug use among older adults: A review. *J Aging Health*. 2011;23(3):481–504.

Wurcel AG, Burke D, Skeer M, et al. Sex work, injection drug use, and abscesses: Associations in women, but not men. *Drug Alcohol Depend*. 2018 Apr 1;185:293–297. doi:10.1016/j.drugalcdep.2017.12.028. Epub 2018 Feb 20.

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Infections in the alcoholic

Laurel C. Preheim and Manasa Velagapudi

Approximately 18 million adults in the United States meet criteria for alcohol use disorders (AUD). The National Institute on Alcoholism and Alcohol Abuse (NIAAA) has provided a definition of low-risk drinking. Alcohol use above these limits is associated with increased risk for AUD or its associated health complications. For women, low-risk drinking is defined as no more than 3 drinks on any single day and no more than 7 drinks per week. For men, it is defined as no more than 4 drinks on any single day and no more than 14 drinks per week. NIAAA research shows that only about 2 in 100 people who drink within these limits have AUD.

Patients with AUD have an increased susceptibility to bacterial infections such as pneumonia, tuberculosis (TB), peritonitis, and bacteremia. They are also more likely to develop viral hepatitis and HIV disease. Acute and chronic alcohol ingestion exerts direct and indirect effects on host defenses against infection (Box 91.1). Alcohol consumption has been shown to alter the microbial communities of the gastrointestinal tract and the respiratory tree, including the oropharynx, mainstem bronchus, and lower bronchoalveolar spaces. The role of these changes in the microbiome and their influence on the immune response is under intensive investigation. Some studies suggest that the immunotoxic effects of ethanol are due to direct cytotoxicity and to a shift in the balance of cytokines produced from the pro-inflammatory to more immunoinhibitory products. However, the adverse effects of ethanol itself may be indistinguishable from those due to concomitant alcoholic liver disease and other conditions related to AUD, including malnutrition, poor hygiene, adverse living conditions, and abuse of tobacco and other drugs. This discussion includes infections associated with increased frequency or severity in these patients (Box 91.2). Antibiotic suggestions are made according to current treatment guidelines, but therapeutic decisions should always be made with the knowledge that alcoholic liver disease can interfere with the metabolism and excretion of certain agents and that some antimicrobials can cause or exacerbate hepatic dysfunction.

Pneumonia

Bacterial pneumonia usually follows aspiration of oropharyngeal flora into the lungs. Severe intoxication is associated with altered consciousness and a diminished cough reflex. Elevated ethanol levels can interfere with cilial function on the surface of respiratory epithelial cells. Most patients with AUD also smoke cigarettes, which further impairs mucociliary defenses against infection of the respiratory tract. The most frequent bacterial causes of pneumonia in alcoholics include *Streptococcus pneumoniae*, anaerobes, aerobic gram-negative bacilli, and *Haemophilus influenzae*.

Standard diagnostic approaches are used to evaluate alcoholic patients who exhibit signs or symptoms of pneumonia. Organisms seen on sputum Gram stain often can help guide empiric antibiotic therapy. In addition to obtaining sputum and blood cultures, any significant pleural fluid visible on chest radiographs should be sampled for appropriate stains and cultured for aerobic and anaerobic organisms. Serum procalcitonin may be elevated, and urinary antigen testing for *Legionella* and pneumococcus should be considered.

BOX 91.1

Immunodefects and alcohol use disorders

Microbiome alterations (dysbiosis and/or overgrowth)
- Gut (small and large intestine)
- Respiratory tract (oropharynx, mainstem bronchus, alveoli)

Mechanical defects (lung)
- Diminished cough reflex
- Impaired glottal closure
- Lung atelectasis due to ascites
- Decreased ciliary function

Mechanical defects (gut)
- Increased intestinal permeability

Humoral immunity
- Increased serum immunoglobulins
- Decreased alveolar IgG subclasses
- Decreased complement activity
- Decreased serum bactericidal activity

Cell-mediated immunity
- Decreased skin test reactions
- Decreased numbers of T lymphocytes
- Alterations in T-lymphocyte subsets
- Altered cytokine production
- Decreased suppressor cell activity
- Decreased lymphocyte mitogenic response
- Decreased natural killer cell function
- Altered antigen presentation by macrophages and dendritic cells

Phagocytes
- Granulocytopenia (rare)
- Decreased granulocyte chemotaxis
- Decreased granulocyte bactericidal activity
- Decreased macrophage phagocytosis
- Decreased macrophage bactericidal activity

Abbreviation: IgG = immunoglobulin G.

BOX 91.2

Infections in alcoholics

Bacterial pneumonia
- *Streptococcus pneumoniae*
- Anaerobes
- *Klebsiella pneumoniae*
- *Haemophilus influenzae*

Tuberculosis

Spontaneous bacterial peritonitis
- *Escherichia coli*
- *K. pneumoniae*
- *S. pneumoniae*

Bacteremia
- *E. coli*
- *S. pneumoniae*
- *Streptococcus pyogenes*
- *Clostridium perfringens*
- Non-01 *Vibrio cholerae*
- *Vibrio vulnificus*
- *Salmonella*
- *Bartonella quintana*

Endocarditis
- Gram-negative bacteria
- *S. pneumoniae*
- **Meningitis**

Pancreatic abscess

Hepatitis B and C

HIV infection and AIDS

Abbreviations: HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.

Because the severity of bacterial pneumonia is increased in patients with AUD, hospitalization for parenteral antibiotic therapy is usually indicated. The length of hospital stay and the need for intensive care units are likely to be higher, and the expected mortality rate is greater than twice that for nonalcoholics.

Pneumococcal pneumonia

Streptococcus pneumoniae, or pneumococcus, remains the most common cause of both community-acquired bacterial pneumonia and bacterial meningitis in adults. Outbreaks of pneumococcal pneumonia have occurred among residents of shelters and prisons, where close proximity enhances the risk of transmission. Patients with AUD have the usual signs and symptoms of pneumococcal pneumonia, including a sudden onset, often with a single shaking chill, fever, and subsequent productive cough. Secondary complications, including acute respiratory distress syndrome (ARDS), empyema, and bacteremia, are common in alcoholics, particularly those with liver disease. Despite appropriate therapy, the reported overall mortality for adult bacteremic pneumococcal pneumonia increases from approximately 20% to >50% in patients with cirrhosis. The Advisory Committee on Immunization Practices recommends pneumococcal polysaccharide vaccine for all alcoholics. However, the antibody responses may be blunted, and the efficacy of the vaccine has been questioned in this high-risk population.

Current guidelines on the management of community-acquired pneumonia in adults with AUD recommend either the empiric use of a respiratory fluoroquinolone such as moxifloxacin or levofloxacin, or the combination of a β-lactam agent such as ceftriaxone or ampicillin-sulbactam with a macrolide such as azithromycin. For less severe cases not requiring inpatient treatment, combination therapy is recommended using an oral β-lactam agent (e.g., high-dose amoxicillin, amoxicillin-clavulanate, or cefuroxime) *plus* either a macrolide (azithromycin or clarithromycin) or doxycycline. Alternatively, an oral respiratory fluoroquinolone could be used.

Anaerobic pneumonia

Anaerobic oropharyngeal bacteria, including peptostreptococci, *Fusobacterium* spp., and *Prevotella melaninogenica*, are commonly involved in aspiration pneumonia and can cause lung abscess and empyema. Intoxication interferes with several host defenses against aspiration of oropharyngeal contents. Elevated circulating ethanol levels can disrupt the coordinated beating of cilia on respiratory epithelium and thus impair mucociliary clearance of inhaled or aspirated organisms. Inebriation also can be associated with diminished gag and cough reflexes. Alcoholics frequently have severe periodontal disease, which can increase the number of anaerobic organisms in the aspirated inoculum. Clinical signs and symptoms of anaerobic pneumonia commonly progress slowly over weeks or months before patients present with malaise, low-grade fever, cough producing foul-smelling sputum, and/or weight loss. Recommended therapy includes a β-lactam/β-lactamase inhibitor such as piperacillin-tazobactam, ampicillin-sulbactam, or amoxicillin-clavulanate. Alternatively, a carbapenem may be used such as ertapenem or meropenem. Clindamycin is indicated for anaerobic pleuropulmonary infections in patients who are allergic to penicillin.

Gram-negative pneumonia

Gram-negative bacilli such as *Klebsiella pneumoniae* and *Enterobacter* spp. are more likely to colonize the oropharynx and cause pneumonia in alcoholics than in nonalcoholics. The combination of bloody sputum and an upper lobe infiltrate with a bulging fissure that has been classically associated with *Klebsiella* pneumonia is rarely seen today. Mortality with gram-negative bacillary pneumonia exceeds that of pneumococcal pneumonia and increases further if neutropenia is also present. For pneumonia due to Enterobacteriaceae, recommendations include either a third-generation cephalosporin such as ceftriaxone, a fourth-generation cephalosporin such as cefepime, or a carbapenem such as ertapenem or meropenem. If the pathogen is an extended-spectrum β-lactamase producer, a carbapenem should be used. Alternative antimicrobials include β-lactam/β-lactamase inhibitor combinations or a fluoroquinolone.

For patients with pneumonia due to *Pseudomonas* who are not in septic shock or at high risk for death and for whom the results of antimicrobial sensitivity testing are known, monotherapy with an effective antipseudomonal β-lactam such as piperacillin, cefepime, ceftazidime, aztreonam, or imi-, mero-, or doripenem is recommended. For patients who remain in septic shock or at risk of death when results of susceptibility testing are known, combination therapy using one of the preceding antibiotics with either an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside such as gentamicin is recommended. An alternative regimen would be an aminoglycoside plus the antipseudomonal fluoroquinolone. For a patient whose septic shock resolves when antimicrobial sensitivities are known, continued combination therapy is not recommended. The coccobacillus *H. influenzae* frequently causes pneumonia in alcoholics. Resistance to antibiotics other than penicillin and ampicillin is rare. Recommendations include either a third-generation cephalosporin such as ceftriaxone, a β-lactam/β-lactamase inhibitor, a carbapenem, or a fluoroquinolone.

Acute respiratory distress syndrome

The incidence of ARDS in patients with AUDs has been reported to be 70% compared with 31% in patients without AUDs. AUD patients are approximately four-fold more likely than nonalcoholic patients to develop ARDS. In addition, alcohol-related ARDS is associated with poorer outcomes, including combined outcomes of death or persistent hospitalization. Gut-associated bacteria are enriched in the lung microbiome of both an experimental sepsis model as well as in humans with ARDS. This suggests that gut–lung translocation and dysbiosis of the lung microbial communities may contribute to the development of ARDS.

Tuberculosis

TB has historically been associated with ethanol abuse, and alcoholics have 15 to 200 times the TB incidence rates of nonalcoholics. A 2017 meta-analysis found that there were about 10.4 million TB cases around the world in 2015, and it was associated with about 1.4 million deaths. In all studies, on average, abusing alcohol increased the risk of contracting TB by 35%. The Biomed central public health study reported that people who drank >40 g of alcohol per day dramatically increased their risk of contracting TB. Alcohol abuse is associated with malnutrition, which increases the risk of TB.

Homelessness and immunocompromising conditions such as HIV disease have also been linked to an increased incidence of TB. Most cases occur in urban areas, where outbreaks of TB have occurred among indigent alcoholics housed in shelters.

After decades of steady decline, the number of new cases of TB in the United States started to rise in the late 1980s and continued to climb into the early 1990s. Due to renewed control efforts, the number of new cases has again declined annually since 1992.

Most individuals remain asymptomatic early in the disease. They may note a gradual onset of malaise, fatigue, anorexia, weight loss, afternoon fevers, or night sweats. Cough is frequent, generally producing mucopurulent sputum that may be blood tinged. The most common abnormality on chest radiographs is multinodular cavitary infiltrates in the apical or subapical posterior areas of the upper lobes or in the superior segment of a lower lobe. Pleural effusions may be present. Findings of TB are confined to the lower lung fields in up to 18% of patients.

Hospitalized patients suspected of having active pulmonary TB should be placed under airborne infection precautions. The diagnosis of TB depends on isolation of *Mycobacterium tuberculosis* from clinical specimens. For evaluation of active pulmonary TB, sputum samples are helpful, but yield is increased by more direct collection methods such as via bronchoalveolar lavage. Susceptibility testing should be performed on *M. tuberculosis* isolates from any clinical specimen.

Several tests are available for the evaluation of clinical specimens in the diagnosis of active TB. Culture, the gold standard for isolating *M. tuberculosis*, provides organisms for speciation, strain identification, and susceptibility testing but may require up to 2 months. Acid-fast stains should be performed on clinical samples the day of collection. They are helpful in ruling out mycobacterial disease but are less sensitive than culture. Positive acid-fast stains do not distinguish between *M. tuberculosis* and other mycobacteria.

Newer assays employ nucleic acid amplification directly on clinical samples. They offer same-day results, more sensitivity than acid-fast stains, and the ability to detect members of the *M. tuberculosis* complex. Nucleic acid probes on culture isolates are even more sensitive. These nucleic acid probes complement other tests and are helpful in initiating therapy. However, cultures are still needed for species identification within the *M. tuberculosis* complex and for susceptibility testing.

Although there is no convincing evidence that alcohol abuse is associated with increased risks of extrapulmonary TB infection, miliary TB should remain in the differential diagnosis of fever of unknown origin in an alcoholic patient.

Alcoholic patients are less likely than nonalcoholics to be compliant with therapy for TB and thus are more likely to relapse. Current treatment guidelines with special emphasis on directly observed therapy should be followed to reduce risks of both therapeutic failure and emergence of drug-resistant strains (see Chapter 155, "Tuberculosis"). Recent medical literature supports the effectiveness of integration of AUD treatment into routine TB care.

Peritonitis

Up to 30% of patients with alcoholic liver disease and ascites develop spontaneous bacterial peritonitis (SBP). In this condition bacterial cultures of ascitic fluid are positive, the fluid contains >250 neutrophils/mm^3, and there is no evident intra-abdominal source of infection. Aerobic gram-negative bacilli, especially *Escherichia coli*, cause approximately 75% of SBP infections. Aerobic gram-positive cocci, including *S. pneumoniae, Enterococcus faecalis*, other streptococci, and *Staphylococcus aureus*, are responsible for most other SBP cases. Anaerobes cause only 6% of SBP cases, presumably because of the relatively high pO_2 of ascitic fluid.

Because enteric bacteria predominate in SBP, it is thought that the gut is the major source of organisms for this infection. Several mechanisms have been proposed to explain the movement of organisms from the intestinal lumen to the systemic circulation. Cirrhosis-induced depression of the hepatic reticuloendothelial system impairs the liver's filtering function, allowing bacteria to pass from the bowel lumen to the bloodstream via the portal vein. Cirrhosis also is associated with a relative increase in aerobic gram-negative bacilli in the jejunum. A decrease in mucosal blood flow due to acute hypovolemia or drug-induced splanchnic vasoconstriction may compromise the intestinal barrier to enteric flora, thereby increasing the risk of bacteremia. Finally, bacterial translocation may occur with movement of enteric organisms from the gut lumen through the mucosa to the intestinal lymphatics. From there, bacteria can travel through the lymphatic system and enter the bloodstream via the thoracic duct. It is assumed that SBP caused by nonenteric organisms is also due to bacteremia secondary to another site of infection, with subsequent seeding of the peritoneum and ascitic fluid.

Patients with severe acute or chronic liver disease have decreased serum complement levels, diminished serum bactericidal activity, and reduced bacterial clearance by macrophages of the reticuloendothelial system. Because the ability of ascitic fluid to opsonize bacteria and thus facilitate phagocytosis correlates closely with total protein concentration, patients with low ascitic fluid protein levels are at particular risk for SBP. Other risk factors have been associated with SBP, including gastrointestinal bleeding, fulminant hepatic failure, and invasive procedures such as the placement of peritoneovenous shunts for the treatment of ascites. An elevated bilirubin level is also correlated with a high risk of peritonitis in patients with cirrhosis.

Many patients exhibit other findings of end-stage liver disease such as hepatorenal syndrome, encephalopathy, and variceal bleeding. Other clinical features include fever, vomiting, abdominal pain, and physical signs of peritonitis. However, signs or symptoms of infection are absent in approximately one-third of patients with SBP, so diagnostic paracentesis is indicated for all alcoholic patients with ascites. Fluid should be submitted to the laboratory for chemistry tests, cell count and differential, and microbiologic stains and cultures. Centrifugation of ascitic fluid and Gram stain of the sediment will reveal organisms in 25% to 68% of patients with SBP. Some authorities recommend that a portion of ascitic fluid be inoculated directly into blood culture bottles at the bedside. Peripheral blood cultures should be performed if SBP is suspected.

Empiric therapy should be directed against the most likely gram-negative and gram-positive pathogens discussed earlier. Recommended choices include either a third-generation cephalosporin, β-lactam/β-lactamase inhibitor combination, or a carbapenem (see Chapter 57, "Peritonitis").

Tuberculous peritonitis can occur in patients with alcoholic liver disease. Clinical findings resemble those of bacterial peritonitis, and acid-fast stains of ascitic fluid are usually negative. The diagnosis is best made with stains and cultures of peritoneal tissue, especially when obtained by peritoneoscope-directed biopsy. The treatment regimen is the same as for pulmonary TB.

Bacteremia and sepsis

The liver plays a major role in clearing bacteria from the bloodstream. Alcoholic cirrhosis adversely affects hepatic reticuloendothelial system function. Both intrahepatic and extrahepatic arteriovenous shunts divert blood from macrophages that line liver capillary beds. In addition, both acute intoxication and cirrhosis interfere with bactericidal activity of these tissue phagocytes. Complications of liver cirrhosis including hypocomplementemia, neutropenia, and reduced serum bactericidal activity may also contribute to bacteremia in these patients.

E. coli is the most common cause of spontaneous bacteremia in alcoholic and cirrhotic patients. Additional organisms

causing bacteremia or sepsis include other gram-negative bacilli, *S. pneumoniae*, group A streptococci, and *Clostridium perfringens*.

Alcoholics with cirrhosis are particularly susceptible to sepsis caused by non-01 *Vibrio cholerae* and *Vibrio vulnificus*, an opportunistic pathogen found in marine waters. Bacteremia can follow ingestion of contaminated shellfish, or exposure to seawater can result in a cutaneous infection. The latter may progress from erythematous or ecchymotic patches to bullae formation, subcutaneous necrosis, and bacteremia. *V. vulnificus* infections are associated with high mortality rates. The recommended antibiotic therapy includes doxycycline with ceftazidime. Alternative regimens include cefotaxime or ciprofloxacin.

Nontyphoidal salmonella septicemia, especially due to *Salmonella typhimurium* and *S. choleraesuis*, has been associated with alcoholic liver disease. Homeless people and alcoholics are also at increased risk for bacteremia due to *Bartonella quintana*, and the seroprevalence for this organism is high among homeless people in both the United States and Europe.

Bacteremia with or without sepsis syndrome is associated with increased mortality among alcoholics. A multicenter study conducted in four US urban university hospitals confirmed that a history of chronic alcohol abuse substantially increases the risk of ARDS for critically ill patients with septic shock. These patients also experienced greater frequency and severity of nonpulmonary organ dysfunction and, for survivors, an increased length of hospital stay.

Chronic alcoholic patients also have a three-fold or greater increased risk for developing a severe infection or septic shock after surgery. A German study evaluated patients with and without a history of chronic ethanol abuse who developed severe sepsis. At the onset of infection and during early septic shock, chronic alcoholic patients had lower plasma levels of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and IL-8. The authors concluded that ethanol abuse altered proinflammatory cytokine production and thus the host's immune defenses to infection.

Endocarditis

Alcoholism is one of the strongest risk factors for pneumococcal endocarditis, and reports link cirrhosis with increased frequency and severity of endocarditis due to other bacteria. It is a less common but significant complication of cirrhosis, seen in up to 14% of cirrhotic patients. The aortic valve is most likely to be involved, and many patients have no demonstrable underlying cardiac valvular abnormalities. Compared with that in nonalcoholics, endocarditis in cirrhotic patients is also more likely to involve gram-negative bacilli such as *E. coli* and less likely to be caused by α-hemolytic streptococci.

Other infections

Meningitis

Numerous studies have identified ethanol abuse as a risk factor for bacterial meningitis. In one series, seizures were a presenting symptom in 18% of 88 alcoholic patients, 23% had coexisting infection (pneumonia, 23%; endocarditis 9%), 40% developed respiratory failure, 58% had unfavorable outcome, and 25% died. The most common causative organisms were *S. pneumoniae* (76%). *Listeria monocytogenes* (8%), and *Neisseria meningitidis* (6%). Other less common causes of bacterial meningitis that have been linked to AUDs include *Capnocytophaga canimorsus,* group B streptococcus, aerobic gram-negative bacilli, and anaerobes. In addition, ethanol abuse has been linked to increased risk of severe infection by West Nile Virus, including meningitis and encephalitis.

Pancreatitis and pancreatic abscess

Alcohol abuse is a common cause of acute and chronic pancreatitis, and infectious complications including development of a pancreatic abscess are potentially catastrophic. Primary abscesses characteristically evolve rapidly and culminate in severe sepsis. Secondary abscesses, which may present weeks after the acute inflammation, commonly involve infection of a pancreatic pseudocyst.

The cardinal signs of a pancreatic abscess are high fever, septicemia, a rapidly enlarging abdominal mass, and multisystem organ failure in severe cases. Early surgical drainage is important. Initial empiric antibiotic therapy should be aimed at the most common pathogens, including *E. coli*, other enteric aerobes, and anaerobic gram-negative bacilli. Recommended choices include a β-lactam/β-lactamase inhibitor combination or a carbapenem.

Viral hepatitis

Hepatitis viruses and alcohol abuse are the two main causes of liver cirrhosis. In patients with chronic infection due to hepatitis B virus (HBV), the prevalence of e antigen tends to be higher, and levels decrease more slowly in alcoholics versus nonalcoholics. Current evidence suggests that alcohol use may adversely affect cellular immune responses to the virus and is associated with increased risks of cirrhosis and hepatocellular carcinoma in chronic HBV infection. In addition, alcoholics have a lower rate of responsiveness to the hepatitis B vaccine.

Hepatitis C virus (HCV) is found at a high incidence in alcoholic patients, and 20% to 30% of patients infected with hepatitis C will progress to cirrhosis. The interaction between HCV and alcohol use that affects immune responses, cytotoxicity, and oxidative stress results in more persistent HCV infection and more extensive liver damage. Some studies suggest that even moderate alcohol consumption may accelerate liver damage and hasten the clinical progression of hepatitis C infection. In a meta-analysis, the relative risk of progression to cirrhosis or decompensated liver disease was 2.3 times higher among patient with HCV and AUD compared to abstainers. Abstinence from alcohol also has been shown to result in a reduction of viremia. HCV infection in patients with AUD is associated with poorer outcomes such as longer hospital stays and elevated overall and liver-related mortality.

Alcohol abuse is considered a relative contraindication to interferon-based therapy of hepatitis C due to concerns regarding patient compliance. Response rates to interferon therapy are diminished by alcohol use, and the effectiveness is further reduced

if alcohol consumption is increased. Response to direct antiviral agents is not affected by alcohol use. Alcohol consumption not a contraindication to start treatment with a direct antiviral agent, although it is very important to emphasize the importance of abstinence. Adults with hepatitis C infection tend to consume greater amounts of alcohol than do nonalcoholics.

Human immunodeficiency virus infection

Individuals with HIV infection have significantly higher rates of alcohol use than the general population. Studies have reported the prevalence of alcohol abuse or dependence to range from 20% to 40% among HIV-infected patients.

Use of alcohol and recreational drugs can lead to risky behaviors including unprotected sex that increase the chances of exposure to and transmission of HIV infection. It is not certain whether alcohol consumption increases the rate of HIV replication within the host, although ethanol intake has been shown in some studies to increase HIV replication in isolated human blood mononuclear cells. It is likely that the well-described adverse effects of ethanol on cell-mediated immune function may reduce host defenses against HIV infection.

Aside from the direct effects of acute alcohol ingestion, the concomitant malnutrition and liver disease seen with chronic alcoholism may amplify the immunosuppressive effects of ethanol and hasten the progression from asymptomatic HIV infection to manifestations of AIDS.

The effect of ethanol ingestion on progression from asymptomatic HIV infection to AIDS-defining opportunistic infections has not been clearly established, but there are recent studies showing associations between heavy alcohol consumption with declines of CD4 cell counts and decreased ability to suppress HIV viral load. Heavy alcohol users receiving antiretroviral therapy are twice as likely to have CD4 counts of <500 than are light or nondrinkers, and antiretroviral-treated heavy alcohol users are four times less likely to achieve a positive virologic response. Furthermore, there is evidence that any alcohol use among HIV-infected patients is associated with diminished compliance with antiretroviral therapy.

Suggested reading

Bishehsari F, Mango E, Swanson G, et al. Alcohol and gut-derived inflammation. *Alcohol Res* 2017;38:163–171.

Boule LA, Kovacs EJ. Alcohol, aging, and innate immunity. *J Leukoc Biol* 2017;102:41–55.

Chan C, Levitsky J. Infection and alcoholic liver disease. *Clin Liver Dis*. 2016;20:595–606.

Daniel F, Jeffrey S. Alcohol use in patients with chronic liver disease. *N Engl J Med* 2018;379:1251–1261.

Fan X, Peters BAS, Jacobs EJ, et al. Drinking alcohol is associated with variation in the human oral microbiome in a large study of American adults. *Microbiome*. 2018;6:59.

Hahn JA, Samet JH. Alcohol and HIV disease progression: Weighing the evidence. *Curr HIV/AIDS Rep*. 2010;7:226–233.

Imtiaz S, Shield KD, Roerecke M, et al. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. *Eur Respir J*. 2017;50:216–217.

Mehta AJ. Alcoholism and critical illness: a review. *World Crit Care Med*. 2016;5:27–35.

Samuelson DR, Burnham EL, Maffei VJ, et al. The respiratory tract microbial biogeography in alcohol use disorder. *Am J Physiol Lung Cell Mol Physiol*. 2018;314:L107–L117.

Simet SM, Sisson JH. Alcohol's effect on lung health and immunity. *Alcohol Res* 2015;37:199–208.

Szabo G, Wands JR, Eken A, et al. Alcohol and hepatitis C virus: Interactions in immune dysfunctions and liver damage. *Alcohol Clin Exp Res*. 2010;10;1675–1686.

van Veen KEB, Brouwer MC, van der Ende A, et al. Bacterial meningitis in alcoholic patients: A population-based prospective study. *J Infection*. 2017;74:352–357.

92

Infection in the elderly

Kent Crossley

Although virtually all significant infections are discussed throughout this book, certain aspects of infectious diseases in older individuals need to be emphasized. This chapter stresses the unique aspects of infection in the elderly (defined here as >65 years of age). Infections that occur in long-term care institutions are briefly discussed.

Infections in the aged are an important area of concern for medicine. The number of individuals who are older than 65 is increasing dramatically and is disproportionate because of lower birth rates. Although representing only 13% of the US population at present, the elderly consume 25% of all prescription medications and a similarly excess amount of other healthcare services. With few exceptions (some viral infections and venereal diseases), most common infections occur more often in older individuals.

Although mortality associated with many infections is increased in the elderly, age alone is now seen as a relatively unimportant risk factor for infection-related death or serious morbidity. Rather, it is the variety of comorbid conditions that are increasingly common with advancing age that appears to be closely associated with greater morbidity and mortality from infection.

Since the early 1990s, it has become clear that there is a general hyporesponsiveness of the immune system in elderly individuals. This is the most likely explanation for the muted symptoms and signs that are a common denominator of infections in the aged. In a number infectious illnesses, maximum temperatures, white blood cell count elevations, and the overtness of clinical signs and symptoms are all less pronounced in older individuals. In clinical terms, this means that an elderly patient may have a serious bacteremic infection without chills, fever, or leukocytosis.

Principles of antibiotic use

Table 92.1 summarizes recommendations for treatment of common infections in the elderly. Important points include the following:

1. Aminoglycoside antibiotics are best avoided in older individuals because of their toxicity. Although probably appropriate in neutropenic, immunocompromised elderly or in the presence of documented *Pseudomonas* infection, try to use other agents when possible. With careful monitoring, once-daily administration of these drugs for at least 10 days does not appear to be associated with more side effects in the elderly.
2. Because most antibiotics (quinolones, aminoglycosides, and most penicillins are examples) are excreted by renal routes and because of the decline in renal function with increasing age, higher dosages may be potentially more toxic in the elderly.
3. Broad-spectrum therapy is appropriate initially in the treatment of serious infection if the cause is unclear. Older individuals lack the physiologic reserve of younger adults and usually have one or more comorbid diseases. In the presence of a serious infection, the elderly can rapidly deteriorate. Using drugs that are active against most of the likely causes of the infection (with the least possible toxicity) is the best approach.

TABLE 92.1 **ANTIBIOTICS RECOMMENDED FOR INITIAL (EMPIRIC) THERAPY FOR THE ELDERLY**

Infection	Antibiotics	Comments
Acute fever, unidentified source	Ertapenem, 1 g q24h IV, or imipenem, 0.5 g q6h IV, or meropenem, 1.0 g q8h IV plus vancomycin 15 mg/kg q12h IV	Broad spectrum, limited toxicity. For critically ill patients needing empiric therapy.
Urinary tract infection	*Gram-negative organisms*: Third-generation cephalosporin (e.g., ceftazidime, 2.0 g q8–12h), or broad-spectrum penicillin with β-lactamase inhibitor (e.g., piperacillin–tazobactam, 3.375 g IV q6h), or imipenem, or meropenem, or quinolone (e.g., ciprofloxacin, 400 mg IV q12h) *Gram-positive organisms*: Vancomycin, 10–15 mg/kg q12h IV	Consider imipenem or meropenem if in LTCF or a recurrent infection; use in combination with low-dose aminoglycoside (e.g., gentamicin, 40–60 mg/d) if resistant organisms are probable Oral quinolone (e.g., ciprofloxacin, 250 mg BID) appropriate if not seriously ill Vancomycin is active against enterococci, staphylococci, and streptococci
Pneumonia	Third-generation cephalosporin (ceftriaxone, 1 g IV q12h) or ertapenem, 1 g IV q24h plus a macrolide (e.g., azithromycin, 0.5 g/24h IV)	Consider using ceftazidime or imipenem for nosocomial pneumonia Macrolide (preferably azithromycin, 500 mg on day 1, then 250 mg on days 2–4), or quinolone with antipneumococcal activity (e.g., levofloxacin, 500 mg/d) for oral therapy in less seriously ill patients
Pressure sores	Broad-spectrum β-lactam agent with β-lactamase inhibitor (e.g., piperacillin–tazobactam), ertapenem or imipenem (doses as above)	Other treatment regimens active against Bacteroides, and enteric gram-negative organisms, may be used. Add vancomycin if gram-positives present in wound
If a patient is not acutely ill, treatment can wait until specimens for culture have been obtained. All sores will be colonized. A decision to treat as infected is based on presence of signs of infection (such as purulence, local inflammation, and systemic response such as fever or leucocytosis).		
Infective endocarditis	Vancomycin, 15 mg/kg IV q12h with gentamicin 1 mg/kg IV or IM q8h	Modify as appropriate after results of cultures and antibiotic susceptibility testing are available
Infectious (bacterial) diarrhea	Ciprofloxacin (500 mg PO BID) or other quinolone for 1–3 days. Azithromycin if recent travel to Southeast Asia	Consider *Clostridium difficile* if recent antibiotic use.
Meningitis	Third-generation cephalosporin (e.g., ceftriaxone, 2 g IV q12h) plus ampicillin, 2 g IV q4h plus vancomycin 10–15 mg/kg IV q6h	*Listeria monocytogenes* is not susceptible to cephalosporins
Septic arthritis	Vancomycin 10–15 mg/kg IV q6h plus ceftazidime 1–2 g IV q8–12h	Gram stain may be used to narrow therapy.

Abbreviation: LTCF = long-term care facility.
Therapy should be modified as appropriate after results of Gram stain, culture, and antibiotic susceptibility testing are available. Renal function in patients receiving vancomycin and gentamicin therapy must be carefully monitored.

Urinary tract infection

Urinary tract infection (UTI) is increasingly common with increasing age. This reflects obstruction from prostatic enlargement in men and a variety of changes in the defense mechanisms of the female urinary system. The risk of instrumentation and catheterization, procedures often associated with development of infection also increases in the elderly population.

Asymptomatic bacteriuria is more common in both elderly men and women than in younger subjects. Multiple studies have demonstrated that treatment of bacteriuria is without value, primarily because it usually recurs after therapy.

Escherichia coli accounts for the bulk of UTIs in young women. In older individuals, the bacteriology is more complex. Infecting organisms include *E. coli* but also bacteria from other genera (e.g., *Serratia* and *Pseudomonas*) that are often resistant to multiple antibiotics. For this reason, urine culture and sensitivity should always be done before initiating therapy in an elderly individual.

Recent studies indicate that treatment of lower UTI in elderly women may be safely done with 3-day therapy. In men, a 2013 study examining 40,000 episodes of UTI showed that shorter course therapy (<7 days) was as effective as longer periods of treatment. While trimethoprim-sulfamethoxazole (TMP-SMX) or a quinolone are good initial choices for treatment of a lower UTI, resistance to these drugs is increasing in frequency and a drug such as fosfomycin may be required.

For patients with upper tract infection and for those who are seriously ill, therapy should be initially parenterally. Selection should

be guided by Gram stain of the urine. If gram-negative organisms are present, a broad-spectrum β-lactam agent with activity against *Pseudomonas aeruginosa* (e.g., piperacillin-tazobactam) or a quinolone would be an appropriate initial choice. If a gram-positive organism is present in the Gram stain (nearly always representing staphylococci or enterococci), vancomycin would be the most appropriate antibiotic to start, pending culture and susceptibility results. Multiply resistant gram-negative organisms may cause infection in patients with previous UTIs, those who have recently taken antibiotics, nursing home residents, and immunosuppressed patients. In these situations (and in documented *Pseudomonas* infections), imipenem, meropenem, or another broad-spectrum β-lactam should be given with an aminoglycoside. Often a transition to oral therapy can be made after 48 to 72 hours.

Infections in individuals with chronic indwelling urinary catheters should be treated only when symptomatic. Virtually all catheterized patients will have asymptomatic bacteriuria. Treatment of catheterized patients with symptomatic infection should be based on culture and sensitivity. Catheter replacement is often done before initial therapy for these infections and is associated with better outcomes.

Pneumonia

Pneumonia is an increasingly common problem with increasing age. *Streptococcus pneumoniae* is the single most common cause in the elderly. Patients who are 65 or older should receive both the newer pneumococcal vaccine (PCV13) as well as the older 23 valent. Recommendations by the US Centers for Disease Control and Prevention (CDC) on timing of dosing should be consulted. Gram-negative organisms (e.g., *Haemophilus influenzae, Moraxella*, and, less often, enteric organisms such as *E. coli*) are also causal. Nonbacterial organisms such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are also recognized as important causes of pneumonia in older adults. *M. pneumoniae* and *C. pneumoniae* may each account for up to 10% of episodes of acute pneumonia in the elderly. Respiratory syncytial virus (RSV) was recently recognized as a significant cause of pneumonia in the aged. Although RSV-associated illness is similar to clinical influenza, bronchospasm is more common. Rhinoviruses also occasionally cause pneumonia in older individuals.

Because of the variety of agents that may cause pneumonia in the elderly, attempts to document the etiology of the infection by sputum cultures (and blood cultures if the patient is seriously ill) are important. Sputum cultures after initiation of treatment are usually of no value; appropriate cultures need to be obtained before starting therapy.

In an otherwise healthy elderly adult living in the community, initial therapy for pneumonia could be with either a macrolide or a quinolone. The newer quinolones (e.g., levofloxacin) have activity against *S. pneumoniae*, many gram-negative organisms and atypical agents such as *Mycoplasma*. Because of their broad spectrum and once-daily dosing, these agents have become increasingly popular in the outpatient therapy of pneumonia in elderly individuals. The quinolones are preferred over macrolide in elderly patients with significant comorbidities or in those who live in an institution.

For patients with community-acquired pneumonia who are hospitalized, empiric treatment should be broad-spectrum and effective against gram-positive and gram-negative bacteria as well as atypical agents. Broad-spectrum parenteral β-lactams, such as a third-generation cephalosporin (e.g., ceftriaxone) or a penicillin/β-lactamase inhibitor combination (e.g., piperacillin–tazobactam) in conjunction with a parenteral macrolide (e.g., azithromycin), represent optimal therapy. Although limited data are available, in a patient with a functioning gastrointestinal tract, oral therapy with a newer quinolone (such as levofloxacin) may be a possible option. While parenteral therapy is most often appropriate in patients who are ill enough to be hospitalized, the nearly complete absorption of the quinolones after oral dosing and their broad spectrum suggest this may become a convenient and cost-effective approach.

Tuberculosis

About one-quarter of tuberculosis (TB) cases in the United States occur in individuals >65. This is a special problem for nursing homes because the incidence in long-term care is about four times that in the community. Older individuals with a positive tuberculin skin test or a positive TB blood test who have one of a number of additional risk factors (e.g., recent steroid therapy, living in a high risk setting [e.g., shelters or prisons], or immigrants from countries with a high prevalence of TB) or who have recently converted their test need to be treated with isoniazid, 300 mg/d for 9 months, or rifampin for 4 months. Managing clinical tuberculosis in an elderly individual is similar to that in a younger patient. Monitoring for hepatic toxicity is advisable.

Pressure ulcers

Efforts to attempt to prevent pressure-associated ischemia are extremely important. Once an ulcer develops, infection often follows. Topical antimicrobials are ineffective in the management of these lesions. Systemic antimicrobials should be used if clinical cellulitis is evident at the margin of a pressure ulcer or if there is evidence of deep infection or osteomyelitis. Therapy needs to be effective against anaerobic bacteria and both gram-negative and gram-positive organisms. Oral therapy might include a combination of an oral cephalosporin and metronidazole or amoxicillin-clavulanate. Appropriate parenteral therapies include imipenem, piperacillin-tazobactam, or one of the broader spectrum cephalosporins (e.g., ceftriaxone and cefotaxime) or a quinolone combined with metronidazole or clindamycin for anaerobic coverage. If material can be obtained for culture (usually best done by needle aspiration), therapy can be modified when results are available.

Most other skin and soft tissue infections in the aged, as in younger individuals, are caused by group A β-hemolytic streptococci or *Staphylococcus aureus*. Treatment of these infections is not

significantly different in older individuals. Community-acquired methicillin-resistant *S. aureus* (MRSA) is of concern in all patients with skin and soft tissue infection. For seriously ill patients, vancomycin is appropriate. In outpatient treatment, TMP-SMX should be used.

Bacteremia

In one recent study, nearly 15% of the cases of community-acquired bacteremia were in individuals >84 years. Usual primary sites of infection include the urinary tract, intra-abdominal sites, the lower respiratory tract, and skin and soft tissue. Evaluation should rule out abscess or obstruction of an airway or hollow viscus.

Meningitis

Streptococcus pneumoniae remains the most common cause of meningitis in older adults. The second most common cause is *Listeria monocytogenes*. This is important to know when selecting therapy because *Listeria* is not killed by cephalosporins, and initial therapy of meningitis of unknown cause in an elderly individual must include ampicillin, which is active against *L. monocytogenes*.

Infections in residents of long-term care facilities

All the infections that occur in older individuals may develop in residents of long-term care facilities (LTCFs). MRSA and, in some areas of the United States, vancomycin-resistant enterococci (VRE) have a strong association with LTCF residency. Residents are also especially prone to epidemic respiratory or gastrointestinal diseases, particularly in winter months. Selecting antibiotic therapy for patients who reside in LTCFs requires an awareness that resistant gram-negative organisms, MRSA, and VRE are all potential pathogens. Overuse of antibiotics and antimicrobial stewardship in LTCFs are recognized as increasingly important.

Suggested reading

Boyko TV, Longaker M, Yang GP. Review of the current management of pressure ulcers. *Adv Wound Care (New Rochelle)*. 2018;7:57–67.

Bradley SF. Principles of antimicrobial therapy in older adults. *Clin Geriatr Med*. 2016;32:443–457.

Crossley KB, Peterson PK. Infections in the elderly. In Mandell GL, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 8th ed. New York: Churchill Livingstone; 2015:3459–3465.

Drekonja DM, Rector TS, Cutting A, Johnson JR. Urinary tract infection in male veterans: Treatment patterns and outcomes. *JAMA Intern Med*. 2013;173(1):62–68.

Henig O, Kaye DS. Bacterial pneumonia in older adults. *Infect Dis Clin N Am*. 2017;31:689–713.

High KP, Bradley SF, Gravenstein S, et al. Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Disease Society of America. *Clin Infect Dis*. 2009;48:149–171.

Jump RLP, Crnich CJ, Mody L, Bradley SF, Nicolle LE, Yoshikawa TT. Infectious diseases in older adults of long-term care facilities: Update on approach to diagnosis and management. *J Am Geriatr Soc*. 2018;66:783–803.

Norman DC. Clinical features of infection in older adults. *Clin Geriatr Med*. 2016;32:433–444.

Weinberger B, Grubeck-Loebenstein B. Vaccines for the elderly. *Clin Microbiol Infect*. 2012;18(5):100–108.

Yahav D, Eliakim-Raz N, Leibovici L, Paul M. Bloodstream infections in older patients. *Virulence*. 2016;7:341–352.

93

Neonatal infection

Patrick G. Gallagher and Robert S. Baltimore

Bacterial infections

Epidemiology

Neonatal infections are usually classified according to time and mode of onset in three categories: (1) prenatal, (2) perinatal (early onset), and (3) nursery-acquired (late onset). The division in time between early and late onset is usually 2 to 7 days of age (Table 93.1). Different investigators have divided early-onset from late-onset infections at different days of life but most early-onset infections are evident during the first day of life. Infections that begin within the first month of life are considered neonatal, but many intensive care units for neonates provide continuing care for infants several months of age with complex problems that are the result of prematurity and complications of neonatal disorders. Therefore, neonatal nursery-associated infections may occur in infants up to a year or more of age. Bacterial infections due to rapidly dividing high-grade pathogens that set in substantially before birth usually result in a stillbirth. Often it is difficult to distinguish infections acquired shortly prior to birth from those acquired as a result of contact with maternal vaginal, fecal, or skin flora during delivery.

Neonatal sepsis occurs in approximately 2 to 4 per 1000 live births in the United States. Worldwide reports vary from <2 to 50 per 1000 live births. The rates of early-onset sepsis have fallen to <1.0/1000 in the United States and Western Europe. Risk factors noted in Table 93.1 have a very strong predictive influence on infection rates. Full-term infants born without incident have a very low incidence of infection, lower than any other population of hospitalized patients. Infants susceptible to early-onset postnatal infections are primarily those born prematurely. Those premature infants born to mothers with an infection or whose membranes rupture more than 18 hours before delivery may have an infection rate of 20% or more. In extremely premature infants extra vigilance is required for early recognition and treatment of infection. Premature infants are much more likely to develop sepsis as a consequence of the amnionitis caused by ascending infection than are full-term infants. Similarly, premature infants are at a greater risk for developing an invasive infection if born to a mother with peripartum infection than are full-term infants. The practice of treating parturient women suspected of having amnionitis with antibiotics is probably an important factor in the decrease in early-onset sepsis observed in the United States.

Hospital-acquired infection in the nursery is an important and growing problem, and now represents most of the infections seen in neonatal units. As the technology for treating very premature and very sick infants has increased, so too has the population of surviving immunocompromised infants who require therapy with ventilators, intravascular catheters, total parenteral nutrition, and various surgical interventions, each of which carries a substantial risk of infection (see Table 93.1). The liberal use of broad-spectrum antibiotics in neonatal care units increases the risk of acquisition of pathogens by interfering with the development of normal flora in these infants. Recent data suggest that antibiotic treatment early in life increases the risk of developing neonatal necrotizing enterocolitis. In contrast, the risk of acquiring hospital-acquired viral infections appears to depend mostly on the chances of contact with the virus and not pre-existing disease

TABLE 93.1 **CHARACTERISTICS OF PRENATAL, EARLY-ONSET, AND LATE-ONSET NEONATAL INFECTIONS**

	Prenatal onset	Early-onset infections	Late-onset infections
Age at onset	Prior to birth	Birth to 2–7 days	2–7 to 30 days
Primary route of transmission	Transplacental or ascending	Maternal flora transmitted peripartum	Hospital-acquired
Risk factors	Maternal infection Prolonged premature rupture of membranes	Prolonged premature rupture of membranes Septic or traumatic delivery Maternal infection, especially urogenital Fetal anoxia Male sex Maternal factors (poverty, pre-eclampsia, cardiac disease, diabetes)	Extreme prematurity Mechanical ventilation Contact with hands of colonized personnel Contact with aerosols of bacteria Contaminated equipment (e.g., isolettes, ventilators, IV lines) Debilitating illness, including bronchopulmonary dysplasia and short gut syndrome Congenital anomalies Surgery (including necrotizing enterocolitis) Prior exposure to broad-spectrum antibiotics
Most common pathogens	Cytomegalovirus Syphilis *Toxoplasma* Maternal vaginal flora Human immunodeficiency virus	*Escherichia coli* Group B streptococci, *Klebsiella* spp. *Enterococcus* spp., *Listeria monocytogenes* Other Enterobacteriacae (*Proteus, Citrobacter, Enterobacter*)	Those causing early-onset infections *Staphylococcus aureus* Coagulase-negative staphylococci *Pseudomonas aeruginosa* and other gram-negative rod species resistant to first-line antibiotics *Candida* spp.

Abbreviation: IV intravenous.

in the infant. Infants with chronic lung disease or congenital cardiac conditions are particularly susceptible to severe infection with respiratory syncytial virus and human metapneumovirus. Therefore, community activity of respiratory and gastrointestinal viruses and defects in the barriers to prevent spread, especially poor adherence to handwashing, within the unit appear to be the most important risk factors for viral infection.

Microbiology

Table 93.1 lists the major bacterial organisms responsible for early and late postnatal sepsis. The organisms that cause meningitis in the neonate are the same. *Escherichia coli* and group B streptococci have accounted for about 80% of early-onset sepsis and meningitis in the past. The rate of group B streptococcal infection has declined about 80% since the widespread adoption of intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal disease.

Since the early 1990s the microbiology of late-onset sepsis has shifted, with an increase in commensal organisms, particularly staphylococci and *Candida* spp. This shift appears to be due to the increased survival of extremely premature infants with increased utilization of mechanical ventilation, central venous catheters, parenteral alimentation, and broad-spectrum antibiotics. Empiric therapy is guided by published information on the microbiology of neonatal infections as well as information about local bacterial and fungal isolates which should be kept by hospitals with neonatal units.

Antimicrobial therapy

Empiric therapy for early-onset sepsis

Antibiotics for early-onset infections are generally commenced prior to the identification of the infecting organism. Neonates, especially premature ones, typically fail to manifest classic signs and symptoms of infection. Thus, many schemata have been developed for empiric antibiotic treatment of infants with multiple epidemiologic risks alone or nonspecific signs and laboratory test abnormalities plus epidemiologic risk factors. The common features of these schemata are recognition of the risk factors listed in Table 93.1; the possibility that severe infection may present as temperature instability or other vital sign changes, unexplained hyperbilirubinemia, vomiting, or changes in feeding; and the recognition that a very short delay in treatment may result in overwhelming sepsis and death. Such schemata vary from hospital to hospital according to the population served, the type of hospital, and resources for screening. Screening tests may also include hematologic findings such as white blood cell count, the ratio of immature to mature cells of the granulocyte series, acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, procalcitonin, mannose-binding lectin, and serum amyloid A, upregulation of neutrophil cell surface adhesion molecules such as CD64 and CD11b, and concentrations of certain lymphokines such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor-α, and each has been reported to have moderate positive and negative predictive values.

TABLE 93.2 **EMPIRIC ANTIBIOTIC TREATMENT FOR PRESUMED NEONATAL SEPSIS (WITH OR WITHOUT MENINGITIS)**

Age and location of infant at onset	Antibiotic regimen	Alternative regimens
Early-onset sepsis	Ampicillin *plus* gentamicin[a]	Ampicillin *plus* cefotaxime
Late-onset sepsis (up to 1 month)		
Readmission from the community	Ampicillin *plus* cefotaxime (or ceftriaxone[b])	Ampicillin *plus* gentamicin[a] *with* or *without* cefotaxime (or ceftriaxone[b])
In the hospital, with no intravenous catheter(s)	Ampicillin *plus* gentamicin[a]	Ampicillin *plus cefotaxime* (or ceftriaxone[b])
In the hospital, with intravenous catheter(s)	Oxacillin or vancomycina *plus* gentamicin[a]	Vancomycin[a] *plus* cefotaxime (or ceftriaxone[b])

[a] Adjust dose according to concentration of the antibiotic in the blood once a steady state has been achieved.
[b] Ceftriaxone can displace bilibrubin from albumin thus intensifying hyperbilirubinemia and may also cause deposition of sludge in the gallbladder so it should be used with caution in newborns.

Treatment is designed to provide adequate antimicrobial activity against the organisms listed in Table 93.1. Often the focus of infection is unknown initially but in the absence of a detectable extravascular source, therapy is directed against bacteremia and meningitis because experience demonstrates that these are the most likely foci. If pneumonia or a urinary tract infection is present, physical exam or screening tests, chest radiograph, and urinalysis will demonstrate these foci. Tables 93.2 and 93.3 list the antibiotics found to be effective and commonly used for neonatal infections. The recommended dosing (Table 93.3) takes into consideration the absorption, metabolism, distribution, and excretion, which differ from those of older children and change rapidly during early life.

Empiric treatment is generally an extended-spectrum penicillin with an aminoglycoside or extended-spectrum (third-generation) cephalosporin (Table 93.2). A majority of pediatric infectious disease practitioners continue to use an extended-spectrum penicillin, usually ampicillin, with an aminoglycoside, usually gentamicin. The advantages of this combination are low cost, considerable experience, and low toxicity. The advantages of the extended-spectrum cephalosporins are greater activity against many of the pathogens and excellent central nervous system penetration in the presence of inflammation. There is concern, however, about the development of resistant flora if these agents are used routinely. Prior treatment with third-generation cephalosporins increases the risk for invasive infections due to *Candida* species. Also *Listeria* and *Enterococcus* species which occur in ill neonates are resistant to the cephalosporins. If gram-negative bacillary meningitis is diagnosed, it is reasonable to use ampicillin plus an extended-spectrum cephalosporin as a first choice until the pathogen is identified.

When transmission of *Staphylococcus* from mother to infant is suspected, an anti-staphylococcal agent should be included.

Empiric therapy for late-onset sepsis

The neonates most likely to have late-onset infections are ill residents of an intensive care nursery. Ideal empiric antibiotic therapy takes into consideration the resident flora of the nursery, especially isolates from previously infected neonates, and the particular risk factors of the patient. If intra-vascular cannulas have not been used, if the infant has not been treated for a previous infection, and if there have not been isolates of gentamicin-resistant gram-negative aerobic bacilli, it is appropriate to use the same empiric treatment as for early-onset sepsis (see Table 93.2). In fact, this is usually not the case, and another regimen is often more appropriate. Ill infants frequently have one or more intravascular catheters in place, and these may be the focus of infection. The most common bacterial species causing catheter-associated infections are coagulase-negative staphylococci and *Staphylococcus aureus*. Although penicillinase-resistant semisynthetic penicillins (oxacillin, nafcillin) are usually the agents of choice against staphylococci, resistance to this class, commonly called methicillin-resistant *S. aureus* (MRSA), is rising in many institutions. Some institutions report high endemic rates of MRSA in neonatal intensive care units (NICUs). In addition, coagulase-negative staphylococci appear to have a higher incidence in very-low-birth-weight infants, and these pathogens are more likely to show methicillin resistance. Therefore, in institutions with substantial methicillin resistance of staphylococci it is reasonable to use vancomycin for empiric treatment of late-onset catheter-associated infections until susceptibility is known. Generally an aminoglycoside is added. If an infant develops new symptoms of infection while receiving gentamicin, either amikacin or third-generation cephalosporin is substituted.

Penicillin is used for group B streptococci; ampicillin or ampicillin plus gentamicin is used for *Enterococcus* species or *Listeria*. For gram-negative bacillary infections ampicillin or ampicillin plus an aminoglycoside or third-generation cephalosporin (depending on susceptibility) is continued for 7 to 10 days unless there is a focal infection in addition that requires a longer duration of treatment. For peritonitis due to necrotizing enterocolitis, the addition of clindamycin to the regimens recommended for sepsis may be of value for treatment of staphylococci and gram-negative rod anaerobes. The duration is determined based upon response to treatment.

If *Pseudomonas aeruginosa* is a likely pathogen, tobramycin is preferred to gentamicin because of higher activity. Extended-spectrum β-lactam agents such as ceftazidime and piperacillin–tazobactam are also used for *Pseudomonas* species. If infections

TABLE 93.3 **DOSE SCHEDULES OF FREQUENTLY USED PARENTERAL ANTIBIOTICS FOR NEONATAL INFECTIONSA**

	<7 days of age		>7 days of age	
ANTIBIOTIC AGENT	**DAILY DOSE (per kg)**	**DOSES/DAY**	**DAILY DOSE (per kg)**	**DOSES/DAY**
Penicillins				
Penicillin G	50 000–100 000 units[b]	2–3[c]	100 000–200 000 units	3–4
Ticarcillin, ticarcillin–clavulanate	150–225 mg	2–3	225–300 mg	3–4
Piperacillin, piperacillin–tazobactam	150–225 mg	2–3	225–300 mg	3–4
Penicillinase-resistant penicillins (oxacillin, nafcillin)	50–100 mg	2	100–200 mg	3–4
Ampicillin	50–150 mg	2–3	100–200 mg	3–4
Aminoglycosides				
Amikacin[d]	7.5–20 mg	1–2	22.5–30 mg	3
Gentamicin[d]	5 mg	2	7.5 mg	3
Tobramycin[d]	5 mg	2	7.5 mg	3
Cephalosporins				
Cefotaxime	100 mg	2	100–200 mg	3
Ceftazidime	100–150 mg	2–3	100–150 mg	3
Ceftriaxone	50 mg	1	50–75 mg	1
Miscellaneous antibiotics				
Clindamycin	10–15 mg	2–3	15–20 mg	3–4
Vancomycin[d]	20–30 mg	2	30–45 mg	3
Chloramphenicol[d]	25 mg	1	25–50 mg	1–2
Aztreonam	60–90 mg	2–3	90–120 mg	3–4
Metronidazole	7.5–15 mg	1–2	15–30 mg	2
Antifungal agents				
Amphotericin B	0.5–1.0 mg	1	0.5–1.0 mg	1
Amphotericin B lipid complex or liposomal	3–5 mg	1	3–5 mg	1
Flucytosine (oral)[e]	100–150 mg	4	100–150 mg	4
Fluconazole[f]	3–12 mg	1	3–12 mg	1
Antiviral agents				
Acyclovir	45–60 mg	2–3	45–60 mg	2–3

[a] Dosing of very small premature infants (1200 g birth weight) may require longer dose intervals, and specialized literature or a pharmacy specialist should be consulted.
[b] Where there is a dose range the higher figure is used for treatment when meningitis is present. For sepsis without meningitis the higher end of the dose range is recommended for more severe infections or when the measured serum antibiotic concentration is lower than the therapeutic range.
[c] Where there is a range of number of doses/day the greater number and higher dose is used for neonates with a birth weight over 2 kg and the lower number doses with lower daily dose are for neonates with a birth weight under 2 kg.
[d] Dosing should be guided by laboratory determination of serum antibiotic concentrations once a steady state has been reached.
[e] Limited data on dosing neonates. Dose indicated is from cases in the literature.
[f] Limited data in neonates. Child dose is listed.

due to gentamicin-resistant gram-negative bacilli have recently been encountered in the unit, amikacin or netilmicin are the aminoglycosides of choice. Ideally, each neonatal treatment unit would monitor pathogens isolated and adjust empiric treatment accordingly.

Isolation of *Candida* from blood or a closed space requires prompt institution of antifungal treatment. For candidemia, first remove intravascular catheters and treat with amphotericin B or one of the lipid-associated forms of amphotericin. Once there has been speciation, one may consider treatment with fluconazole or other azoles if it is a susceptible species. Although it is controversial, there is evidence that fluconazole prophylaxis is effective at reducing neonatal candidiasis and candidemia in NICUs. At this time, prophylaxis with fluconazole (3 or 6 mg/kg/day, twice weekly) is

recommended primarily for neonates with a birth weight of <1000 g in units having a high rate of candidal infections.

Adjunctive therapy of sepsis

In addition to antibiotic therapy, infants with sepsis require intensive medical management. Care should be provided to address fluid and electrolyte, metabolic, nutritional, respiratory, cardiovascular, renal, and hematologic needs. Extracorporeal therapies, including continuous renal replacement therapy (CRRT), plasma-based removal techniques, and extracorporeal membrane oxygenation (ECMO), have been explored in the treatment of neonatal sepsis. The most experience is with ECMO, which has been used successfully for the treatment of refractory septic shock in neonates. The use of agents to support or enhance the neonate's immune response is controversial. Exchange transfusion, transfusion of concentrated white blood cells when there is severe neutropenia and bone marrow failure, commercial intravenous immunoglobulin preparations, and organism-specific immunoglobulin preparations are either ineffective or only slightly better than placebo. Hematopoietic growth factors, such as granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF), have been studied in septic neonates with neutropenia, but results are inconclusive, and their use is not currently recommended. Steroids have not been proven to be of benefit in neonatal sepsis or meningitis.

Therapy and management of other focal infections

Meningitis

The doses of some antibiotics are increased when treating meningitis to allow for lower antibiotic concentrations in central nervous system tissue and cerebrospinal fluid (CSF) due to the blood–brain barrier. Bactericidal antibiotics are preferred to bacteriostatic agents. Routine intrathecal or intraventricular administration of antibiotics does not improve outcome. Intraventricular instillation may occasionally be warranted when resistant organisms are not eradicated using conventional antibiotics.

Ampicillin plus gentamicin or cefotaxime are recommended for empiric treatment of neonatal meningitis. Cefotaxime is preferred over ceftriaxone because the latter antibiotic has high protein binding which can increase free bilirubin in the blood. Complications and delayed sterilization are more common with gram-negative bacillary meningitis in the newborn than with meningitis in children beyond the neonatal period caused by the usual organisms for that age group. In evaluating the infant being treated for bacillary meningitis, it is recommended to repeat the lumbar puncture every 48 hours until the CSF is sterile to monitor antibiotic efficacy. Continued positive cultures may signal the need to change antibiotics or look for a focus such as a brain abscess with cranial imaging. Assuming no complications, antibiotics are usually continued for 3 weeks. For group B streptococcal meningitis repeat lumbar puncture has little value when there is a good clinical response and no late complications. Resistance of group B streptococci to penicillin and ampicillin has not been reported. Length of treatment is 2 to 3 weeks. Hydrocephalus is an unfortunately common complication of neonatal meningitis, usually associated with severe ventriculitis, and it is important to monitor the head circumference and serial head ultrasound examinations, if indicated, throughout therapy. Infants who develop an increase in ventricular size should be evaluated by a neurosurgeon. At this time there are no data to suggest that adjunctive steroid treatment is either safe or beneficial for neonatal meningitis.

Pneumonia

Neonatal pneumonia can occur prenatally, in association with early-onset sepsis, as a complication of a noninfectious respiratory condition such as respiratory distress syndrome or meconium aspiration, or as a nosocomial pneumonia associated with mechanical ventilation. Prematurely born infants > 1 month of age may develop chronic lung disease of prematurity, which has not been determined to be an infectious disease. Rarely is diagnostic lower-lung tissue or sputum of good quality available for microbiologic diagnosis. Thus there is little information on optimal therapy for pneumonia as an isolated infection. In general, the bacterial pathogens are the same as those for early- and late-onset sepsis, and empiric antimicrobial treatment is the same. Antibiotic therapy is usually for 10 to 14 days and extended to 21 days for the rare cases of staphylococcal pneumonia. In addition, organisms of maternal origin such as *Chlamydia trachomatis*, which can be treated with erythromycin or sulfisoxazole, and genital mycoplasmas such as *Mycoplasma hominis* and *Ureaplasma urealyticum*, for which there is no proven treatment, may be encountered. There are reports of treatment of *U. urealyticum* with macrolide antibiotics but so far little convincing evidence of efficacy.

Urinary tract infection

Percutaneous bladder puncture is the best method of culture to avoid contamination. Bladder catheterization is acceptable but is more likely to result in contamination of the urinary tract. If the same organism is recovered from the urine and the blood, it may not be clear whether the urinary tract was the initial focus of infection or was seeded from blood unless there is an obvious urinary tract anatomic abnormality. Late-onset urinary tract infections may be associated either with a congenital malformation or urinary tract instrumentation or be spontaneous, with no discoverable underlying cause. Initial antibiotic treatment should be similar to the approach to the neonate with sepsis according to Table 93.2 and, following identification of the pathogen continued with one of the agents listed in Table 93.3, according to the susceptibility of the isolate. Due to unpredictable absorption of oral antibiotics the treatment is generally with parenterally administered drug. Although treatment for 10 to 14 days with an agent that has renal concentration and excretion is conventional, the neonate, like older individuals, may have a poor response or relapse in the presence of obstruction, a foreign body, or incomplete voiding. Due to the high rate of congenital malformations in neonates with urinary tract infections or vesicoureteral reflux, imaging studies should be part of the evaluation and management.

Skeletal infections

Septic arthritis and osteomyelitis in the neonate are generally secondary to bacteremia. *S. aureus* is the most frequently isolated organism, and group B streptococci and gram-negative aerobes, especially *E. coli*, are also encountered. *S. aureus* skeletal infections in the neonate are often severely destructive and associated with later disabilities, and may be associated with multiple foci and rupture through the incompletely formed epiphyseal plate. Magnetic resonance imaging helps evaluate arthritis and osteomyelitis because metabolic bone disease of prematurity may make interpretation of radiographs difficult. Empiric therapy is similar to sepsis, but an agent active against *S. aureus* such as oxacillin or nafcillin (or vancomycin if MRSA is suspected) should be added. Management includes aspiration of infected bone or septic joint, and open drainage should be considered if aspiration is insufficient to drain the focus. Length of treatment is generally at least 3 weeks for septic arthritis and at least 4 weeks for osteomyelitis. A longer course may be necessary if there is delayed sterilization, late appearance of a second focus, unusual organism, or other complications. There is too little experience with oral agents for skeletal infections in the neonate to recommend this route.

Viral infections

Herpes simplex infections

Herpes infections of the newborn are transmitted from the mother's genital tract to the infant, usually at delivery but, rarely, ascending infection may occur in utero. The incidence is approximately 1 in 3000 to 5000 deliveries although published rates vary considerably. Infants of mothers with primary genital herpes lesions at the time of delivery rather than recurrent herpes are at highest risk, but mothers of infants with herpes infection are often unaware of ever having had genital herpes. The incubation period is generally from 3 or 4 days to a month after birth. Most neonatal herpes infections are due to herpes simplex virus type 2. The presentation of neonatal herpes may include (1) only cutaneous, eye, and mucous membrane manifestations (vesicles); (2) only central nervous system infection; or (3) disseminated visceral infection. Combinations of the three may also occur. Severity and prognosis are worst for disseminated visceral disease and best for cutaneous disease.

Acyclovir is the antiviral agent of choice. Moderately ill infants who are treated early in the course of infection benefit most. The recommended dose is now higher than that previously recommended. The usual dose in a term infant is 60 mg/kg/day divided every 8 hours. The optimal duration of treatment is unknown, but although early studies used a duration of 10 days, most practitioners extend the course to 14 to 21 days (the latter when the infection is disseminated or the central nervous system is involved) because of reports of recurrences with the shorter regimen. Some recommend repeat lumbar puncture to follow the polymerase chain reaction (PCR) and to extend treatment until the CSF PCR is negative.

Cytomegalovirus infection

Cytomegalovirus (CMV) infection of the neonate usually derives from mother to infant during gestation, but CMV may also be acquired by the infant at the time of delivery or postnatally. The diagnosis of congenital CMV infection is established by detecting virus by culture or other techniques in urine, blood, or other tissues during the first 3 weeks of life. Many laboratories utilize rapid culture techniques combined with direct immunofluorescence detection using antibodies against intermediate-early or early CMV antigens but PCR tests have taken over for diagnosis in some laboratories. The use of PCR and quantitative antigenemia in the blood, which have been useful in following older immunocompromised individuals, may be useful in confirming neonatal infection as well as in following the course of infection.

Numerous antiviral agents treat CMV infection, including ganciclovir, valganciclovir, foscarnet, cidofovir, and CMV immunoglobulin. However, there is limited experience in treating congenital infection with these agents. One study showed that infants with symptomatic congenital CMV infection and evidence of central nervous system involvement treated for 6 weeks with ganciclovir (6 mg/kg intravenously every 12 hours) have less hearing loss at 6 months and fewer developmental delays at 12 months compared to untreated controls. Concerns of marrow suppression and other potential long-term effects, such as germ cell toxicity and carcinogenicity, have led many to restrict the use of ganciclovir to treatment of congenital CMV with central nervous system involvement. A recent study demonstrated superiority of oral valganciclovir for 6 months compared to 6 weeks of treatment for congenital CMV disease.

Varicella-zoster virus

Infants born of mothers who have active varicella are in danger of developing overwhelming infection due to varicella-zoster virus (VZV) if the mother's lesions appear in the period between 5 days before delivery and 2 days after delivery. The rationale is that infants exposed during this period may have received a large dose of VZV intravenously by transplacental exposure. Infants exposed earlier in utero receive antibody transplacentally from the mother and generally develop a mild infection. Infants exposed after birth also develop mild varicella. If an infant is exposed to VZV during the critical perinatal period described above, treatment with varicella-zoster immunoglobulin (VariZIG) 125 units (one vial) or immune globulin, intravenous given as soon as possible after delivery or exposure is recommended. Neonates who develop severe perinatal VZV infections can be treated with acyclovir at a dose of 45 mg/kg/day in three divided doses for 5 to 7 days.

Viral pneumonia

Respiratory syncytial virus, influenza viruses, parainfluenza viruses, and adenoviruses can cause severe respiratory disease in neonates, and the diagnosis is made by viral culture or rapid antigen tests. In general, antimicrobial treatment is not available. Ribavirin by aerosol, which in earlier studies appeared to shorten the course of

respiratory syncytial virus-associated bronchiolitis in infants, is no longer recommended for routine use because subsequent studies cast doubt on the efficacy of ribavirin even for older infants.

Suggested reading

Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928–2003. *Pediatrics*. 2005;116:595–602.

Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of sepsis. *Pediatr Clin North Am*. 2013;60:367–389.

Kimberlin DW, Lin CY, Sanchez PJ, et al.; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr*. 2003;143:16–25.

Kimberlin DW, et al. Six months versus six weeks of oral valganiclovir for infants with symptomatic congenital CMV disease: results of a Phase III, randomized double-blind placebo-controlled study. Presented ID Week 2013. San Francisco, CA, October 2–6 2013 (Abstract LB-1).

Pickering L, ed. *Red Book: Report of the Committee on Infectious Diseases*, 29th edn. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

Pinninti SG, Kimberlin DW. Maternal and neonatal herpes simplex virus infections. *Am J Perinatol*. 2013;30:113–119.

Plosa EJ, Esbenshade JC, Fuller MP, Weitkamp JH. Cytomegalovirus infection. *Pediatr Rev*. 2012;33:156–163.

Polin RA; Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2012;129:1006–1015.

Remington JS, Klein JO, Wilson CB, Nizet V, Maldonado YA. *Infectious Diseases of the Fetus and Newborn Infant*, 7th edn. Philadelphia, PA: Saunders; 2011.

Whitley RJ. The use of antiviral drugs during the neonatal period. *Clin Perinatol*. 2012;39:69–81.

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Pregnancy and the puerperium

Infectious risks

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Infectious diseases that occur during pregnancy and the puerperium pose special risks to the mother, fetus, and infant. Any intervention must be weighed against possible side effects.

Urinary tract infections

For pregnant women it is recommended to culture urine at the first prenatal visit. Treatment should be provided if the urine culture is positive.

Short courses (3 days) of antimicrobial therapy are usually effective in eradicating asymptomatic bacteriuria. Penicillins, cephalosporins, aztreonam, ertapenem, imipenem, and meropenem are considered safe. Sulfonamides, including TMP–SMX, are avoided in the first trimester and near term (because of kernicterus).

Recommended regimens include amoxicillin, 500 mg orally three times a day; amoxicillin–clavulanate, 875 mg twice a day; nitrofurantoin, 100mg every 12 hours; sulfisoxazole, 500 mg three times a day; cephalosporins, such as cefuroxime–axetil, 250 to 500 mg every 12 hours, or cefpodoxime, 100 mg every 12 hours, can also be used. Fosfomycin, 3 g PO as a single dose, was shown to be effective when compared with other drugs administered for a longer time.

Urine culture should be performed 1 week after therapy and monthly until the end of pregnancy. Suppressive therapy until delivery is recommended for women who have persistent bacteriuria after two or more courses of therapy.

In acute cystitis, pyuria is found in most patients, and urine culture should be performed. Patients should be treated for 3 to 7 days if symptoms suggesting pyelonephritis are absent. The same antibiotic regimens suggested for asymptomatic bacteriuria can be utilized. Quinolones are contraindicated in pregnancy. Follow-up urine culture should be obtained 1 week after therapy. For recurrent infections, antimicrobial prophylaxis should be considered for the duration of pregnancy.

When acute pyelonephritis is the presumptive diagnosis, we admit pregnant patients to the hospital, culture urine and blood, and treat with intravenous antibiotics until the patient is afebrile for 24 hours. Then, oral therapy can be used to complete 10 to 14 days of therapy. If fever and symptoms persist >48 hours after treatment imaging studies of the urinary tract and repeat urine culture should be obtained. Antibiotic prophylaxis should be considered in patients with recurrent pyelonephritis, with periodic urine cultures for the remainder of the gestation.

Empiric treatment of acute pyelonephritis includes the following: ceftriaxone, 1 g IV every 24 hours, ceftazidime, 2 g IV every 8 hours, cefepime, 2 g IV every 12 hours, piperacillin–tazobactam, 4.5 g IV

every 8 hours, ertapenem, 1 g IM every 24 hours, meropenemand aztreonam, 1 to 2 g IV every 8 hours. We avoid aminoglycosides whenever possible.

Premature rupture of fetal membranes and intra-amniotic infection

Premature rupture of fetal membranes (PROM) can occur at any time before uterine contractions and labor start. Subclinical infection or inflammation of the chorioamniotic membranes causes an important proportion of cases. Intra-amniotic infection (IAI), present in 40% to 75% of women with PROM, is the infection of the membranes, the amniotic fluid, the placenta, and/or the uterus. It is associated with a 50% rate of preterm deliveries before gestation week 30.

Maternal fever and tachycardia and fetal tachycardia are common manifestations of IAI. Maternal leukocytosis is common. Maternal bacteremia occurs in up to 10% of cases but is more common when virulent organisms (*Escherichia coli* 15%, group B streptococcus 18%) are causing the infection. Abnormal labor, necessity for C-section, hemorrhage, wound infection, and endometritis are maternal complications. Fetal and neonatal complications include sepsis, pneumonia, respiratory distress, intraventricular hemorrhage, and low apgar score.

When IAI is suspected amniocentesis is performed. Amniotic fluid is obtained for aerobic (group B streptococcus, *E. coli*, enterococci) and anaerobic (*Peptostreptococcus, Bacteroides*, and *Fusobacterium* species, *Gardnerella vaginalis*, and *Mobiluncus* species) cultures. Samples for Gram stain (48% sensitivity, 99% specificity), glucose level (sensitive when below 15 mg/dL), white blood cell count (above 30/mm^3), and leukocyte esterase activity (trace or greater) and measurement of amniotic fluid cytokines (interleukin [IL]-1a, IL-6, IL-8, and tumor necrosis factor [TNF]) can be obtained at the same time. Antibiotics are used immediately. Ampicillin, 2 g IV every 6 hours, plus gentamicin, 5.1 mg/kg once daily, continued for 1 dose after delivery; clindamicin, 900mg IV every 8 hours, can be added after cord clamping in cesarean deliveries to reduce endometritis. Alternatives include ampicillin–sulbactam, 1.5 to 3 g every 6 hours; or piperacillin–tazobactam, 3.375 to 4.5 g every 6 hours. For serious infections due to resistant bacteria, such as extended-spectrum β-lactamase-producing gram negatives, carbapenems (meropenem, doripenem, ertapenem) can be substituted.

Mycobacterial infection in pregnancy

The diagnosis and treatment of pregnant women with active tuberculosis (TB) follows the same steps as in the nonpregnant individual. A human immunodeficiency virus (HIV) serology is mandatory. PPD is safe and accurate during pregnancy. Provided no multidrug resistance is suspected, the initial regimen consists of isoniazid (with pyridoxine 50 mg/day), rifampin, and ethambutol, for 2 months, followed by rifampin and isoniazid for 7 months. Isoniazid may exhibit increased maternal liver toxicity during pregnancy. Pyrazinamide is not currently recommended in the United States for routine use. Expert consultation is advised.

Therapy for latent TB infection (LTBI) may be started even during the first trimester, with isoniazid (5 mg/kg/day, maximum 300 mg) for 9 months (supplemented with pyridoxine) or rifampin (600 mg/day) for 4 months. Breastfeeding is not discouraged.

In pregnant AIDS patients, the treatment of disseminated disease due to *Mycobacterium avium* complex (MAC) is difficult. Azithromycin (Food and Drug Administration [FDA] category B) is the preferred macrolide for MAC prophylaxis and treatment (see Chapters 157, Tuberculosis, and 158, Nontuberculous mycobacteria). Again, expert consultation is advised.

Malaria and pregnancy

Pregnant women are more vulnerable to high parasitemia, severe infection, and mortality; fetuses are more vulnerable to low birth weight (LBW), prematurity, stillbirth, congenital disease, and death. Hence, exposure to malaria should be avoided, and diagnosis and treatment of identified cases should be prompt. The geographic distribution of drug-resistant malaria parasites, the clinical features in obstetric patients, and the laboratory diagnosis are the same as described in Chapter 200, Malaria. We recommend hospitalization for all pregnant women with malaria. All antimalarial drugs have potential fetal toxicity. Chloroquine phosphate, the blood schizonticide of choice for oral prophylaxis (500mg [300mg base] once a week beginning a week prior to potential exposure and continued for 4 weeks afterwards) and therapy (1 g [600mg base] stat, and then 500 mg in 6 hours and 500mg daily for two doses) is generally considered safe and is effective for treatment of plasmodial species other than chloroquine-resistant *Plasmodium falciparum*. Pregnant women should receive chloroquine once a week until the end of pregancy when primaquine can be administered to eradicate dormant hypnozoites that may be in the liver. Mefloquine appears safer than other antimalarial drugs, but concerns remain about stillbirth, LBW, and neuropsychiatric and cardiac side effects. Tetracyclines are contraindicated during pregnancy, but IV clindamycin (10mg/kg followed by 5mg/kg every 8 hours) is an alternative. Artesunate plus clindamycin is indicated during any trimester of pregnancy; for treatment in the second or third trimester, an artemisinin-based combination regimen known to be effective in the region of acquisition of malaria may be preferable. Atovaquone (250mg) combined with proguanil (100mg) is highly effective against chloroquine- and mefloquine-resistant *P. falciparum* malaria, but data in pregnancy are scarce. Rescue has been successful with atovaquone–proguanil combined with artesunate in multidrug-resistant *P. falciparum* infections without recorded toxicity. Small studies suggest that artemisinin-derived antimalarials are well tolerated. Quinine sulfate or quinidine gluconate with or without clindamycin are alternative regimens that require continuous monitoring of vital signs, blood glucose, and electrocardiogram (ECG). For severe malaria

in the second and third trimester, parenteral artesunate is preferred over quinine/quinidine. Treatment should be started immediately with the most readily available drugs. Exchange transfusions might be added in severe malaria during pregnancy, but their benefit is controversial.

During pregnancy, chloroquine alone or with proguanil remains preferred for chemoprophylaxis where still effective; where not, mefloquine may be used. Doxycycline and primaquine must be avoided. Pregnant women should not visit malarial zones; when unavoidable, dedicated chemoprophylaxis, intermittent preventive treatment, and antivector strategies that include insecticide-treated nets are paramount.

Toxoplasmosis

The rationale for early treatment of toxoplasmosis acquired during gestation is to decrease fetal infection. When the maternal diagnosis is established during pregnancy, spiramycin, a macrolide antibiotic with an antibacterial spectrum similar to erythromycin (1 g orally three times a day) reduces the rate of transmission of infection to the fetus by approximately 60%. The drug, available in the United States through the FDA (1–301827–2335), is continued until delivery, assuming fetal infection has been excluded. If fetal infection is confirmed (the diagnostic method of choice is amniotic fluid polymerase chain reaction [PCR] examination for *Toxoplasma gondii* DNA after 18 weeks of gestation), oral pyrimethamine, 25 mg/day, plus sulfadiazine, 4 g/day, is superior and therefore should be started together with folinic acid, 10 mg/day, as soon as the diagnosis is established.

Serologic screening is to be performed before pregnancy or at the first prenatal visit, before gestational week 22, and finally near term in previously seronegative women. If the tests are or become positive, acute immunoglobulin M (IgM) (requires confirmation in a reference laboratory), IgA, or IgE can prove recent infection and mandate therapy. Maintenance trimethoprim–sulfamethoxazole (TMP–SMX) for *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP) prophylaxis may prevent toxoplasmosis.

Herpes simplex virus infection of the genital tract

Maternal fetal transmission occurs by direct contact during vaginal delivery. Ascending or transplacental infection rarely occurs. Acyclovir, an antiviral drug with an excellent safety profile, has been used in pregnancy including the first trimester. The same experience is accumulating with the use of valacyclovir and famciclovir.

For primary genital infection, acyclovir is recommended at a dose of 400 mg PO, three times a day for 10 to 14 days. For one or more symptomatic recurrences of genital herpes simplex virus during pregnancy, acyclovir, 400 mg PO three times a day, given at 36 weeks through delivery is beneficial. In preterm premature rupture of membranes at less than or equal to 31 weeks in women with active genital herpetic lesions, expectant management is warranted, and acyclovir therapy may shorten the duration of the lesions, but no further data are available.

The greatest risk for neonatal herpes is in women who shed virus during delivery, which is most common in those who acquired herpes in the third trimester. Additional risk factors include mothers younger than 21 and the use of fetal scalp electrodes. Although cesarean section does not prevent all neonatal lesions, for women with a history of genital herpes and either active genital lesions, vulvar pain, or burning at the time of delivery, cesarean section should be offered.

Prophylactic cesarean delivery is not indicated for women with a history of recurrent herpetic lesions and no evidence of active lesions at the time of delivery. In such women, acyclovir prophylaxis from week 36 is preferred to cesarean delivery.

The use of antiviral therapy during delivery is controversial; antiviral therapy can reduce the rates of viral shedding (and thereby reduce newborn exposure) but data are incomplete and the approach should be individualized. The benefit of treating asymptomatic mothers at delivery is unknown. After delivery, a high index of suspicion and immediate isolation and treatment of infants with early infections are warranted.

Vaccination during pregnancy

Yearly inactivated influenza vaccine (IIV) is indicated during pregnancy; Tdap vaccination is recommended during each pregnancy regardless of the interval since prior dose. Antipneumococcal vaccination may be given if other risk factors are present; meningococcal and hepatitis vaccines may be indicated on the basis of medical or epidemiologic indications. Live-virus vaccines such as varicella, zoster, and MMR are contraindicated. Always consult the current vaccine recommendations and updates.

Influenza

The risk of complications is increased in pregnant women with influenza. Vaccination is the best protection for the mother and protects the infant for 6 months. The Centers for Disease Control and Prevention (CDC) recommends influenza vaccination to all women who are pregnant or will be pregnant during influenza season regardless of trimester. Live attenuated influenza vaccine (nasal route) should not be utilized during pregnancy. A trivalent or tetravalent vaccine should be utilized.

The diagnosis during pregnancy is clinical and treatment should be initiated within 2 days of symptoms, although data suggest a benefit of treatment if started later. Treatment of influenza outweighs the potential risk to the fetus. Women within 2 weeks postpartum should also be treated promptly. Pregnant women with presumptive influenza should be treated with antivirals, despite an updated vaccination history, since vaccine is not 100% effective.

Oseltamivir and zanamivir are antiviral drugs to which the majority of influenza viruses are susceptible since 2009. Although they are Pregnancy Category C drugs, prenatal exposure to these drugs has not shown increased fetal risk.

Oseltamivir is preferred to inhaled zanamivir because of greater experience using the drug during pregnancy. The dosing for oseltamivir is 75 mg orally every 12 hours and for zanamivir 10 mg (2 inhalations) every 12 hours administered for 5 days. Longer treatments have been used in patients who persist very ill after 5 days of therapy. Antiviral prophylaxis should be considered for pregnant women and for women up to 2 weeks postpartum. Zanamivir is considered the drug of choice for prophylaxis in pregnancy due to its low systemic absorption. Secondary respiratory complications may be seen especially in asthmatic patients. The dose recommended for prophylaxis is zanamivir 10mg (2 inhalations) once a day for 10 days or oseltamivir 75mg orally daily for 10 days. When fever develops during the first trimester, acetaminophen should be added to the antiviral therapy.

Human immunodeficiency virus (HIV) infection

Antiretroviral therapy during gestation includes two separate issues: treatment of maternal HIV infection and prevention of prenatal transmission. Treatment with antiretrovirals during pregnancy reduces the HIV viral load to undetectable levels and lowers the risk of perinatal infection from 25% to 30% without therapy to less than 2%. Therefore, combination antiretroviral therapy is indicated to all pregnant women with HIV regardless of the baseline CD4 count and HIV viral load. The goal of therapy is to achieve an undetectable HIV viral load using the most sensitive assay. Certain antiretroviral drugs should be avoided in pregnancy, e.g., efavirenz, because of teratogenic effects; didanosine and stavudine are more toxic than the available preferred nucleoside reverse transcriptase inhibitors (NRTI). Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), has caused hepatotoxicity in women with CD4 counts >250 cells/mm^3. The recommendations for the use of antiretroviral drugs to prevent or reduce perinatal transmission of HIV are updated periodically, and the reader is encouraged to consult the web site http://AIDSinfo.nih.gov for current guidelines.

For HIV-infected pregnant women on antiretroviral therapy and failure of virologic suppression, there is no clear recommendation. Raltegravir has been used later in pregnancy; however, the reports on safety and efficacy are anecdotal. Intrapartum care using IV zidovudine as therapy or prophylaxis depends on the maternal viral load. If the patient receiving antiretroviral combination has a viral load < 400 copies/mL, IV zidovudine is no longer necessary. However, if the viral load is > 400 copies/mL or unknown at the time of delivery, IV zidovudine is indicated during labor, regardless of the mode of delivery or antiretroviral regimen. IV zidovudine during labor and delivery or before a cesarean section (started 3 hours prior to surgery) should be initiated at the following doses: 2 mg/kg IV as a loading dose followed by continuous IV infusion of 1 mg/kg/hour until delivery. Continue other antiretrovirals on schedule and minimize the duration between rupture of membranes and delivery through stimulating labor. Additionally, cesarean section at 38 weeks of gestation is recommended to all patients if the viral load is above 1000 copies/mL near the time of delivery.

Parvovirus B19 infection

Infection with parvovirus B19 during pregnancy can lead to vertical transmission complicated by fetal heart failure, anemia, hydrops fetalis, and death.

All pregnant women exposed to or with symptoms suggestive of parvovirus infection should have IgM and IgG antibody testing. Those found to have a positive IgM who are beyond 20 weeks of gestation should have weekly ultrasounds for at least 8 weeks after the acute infection to look for signs of fetal hydrops. When hydrops fetalis develops, usually maternal IgM antibodies are absent. If pregnant women with recent parvovirus B19 exposure have negative IgM and IgG serologies, then testing maternal plasma for parvovirus B19 DNA should be performed, since it is a more sensitive test. There is no effective drug treatment for parvovirus B19 infections and it is difficult to avoid contact with infected individuals since they are contagious before symptoms develop; hand washing and avoiding sharing drinks, food, or utensils, may reduce transmission.

Postpartum endometritis

Infection of the uterine cavity remains a significant cause of postpartum fever. Fever, tachycardia, suprapubic pain reflecting uterine tenderness, and purulent cervical drainage are characteristic findings. Purulent foul-smelling lochia and uterine subinvolution are also found in some women. A fever of greater than or equal to 38° C after 24 hours of delivery and within 10 days postpartum is significant. Endometrial cultures are not routinely done since it is difficult to obtain uncontaminated samples through the cervix. Cervical cultures for gonorrhea and samples for chlamydia nucleic acid amplification should be obtained if not done previously, as well as blood and urine cultures.

Early onset of suspected infection suggests group A streptococci; onset between day 3 and 7 postpartum suggests enteric bacteria and anaerobes and late onset after 7 and even 14 days suggest *Chlamydia* infection. Cesarean delivery, especially after the onset of labor, is more frequently associated with endometritis.

Ultrasound and/or computed tomography can establish the presence and characteristics of a mass, especially if palpated, and guide decisions for aspiration or further procedures. Therapy includes draining pelvic collections and the uterus if indicated. Initial antibiotic therapy is empiric and should be broad spectrum covering aerobes and anaerobes.

Clindamycin and gentamicin are commonly used; alternative drugs with similar efficacy include piperacillin–tazobactam and carbapenems (imipenem, meropenem, doripenem, or ertapenem). Doxycycline should be added to the previous antibiotics if *Chlamydia* is suspected or diagnosed. Therapy is continued until the patient is clinically improved and afebrile for at least 24 hours; oral antibiotics are rarely prescribed after successful parenteral therapy. If bacteremia is present, at least 7 days of antibiotic therapy is recommended, switching to PO therapy if appropriate oral alternatives are available. Defervescence is expected after 48 to 72 hours of therapy; persistent fever may suggest resistance, abscess, absence of therapeutic drug blood levels, or septic pelvic thrombophlebitis.

Cesarean section

The risk of infection after cesarean delivery is higher than after vaginal delivery. Surgical site infections usually develop between 4 and 7 days after the surgical procedure and wound infections are diagnosed in 2.5% to 16% of these patients. It has been reported that a subcutaneous hematoma is a major risk factor for infection in a high percentage of patients after discharge. Group A or B β-hemolytic streptococci usually cause an early infection manifested by fever and cellulitis. Infections caused by *Staphylococcus aureus*, enteric bacteria, or vaginal flora usually appear later. A wound containing pus may require drainage, debridement, irrigation, and vacuum wound therapy may also be useful once local infection is controlled. Cellulitis at the wound site can be treated with broad-spectrum antibiotics alone if there are no signs of fluid collections.

For severe infections, especially if deeper tissue extension is suspected, broad-spectrum antibiotics covering *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]) and microbial flora at the site of surgery should be started immediately. This can be accomplished with vancomycin or daptomycin. The antibiotic therapy for deeper pelvic infections is described in the section on postpartum endometritis.

Lactational mastitis

Acute breast infections during breastfeeding cause fever and breast discomfort, and occur in 2% to 10% of lactating women. Risk factors include nipple excoriations or cracking, prolonged unilateral engorgement with inadequate milk drainage, and previous mastitis. *S. aureus*, and more frequently MRSA have become the most important pathogens. Group A or B streptococcus, *E. coli*, anaerobes (*Bacterioides* species), coagulase-negative staphylococci and *Corynebacterium* species are frequently isolated. These microorganisms penetrate the nipple, colonize the stagnant milk, and then produce mastitis. Ultrasound is an effective method to diagnose abscesses and is useful to guide abscess drainage.

In patients with mild to moderate infection and with risk factors for MRSA, trimethoprim–sulfamethoxazole DS (1 tablet PO every 12 hours) or clindamycin (300 to 450 mg PO every 6 hours) can be used. Linezolid (600mg PO every 12 hours) is also an acceptable effective alternative. In patients with mild to moderate infections and with no risk factors for MRSA, dicloxacillin (500mg PO every 6 hours), or clindamycin (300 to 450 mg PO every 6 hours) can be used if the patient is allergic to β-lactam drugs.

In patients with severe infections (systemic toxicity, hemodynamic instability) vancomycin at 15 mg/kg IV every 12 hours should be immediately started, and if Gram stain of the abscess or drainage shows the presence of gram-negative bacilli, broad-spectrum empiric antibiotic therapy including a third-generation cephalosporin or a β-lactam/β-lactamase inhibitor combination should be promptly added. Patients should be treated for at least 10 days. Continuation of lactation is encouraged during therapy. Breast pumps are useful until the mother can resume nursing.

Hepatitis

Acute hepatitis A during pregnancy is similar to the nonpregnant population. So far, there has not been perinatal transmission reported. Premature labor is a risk if severe disease develops during the third trimester. Other complications include PROM, premature contractions, vaginal bleeding, and placental detachment. Overall, children have a favorable outcome. When acute hepatitis B is diagnosed during gestation, it is usually not linked to high mortality or fetal malformations. The infection is not severe and termination of pregnancy is not considered. If hepatitis B occurs earlier in pregnancy, there is a 10% transmission rate during the perinatal period; however, transmission increases significantly if the acute infection is diagnosed near or at the time of delivery. Perinatal transmission occurs most efficiently when the infant mucosal membrane comes in contact with infected maternal secretions during birth, especially if the mother is HBeAg positive. Transmission can also happen in utero or after birth.

Universal maternal screening for hepatitis B virus infection is strongly recommended, and any women in labor with known hepatitis B status should be considered potentially infectious. The use of prophylactic hepatitis B immunoglobulin immediately after birth followed by hepatitis B recombinant vaccine within 12 hours, and completion of three doses within the first 6 months of life, reduces hepatitis B virus transmission to rates of 10% or less. Hepatitis B maternal vaccination is not contraindicated during pregnancy or lactation.

Hepatitis D coinfection during pregnancy is managed as described for hepatitis B. The risk of transmission of hepatitis C from mother to infant is approximately 2%. Cesarean section delivery and avoidance of breastfeeding are not recommended for hepatitis C-infected women.

Hepatitis E virus infection and fulminant hepatic failure have a mortality rate of 10% to 25% in women during the third trimester. Vaccines are presently in development. Also, there is no evidence that immunoglobulin protects against hepatitis E, including lots produced where infection is endemic.

Varicella

Varicella-zoster virus infection is more severe during pregnancy. The risk of congenital varicella syndrome appears to be low, between 0.4% and 2%.

Varicella pneumonia during gestation is a severe disease, usually developing within 1 week of the rash, may rapidly progress to respiratory failure, and it is a medical emergency. Patients are febrile, hypoxemic, with chest x-rays showing diffuse nodular infiltrates. Intravenous acyclovir is indicated at a dose of 10 mg/kg every 8 hours.

Uncomplicated varicella infections in a pregnant female can be treated with acyclovir (20mg/kg PO every 6 hours) for 5 days. Although the use of this drug has not been studied in pregnancy, a prospective registry of acyclovir use during gestation has not revealed an increased rate of birth defects.

Pregnant women who have been exposed to varicella-zoster virus are eligible for prophylaxis with varicella immune globulin, if they have no history of disease or negative serologic evidence of prior exposure. VariZig, which is a purified immune globulin made from plasma containing a high level of antivaricella antibodies, should be administered within 10 days of exposure. The dose recommended is 125 units/10 kg of body weight given intramuscularly, the maximum dose is 625 units. There are no data to support the use of acyclovir for reducing the risk of varicella in exposed pregnant women.

Neonatal varicella-zoster virus infection is a serious disease that results from the transmission of the virus from the mother to the fetus within 5 days before to 2 days after delivery. The management of newborns exposed to varicella-zoster virus is discussed in Chapter 94, Neonatal infection.

Suggested reading

Bizjak G, Blondin D, Hammer R, et al. Acute infection with parvovirus B19 in early pregnancy. *Ultrasound Obstet Gynecol*. 2009;34(2):234–235.

Chen HL, Lin LH, Hu FC. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. *Gastroenterology*. 2012;142:773–781.

Ergaz Z, Ornoy A. Parvovirus B19 in pregnancy. *Reprod Toxicol*. 2006;21(4):421–435.

Faro C, Faro S. Postoperative pelvic infections. *Infect Dis Clin North Am*. 2008;22:653–663.

Haberg SE, Trogstad L, Gunnes N, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. *N Engl J Med*. 2013;368:333–340.

Louie JK, Yang S, Acosta M, et al. Treatment with neuraminidase inhibitors for critically ill patients with influenza A (H1N1). *Clin Infect Dis*. 2012;55(9):1198–1204.

Schoenfeld EM, McKay MP. Mastitis and methicillin-resistant *Staphylococcus aureus* (MRSA): the calm before the storm? *J Emerg Med*. 2010;38(4):e31–e34.

Shrestha MP, Scott RM, Joshi DM. Safety and efficacy of a recombinant hepatitis E vaccine. *N Engl J Med*. 2007;356(9):895–903.

Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA*. 2010;303:1517–1525.

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Dialysis-related infection

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Data from the US Renal Data System (USRDS) 2018 Annual Report show that the crude incidence rate for end-stage renal disease (ESRD) was 378 per million persons. On December 31, 2015, there were 703,243 prevalent cases of ESRD. In 2015, 87.3% of incident individuals began hemodialysis (HD), 9.6% started peritoneal dialysis (PD), and 2.5% received a preemptive kidney transplant. In 2015, 80% of patients who initiated HD used a catheter for vascular access. Infections remain a common cause of death among patients receiving long-term dialysis and a leading cause of hospitalization. Sepsis is responsible for >75% of these deaths. Abnormalities of cellular immunity, neutrophil function, and complement activation are associated with chronic renal failure and cited as risk factors for the increased susceptibility to infection. Additional predispositions for bacteremia include comorbid conditions (diabetes mellitus, hepatitis C infection), receipt of immunosuppressive therapy, and anemia. Most dialysis-related infections are caused by common microorganisms rather than by opportunistic pathogens and are primarily related to access site for both HD and PD. This chapter focuses on the treatment of infections related to dialysis access devices.

Types of access devices for dialysis

The catheters available for hemodialysis (Table 95.1) differ according to the duration of use (acute versus chronic), tunneled versus non-tunneled, cuffed versus non-cuffed, and, with regards to PD catheters, intraperitoneal versus extraperitoneal designs. An arteriovenous (A-V) fistula is an anastomosis most frequently of the radial artery to the cephalic vein. Other vessels in the arm can also be used. An A-V graft uses a tube made of polytetrafluoroethylene (PTFE, Teflon) to make the A-V connection. There are two types of HD catheters: non-cuffed, non-tunneled, for acute use (<2 weeks) and cuffed, tunneled catheters for chronic use. Catheters are made of either silicone or polyurethane; the specific material does not affect infection rates. Peritoneal catheters for acute use (≤3 days) have the same basic design: a relatively stiff length of straight or slightly curved nylon or polyethylene tubing with side holes at the distal portion. They are placed at the bedside, inserted over a guidewire. These catheters lack cuffs which may protect against bacterial migration from the skin to the outer surface of the catheter and consequently have a high rate of infection when used for longer than 3 days. There are multiple PD catheter designs for chronic use. The subcutaneous segments can be straight or curved (swan-neck) and may have one or two cuffs. The intraperitoneal configuration may be straight or coiled. They are made of silicone rubber or polyurethane with side holes at the distal end. PD catheters can be placed by use of guidewire and dilators, peritoneoscopy, or, less frequently, laparoscopy. Infection rates are not affected by specific mode of placement. The silicone rubber or polyurethane surface elicits growth of squamous epithelium in the subcutaneous tunnel and at the catheter's entry and exit sites. The Dacron cuffs provoke a local inflammatory response resulting in the formation of fibrous and granulation tissues within 4 weeks. Both epithelial and fibrous tissues inhibit bacterial migration along the tunnel. Additionally, the fibrous tissue anchors the catheter, which may decrease infection rates. Examples of peritoneal catheters for chronic use include the straight or curled Tenckoff catheter, which is widely used in the United States, the swan-neck Missouri, and the Toronto Western Hospital catheters. It

TABLE 95.1 **VASCULAR ACCESS DEVICES FOR HEMODIALYSIS**

Temporary venous access (usually <2–3 weeks) for ESRD	Permanent access for ESRD
Single- or double-lumen venous catheter inserted over guidewire into the internal jugular vein, femoral vein[a], or less frequently subclavian vein	Arteriovenous fistula using autogenous saphenous vein or graft using PTFE
Silastin-Teflon shunt for CAVH or CAVHD	Dacron-cuffed double-lumen silicon catheter (Permcath) surgically inserted into the subclavian or internal jugular vein through a subcutaneous tunnel.
Twin wide-bore femoral catheter for CAVH or CAVHD	Scribner arteriovenous shunt (historical interest).

Abbreviations: ESRD = end-stage renal disease, PTFE = polytetrafluoroethylene; CAVH = continuous arteriovenous hemofiltration; CAVHD = continuous arteriovenous hemodialysis.
[a] Femoral vein placement is associated with high rate of infection, so it is usually removed by 72 hours.

has not been shown that any of these newer catheters provide any advantage over the Tenckoff design.

Infectious complications of vascular access devices

Chronic venous catheter use may be complicated by exit site infection, tunnel infection, and catheter-related blood stream infections (CRBSIs). Each dialysis session requires four tubing connections and thus presents a high risk for introduction of microbes through the hub and lumen of catheters. CRBSIs infection rate ranges from 3.8 to 6.6 episodes per 1,000 days for nontunneled catheters versus 1.1 to 5.5 episodes per 1,000 days for tunneled catheters, both of which are markedly higher than for A-V fistulas and grafts. The relative risk for infection-related hospitalization and death is increased two- to three-fold for catheter-dependent HD patients compared to those with A-V fistulas, and the relative risk for CRBIs is estimated to be 10 times higher. Local infections occur at the exit site or along the tunnel of percutaneously inserted catheters. The clinical presentations of exit site infection include pain, erythema, tenderness, induration, and purulent discharge within 2 cm of the site. Tunnel infections are associated with pain, erythema, tenderness, or induration involving the subcutaneous tract of the catheter. Infection of autologous A-V fistulas and prosthetic PTFE A-V grafts manifests as cellulitis, perifistular abscess, false aneurysm, draining sinus, and, in PTFE fistulas, bleeding when the graft's suture lines are involved. Fever, leukocytosis, or left shift in the differential leukocyte count may be present. Other clinical manifestations of CRBSIs may include hemodynamic instability, hypothermia, altered mental status, nausea and vomiting, malaise, and catheter dysfunction.

Both exit site and tunnel infections may be complicated by concomitant bacteremia, sepsis, and suppurative thrombophlebitis. Bacteremia may lead to metastatic foci of infection, including septic arthritis, septic pulmonary emboli, endocarditis, osteomyelitis, brain abscess, and splenic abscess. Bacteremia and sepsis often present without signs or symptoms of infection at the vascular access site. Catheter-related colonization without clinical manifestations of infection has been reported in up to 55% of HD catheters. Most CRBSIs arise from the lumen following bacterial colonization and biofilm formation. Eradication of bacteria in endoluminal biofilm requires very high concentrations of antibiotics (up to 1,000 times the concentrations needed to kill bacteria in solution). Systemic antibiotic therapy alone without catheter removal yields cure in only one-third of these CRBSIs.

Microbiology

A specific microbiologic diagnosis of access-related infection can frequently be made by Gram stain and culture of purulent material from the cannula exit site or with A-V fistulas from needle exit sites or abscess fluid. Blood cultures drawn from the vascular access device along with other peripheral sites (e.g., from vessels not intended to create future HD fistula, for example hand veins) should be obtained to aid in identification of the access site as the origin of infection if possible. If peripheral blood cultures cannot be obtained a blood culture drawn during dialysis from the HD circuit should be obtained. Access site origin of bacteremia is suggested if catheter blood cultures have an earlier time to positivity (at least 2 hours) compared to the time to positivity of blood cultures from another site. Other sources of bacteremia should be excluded. The organisms responsible for access device infection are shown in Table 95.2.

TABLE 95.2 **MICROBIOLOGY OF ACCESS DEVICE INFECTIONS**

Hemodialysis	Peritoneal dialysis
Staphylococcus aureus (40–80%)	*Staphylococcus epidermidis* and *S. aureus* (50%)
Other gram-positive bacteria (*S. epidermidis*, streptococci, including enterococci, diphtheroids), Gram-negative organisms (*Escherichia coli, Pseudomonas aeruginosa, Acinetobacter* spp., and other enteric gram-negative bacteria) (20–40%), polymicrobial (10-20%), fungi (<5%).	Other gram-positive bacteria (streptococci, including enterococci, diphtheroids) Gram-negative organisms (*E. coli, P. aeruginosa, Acinetobacter* spp., and other enteric gram-negative bacteria) occasionally fungi.

Percentages in parentheses are approximate proportional incidence from numerous references.

Therapy

Therapy is based on the results of cultures obtained from infected sites and blood. Initial management plans are shown in Table 95.3. Additionally, relative indications for removal of either catheter or A-V fistula or graft include suppurative thrombophlebitis; septicemia; bacteremia with metastatic foci of infection; infections caused by *Staphylococcus aureus, Pseudomonas aeruginosa*, mycobacteria, and fungi; lack of response to medical therapy within 48 to 72 hours; and recurrent infection in a catheter with the same pathogen. Tunnel infection requires removal of the catheter. Any associated fluid collections associated with an A-V fistula or graft should be drained. In the absence of exit site and tunnel infection, sepsis, or metastatic foci of infection, exchange of the catheter over a guidewire may be attempted. If there is no resolution of fever, bacteremia, or fungemia in 48 to 72 hours, the catheter should be removed. CRBSIs caused by coagulase-negative staphylococci (not *S. aureus* or fungi) seem very amenable to guidewire exchange. Intravenous (IV) vancomycin is often used in initial therapy for access device infections as methicillin-resistant *S. aureus* (MRSA) is the most common pathogen. The type of dialyzer, dialysis flow rate, patient size, and level of residual renal function can make vancomycin serum levels difficult to predict. Therapy should be initiated with a loading dose of 15 to 25 mg/kg of vancomycin given preferably after dialysis. The second dose, 5 to 10 mg/kg, is given after the next dialysis session. Before the third dialysis session, a predialysis serum vancomycin level should be done to determine the vancomycin dose to be given after the third dialysis session. A standard postdialysis dose can be started once target serum concentrations have been achieved. Other antimicrobials with good activity against staphylococci are alternatives to vancomycin. Linezolid or daptomycin can be used in patients with allergy to vancomycin or for organisms with reduced sensitivity to vancomycin. Daptomycin dosing is 6 mg/kg, every 48 hours (preferably after dialysis), and for linezolid, 600 mg by mouth or IV every 12 hours. Methicillin-sensitive staphylococci (MSSA) should be treated with cefazolin 20 mg/kg after each HD session rather than nafcillin, which requires administration every 6 hours and placement of a separate IV line. Duration of therapy is 3 to 4 weeks if there is no evidence of endocarditis or other metastatic focus of infection.

Fifteen to thirty percent of infections are caused by gram-negative bacilli. If gram-negative organisms are suspected, an aminoglycoside, cefepime, or aztreonam should be used in combination with the antibiotics noted earlier for suspected infection caused by gram-positive organisms; treatment duration is 2 weeks. Vancomycin-resistant enterococci (VRE) resistant to ampicillin should be treated with IV daptomycin 6 mg/kg every 48 hours (preferably after dialysis) or linezolid 600 mg by mouth or IV every 12 hours. The initial choice of antimicrobials should be influenced by the sensitivity of organisms prevalent in the patient's geographic region. Surveillance blood cultures should be obtained 1 week after completion of antimicrobial therapy if catheter is not removed.

When catheter salvage is attempted, antibiotic lock therapy (ALT) has been recommended in addition to parenteral antibiotics for uncomplicated catheter infections. The rationale for this is the known difficulty to eradicate bacteria in endoluminal biofilm with parenteral therapy. With ALT the catheter lumen is filled with several milliliters of antimicrobial solution at concentrations several fold higher than the minimum inhibitory concentration (MIC) of the antibiotic for the infecting organism in combination with 50 to 100 U of heparin. Vancomycin (1–5 mg/mL), gentamicin, or amikacin (1–2 mg/mL); ciprofloxacin (0.2 mg/mL); and cefazolin (5 mg/mL) have been used most often. The solution is allowed to remain (lock) in the catheter for as long as possible and changed every 48 hours. The same volume of solution is removed before the next dose of antibiotic or other medications or solutions are administered. The optimal duration of ALT is not known, but it has been used most frequently for 10 to 14 days after each dialysis session. ALT is also used to prevent CRBSIs. Well-designed, appropriately powered, randomized, controlled trials that show efficacy of ALT to treat CRBSIs are lacking.

Lock therapy rather than catheter removal should not be used when the patient has sepsis, septic thrombophlebitis, endocarditis, osteomyelitis, neutropenia, *S. aureus*, mycobacterial or fungal infection, or exit site or tunnel infections.

TABLE 95.3 **TREATMENT OF HEMODIALYSIS ACCESS-SITE INFECTIONS**

Type of infection	Therapy
Exit-site infection in a temporary access device with or without bacteremia[b]	Catheter removal and vancomycin,[a] 1 g IV; subsequent doses based on serum levels; aminoglycosides or broad-spectrum β-lactam antibiotics if gram-negative organisms suspected
Tunnel infection[b]	Catheter removal and antibiotics as above
Catheter-related sepsis	Catheter removal; empiric broad-spectrum antimicrobial therapy with vancomycin and gentamicin, 1.5 mg/kg IV in a single dose; subsequent antimicrobial therapy based on pathogen and sensitivity pattern
Suppurative thrombophlebitis	Catheter removal, antimicrobial therapy based on pathogen and sensitivity pattern; surgical consultation for possible exploratory venotomy
Arteriovenous fistula infection	Vancomycin and gentamicin as above; incision and drainage of abscess; ligation or removal of prosthetic arteriovenous fistulas if response to treatment is not prompt; surgical repair of a malfunctioning infected shunt may be possible

[a] Alternatives to vancomycin include daptomycin and linezolid (see text).
[b] 10–14 days is often used for exit and tunnel infections with catheter removal; if the catheter remains in place, 2–3 weeks of antimicrobials and repeat blood culture 1 week after antimicrobial therapy completed.

Infections associated with peritoneal dialysis catheters

There are two main types of chronic PD: continuous ambulatory PD (CAPD) and automated PD (APD). Whether PD catheter infections are less frequent with CAPD or APD remains unproved. Thirty percent of patient transfers from PD to HD are a consequence of catheter complications and peritonitis. PD catheter exit site and particularly tunnel infections may result in peritonitis and catheter loss. Peritonitis accounts for 15% to 35% of hospital admissions for patients on PD. Quality standards set an infection rate of <0.67 episodes per patient per year on dialysis, while reported rates from different centers vary from 0.24 to 1.66 episodes per patient per year. About 18% of episodes result in catheter removal; 3.5% result in death.

Exit site infections present with purulent discharge from the exit site, and erythema may or may not be present. Pericatheter erythema without purulent drainage may be an early sign of infection particularly if >14 mm in diameter around the exit site. A tunnel infection, which usually occurs in the presence of an exit site infection, can present with erythema, induration, tenderness, and abscess in the area between the catheter cuffs but is often occult, as demonstrated by ultrasonography. Ultrasonography will reveal an area of hypoechogenicity (fluid collection) between the tube or the cuff of the catheter and surrounding tissues. Indications for tunnel sonography include presence of exit site infection, recurrent peritonitis, and for assessment of the efficacy of therapy and prognosis of tunnel infections. A sonolucent area around the exit site >1 mm thick following therapy and the involvement of the proximal cuff are associated with poor outcome. A specific microbiologic diagnosis can be made by performing a Gram stain and culture of purulent exudate. The organisms responsible for PD catheter infections are shown in Table 95.2. *S. aureus* and *P. aeruginosa* exit site infections are frequently associated with concomitant tunnel infections and often result in catheter-associated peritonitis.

Therapy

Therapy is ultimately based on the results of microbiologic culture data. Initial management plans are shown in Table 95.4. Therapy should be continued until the exit site appears normal. Indications for catheter removal include peritonitis, bacteremia, sepsis, recurrent peritonitis with same pathogen, and infection caused by fungi. Relative indications for catheter removal are tunnel infections (particularly if there is no response to therapy noted on serial ultrasound examinations), involvement of the deep cuff (which often leads to peritonitis), chronic exit site infections (no cure after 2–4 weeks of therapy), and exit site infections associated with involvement of the superficial cuff as noted on ultrasound. Ultrasonographic evidence of tunnel involvement is associated with frequent catheter loss (50%) because of refractory or recurrent peritonitis. A ≥30% decrease in the size of the fluid collection after 2 weeks of therapy is often associated with catheter salvage. Prolonged courses of antimicrobial therapy, although sometimes necessary, should be avoided to decrease the chance of development of antimicrobial resistance. Infections with VRE and, more ominously, vancomycin-insensitive strains of *S. aureus* and *S. epidermidis* reported in dialysis patients receiving prolonged (months of) treatment make the judicious use of this drug imperative. In chronic exit site infections, adjunctive surgical therapy may help control infection and result in catheter salvage. Surgical procedures that have been used include cuff shaving (removal of the external cuff), debridement and curettage of the exit site and sinus tract, incision, and debridement along the subcutaneous tunnel with exteriorization of the superficial cuff and relocation of the exit site. It is not known which of these is most effective. Among gram-positive organisms, *S. aureus* is more

TABLE 95.4 **TREATMENT OF PERITONEAL DIALYSIS ACCESS DEVICE INFECTIONS**

Type of infection	Therapy
Exit site erythema without purulent discharge	Topical mupirocin, chlorhexidine, hydrogen peroxide, or povidone iodine BID; avoid mupirocin with polyurethane catheter
Gram-positive exit site infection	For MSSA dicloxacillin, 250–500 mg PO q6h, or cephalexin, 500 mg PO BID, or trimethoprim-sulfamethoxazole, 160/800 mg PO BID. Clindamycin may also be used. IV or IP route can be used. For methicillin-resistant staphylococci: vancomycin, IV 1 g every 3–5 days depending on blood levels. Rifampin, 600 mg PO qd, can be added for possible synergistic effect. Ultrasound to rule out tunnel or cuff involvement; 2–3 weeks of therapy generally recommended; shave external cuff and explore tunnel if infection persists; if this fails, catheter removal
Gram-negative exit site infection	*Pseudomonas aeruginosa* should be suspected pending culture results. Ciprofloxacin, 250 mg PO BID; not to be taken within 2 hours of phosphate binders or antacids; alteration of therapy based on culture and sensitivity results. If infection is slow to resolve or recurrent *Pseudomonas* infection add a second drug such as IP aminoglycoside, cefepime, piperacillin–tazobactam, or a carbapenem. Therapy should be continued for 2–3 weeks. Catheter removal if infection persists beyond 2–3 weeks; early catheter removal should be considered if *Pseudomonas* or *Stenotrophomonas* isolated.
Tunnel infection	Antimicrobials as for exit site infections with removal of catheter.

Abbreviations: BID = twice a day; MSSA = methicillin-sensitive *Staphylococcus aureus*; PO = orally; IV = intravenously; IP = intraperitoneally.

commonly associated with poor response to medical therapy, tunnel infections, and catheter loss.

Peritonitis

Peritonitis is a common complication of PD. Although the incidence varies from center to center, the average incidence is 1.3 episodes per patient per year. A modest reduction in the incidence of peritonitis has been achieved with use of Y-set transfer kit and twin-bag disconnect systems (particularly infections from skin flora). Bacteria gain entry to the peritoneum from the catheter, often after improper technique in connecting the transfer set to the dialysate bag or the catheter to the transfer set from the outside surface of the catheter; as a consequence of exit site or tunnel infection; or by hematogenous spread or from the bowel or pelvis. Clinical manifestations include abdominal pain, fever, chills, malaise, nausea, vomiting, constipation, or diarrhea with abdominal tenderness, rebound tenderness, and leukocytosis. The peritoneal fluid may appear cloudy and will almost always contain >100 white blood cells per cubic millimeter of fluid after a dwell time of at least 2 hours, with 50% or more polymorphonuclear leukocytes. In any suspected PD infection, including those that appear to be localized to the exit site, a Gram stain and culture and a cell count and differential of the peritoneal fluid should be done.

Microbiology

A single pathogen is usually involved. Polymicrobial infection suggests a perforated viscus or other intra-abdominal or pelvic pathologic process. Most cases of peritonitis (70%) are caused by gram-positive bacteria. Collectively, *S. aureus* and *S. epidermidis* account for almost 50% of infections. *P. aeruginosa* and enteric gram-negative bacilli constitute 20% to 30%, and fungi, mostly *Candida albicans*, <1% to 10%. Some 5% to 20% of cases are culture negative. Though infrequent, fungal peritonitis is associated with significant morbidity and mortality, with death rates as high as 25%. Up to 40% of patients cannot resume PD because of damage to the peritoneal membrane that prevents effective dialysis. Mycobacterial peritonitis may be caused by *Mycobacterium tuberculosis* or non-tuberculous mycobacteria.

Therapy

Antibiotics may be given by the IV, oral, or intraperitoneal (IP) route if compatible with PD fluid. The IP route is preferred because of its convenience. Fourteen days of therapy is usually adequate. Three weeks of therapy is recommended for *S. aureus*, *Enterococcus*, *Pseudomonas/Stenotrophomonas* species, or polymicrobial peritonitis. There is no therapeutic advantage to IV therapy for peritonitis. Helpful information for the initial choice of antimicrobials includes peritoneal fluid Gram stain results, history of microbe-specific peritonitis, coexistent exit site infection, and intra-abdominal pathology. If the Gram stain does not show gram-positive bacteria or gram-negative bacteria or is unavailable, empiric therapy should be initiated with vancomycin and gentamicin.

After 24 to 48 hours, 70% to 90% of dialysate fluid cultures will yield a specific pathogen, and therapy should be modified accordingly. For *S. aureus* or *S. epidermidis* sensitive to nafcillin, this may be given at 125 mg/L in each exchange or a first-generation cephalosporin or clindamycin may be used. Addition of rifampin, 600 mg/d orally, can be considered for patients responding slowly to the initial regimen but should not be used for more than a week as resistance to this drug often develops with prolonged use. In areas where tuberculosis is endemic, the use of rifampin to treat *S. aureus* peritonitis should be avoided. If the patient does not improve within 5 days (refractory peritonitis), the catheter should be removed. Other indications for catheter removal include relapsing peritonitis (recurrence of peritonitis with same pathogen within 4 weeks), fungal peritonitis, and refractory exit site and tunnel infection. For MRSA, vancomycin, 15 to 30 mg/kg IP every 5 to 7 days for CAPD, and for PD a 30 mg/kg loading dose followed by 15 mg/kg every 3 to 5 days. In both, achieving a trough level of >15 μg/mL is recommended. If the patient is not responding to vancomycin, consider substituting linezolid 600 mg IV or orally every 12 hours; IP dosing is not recommended as linezolid is not stable in PD fluid, or daptomycin can be used, 6 to 8 mg/kg every 48 hours especially if the vancomycin MIC is >1 μg/mL. If the organism is sensitive, clindamycin, 300 mg/L loading dose and then 150 mg/L maintenance can be used. For enterococci sensitive to ampicillin, give 125 mg/L IP in each exchange and consider continuing the aminoglycoside although is difficult to do so as these antibiotics cannot be given by IP concomitantly. Oral amoxicillin may also be considered. Recent International Society for Peritoneal Dialysis (ISPD) guidelines recommend using vancomycin, 2 g IP (per week) because of concerns regarding the stability and activity of ampicillin in PD fluid. Vancomycin is recommended for patients with penicillin allergy. Treatment of VRE depends on the antimicrobial sensitivities of the specific organism. If VRE is not ampicillin-susceptible, give linezolid, 600 mg IV or orally every 12 hours, or daptomycin, 4 mg/kg (6–8 mg/kg if bacteremia present) every 48 hours, preferably after dialysis. Because enterococci are part of the intestinal flora, intra-abdominal pathology should be considered. For other gram-positive organisms, therapy should be based on antibiotic sensitivity results. For gram-negative organisms other than *P. aeruginosa* and *Stenotrophomonas maltophilia*, a first-generation cephalosporin may suffice. If the microbe is resistant to cefazolin, the choice of another cephalosporin should be based on sensitivity testing. For *P. aeruginosa* or *S. maltophilia*, consider use of two agents (one being an aminoglycoside) chosen based on sensitivity testing results and continue for at least 3 weeks. However, eighth-nerve toxicity may complicate aminoglycoside use, particularly after 2 to 3 weeks of therapy. If the infection is catheter-related, the catheter should be removed with continued administration of antibiotics for 1 week.

Polymicrobial or anaerobic infections suggest a perforated viscus, and therefore surgical consultation is required. Vancomycin and an aminoglycoside should be continued or changed to a cephalosporin based on sensitivity testing, with addition of metronidazole, 500 mg IV or orally every 8 hours.

If yeast are identified on Gram stain, fluconazole, 200 mg orally or IP daily should be used. The catheter should be promptly removed

and treatment continued for at least 10 more days. Voriconazole, caspofungin, and amphotericin B are alternatives to fluconazole for patients who do not respond or who have organisms insensitive or less sensitive to fluconazole such as *Candida krusei* and *C. glabrata*. After catheter removal, infections with filamentous fungi should be treated with amphotericin B or voriconazole.

Most patients with peritonitis demonstrate significant clinical improvement within 2 to 4 days. Patients who do not respond to therapy should be re-evaluated. Peritoneal fluid should be obtained for cell count and differential, Gram stain, and culture. In addition, intra-abdominal or gynecologic pathology requiring surgical intervention, unusual pathogens (fungi, mycobacteria), and sclerosing peritonitis must be considered. The catheter should be removed and cultures obtained for patients whose original cultures are negative but who remain symptomatic after 2 to 4 days.

Less common pathogens

There are conflicting data regarding the intrinsic risk of dialysis patients for developing tuberculosis. It is likely that any predisposition of patients to pulmonary tuberculosis is related more to the prevalence of tuberculosis in the community than to host factors. However, there is a higher incidence of extrapulmonary tuberculosis in patients receiving PD. Treatment is the same as for patients without ESRD, except that the dosing of some agents must be adjusted for renal failure and others should be avoided. Isoniazid is given at 150 mg/d orally with a supplemental dose after dialysis. Rifampin requires no dosage adjustment. The dosage of ethambutol is 5 mg/kg/d orally with a supplemental dose after dialysis. Some believe that pyrazinamide use should be avoided if possible; ethionamide is given at 250 to 500 mg/d orally.

Listeria monocytogenes septicemia, meningitis, and endocarditis have been rarely described in patients with ESRD, usually as a complication of iron overload or during immunosuppressive therapy. Yersiniosis complicating iron overload has also been reported. Disseminated or rhinocerebral phycomycosis in nondiabetic patients receiving hemodialysis may be related to deferoxamine use. Treatment includes amphotericin B, posaconazole, and surgical debridement of infected sites.

Suggested reading

Allon M. Dialysis catheter-related bacteremia: Treatment and prophylaxis. *Am J Kidney Dis*. 2004;44:779–791.

Goldman M, Vanherweghem JL. Bacterial infections in chronic hemodialysis patients: Epidemiologic and pathophysiologic aspects. *Adv Nephrol*. 1990;19:315–332.

Hansson JH, Watnick S. Update on peritoneal dialysis: Core curriculum 2016. *Am J Kidney Dis*. 2016:67(1):151–164.

Heintz BH, Matzke GR, Drager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009;29 (5):562–577.

Li PK-T, Szeto CC, Piraino B, et al. Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int*. 2010;30:393–423.

Mermel LA, Allon M, Bouza E, et al. Guidelines for diagnosis and management of intravascular catheter-related infection. *Clin Infect Dis*. 2009;49:1–45.

Quittnat Pelletier F, Joarder M, Poutanen SM, et al. Evaluating approaches for the diagnosis of hemodialysis catheter–related bloodstream infections. *Clin J Am Soc Nephrol*. 2016;11:847–854.

United States Renal Data System. *2018 USRDS annual data report: Epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018.

Vychytil A, Lorenz M, Schneider B, et al. New criteria for management of catheter infections in peritoneal dialysis patients using ultrasonography. *J Am Soc Nephrol*. 1998;9:290–296.

96

Asplenia-associated Infections

Larry I. Lutwick

What more thou didst deserve than in thy name,
And free thee from the scandal of such senses
As in the rancor of unhappy spleen
Measure thy course of life, with false pretenses
Comparing by thy death what thou hast been.

– "A Funeral Elegy," W. Shakespeare, 1612

Introduction

The human spleen (Figure 96.1) (in German: *milz*; also, *ohnemilz*: "without a spleen, asplenic") is an organ that at one point had been deemed as nonessential as the appendix and traditionally had been deemed the source of anger and melancholy thoughts. Thus, the expression "venting one's spleen" is to rid oneself of anger caused by someone or something by attacking someone or something other than the source of that anger. A similar therapeutic process, laughter ("If you desire the spleen, and will laugh yourself into stitches, follow me," Shakespeare [Figure 96.2], *Twelfth Night*, Act III, Scene 2), is also linked to the spleen.

It seems ironic, therefore, that these concepts reflect that this collection of immune cells in the left upper quadrant of the abdomen actually do appear to function as a way of cleansing the body. Indeed, Shakespeare's "unhappy spleen," one that has been removed from residence (by splenectomy) or whose function is embarrassed by one or another disease (hyposplenism), predisposes (by not appropriately performing its cleansing function) its former owner to an infectious disease process with substantial morbidity and mortality by becoming *ohnemilz*.

This disease, overwhelming postsplenectomy infection (OPSI), also referred to as postsplenectomy sepsis (PSS), is one of a group of infectious disease processes, such as bacterial meningitis and meningococcemia, for which diagnosis and therapeutic intervention are required immediately to minimize disease impact. Using Ben Franklin's (Figure 96.3) "ounce of prevention is worth a pound of cure" concept, prevention as well as therapeutic intervention is an important part of any discussion of OPSI.

Risks and timing of OPSI

The individual risk of OPSI depends on the cause of splenectomy as well as the time after the procedure. Overall, the lifetime risk of 1% to 2% is estimated related to trauma or idiopathic thrombocytopenic purpura (ITP), 3% for spherocytosis, 6% for Hodgkin's disease and portal hypertension, and as high as 11% for thalassemia. Although some asplenic conditions clearly have a lower risk of OPSI, if OPSI, develops the

FIGURE 96.1 The spleen.

morbidity and mortality are not lower in these cohorts. About 5% to 6% of total OPSI cases occur in individuals with poorly functioning spleens. A partial list of diseases associated with hyposplenism can be found in Box 96.1.

No ideal assay is available to measure adequate splenic function. The presence of Howell–Jolly bodies (nuclear remnants in

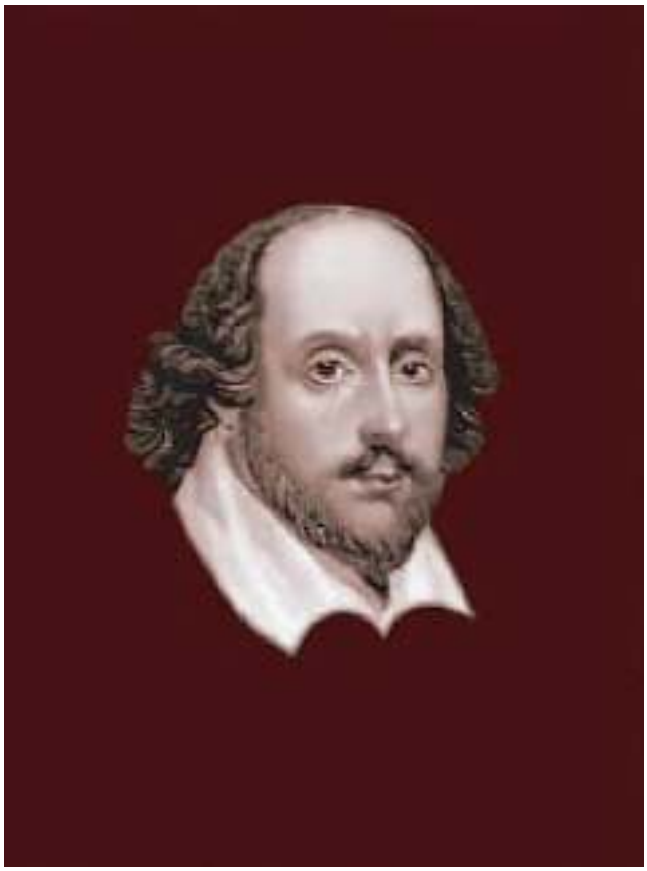

FIGURE 96.2 William Shakespeare.

FIGURE 96.3 Benjamin Franklin.

BOX 96.1

Common causes of hyposplenism

Blood diseases
- Primary thrombocytosis
- Sickle cell hemoglobinopathies

Gastrointestinal diseases
- Celiac disease
- Ulcerative colitis

Splenic infiltration
- Amyloidosis
- Sarcoidosis
- Malignant infiltration

Vasculitic diseases
- Autoimmune thyroiditis
- Lupus erythematosus
- Rheumatoid disease

Others
- Ethanolism
- Long-term parenteral nutrition
- Spleen irradiation
- Splenic vein thrombosis

circulating red blood cells [RBCs]) is too insensitive. Quantification of red cells containing "pocks" (actually vacuoles containing hemoglobin found in older RBCs) as seen by interference microscopy, however, appears to be a valuable tool.

About 50% of cases of OPSI following a splenectomy occur within 2 years of the event and about 75% within 5 years. It is important to know, however, that 2% to 3% of cases occur 20 years or longer after the event, and there have been reports of OPSI four decades after the onset of *ohnemilz*.

Presentation and diagnosis

The classical presentation of OPSI is one that often begins with an alert, relatively nontoxic patient who might walk into an emergency department complaining of fever and chills associated with myalgias and diarrhea. The individual deteriorates quickly, developing lactic acidosis due to organ hypoperfusion, disseminated intravascular coagulation (DIC), and multiorgan failure. This gastroenteritis-like presentation can, but should not, divert attention away from OPSI in the at-risk individual.

The progression to septic shock and death in these individuals can happen within hours of initial presentation. Overall mortality rates are 50% to 60%, with a majority of the deaths within 24 hours. Encouragingly, relatively recent pediatric data suggest that increased survival rates can result from prompt recognition, and overall incidence can decrease with preventative measures. Purpura fulminans (Figure 96.4) has been associated with OPSI as well as with meningococcemia. It causes considerable endothelial injury, resulting in arterial thrombosis and gangrene of one or multiple extremities. If the affected individual survives, multiple extremity amputations can result.

Prompt diagnosis requires knowledge of the issue with spleen function or absence in an appropriately ill patient. Confirmation requires positive blood cultures for the bacterial etiology. Blood cultures are often positive within 6 to 8 hours due to the high initial bacteremia, which is as much as 10,000 times the organism load of a more routine bacteremia. Because of this massive bacteremia, organisms can be found in the buffy coat of the peripheral blood and sometimes on a standard peripheral smear. It should be noted that Wright stain, routinely used on peripheral blood smears, will stain all bacteria blue, even the usual "red" organisms on Gram stain of gram-negative bacteria.

Pathogens

Streptococcus pneumoniae

Pneumococci are without question the most canonical cause of OPSI. This α-hemolytic, polysaccharide-encapsulated, gram-positive diplococcal bacterium has a distinctive morphology on staining, a so-called lancet shape (Figure 96.5). Its capsule is a well-recognized virulence factor, interfering with phagocytosis by preventing effective C3b opsonization of the bacterial cells. Overall, *S. pneumoniae* is involved in 50% to 90% of OPSI cases, with the percentage of pneumococcal OPSI cases tending to increase with age. In series that include single case reports, pneumococci are often underrepresented because many case reports relate to less common causes of infection in asplenic hosts.

No single type or group of the 90 different capsular types appears to be more associated with OPSI than other forms of invasive pneumococcal disease. With the use of pneumococcal polysaccharide vaccination, however, especially in places with universal immunization using the newer 13-valent conjugated product, a shift of serotypes can occur.

It is important to note that antimicrobial drug resistance has become increasingly prevalent. Some isolates are only less sensitive to penicillin (particularly relevant in bacterial meningitis), some are fully resistant to penicillin, and some may be resistant to penicillin as well as the extended-spectrum cephalosporins such as ceftriaxone. The local epidemiology of pneumococcal resistance must be considered in the empiric treatment of OPSI. High levels of penicillin resistance are reported in Spain, parts of eastern Europe, and South Africa (Figure 96.6). In the United States, resistance is more prevalent in

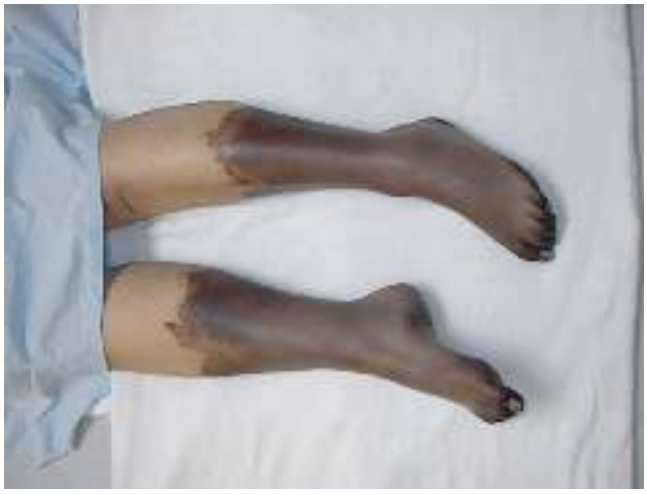

FIGURE 96.4 Purpura fulminans.

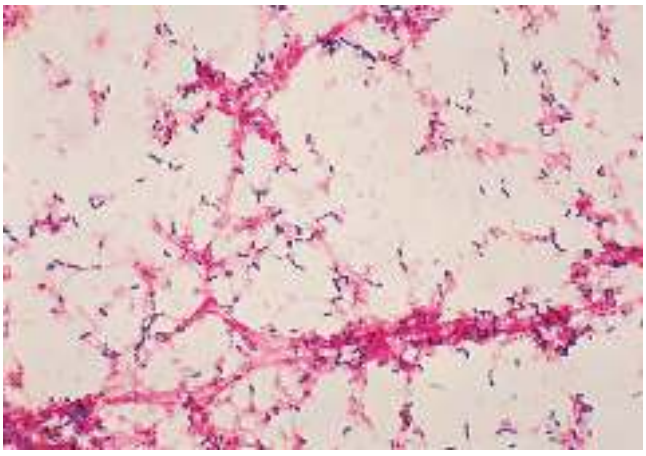

FIGURE 96.5 Pneumococcus.

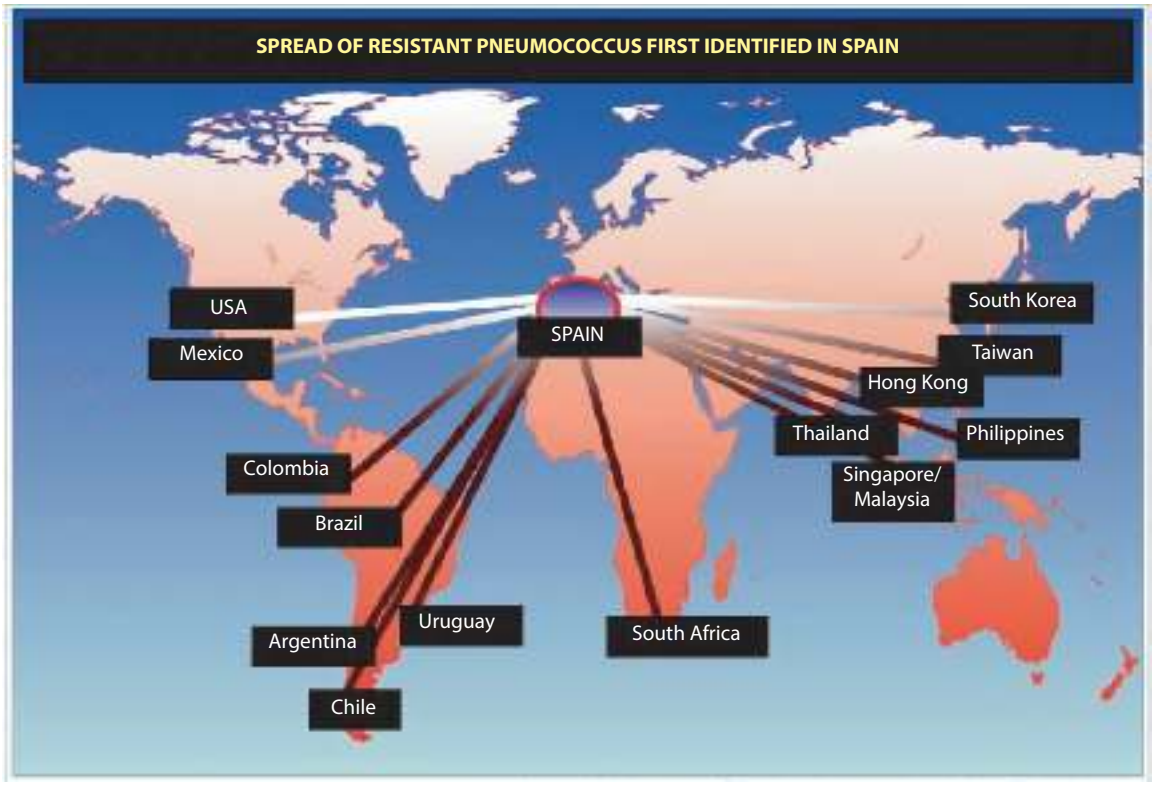

FIGURE 96.6 Spread of resistant pneumococcus.

Alaska and the South but can be found anywhere. It is yet to be determined whether changes in serotypes in the post-conjugate vaccine era will in the long run increase or decrease antimicrobial resistance.

Haemophilus influenzae type b

Although studies report the frequency of *Haemophilus influenzae* type b (Hib)-associated OPSI to be about 10 times lower than that of pneumococcus, Hib is classically the second most common cause of OPSI. It has primarily affected children <15 years. *H. influenzae* is a small polysaccharide-encapsulated pleomorphic gram-negative coccobacillus (Figure 96.7) that can be confused with pneumococcus if the Gram stain technique is poor (over- or underdecolorized). Like pneumococcus, the type b capsule is a major virulence factor for invasive disease.

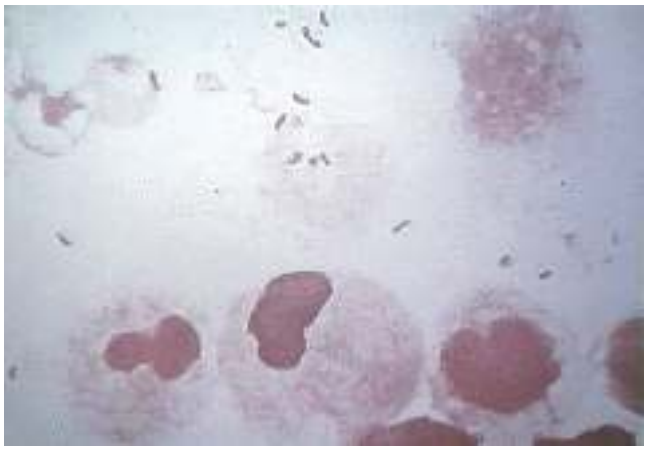

FIGURE 96.7 *Haemophilus influenzae*.

The incidence of invasive Hib disease (and correspondingly of Hib-related OPSI) has dramatically decreased because of the use of the conjugated Hib vaccine. Neither nontypeable strains nor non-b capsular organisms have been found to be significant causes of OPSI, although nontypeable organisms may cause usually non-invasive infection in the human respiratory tract. When choosing antimicrobial therapy, it is important to know that many *H. influenzae* strains produce β-lactamases.

Other bacterial organisms

Capnocytophaga canimorsus, a fastidious gram-negative rod formerly referred to as CDC group DF-2, is usually transmitted to humans from dog bites. Human infection with this part of canine and feline oral normal flora is relatively mild when occurring in the eusplenic host. Of reported severe cases, however, predisposing conditions can be identified in 80%, primarily asplenia or a hyposplenic condition. The presence of an eschar at the bite site 1 to 7 days after the bite or observation of gram-negative bacilli in the blood buffy coat or peripheral smear is highly suggestive of *C. canimorsus* infection.

The organism does not have a capsule as the pneumococcus and Hib do but appears to escape from immune surveillance by blocking the typical proinflammatory response of human macrophages, perhaps related to the inability of Toll-like receptor 4 to respond to the organism. β-lactamase activity can be seen in 30% of strains.

Although *Neisseria meningitidis* (the meningococcus) is often cited as the third most common cause of OPSI and does occur in the asplenic host, it does not appear that meningococcemia is either more severe or more frequent than in eusplenic individuals. Because meningococci are encapsulated and can cause quite severe invasive infection, most authorities include preventative strategies for it in dealing with the noneusplenic person.

Salmonellosis has been associated with, but does not play a large role in, OPSI. Most reports are associated with illnesses where cell-mediated immunity defects from either the illness or its treatment predispose to salmonellosis, as in children with sickle cell anemia. Sickle cell disease, however, does cause hyposplenism, as previously noted.

Intraerythrocytic parasitemias

The human spleen plays a key role in malarial parasite clearance by removal of intraerythrocytic parasites from the RBC without red cell destruction (pitting). Because pitting is absent or much diminished in the splenectomized or hyposplenic person, removal of malarial parasites (either killed by medication or viable) is delayed and disease may falsely appear to be more severe. During antimalarial therapy, delayed clearance in the noneusplenic does not, therefore, necessarily reflect antimalarial resistance. In partially malaria-immune individuals, the course of *Plasmodium falciparum* infection is not much changed by asplenia, but more fever and higher levels of parasitemia occur and there seems to be a risk for more symptomatic malaria episodes. How this relates to the nonimmune splenectomized person traveling into a malarious area is not clear, but appropriate prophylaxis is indicated regardless of splenic function.

In babesiosis, however, splenectomized patients are clearly at higher risk for illness with much higher levels of parasitemia (Figure 96.8) due to the lack of a spleen. This high parasitemia is associated with significant hemolysis. In the United States, infections have been reported from many states, but the most endemic areas are the islands off the coast of Massachusetts (including Nantucket and Martha's Vineyard) and New York (including eastern and south-central Long Island, Shelter Island, and Fire Island) and in Connecticut. Many of the initial individuals diagnosed with babesiosis were asplenic prior to the recognition that mild and even asymptomatic infections with babesiosis may occur in areas of endemicity for this tick-borne organism. These noneusplenic individuals are responsible for most cases of morbidity and mortality related to babesiosis. These individuals may also acquire the infection by blood transfusion without travel into a highly endemic area because their underlying diseases associated with noneusplenism may cause the need for transfusion.

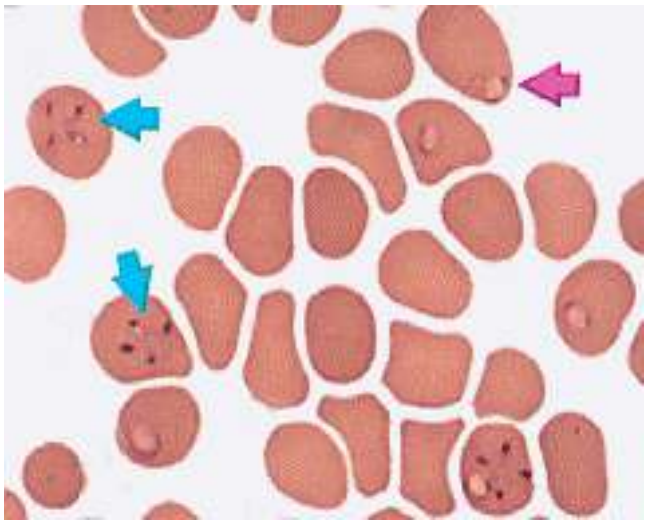

FIGURE 96.8 Babesiosis.

Therapeutic interventions

Active intervention early on in the form of antimicrobial therapy administration is crucial to patient survival. For this reason, two modalities should be utilized in the prehospital stage of this process, both aimed at shortening the time to first dose of antimicrobial treatment. For these to be relevant, the asplenic or hyposplenic person has to be aware of the condition and communicate this knowledge to the physician involved. One modality often mentioned in reviews of this infection is having the asplenic person fill, keep current, and carry with him or her a prescription for an appropriate orally administered antimicrobial agent (Box 96.2). The drug should be taken, ideally after talking with a physician by telephone, if a febrile

BOX 96.2

Suggested regimens for initial extramural oral therapy[a]

Ampicillin or amoxicillin
- Dose: 2 g
- Contraindicated in β-lactam hypersensitivity
- Not active against β-lactamase-producing organisms
- Not active against penicillin-resistant pneumococci

Amoxicillin-clavulanate
- Dose: Two 875 mg amoxicillin/125 mg clavunate tablets
- Contraindicated in β-lactam hypersensitivity

Trimethoprim-sulfamethoxazole
- Dose: Two 800 mg sulfamethoxazole/160 mg trimethoprim tablets
- Contraindicated in sulfonamide hypersensitivity
- Inconsistent activity for pencilling-resistant pneumococci

Clarithromycin or azithromycin
- Dose: 2 g
- Inconsistent activity for pencilling-resistant pneumococci

Moxifloxacin
- Dose: 800 mg

[a] Minimal to no data on any of these regimens in overwhelming postsplenectomy infection.

BOX 96.3

Treatment options for suspected bacterial overwhelming postsplenectomy infection (OPSI)

Rationale: Adequate coverage for *S. pneumoniae* and *H. influenzae*
Ceftriaxone 2 g IV q12h
Alternative in severe β-lactam allergy
Moxifloxacin 400 mg IV q24h
Plus
Vancomycin 1 g IV q12h
Alternatives in vancomycin-intolerant patients
Moxifloxacin 400 mg intravenously q24h

illness develops, especially with prostration while the person is coming to seek healthcare. It is not a substitute for medical care. The second prehospital modality comes into play when a potential OPSI case presents at a physician's office. Similar to suggestions for a patient with suspected bacterial meningitis, if available, a dose of an antimicrobial such as ceftriaxone should be given intravenously or intramuscularly. This should be done even if blood cultures cannot be performed. For obvious reasons, no controlled trials of these methods of early treatment have been or will be done.

Upon emergency department arrival, it is imperative for the patient to impart the appropriate information regarding the spleen and the new symptoms at once to facilitate immediate triage. Specific therapy (Box 96.3) could consist of an extended cephalosporin such as ceftriaxone, a β-lactam/β-lactamase inhibitor, a newer fluoroquinolone, and/or vancomycin. The therapy must afford adequate activity against the encapsulated pathogens commonly implicated in OPSI. Choice of initial antimicrobial therapy should be guided by the community antimicrobial resistance profile.

In addition to antimicrobial therapy, aggressive cardiovascular and hemodynamic support is given as needed. Whether adjuvant immunologic interventions decrease morbidity and/or mortality is not known, but, in animal models, granulocyte-stimulating factor and intravenous immunoglobulin have been studied.

If an intraerythrocytic protozoan is involved, therapy should be directed in that direction. Box 96.4 lists some of the current therapies for falciparum malaria and babesiosis. Response to therapy for babesiosis in the noneusplenic person, however, clinically appears to be much slower, independent of the delayed clearance of parasitized erythrocytes.

BOX 96.4

Treatment options for intraerythrocytic protozoa in overwhelming postsplenectomy infection (OPSI)

Babesiosis
(The usual adult dose treatment is for 1 week, but consider longer lengths of treatment in asplenic patients with significant hemolysis. Exchange transfusions have been used as an adjunct in severe cases.)
Atovaquone 750 mg PO q12h
Plus
Azithromycin 500 mg PO on day 1 then 250 mg PO per day
Or
Clindamycin 600 mg PO q8h
Plus
Quinine 650 mg PO q8h

Falciparum malaria
(Most strains except from parts of Central America, the Caribbean, and the Middle East should be considered to be chloroquine-resistant and that antimalarial should not be used except with cases from known "sensitive" areas.)
Usual adult dose oral therapies (for parenteral treatment of severe falciparum malaria, consult WHO reference)
Atovaquone-proguanil fixed combination
4 tablets daily for 3 d
Or
Artemether-lumefantrine fixed combination[a]
4 tablets BID for 3 d
Or
Quinine 650 mg q8h for 7 d
Plus
Doxycycline 200 mg daily for 7 d
Or
Clindamycin 600 mg 2× daily for 7 d

[a] Not US Food and Drug Administration (FDA) approved.

Abbreviations: OPSI = overwhelming postsplenectomy infection; PO = orally; WHO = World Health Organization.

Prevention

Education

The importance of patient (and the respective family) education cannot be overemphasized. A philosopher once reflected that the half-life of truth is 8 months, underscoring the importance of physicians to continue to remind asplenic or hyposplenic patients and/or their families to tell any physician involved in their medical care of the splenic defect. A medical alert bracelet or necklace could also assist in this task. Early knowledge of asplenia can prompt earlier treatment of presumptive OPSI.

The widespread knowledge of OPSI has also changed the landscape of surgical splenectomy. Whenever possible, the organ or part of it is retained in an effort to provide adequate organ function. In trauma situations, repair instead of removal is preferred. Splenectomy, however, can still be required in the management of a variety of disease states.

Vaccination

The current Centers for Disease Control and Prevention (CDC) guidelines recommend administering the 23-valent unconjugated pneumococcal polysaccharide vaccine (PPV23) to all children >2

years with anatomic or functional asplenia at least 8 weeks after the last 13-valent conjugated pneumococcal vaccine (PCV13). A second dose 5 years later is then suggested. In asplenic adults who have been previously immunized with PPV23, a dose of PCV13 should be given 1 or more years after the last PPV23. If no PPV23 had been given, a single dose of PCV13 should be given followed by a PPV23 at least 8 weeks later. Another PPV23 can be given 5 years later and again at age 65. It is not unreasonable to consider more frequent revaccination with these vaccines. Additional repeated immunizations with this vaccine are not recommended by the CDC, probably due to the lack of adequate safety studies (Box 96.5). A number of case reports have surfaced documenting occurrence of OPSI with vaccine-related strains of pneumococci sepsis despite administration of the pneumococcal polysaccharide vaccine. This may be related to lack of an adequate response to the polysaccharide of the infecting type.

The quadrivalent meningococcal A, C, Y and W-135 polysaccharide vaccine, the monovalent type B outer membrane vaccine and the Hib conjugated vaccines are also part of CDC recommendations for asplenic adults. The reader is referred to the most recent CDC guidelines for the most up-to-date immunization advice.

Hyposplenia or functional asplenia is not a contraindication to receiving any otherwise indicated live, attenuated vaccines such as measles, mumps, and rubella (MMR), varicella-zoster virus (either for varicella or zoster), or yellow fever. Influenza vaccine should be administered yearly.

Antimicrobial prophylaxis

Prophylactic antimicrobial therapy after splenectomy has been advised by some experts, but this has primarily been advocated in the pediatric population. Children are usually started on penicillin prophylaxis for the first 2 years, and studies conducted in sickle cell disease patients have demonstrated significant reduction in the incidence of pneumococcal sepsis. Sustained lifelong prophylaxis has been advocated by some authorities, but the issues of noncompliance and selection of resistant strains along with adverse drug reactions have prevented this from becoming the rule. There are no controlled trials to recommend lifelong antimicrobial prophylaxis in asplenic adults; however, the practice should be strongly considered if a patient has had an episode of OPSI.

BOX 96.5

Bacterial vaccines to consider in patients with asplenia/hyposplenia

23-valent unconjugated pneumococcal vaccine
Contains types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F
13-valent conjugated pneumococcal vaccinea
Contains types 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
Conjugated H. influenzae vaccine
Contains type b
Quadrivalent meningococcal vaccine
Contains types A, C, Y, and W-135a
Monovalent outer membrane protein meningococcal vaccine
ContainsType B

[a] Not formally approved by the US Food and Drug Administration (FDA) for adults <65 years of age.

Acknowledgments

This chapter includes contributions from Amy Wecker and Monica Panwar.

Suggested reading

Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP) immunization schedules for persons aged through 18 years and adults 19 years and older—United States, 2021. *MMWR Morb Mortal Weekly Rep*. 2021;70:189–192, 193–196.

Childers BJ, Cobanov B. Acute infectious purpura fulminans: A 15-year review of 28 consecutive cases. *Am Surg*. 2003;69:86–90.

Chong J, Jones P, Spelman D, Leder K, Cheng AC. Overwhelming post-splenectomy sepsis in patients with asplenia and hyposplenia: A retrospective cohort study. *Epidemiol Infect*. 2017;145:397–400.

Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia: A randomized trial. *N Engl J Med*. 1986;314:1593–1599.

Holdsworth RJ, Irving AD, Cuschieri A. Post-splenectomy sepsis and its mortality rate: Actual versus perceived risks. *Br J Surg*. 1991;78:1031–1038.

Jugenburg M, Haddock G, Freedman MH, et al. The morbidity and mortality of pediatric splenectomy: does prophylaxis make a difference? *J Pediatr Surg*. 1999;34:1064–1067.

Molrine DC, Silber GR, Samra Y, et al. Normal IgG and impaired IgM responses to polysaccharide vaccines in asplenic patients. *J Infect Dis*. 1999;179:513–517.

O'Neal HR, Niven AS, Karam GH. Critical illness in patients with asplenia. *Chest*. 2016;150:1394–1402.

Styrt B. Infection associated with asplenia: risks, mechanisms, and prevention. *Am J Med*. 1990;88(5N):33N–42N.

Vernacchio L, Neufeld EJ, MacDonald K, et al. Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell anemia. *J Pediatr*. 1998;133: 275–278.

Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med*. 2003;348:1737–1746.

World Health Organization. *Guidelines for the treatment of malaria*. Geneva: World Health Organization; 2006.

Section 12

HIV

97

HIV infection

Initial evaluation and monitoring

Aaron E. Glatt, Andréa Sciberras, and Steven M. Weiss

Infection with human immunodeficiency virus (HIV) can be devastating news to newly diagnosed patients. However, with earlier recognition of the infection and the advent of simple one-pill combination antiretroviral regimens, HIV is now considered a chronic disease process, and those infected and treated can expect a relatively normal life and life expectancy.

More than 36 million people worldwide, and more than 1 million in the United States are living with HIV infection. Primary care physicians need to be familiar with the history, clinical presentation, complications, early detection, and treatment of HIV infection, especially during the early stages of the infection. Both the US Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force (USPSTF) made a Grade A recommendation to screen all patients (18–65 years) for HIV in 2006. As a result, primary care physicians will care for a growing population of newly identified, relatively asymptomatic HIV patients, and they will need to be familiar with and adhere to the latest recommendations for early treatment and prevention of transmission.

HIV clinical presentation

Patients can present with different complaints depending on the length of time they have been infected with HIV. Approximately 2 to 6 weeks after acquisition of HIV infection, patients may present with vague complaints consisting of upper respiratory–like illness, fatigue, low-grade fevers, rash, nausea, and/or diarrhea. This "seroconversion illness" may resemble mononucleosis or influenza. However, many patients with newly acquired infection are completely asymptomatic. During the initial presentation, it is important for clinicians to establish the route and risks for acquisition of HIV with open, nonjudgmental questions. This is essential for reducing further transmission of the virus, as well as recognizing any complications. Once the seroconversion illness, when present, resolves, patients enter a mostly asymptomatic latent stage which can last for 10 years or more without treatment and, with proper treatment, can last their entire lifetime. However, if their disease status worsens, the astute physician will first begin to see class B symptoms (see Box 97.1), which will then be followed by opportunistic infections which then signify progression to clinical AIDS (see Box 97.2).

BOX 97.1

Category B conditions in HIV-infected individuals

Candidiasis, oropharyngeal
Candidiasis, vulvovaginal; persistent, frequent or poorly responsive to therapy
Cervical dysplasia (moderate or severe)
Cervical carcinoma *in situ*
Constitutional symptoms, such as fever (38.5°C/101°F) or diarrhea lasting >1 month
Hairy leukoplakia, oral
Herpes zoster (shingles), involving at least 2 distinct episodes or >1 dermatome
Idiopathic thrombocytopenia purpura
Listeriosis
Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
Peripheral neuropathy
Bacillary angiomatosis

BOX 97.2

Category C/AIDS-defining illnesses[a]

Candidiasis of the trachea, bronchi, or lungs
Candidiasis of the esophagus
Cervical carcinoma, invasive
Coccidioidomycosis, disseminated or extra pulmonary
Cryptococcosis, extra pulmonary
Cryptosporidiosis, chronic intestinal (>1 month duration)
Cytomegalovirus (CMV) disease (other than liver, spleen, nodes), CMV retinitis (with loss of vision)
Encephalopathy; HIV related
Herpes simplex: Chronic ulcer(s) (>1 month duration) or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extra pulmonary
Isosporiasis, chronic intestinal (>1 month duration)
Kaposi's sarcoma
Lymphoma, primary brain
Lymphoma (immunoblastic or equivalent term)
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extra pulmonary
Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
Mycobacterium, other species or unidentified species disseminated or extrapulmonary
Pneumocystis jiroveci (*carinii*) pneumonia
Progressive multifocal leukoencephalopathy
Pneumonia, recurrent (not PJP, 3 or more times in 1 year)
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome due to HIV
CD4 count <200

[a] A patient with any one of these conditions is defined as an AIDS patient regardless of CD4 T-cell count.

History and physical examination

HIV infection causes and predisposes to multiple organ diseases. Evaluation should be systematic and comprehensive. After a detailed chief complaint and history of present illness are obtained, a thorough review of past medical, surgical, and social histories; medications; allergies; and systems on all patients is necessary. Obtaining a history of all past antiretroviral therapy (ART) regiments is particularly useful and important. Detailed physical examination, with careful documentation of baseline observations, is essential for early recognition of new problems. It is important to recognize that ART may significantly alter the natural history of HIV infection. In addition, ART may be associated with significant side effects such as lipodystrophy, lipoatrophy, gastrointestinal issues, and other signs and symptoms. However, the majority of these side effects are from older medication regimens that are now used less frequently.

General

Fever, weight loss, malaise, fatigue, shaking chills, night sweats, and loss of appetite can be initial findings of significant illness. They are less common in early HIV infection. They may signify worsening immunosuppression or an acute secondary infection. Weight and nutritional assessment should be recorded at each visit.

Skin

The skin of many HIV-infected persons may be affected secondary to infectious and noninfectious dermatologic disorders. Skin or nail pigmentation and rashes of all varieties can occur in disseminated or localized fashion. Many skin diseases don't follow common "textbook" presentations. They may be clues to underlying serious illness, coinfection, or worsening immunosuppression. Needle tracks or skin popping indicate intravenous drug abuse and are indications to discuss rehab and/or prevention of transmission by not sharing needles (Table 97.1).

Lymph nodes

Nonspecific small, symmetric, mobile nodes are commonly seen in patients with HIV infection; these often reflect nonspecific reactive hyperplasia. Acute generalized lymphadenopathy can be seen during seroconversion. Non-Hodgkin's lymphoma (NHL) and infectious pathogens can present as single or multiple nodes. At each visit, lymph node groups should be assessed for size, quantity, texture, and tenderness. Biopsy is usually not indicated and is not helpful unless the etiology is unclear, the nodes are rapidly enlarging or asymmetric, and/or they are associated with fever and weight loss.

Head, eyes, ear, nose, and throat

Candida and herpes simplex virus often cause painful cheilitis, stomatitis, or pharyngitis and can manifest at any stage of HIV infection. Candida (oral thrush), cytomegalovirus (CMV) (oral ulcers), Epstein–Barr virus (EBV) (oral hairy leukoplakia), varicella-zoster virus, mycobacterial infection, *Cryptococcus neoformans, Histoplasma*

TABLE 97.1 **COMMONLY SEEN CUTANEOUS MANIFESTATIONS IN HIV PATIENTS**

Etiology	Clinical features
Bacterial infection	
Bacillary angiomatosis	Fleshy, friable, protuberant papules-to-nodules that tend to bleed very easily
Staphylococcus aureus	Folliculitis, ecthyma, impetigo, bullous impetigo, furuncles, and carbuncles
Syphilis	May occur in different forms (primary, secondary, or tertiary); chancre may become painful due to secondary infection
Fungal infection	
Candidiasis	Mucous membranes (oral, vulvovaginal), less commonly *Candida intertrigo* or *paronychia*
Cryptococcosis	Most common on the head and neck; typically present as pearly 2–5 mm translucent papules that resemble molluscum contagiosum papules; other forms include pustules, purpuric papules, and vegetating plaques
Seborrheic dermatitis	Poorly defined, faint pink patches, with mild to profuse fine, loose, waxy scales in the nasolabial folds and hair-bearing areas such as the eyebrows, scalp, chest, and pubic area
Arthropod infestations	
Scabies	Pruritus with or without rash; generalized but can be limited to a single digit, more severe in Norwegian type
Viral infection	
Herpes simplex	Painful vesicular lesion in clusters; perianal, genital, orofacial, or digital; can be disseminated
Herpes zoster	Painful dermatomal vesicles that may ulcerate or disseminate (polydermatomal)
HIV	Discrete erythematous macules and papules on the upper trunk, palms, and soles are the most characteristic cutaneous finding of acute HIV infection
Human papilloma virus	Genital warts (may become unusually extensive)
Kaposi's sarcoma (herpesvirus 8)	Erythematous macule or papule, enlarge at varying rates, violaceous nodules or plaques, occasionally painful. Can be seen anywhere on/in body including skin, mucosa, and all major organ systems
Molluscum contagiosum	Discrete umbilicated papules commonly on the face, neck, and intertriginous site (axilla, groin, or buttocks)
Noninfectious	
Drug reactions	Mild rash to Stevens–Johnson syndrome
Nutritional deficiencies	Mainly seen in children and patients with chronic diarrhea; diffuse skin manifestations, depending on the deficiency
Psoriasis	Scaly lesions; diffuse or localized; can be associated with arthritis
Vasculitis	Palpable purpuric eruption (can resemble septic emboli)

Abbreviation: HIV = human immunodeficiency virus.

capsulatum, Kaposi's sarcoma, squamous cell carcinoma, and NHL may be visible on oral examination. Idiopathic aphthous ulcers are a significant cause of troublesome oral pain. Toothache and dental tenderness may indicate periodontal disease or abscess and may cause both fever and headache. Gingival and periodontal infection are particularly aggressive in patients with HIV infection.

Facial pain, nasal obstruction, postnasal drip, and headache can be caused by sinusitis, which occurs frequently in HIV infection. Atopy may coexist.

Blurred vision, scotoma, floaters, and/or decreased visual acuity may suggest CMV retinitis or other opportunistic infectious retinochoroiditis. Complete eye examinations at baseline and when retinitis is a consideration are essential, especially in hosts with CD4 cell count of $<50/mm^3$. This is especially important if ART is not successful and/or patients are noncompliant with ART. CMV retinitis may appear as a "ketchup and cheese," "pizza," or brushfire appearance on ophthalmologic exam.

Headache of new onset or changing character may be an early manifestation of a central nervous system opportunistic process, and a CT or MRI scan of the head is usually warranted.

Cardiopulmonary

Precise baseline pulmonary and cardiovascular examinations are important because of increasing pulmonary and cardiac complications in advancing HIV disease. Shortness of breath at rest or with exertion, its duration and progression, whether a cough is dry or productive, sputum color, amount, and odor may help with the differential

diagnosis. Hemoptysis can be caused by tuberculosis, thrombocytopenia, bacterial pneumonia, or other lung pathology. Chest pain can be caused by pneumonia, spontaneous pneumothorax (often *Pneumocystis*-related), pericarditis, herpes zoster, or HIV-related cardiomyopathy. Palpitations and postural hypotension may suggest symptomatic anemia.

Gastrointestinal

Gastrointestinal diseases are increasingly frequent as HIV disease progresses. Odynophagia, dysphagia, retrosternal chest pain, nausea, anorexia, and weight loss are commonly associated with esophagitis due to *Candida*, herpes simplex, CMV, or, more rarely, lymphoma. Hepatic or splenic enlargement may be an early manifestation of HIV-related complications, and baseline size should be accurately quantified and documented.

Right upper quadrant pain associated with fever and elevated liver enzymes may indicate viral or drug-induced hepatitis, cholelithiasis, or acalculous cholecystitis related to *Mycobacterium avium* complex (MAC), cryptosporidiosis, microsporidia, or CMV.

Epigastric or left upper quadrant pain may indicate drug-induced pancreatitis. Abdominal distension, tenderness, masses, constipation, or fecal incontinence may be caused by Kaposi's sarcoma, lymphoma, carcinoma, gastrointestinal opportunistic infections (CMV, histoplasmosis, tuberculosis), or parasitic infestation. Diarrhea occurs in 30% to 66% of adults with HIV. *Salmonella, Cryptosporidium, Isospora*, CMV, microsporidia, and other enteric pathogens commonly occur. Constipation is commonly seen in patients taking methadone, heroin, or opioids, as well as other medicines. Antibiotic use predisposes patients to *Clostridium difficile* infection. There is also a higher incidence of irritable bowel syndrome among HIV patients, but it is a diagnosis of exclusion.

Painful defecation or rectal pain can be caused by trauma, perirectal abscess, herpes, squamous cell carcinoma, or other sexually transmitted diseases (STD; e.g., lymphogranuloma venereum, LGV), all of which are increased in persons having anal intercourse. Careful, nonjudgmental sexual and social histories may help identify pathogens. Perirectal areas should be carefully examined for lesions, abscess, fissures, proctitis, and ulcerations. Stools should be tested for occult blood.

Genitourinary, obstetric, and gynecologic manifestations

Painful, frequent urination may indicate urinary tract infection, STD, or vulvovaginitis. The latter are more common and possibly more difficult to treat in HIV infection. Recurrent or severe vaginitis, vaginal discharge, and pruritus are common and may not be related solely to sexual practices. Prompt evaluation of all genital discharges, ulcers, and lesions will allow correct identification of any STD.

Women should be queried regarding menstrual history, fertility, method of birth control, and numbers and dates of pregnancies and abortions. Menstruation may become irregular in worsening HIV infection, and fertility declines as well. Prior tubal scarring from salpingitis or pelvic inflammatory disease predisposes to ectopic pregnancy and infertility. An external genital, rectal, and complete pelvic examination (speculum and bimanual), including Pap tests and appropriate cultures and stains, should be performed initially and then annually if exams are normal. Direct HPV testing is replacing Pap smears in many situations because they are more sensitive and specific.

Neurologic

Neuropsychiatric complications occur in many HIV-infected patients, yet symptoms may go unrecognized because of coping strategies and the large reserve available until significant deterioration is noted. Subtle neurologic deterioration, memory loss, and poor concentration may be the only early signs of HIV dementia, which often starts at an earlier age. Central and peripheral neurologic complications may be caused by HIV infection, opportunistic infections, medications, or malignancy. Illness can occur at any stage of HIV infection, albeit with different manifestations. Symptoms depend greatly on the location of the abnormality and the pathophysiology involved. Peripheral neuropathy is still quite common regardless of disease status and can occur years or even decades after seroconversion. With the advent of new and better antiretroviral therapies, progressive multifocal encephalopathy is rarely seen now; however, it also occurs usually years or even decades after seroconversion. Intracranial mass lesions are usually a late complication of HIV disease.

Distal predominantly sensory polyneuropathy, chronic inflammatory demyelinating polyneuropathy, mononeuropathy, herpesvirus and CMV radiculitis, and neuropathies of vitamin deficiency are commonly seen. Neurologic evaluation and appropriate diagnostic testing may differentiate treatable from less responsive pathology. A carefully documented baseline neurologic examination, including mental status assessment; cranial nerve testing; and evaluation of sensation, strength, coordination, and reflexes, should be part of an initial and yearly comprehensive evaluation. Mini-mental status test results should be clearly documented.

Musculoskeletal

Myalgia and proximal muscle weakness, tenderness, and wasting may be manifestations of primary HIV or drug-related myositis. Forms of arthritis that are not uncommon include severe, persistent oligoarthritis, primarily affecting the large lower limb joints with exquisite pain; psoriatic arthritis with erosive changes and crippling deformities; and septic arthritis caused by *Staphylococcus aureus*, especially in substance abusers. Changes in fat distribution secondary to ART may also be present.

Medical history

A clear history of prior HIV-related events, CD4 cell counts, viral load, resistance patterns, ART, complications, opportunistic infections, and malignancies will help stage HIV infection, provide prognostic information, and clarify therapeutic options. Opportunistic infections signify marked immunocompromise and

are discussed at length in Chapter 100, "Opportunistic infections in HIV."

Untreated HIV infection significantly increases the risk of tuberculosis and increases the yearly rate of conversion from latent to active tuberculosis to 7% to 8%, compared with an approximate 10% *lifetime* conversion rate in non-HIV patients. Tuberculosis also makes HIV infection worse, with a more rapid progression to AIDS. Purified protein derivative (PPD) or QuantiFERON-TB status, previous exposure to tuberculosis, and previous prophylaxis or treatment (date, duration, outcome, and medications) are critical. Noncompliance, prior hospitalizations, and geographic and social factors play major roles in the development of drug resistance and the choice of agents for empiric management. Syphilis may increase the rate of HIV acquisition as well as other STDs, and initial presentation can be varied in coinfected patients. Any STD presenting with an ulcer/ulcerations also increases the risk of acquiring HIV.

Medications

Polypharmacy, with prescription agents and vitamin, mineral, and herbal supplements, and alternative medications are very common. They can cause or change disease manifestations and be associated with adverse effects and toxicity, which can be confused with symptoms of HIV-related disease. For example, vitamin overdosing may cause diarrhea, abdominal cramps, peripheral neuropathy, increased intracranial pressure, headache, anorexia, nausea, and vomiting. Drug interactions, sometimes leading to ART failure, are also common and must be diligently sought for both prescription and nonprescription medicines. Patients should be encouraged to bring *all* their pills, both prescribed and over-the-counter, to each office visit.

Allergy

The astute physician should differentiate between *allergic reaction* and *intolerance*, which is commonly misinterpreted as allergy. The specific reaction, duration, and resolution of toxicity for each medication should be noted, as well as a clear temporal relationship with all factors potentially involved. Rash and fevers are the most common type of adverse drug manifestations and must be differentiated from infectious etiologies common in HIV.

Social history

Particular attention must be given to all aspects of the psychosocial history, especially residence status, occupational history, substance abuse, and sexual history. A complete sexual history should be obtained, including orientation, practices, lifetime number of partners, prostitution, and any previous STDs. Care should be taken to take the sexual history in a nonjudgmental fashion and in private. If at all possible, one should never take a sexual history in the presence of the spouse, parent, or immediate family member. In addition, dietary habits and water sources are important risks for certain pathogens.

Travel history

Because certain opportunistic infections occur predominantly in particular geographic regions (e.g., southwestern United States for coccidiomycosis; Ohio River Valley for histoplasmosis), place of birth and a complete travel history are particularly useful in formulating an accurate differential diagnosis. History of travel to developing or tropical countries may raise suspicion of travelers' diarrhea, malaria, leishmania, kala-azar, strongyloidiasis, *Penicillium* infection (Southeast Asia), HIV-2, etc.

Pets

Certain opportunistic infections have been associated with particular animals. Patients should be queried regarding exposure to animals and advised about methods of avoiding zoonoses. *Bartonella* (formerly *Rochalimaea*) species have been associated with cat-scratch disease and bacillary angiomatosis. Exposure to cat feces as well as dirt and unwashed ground foods is associated with toxoplasmosis.

Laboratory studies

Laboratory testing is sometimes the only way to absolutely establish or confirm a diagnosis. Laboratory studies should be individualized, but several general principles apply (Box 97.3 and Table 97.2).

A CBC may reveal mild normocytic, normochromic anemia, which often develops as HIV progresses. Macrocytosis frequently develops while on zidovudine, which is rarely prescribed any more. Pancytopenia may suggest bone marrow involvement or infiltration, isolated thrombocytopenia may be an early finding of HIV infection, and leukopenia and/or a blunted neutrophil response to infection is a common finding. Neutropenia often becomes more pronounced with various drug therapies (e.g., zidovudine, trimethoprim-sulfamethoxazole, pentamidine) and may require treatment with colony-stimulating factors.

Assessment of chemistries, liver function tests, and hepatitis serologies/viral levels are useful in diagnosing new or chronic illnesses, making vaccination recommendations, and as a guide to monitoring drug toxicities. Hepatitis A, B, C, and others are more

BOX 97.3

Purposes of laboratory testing in HIV infection

1. Establish baseline parameters
2. Identify underlying disease
3. Determine appropriate therapy
4. Estimate the likelihood and rate of disease progression
5. Monitor response to therapy
6. Monitor adverse reactions and toxicities
7. Screen for common/preventable illnesses

Abbreviation: HIV = human immunodeficiency virus

TABLE 97.2 **ROUTINE LABORATORY STUDIES GUIDELINES FOR HIV-INFECTED ADULTS**

Test	Indication	Interval
Antitoxoplasma IgG antibody	Screening for previous exposure Guide diagnostic and empiric management	Baseline Yearly in patients with negative results
Chemistry and liver functions	Evaluation of baseline renal and liver function, and nutritional status Diagnosis of concurrent hepatitis Monitoring of drug toxicities Monitoring of efficacy of therapy	Baseline q6–12mo More frequently in patients with advanced disease, baseline abnormalities, or with drug toxicity
Chest radiograph	Screening for disease Diagnosis of active disease	Baseline If pulmonary disease suspected
Complete blood count	Evaluation of anemia, leukopenia, or thrombocytopenia Monitoring of drug toxicities	Baseline q6mo More frequently in patients with abnormalities
Hepatitis profile	Diagnosis of viral hepatitis Evaluation for vaccination Response to vaccination	Baseline During potential acute infection Postvaccination
Lymphocyte subset testing (CD4 cells)	Guiding initiation of prophylactic therapy Prognostic information Monitoring of efficacy of therapy	Baseline q6mo if >500 q3mo if <500
HIV viral load	Diagnostic in acute infection before seroconversion (>10,000/mL) Monitoring of HIV activity Monitoring of efficacy of therapy	Baseline Every month until antiretroviral therapy efficacy is established q3mo if clinically stable
RPR or VDRL	Screening for syphilis Monitoring response to therapy Use specific test (i.e., FTA) for confirmation and/ or false-negative specimen	Baseline Yearly (at least) in patients at risk/prior infection Monthly for 6 mo, and at 9 and 12 mo after therapy
Tuberculosis skin test (TST; purified protein derivative)	Screening for infection or previous exposure	Baseline, then yearly More frequently if at risk
IGRA (interferon-γ release assay)	Identification of new converters Exposed to active tuberculosis (TB) and TST is negative; Those with anergy	

Abbreviations: HIV = human immunodeficiency virus; TB = tuberculosis.

common in HIV infection based upon underlying risk behaviors, and the choice of initial ART may be influenced by coinfections, especially hepatitis B.

Nonspecific syphilis (RPR or VDRL) tests, with confirmatory fluorescent treponemal antibody absorbed (FTA-ABS) tests, should be performed initially and repeated annually in patients at risk. Lumbar puncture may be indicated for patients with reactive serologies (RPR of 1:16 and above), for patients with positive treponemal tests of uncertain duration, late latent syphilis, and/or secondary to symptoms.

A tuberculin skin test (TST) should be placed on initial evaluation and at least annually except in patients with a history of tuberculosis or known prior reactive TST. An induration of 5 mm or more is considered positive in an HIV-infected individual and must be followed by a chest x-ray. Interferon-γ release assay (IGRA; QuantiFERON-TB, TSPOT) is recommended when TST is negative but the HIV-infected patient was exposed to an active tuberculosis patient or is at high risk of tuberculosis infection. Those also with known anergy to TST should receive IGRA testing. An initial chest radiograph is still often obtained to establish baseline status, regardless of TST or IGRA status.

Baseline antitoxoplasma immunoglobulin G (IgG) antibodies may influence prophylaxis decisions and help with the evaluation and empiric treatment of central nervous system mass lesions should they occur. Baseline CMV and EBV serologies, and cryptococcal antigen testing have no value.

Pap smears are recommended initially, at 6 months, and thereafter annually if normal. For high-risk patients based on sexual activity, more frequent evaluation may be prudent, with referral to a gynecologist for atypia or other Bethesda scale findings. The role of screening HPV testing has not yet been finalized, but will possibly replace Pap testing in the future. An anal Pap or equivalent screening test is recommended in those who have engaged in anal sex. The recommended frequency of such testing remains to be finalized.

Testing for STDs including gonorrhea, chlamydia, trichomonas, and syphilis should be performed at initial presentation and then at least annually thereafter. More frequent screening might be appropriate depending on individual risk behaviors and the local epidemiology. Type-specific HSV serologic testing should be considered at initial evaluation as well as at any time the patient presents for concerning lesions.

Cholesterol, lipid, and blood sugar evaluations are important to monitor for the metabolic abnormalities common in patients with HIV, especially those on ART.

CD4 lymphocyte counts (marker of immune status) and viral load counts (marker of disease status and response to therapy) should be obtained initially and at 3-month intervals as a guide for treatment and prophylactic interventions. Resistance status should be obtained at initial evaluation and thereafter as appropriate based on ART, compliance, and other clinical and laboratory factors. There is significant variability in CD4 cell counts; the aggregate picture over time is more useful than a single reading for major therapy decisions.

Viral load testing is essential for monitoring the efficacy of ART, and the most ultrasensitive assays, capable of detecting as low as 10 viral particles per mL, should be used. Viral genotyping and phenotyping are commonly used to detect resistance and to guide the choice of individual ART regimens in treatment-naïve patients and in patients who fail therapy.

Vaccinations

Patients should receive appropriate immunizations as early as possible in the course of HIV infection to optimize response. While clinical efficacy is difficult to prove or even assess, it is assumed that higher CD4 cell counts, preferably >500/mm^3, are associated with better vaccine efficacy (Table 97.3).

In previously unvaccinated patients, pneumococcal vaccine PCV13 (Prevnar 13) is administered first, followed by PPSV23 (Pneumovax 23) 8 weeks thereafter. Some recommend an additional booster PPSV23 after 5 years. If previously vaccinated with PPSV23, PCV13 should be administered 1 year later. Efficacy is very questionable if the CD4 cell count is <200 cells/mm^3. *Haemophilus influenzae* vaccination is not indicated as per the latest recommendations.

Patients without serologic evidence of hepatitis B infection or immunity should be given hepatitis B vaccine. Booster vaccinations, while not proved, are sometimes recommended for healthcare workers (and others) no earlier than 5 years after the initial vaccination series is completed.

TABLE 97.3 **VACCINATION GUIDELINES FOR HIV-INFECTED ADULTS**

Vaccine	Frequency
Pneumococcal vaccine Naïve patients Exposed to PPSV23 All patients	PCV13 first; PPSV23 8 weeks later PCV13 after 1 year PPSV23 booster at 5 years
Hepatitis B vaccine series	Series of three (0, 1, and 6 months) (booster in 5 years)
Influenza	Yearly, only injectable; no live attenuated
Human papillomavirus (HPV4; HPV2)	Three doses: both females and males (through age 26); (males receive HPV4 only)
Diphtheria/tetanus/pertussis	1 shot Tdap, then Td booster every 10 years
Measles (MMR), varicella	1–2 shots, if CD4 >200
Haemophilus influenzae, zoster, anthrax, small pox	Not recommended
Meningococcal, hepatitis A	Vaccination when CD4 cell count is >200 cells/mm^3
VZV	Shingrix only (inactivated); Zostavax contraindicated

Abbreviations: HIV = human immunodeficiency virus; MMR = measles, mumps, and rubella vaccine; CDC = Centers for Disease Control and Prevention, VZV = varicella zoster virus.

Influenza vaccine (*only inactivated*) is recommended annually. Mumps-measles-rubella (MMR) and Zostavax (live, attenuated VZV) are contraindicated in severely immunocompromised patients. On the other hand, Shingrix, an inactive, subunit vaccine for VZV, is considered safe in immunocompromised patients and has better immunogenic potential and should be considered. Inactivated polio vaccine, standard childhood vaccinations, and booster diphtheria and tetanus immunizations can be given as per published guidelines. Hepatitis A vaccine may also be indicated among selected at-risk populations.

Treatment considerations for both HIV and non-HIV infected individuals

Except for certain, rare circumstances, it is now recommended that patients begin ART at the *time of diagnosis* for the best long-term outcomes and survival rates. Careful consideration of the patient's compliance, lifestyle, comorbid conditions and medications, and socioeconomic factors must be made when deciding on what antiretroviral regimen is appropriate.

It is also important to be aware of *immune reconstitution inflammatory syndrome* (IRIS). While not occurring post initiation of therapy for acute initial HIV acquisition, this does occur when patients with particularly severe levels of immunosuppression are started on ART. As their immune systems get a "boost," they may develop on inflammatory response to underlying infections. Such underlying infections may be known and under treatment or previously unknown and first discovered due to IRIS. Patients with IRIS may experience symptoms such as rash, diarrhea, malaise, etc. It is important to differentiate between IRIS and drug allergy or intolerance. IRIS symptoms typically last no more than 4 weeks, and this usually occurs in patients with long-standing HIV illness.

Pre-exposure prophylaxis (PrEP) is now indicated for non–HIV-infected individuals who are at high risk for acquiring HIV. It is recommended that any HIV-negative individual who is in an ongoing sexual relationship with an HIV-positive partner receive PrEP. Other high-risk individuals include

- men who have unprotected anal sex with men
- those with a history of STDs
- heterosexual men and women having unprotected intercourse or a recent bacterial STD
- bisexual males engaging in unprotected intercourse
- injection drug users sharing needles and/or engaging in unsafe sexual practices.

PrEP consists of a combination pill of two nucleoside reverse transcriptase inhibitors, tenofovir disoproxil and emtricitabine, taken as a single daily dose. When taken consistently on a daily basis, PrEP has been shown to reduce the risk of HIV transmission by up to 92%. It is recommended that PrEP be combined with condoms and other prevention tools to provide even greater protection from acquiring HIV. PrEP should only be prescribed to those who will be compliant with the daily regimen as well as with quarterly physician follow-ups.

Guidelines for follow-up

Patients receiving ART need to be followed closely to ensure compliance, efficacy, and optimal management. Stable asymptomatic patients on ART without significant lab abnormalities can be seen every 3 to 4 months if they have no complications and are compliant. Symptomatic HIV patients should be examined and reevaluated as frequently as indicated, and testing should occur when immune status worsens. Most patients have numerous psychosocial needs that also must be addressed; referral to the appropriate staff is essential for complete and compassionate care.

Suggested reading

Centers for Disease Control and Prevention (CDC). Updated guidelines for using IGRA to detect *Mycobaterium tuberculosis* infection, United States. *MMWR Morb Mortal Wkly Rep*. 2010;59(RR-05):1–25.

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices. Recommended adult immunization schedule, United States 2012. *MMWR Morb Mortal Wkly Rep*. 2012;61(04):1–7.

Centers for Disease Control (CDC). Recommendations for HIV prevention with adults and adolescents with HIV in the United States, 2014: Summary for clinical providers. December 11, 2014 (amended December 30, 2016).

https://www.cdc.gov/hiv/risk/prep/index.html

https://aidsinfo.nih.gov/guidelines Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2017 Update

Dikman AE, Schonfeld, E et al. Human immunodeficiency virus-associated diarrhea: Still an issue in the era of antiretroviral therapy. *Digest Dis Sci*. 2015; 60(8): 2236–2245.

Martin EG, Schachman BR. Upgrading the HIV testing guidelines. *N Engl J Med*. 2013; 368:884–886.

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HIV

Antiretroviral therapy

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Introduction

The syndrome now known as AIDS was first described in 1981 in Centers for Disease Control and Prevention (CCD) journal, *Morbidity and Mortality Weekly Report* (MMWR) through a case series of five young gay men in Los Angeles who were diagnosed with *Pneumocystis carinii* pneumonia. This was quickly followed by other reports from around the country of unusual infections usually found in extreme immune suppression now occurring in other populations with no known cause of immunosuppression. The causative agent of this immunosuppression, the HIV virus, was discovered in 1984 by Francoise Barré-Sinoussi and Luc Montagnier, a discovery for which they would later win the Nobel Prize. No effective treatment was available for this deadly virus until 1987, when zidovudine (AZT) was approved by the US Food and Drug Administration (FDA); its discovery, clinical trials, and approval were pushed forward by people living with HIV. The approval of zidovudine ushered in a new age in HIV management and brought new hope for a cure or for long-term viral suppression. Single-drug therapy was quickly found to lack long-term durability however, as treatment-associated resistance began to emerge, usually in 6 to 12 months after initiation of the drug. Luckily, the advent of new agents led to dual and then triple therapy as new options, and these were able to demonstrate long-term suppression. With the approval of the first protease inhibitor (PI) in 1995 and the first non-nucleoside reverse transcriptase inhibitor in 1996, triple therapy became the standard of care. At the time called *highly active antiretroviral therapy* (HAART) and later *combination antiretroviral therapy* (cART)—and now simply referred to as ART—this multiple-drug approach to treatment brought long-term viral suppression to patients and has remained the standard of care for nearly all patients.

The growing pantheon of drugs used to treat HIV brought with them new challenges as well—side effects, high pill burdens, drug toxicities, and drug-resistant viral strains all emerged. Initial regimens often required dosing multiple times daily with multiple pills and were often associated with both immediate side effects—nausea, diarrhea, and rash were common—and long-term effects that could be disfiguring and permanent, among them lipodystrophy, lipoatrophy, neuropathies, and loss of bone density. Refining these regimens to simplify dosing requirements, reduce toxicities and drug–drug interactions, and raise the genetic barrier to resistance have all been significant advances to transforming HIV from a deadly disease to a chronic disease that can be well-managed with a very tolerable, often single-pill, daily regimen. The first once-monthly injectable therapy was recently approved, and will usher in a new era of even more treatment options for people living with HIV. We do not yet have a cure for HIV, but the goal of long-term viral suppression with simple, well-tolerated regimens has in many ways been achieved.

This chapter provides a brief overview of HIV replication along with a more detailed review of the commonly prescribed, currently approved ART medications and classes, and their indications and combinations.

Use of ART in the setting of a variety of host and viral characteristics, monitoring, and a brief discussion of the immune reconstitution inflammatory syndrome (IRIS) are included as well.

HIV replication cycle

The HIV replication cycle is illustrated in Figure 98.1. Defining and understanding the HIV viral replication cycle has led to the identification of unique drug targets specific to the HIV virus or host proteins that are necessary for viral replication. Current ART medications inhibit entry of virus into host cells, reverse transcription of viral DNA from an RNA template, integration of this viral DNA into the host genome, and processing of newly transcribed viral proteins.

The viral replication cycle begins with attachment and fusion of the HIV virus to the host cell membrane. The attachment and fusion process is complex, orchestrated by viral glycoproteins 120 and 41 attaching to host cell CD4 receptors and CCR5 or CXCR4 co-receptors (Figure 98.2). Once attachment occurs, the viral membrane fuses to the cellular membrane, and release of the contained viral RNA and viral proteins into the host cell occurs. Within the host cytoplasm, viral RNA undergoes reverse transcription via the viral reverse transcriptase enzyme (RT). RT utilizes host cell nucleotides to construct a viral complementary DNA (cDNA). Viral cDNA interacts with the viral integrase protein in the host cell cytoplasm. Viral cDNA is then transported into the nucleus of the host cell, where integrase incorporates viral cDNA into the host DNA genome. Once incorporated into the host genome, viral DNA is transcribed and translated into polyproteins using host enzymes and ribosomes. Viral proteases then cleave these polyproteins into functional and mature viral proteins. Full HIV virions are constructed. These new virions then bud from the host cell surface, detach, and infect new host cells, repeating the cycle (Figure 98.1).

HIV pharmacotherapy

Pharmacotherapy for the treatment of HIV includes eight pharmacologic classes, each disrupting one of the critical steps in the viral replication cycle. Classes include fusion inhibitors, CCR5 antagonists, post-attachment inhibitors, and attachment inhibitors, collectively known as the "entry inhibitors"; reverse transcriptase inhibitors, including both nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs); integrase strand transfer inhibitors (INSTIs) or "integrase inhibitors"; and PIs. Pharmacokinetic (PK) enhancers, or "boosters," are combined with PIs and the integrase inhibitor elvitegravir to allow for once daily dosing but are not considered active agents within a regimen.

Modern-day regimens generally combine an NRTI pair, most commonly tenofovir/emtricitabine or abacavir/lamivudine, with an additional active agent from the INSTI, PI, or NNRTI class. Integrase inhibitors have become the preferred third agent for most treatment-naïve individuals owing to the excellent tolerability and efficacy of this class. Entry inhibitors are not recommended for use as initial therapy, and all are only used in the setting of salvage therapy. Though the majority of first-line regimens combine three agents, select two-drug regimens are approved for use in certain scenarios; these regimens combine an agent with a high genetic barrier to resistance with an additional agent from another class, such as a second-generation INSTI with an NRTI or NNRTI, or an INSTI with a PI.

Newer agents within each class often demonstrate significant advantages over first-generation antiretrovirals in terms of tolerability, safety, efficacy, and pill-burden. The following sections will review the pharmacologic classes and individual agents with a focus on modern ART and regimens that are most frequently prescribed today. Fixed-dose combinations (FDCs), which comprise part of a regimen, and single-tablet regimens (STRs), which are considered a complete regimen alone, will be referenced throughout. Tables 99.5 and 99.6 provide a detailed description of the available products and their co-formulations.

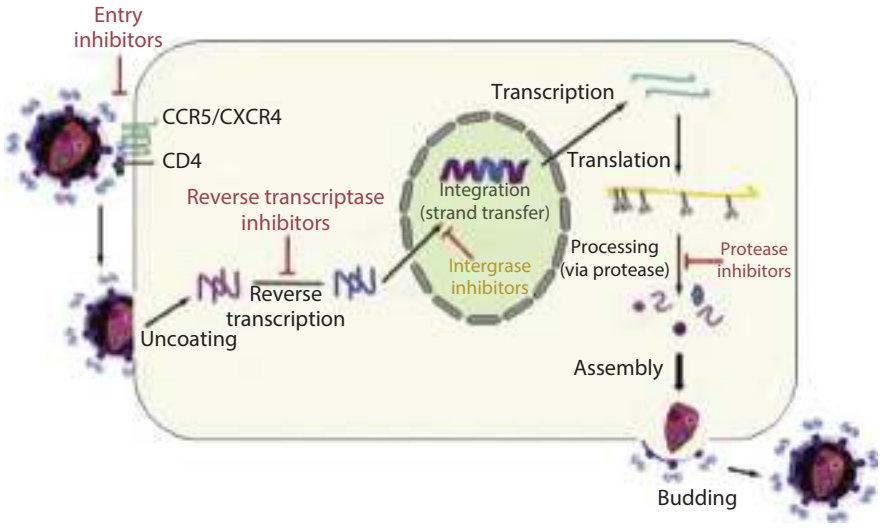

FIGURE 98.1 HIV replication cycle

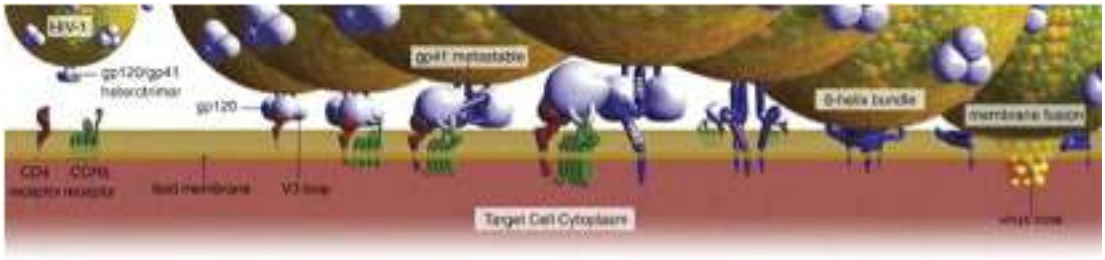

FIGURE 98.2 Fusion of the viral and host membranes

Nucleoside and nucleotide reverse transcriptase inhibitors

NRTIs are chemical derivatives of native nucleosides or nucleotides and inhibit reverse transcription of viral cDNA from HIV RNA. Apart from tenofovir, all NRTIs lack a 3′-hydroxyl (OH) group on their ribose ring, which prevents chain elongation and terminates proviral cDNA synthesis. NRTIs include the cytosine analogs lamivudine (3TC) and emtricitabine (FTC); adenosine analogs didanosine (ddI), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF); the guanosine analog abacavir (ABC); and the thymidine analogues stavudine (d4T) and zidovudine (AZT or ZDV). First-generation NRTIs (specifically ddI, d4T, and AZT) have a high affinity for host cellular mitochondrial DNA polymerase in addition to viral RT and consequently are associated with mitochondrial toxicities, including peripheral neuropathy, pancreatitis, lactic acidosis, hepatic steatosis, and lipoatrophy. They have largely been replaced by the second-generation class, which are better tolerated with fewer toxicities.

Apart from two-drug regimens, a dual NRTI backbone comprises two of the three agents in an ART regimen for a treatment-naïve individual. Preferred NRTI pairs include tenofovir/emtricitabine and abacavir/lamivudine. Due to their chemical similarities, emtricitabine and lamivudine are utilized interchangeably and therefore should never be combined. Table 98.1 presents a summary of the preferred NRTIs that will be discussed in this section.

Lamivudine and emtricitabine (3TC and FTC)

Lamivudine (3TC, trade name Epivir) and emtricitabine (FTC, trade name Emtriva) are structurally similar, roughly interchangeable cytosine analogs. Lamivudine is administered 300 mg orally once daily, while emtricitabine is administered 200 mg orally once daily. The cytosine analogs are very well-tolerated, with the rare exception of hyperpigmentation or skin discoloration of the palms and the soles with FTC. Both agents undergo renal elimination and require renal dose adjustment per package labeling, which typically necessitates breaking up FDCs or STRs into their individual components. However, results from a Phase 3b single-arm switch study in a small number of patients receiving chronic hemodialysis (HD) on the STR elvitegravir 150 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg (trade name Genvoya) demonstrated that these agents are tolerable without renal dose adjustment. Based on limited data, this practice might be considered in scenarios where maintaining an STR is preferable for adherence. Both medications have activity against hepatitis B virus (HBV) and can be utilized in combination with tenofovir for HIV/HBV coinfection. Monotherapy for HBV with FTC or 3TC is not recommended due to the rapid development of resistance.

Tenofovir (TFV)

Two tenofovir prodrug formulations are commercially available, TDF (trade name Viread) and TAF (trade name Vemlidy). TDF is administered 300 mg orally once daily in those with normal renal function, whereas TAF is administered 10 mg orally once daily when co-formulated with cobicistat and 25 mg once daily in all other scenarios. Tenofovir is most frequently co-formulated with FTC, but co-formulations with 3TC have recently been approved.

TDF has been associated with rare instances of kidney and bone disease, including new onset or worsening renal impairment, proximal renal tubulopathy, Fanconi syndrome, and bone demineralization. Adverse effects are more pronounced when TDF is combined with PK boosters (ritonavir or cobicistat) due to increased levels of TDF through inhibition of the drug transporter P-glycoprotein. Additional risk factors for toxicity include preexisting renal dysfunction, advanced HIV, longer treatment history, and low body weight. In comparison, TAF exhibits 6.5 times higher intracellular concentrations and 90% lower serum concentrations of the active moiety, tenofovir diphosphate, when compared to TDF, and, because of this, it has demonstrated more favorable effects on renal biomarkers and percentage change in bone mineral density in clinical trials. TDF has been noted to have a more favorable lipid profile than TAF; however, the clinical significance of this is unknown. TAF has been associated with greater weight gain than TDF and ABC in treatment-naïve individuals. This is an ongoing area of investigation, and additional data are needed to fully comprehend the pathophysiological mechanism and clinical impact of this finding.

TDF and TAF have differing PK properties and toxicity profiles and should not be considered interchangeable in every scenario. TAF is the preferred formulation in individuals with chronic kidney disease or osteoporosis; however, avoiding tenofovir products entirely and utilizing an NRTI-sparing

TABLE 98.1 SUMMARY OF PREFERRED NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS)

Generic (Abbreviation) *Trade Name* Analog	**Adult Dosing, Formulations, Coformulations** *Trade Name* (Abbreviation)	**Metabolism, Dose Adjustments, Major Drug-Drug Interactions**	**Resistance Pathways**	**Adverse Effects, Considerations for Use**
Abacavir (ABC) *Ziagen* Guanosine	Dosing: 600 mg PO qd, or 300 mg PO BID Formulations: 300 mg tablet 20 mg/ mL oral solution FDCs: *Epzicom* (ABC/3TC) *Trizivir* (ABC/ZDV/3TC) STRs: *Triumeq* (DTG/ABC/3TC)	Alcohol dehydrogenase and glucuronyl transferase; renal elimination Dose adjustment: Renal: N/A Hepatic: CTP A: 200 mg BID CTP B or C: **Contraindicated** Major DDIs: none	K65R L74V Y115F M184V 69 insertion Q151M	Headache, fatigue, nausea **HLA-B*5701 testing required prior to use**; avoid use if positive—highest risk for hypersensitivity reaction **Increased CV events** associated with ABC in some cohort studies; **avoid if high CV risk**
Emtricitabine (FTC) *Emtriva* Cytosine	Dosing: Capsule: 200 mg PO qd Oral solution: 240 mg (24 mL) PO qd Formulations: 200 mg hard gelatin capsule 10 mg/ mL oral solution FDCs: *Descovy* (TAF/FTC) *Truvada* (TDF/FTC) STRs: *Atripla* (EFV/TDF/FTC) *Biktarvy* (BIC/TAF/FTC) *Complera* (RPV/TDF/FTC) *Genvoya* (EVG/c/TAF/FTC) *Odefsey* (RPV/TAF/FTC) *Stribild* (EVG/c/TDF/FTC) *Symtuza* (DRV/c/TAF/FTC)	Renal elimination Dose adjustment: Renal: CrCl <50 mL/min: dose adjustment recommended; limited data suggest tolerability without adjustment Hepatic: N/A Major DDIs: None	M184V/I; (often continued in setting of M184V mutation) K65R 69 insertion Q151M	Minimal toxicity; Hyperpigmentation/skin discoloration HBV activity; not for HBV monotherapy (high resistance) Used interchangeably with 3TC
Lamivudine (3TC) *Epivir* Cytosine	Dosing: 300 mg PO qd, or 150 mg PO BID Formulations: 150 and 300 mg tablets 10 mg/ mL solution FDCs: *Cimduo* (TDF/3TC) *Combivir* (ZDV/3TC) *Epzicom* (ABC/3TC) *Temixys* (TDF/3TC) *Trizivir* (ABC/ZDV/3TC) STRs: *Delstrigo* (DOR/TDF/3TC) Dovato (DTG/3TC) *Symfi* (EFV/TDF/3TC) *Symfi Lo* (EFV/TDF/3TC) *Triumeq* (DTG/ABC/3TC)	Renal elimination Dose adjustment: Renal: CrCl <50 mL/min: dose adjustment recommended; limited data suggest tolerability without adjustment Hepatic: N/A Major DDIs: None	M184V/I; (often continued in setting of M184V mutation) K65R 69 insertion Q151M	Minimal toxicity HBV activity; not for HBV monotherapy (high resistance) Used interchangeably with FTC

TABLE 98.1 CONTINUED

Generic (Abbreviation) *Trade Name* Analog	Adult Dosing, Formulations, Coformulations *Trade Name* (Abbreviation)	Metabolism, Dose Adjustments, Major Drug-Drug Interactions	Resistance Pathways	Adverse Effects, Considerations for Use
Tenofovir alafenamide (TAF) *Vemlidy* Adenosine	Dosing: 25 mg PO qd, or 10 mg PO qd with cobicistat Formulations: 25 mg tablet FDC: *Descovy* (TAF/FTC) STRs: *Biktarvy* (BIC/TAF/FTC) *Genvoya* (EVG/c/TAF/FTC) *Odefsey* (RPV/TAF/FTC) *Symtuza* (DRV/c/TAF/FTC)	<1% renal elimination Dose adjustment: Renal: CrCl ≥15 mL/min or on HD; not required CrCl <15 mL/min and not on HD: use not recommended Hepatic: N/A Major DDIs: Avoid with **strong inducers**[a] rifapentine, and rifabutin	K65R TAM1 69 insertion	Diarrhea, nausea, headache Lower risk of renal insufficiency, Fanconi syndrome, or proximal renal tubulopathy than TDF Lower risk of osteomalacia or decreased BMD than TDF **HBV activity; preferred NRTI in HIV/HBV coinfection**
Tenofovir disoproxil fumarate (TDF) *Viread* Adenosine	Dosing: 300 mg PO qd 7.5 level scoops (300 mg) of oral powder PO qd Formulations: 150, 200, 250, and 300 mg tablets 40 mg/g oral powder FDCs: *Cimduo* (TDF/3TC) *Temixys* (TDF/3TC) *Truvada* (TDF/FTC) STRs: *Atripla* (EFV/TDF/FTC) *Complera* (RPV/TDF/FTC) *Delstrigo* (DOR/TDF/3TC) *Stribild* (EVG/c/TDF/FTC) *Symfi* (EFV/TDF/3TC) *Symfi Lo* (EFV/TDF/3TC)	Renal elimination Dose adjustment: Renal: CrCl <50 mL/min: required Hepatic: N/A Major DDIs: HIV/HCV protease inhibitors and PK boosters may increase levels of TDF; TDF reduces levels of unboosted atazanavir	K65R TAM1 69 insertion	Diarrhea, nausea, vomiting, flatulence, headache, asthenia Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy; avoid in CKD Osteomalacia, decreased BMD; avoid in osteoporosis **HBV activity; preferred NRTI in HIV/HBV coinfection** Preferred tenofovir formulation in pregnancy, PEP, or with concomitant strong inducers[a]

Abbreviations: BMD = bone mineral density; CKD = chronic kidney disease; CrCl = creatinine clearance; CTP = Child-Turcotte-Pugh; CV = cardiovascular; FDC = fixed-dose combination; HBV = hepatitis B virus; HCV hepatitis C virus; HD = hemodialysis; NRTI = nucleoside and nucleotide reverse transcriptase inhibitor; PEP = post-exposure prophylaxis; P-gp = p-glycoprotein; PK = pharmacokinetic; STR = single-tablet regimen; TAM1 = thymidine analog mutation 1 pathway (positions 41, 210, and 215)
[a]Examples of strong inducers include rifampin, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin
The NRTI class also includes zidovudine (AZT or ZDV), didanosine (ddI), stavudine (d4T), and zalcitabine (ddC). These agents are no longer in clinical use except in very rare instances (usually based on patient preference not to change from an older regimen). Given their extremely limited clinical use in the modern era, they have not been included in this table.

regimen would also be clinically appropriate. TDF requires renal dose adjustments, while TAF does not, with <1% renal elimination. TDF is currently the preferred formulation in pregnancy, for post-exposure prophylaxis, and in the setting of concomitant P-glycoprotein inducers. In the future, it may be important to consider an individual's risk for weight gain when selecting between TAF and TDF in certain patient populations; studies are ongoing to determine the significance of this effect. Both formulations have excellent activity against HBV and are preferred NRTIs in the setting of HBV coinfection. Caution is advised when discontinuing tenofovir products in those with chronic HBV due to risk of hepatitis flare.

Abacavir (ABC)

Abacavir (trade name Ziagen) is most frequently paired with 3TC (FDC trade name Epzicom). ABC is administered 600 mg orally once daily but requires dose reduction to 200 mg twice daily in mild hepatic impairment (Child-Turcotte-Pugh A), and its use is contraindicated in those with moderate to severe hepatic impairment (Child-Turcotte-Pugh B or C). ABC is metabolized in part by alcohol dehydrogenase, and levels may be increased in the setting of concomitant alcohol consumption. ABC lacks activity against HBV, and regimens including tenofovir are preferred in the scenario of HIV/HBV coinfection.

Common side effects of ABC include headache, fatigue, and nausea. The most well-known toxicity linked to ABC is a potentially fatal hypersensitivity reaction (HSR) in the presence of human leukocyte antigen allele, HLA-B*5701. Testing for HLA-B*5701 allele must be performed prior to use of ABC. If the result is positive, the risk of HSR is approximately 50%, and ABC therapy should be avoided and listed as an allergy in the medical record. For this reason, ABC-containing regimens are not commonly utilized when rapid initiation of ART is desired. A controversial association exists between ABC use and myocardial infarction, which was first reported in a large multinational observational study. Since the initial report, some cohorts have corroborated this finding whereas others have not. The US Department of Health and Human Services (DHHS) Guidelines recommend cautious use or avoidance of ABC in those with known high cardiovascular risk.

An abacavir-based NRTI backbone may be inferior to a tenofovir-based NRTI backbone in certain scenarios. The AIDS Clinical Trials Group (ACTG) 5202 trial compared the NRTI backbones ABC/3TC versus TDF/FTC when given in combination with efavirenz or ritonavir-boosted atazanavir. Results demonstrated higher virologic failure with ABC/3TC compared to TDF/FTC in patients with pretreatment viral loads of >100,000 copies/mL. Of note, this outcome was not observed in other trials, including a separate trial when ABC/3TC was given in combination with dolutegravir (this regimen is co-formulated and marketed as Triumeq). However, based on these data, in patients with high pretreatment HIV RNA, the combination of ABC/3TC with efavirenz or atazanavir/ritonavir, specifically, should be avoided.

NRTI administration requirements and interaction potential

All second-generation NRTIs can be administered without regard to meals. Limited drug–drug interactions exist for the NRTI class; however, it is important to note that the two tenofovir pro-drugs differ in interaction profiles. For example, the combination of TDF with nephrotoxic medications may increase risk for renal injury, particularly in those with additional underlying risk factors. Additionally, certain medications and combinations can increase TDF levels thereby increasing risk for TDF toxicity, such as the combination of TDF with ritonavir- or cobicistat-boosted darunavir or atazanavir. Due to lower peripheral exposure, these concerns are not clinically relevant with TAF. On the other hand, TAF should not be combined with P-glycoprotein inducers, including rifamycins, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, or St. John's Wort, a drug–drug interaction that is not clinically relevant with TDF or any other preferred NRTI. Concomitant administration could lead to reduced TAF concentrations, therapeutic failure, and HIV resistance.

NRTI resistance mechanisms

Resistance to NRTIs occurs most frequently through single point mutations, thymidine analog mutations (TAMs), and β3-β4 insertions and/or deletions. M184V and K65R are the most commonly encountered clinically significant single-point NRTI resistance mutations. M184V confers high-level resistance to 3TC and FTC, whereas K65R confers high-level resistance to tenofovir and intermediate resistance to ABC, 3TC, and FTC. Tenofovir resistance can also occur through the presence of TAMs, which are selected for by thymidine analogs (d4T, AZT). TAMs can occur at positions 41, 210, and 215 (TAM1 pathway) or at positions 67, 70, 215, and 219 (TAM2 pathway). The TAM1 pathway impacts tenofovir activity more significantly than the TAM2 pathway. Presence of the Q151M complex reduces susceptibility to all currently approved NRTIs except tenofovir, and pan-NRTI resistance can occur through the 69 Insertion Complex.

The M184V mutation merits further discussion due to its unique clinical properties. Upon development of the M184V mutation, FTC or 3TC will often be continued in order to maintain its presence as it decreases viral fitness and results in a 0.3 to 0.6 $\log_{10}$ reduction in plasma HIV RNA levels. M184V can also hypersensitize HIV to tenofovir, restore partial sensitivity to tenofovir in the presence of TAMs or K65R, and delay the emergence of additional TAMs.

Non-nucleoside reverse transcriptase inhibitors

NNRTIs are noncompetitive inhibitors of RT that bind to the enzyme at an allosteric site, inducing a conformational change and thereby reducing its activity. In current practice, NNRTI-based regimens are only recommended as initial therapy in certain clinical scenarios due to a lower genetic barrier to resistance, poorer tolerability, and proven inferiority when compared to INSTI-based regimens. The risk for transmitted resistance in ART-naïve individuals is highest with the NNRTI class; therefore, NNRTI-based regimens should not be prescribed without a baseline genotype demonstrating susceptibility. Like NRTIs, the NNRTIs are also divided into two distinct groups, the first- and second-generation NNRTIs. Second-generation NNRTIs were structurally altered to theoretically increase efficacy in resistant HIV, but their most clinically meaningful benefit is an improved safety and tolerability profile. Table 98.2 presents a summary of the NNRTIs that will be discussed in this section.

First-generation NNRTIs

First-generation NNRTIs include delavirdine (DLV), efavirenz (EFV), and nevirapine (NVP). DLV and NVP are not utilized frequently in the United States largely due to inferior clinical efficacy, higher pill burden, and severe toxicities compared to other agents within the class.

Efavirenz at a dose of 600 mg orally daily, in combination with TDF/FTC (trade name Atripla), was the first STR approved for use in 2006, revolutionizing the approach to HIV management at that time. EFV-based regimens have since been removed from the recommended initial treatment options for most people with HIV due to high discontinuation rates and the development of more tolerable and durable agents and classes. This change was driven by an accumulation of data including results from the SINGLE trial,

TABLE 98.2 **SUMMARY OF NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS)**

Generic Name (Abbreviation) *Trade Name* Generation	**Adult Dosing, Formulations, Coformulations** *Trade Name* (Abbreviation)	**Metabolism, Dose Adjustments, Major Drug–drug Interactions**	**Resistance Pathways**	**Adverse Effects, Considerations for Use**
Doravirine (DOR) *Pifeltro* Second generation NNRTI	Dosing: 100 mg PO qd Formulations: 100 mg tablet STR: *Delstrigo* (DOR/TDF/3TC)	Hepatic through CYP3A4 Dose adjustment: Renal: N/A; not studied in ESRD Hepatic: N/A; not studied in CTP C Major DDIs: **Contraindicated with strong inducers[a] and rifapentine** Increase DOR to 100 mg BID with rifabutin	V106A/M Y188L M230L G190E	Nausea, dizziness, abnormal dreams Less neuropsychiatric adverse effects than EFV Administer without regard to meals; does not require acid for absorption
Efavirenz (EFV) *Sustiva* First generation NNRTI	Dosing: 600 mg PO qd, or 400 mg PO qd (low-dose) Formulations: 50 mg and 200 mg capsules 600 mg tablet STRs: *Atripla* (EFV/TDF/FTC) *Symfi* (EFV 600 mg/TDF/3TC) *Symfi Lo* (EFV 400 mg/TDF/3TC)	Hepatic through CYP2B6, 3A4, and 2A6 Dose adjustment: Renal: N/A Hepatic: use with caution in hepatic dysfunction Major DDIs: Induces CYP2B6, 2C19, 3A4 **Extensive DDIs** **EFV, ETV, and NVP reduce levels of many medications**, including certain anxiolytics, antidepressants, antipsychotics, alpha-adrenergic antagonists, anticoagulants, anticonvulsants, antifungals, antiplatelets, cardiac medications, contraceptives, HCV Direct Acting Antivirals, treatments for opioid dependence, and statins ETV, EFV, and NVP levels may be reduced with strong inducers[a], however, EFV 600 mg can be given with rifampin and rifapentine	**K103N/S** K101P L100I V106M V108I Y181C/I Y188L G190S/A P225H M230L	Rash, neuropsychiatric effects, vivid dreams, hepatotoxicity, hyperlipidemia **Take at bedtime on an empty stomach** (to decrease side effects); does not require acid for absorption Lower virologic efficacy when combined with ABC/3TC when HIV RNA >100,000 copies/mL
Etravirine (ETV) *Intelence* Second generation NNRTI	Dosing: 200 mg PO BID Formulations: 25, 100, and 200 mg tablets	Hepatic through CYP3A4, 2C9, 2C19 Dose adjustment: Renal: N/A Hepatic: N/A Major DDIs: Induces CYP3A4 Inhibits CYP2C9 and 2C19 **Extensive DDIs** Similar in profile to EFV, however ETV should not be coadministered with rifampin or rifapentine	Y181C/I/V L100I K101P G190A	Nausea, rash, including SJS, hepatotoxicity **Requires food for absorption**; does not require acid for absorption **Reserved for multidrug resistant HIV**

(*continued*)

TABLE 98.2 CONTINUED

Generic Name (Abbreviation) *Trade Name* Generation	Adult Dosing, Formulations, Coformulations *Trade Name* (Abbreviation)	Metabolism, Dose Adjustments, Major Drug–drug Interactions	Resistance Pathways	Adverse Effects, Considerations for Use
Nevirapine (NVP) *Viramune*, *Viramune XR* First generation NNRTI	Dosing: 200 mg PO qd for 14 days followed by 200 mg PO BID, or 400 mg XR PO qd Formulations: 200 mg tablet 50 mg/5 mL oral suspension 400 mg XR tablet	Hepatic through CYP3A4, 2B6 Dose adjustment: Renal: N/A; administer additional 200 mg after HD Hepatic: contraindicated in CTB B or C Major DDIs: Induces CYP3A4, 2B6 **Extensive DDIs S**imilar in profile to EFV, however, NVP should not be coadministered with rifampin or rifapentine	**K103N** V106A/M Y181C Y188L G190A/S	Rash, including SJS Hepatotoxicity, including fatal hepatic necrosis Symptomatic hepatitis may occur in ARV-naïve females with pre-NVP CD4 counts >250 cells/mm^3 and in ARV-naïve males with pre-NVP CD4 counts >400 cells/mm^3 Administer without regard to meals
Rilpivirine (RPV) *Edurant* Second generation NNRTI	Dosing: 25 mg PO qd Formulations: 25 mg tablet STRs: *Complera* (RPV/TDF/FTC) *Juluca* (DTG/RPV) *Odefsey* (RPV/TAF/FTC)	Hepatic through CYP3A4 Dose adjustment: Renal: N/A Hepatic: N/A; not studied in CTP C Major DDIs: **Requires acid for absorption; contraindicated with PPIs**, and must be appropriately timed with antacids and H2RAs **Contraindicated with strong inducers[a] and rifapentine** Increase RPV to 50 mg daily with rifabutin	**E138K/G** K101E/P/T V90I V179I/L Y181I/C V189I H221I F227C/L M230L	Rash, depression, insomnia, headache, hepatotoxicity May artificially increase creatinine without decreasing renal function **Requires food for absorption**; administer with high calorie meal (390 kilocalories) Avoid use if pretreatment CD4 <200 cells/mm^3 or HIV RNA >100,000 copies/mL Small tablet size, favorable lipid profile

Abbreviations: ARV = antiretroviral; CTP = Child-Turcotte-Pugh; CYP = cytochrome P450; DDI = drug–drug interactions; ESRD = end stage renal disease; HD = hemodialysis; H2RA = histamine type-2 receptor antagonist; NNRTI = non-nucleoside reverse transcriptase inhibitor; PPI = proton pump inhibitor; SJS = Stevens-Johnson syndrome; STR = single-tablet regimen

[a]Examples of strong inducers include rifampin, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin

The NNRTI class also includes delavirdine (DLV). This agent is no longer in clinical use except in very rare instances (usually based on patient preference not to change from an older regimen). Given extremely limited clinical use in the modern era, DLV has not been included in this table.

where EFV in combination with TDF/FTC demonstrated inferiority to dolutegravir in combination with ABC/3TC, a finding that was mainly driven by discontinuations due to adverse effects in the EFV arm.

Adverse effects from EFV leading to discontinuation are typically central nervous system (CNS)-related and may include vivid dreams, insomnia, dizziness, and difficulty concentrating. Depression, suicidal ideation, and psychosis have also been reported, and EFV should be avoided in those with preexisting psychiatric conditions. EFV may also cause dyslipidemia, including elevations in LDL and triglyceride levels. Although EFV has multiple other drug–drug interactions, it has minimal interaction with rifamycins, and efavirenz-based STRs are an option for individuals with mycobacterial coinfection.

In addition to co-formulation with TDF/FTC, EFV is also co-formulated with TDF/3TC (trade name Symfi). A reduced dose of EFV (400 mg) has been co-formulated with TDF/3TC to reduce adverse effects (trade name Symfi Lo). EFV is also available as a non–co-formulated product under the trade name Sustiva.

Second-generation NNRTIs

Second-generation NNRTIs include doravirine (DOR), etravirine (ETV), and rilpivirine (RPV). RPV and DOR are commonly used in scenarios where INSTI-based regimens are non-preferred, poorly tolerated, or contraindicated based on patient-specific factors. RPV and DOR have been associated with fewer adverse CNS effects and more favorable lipid profiles when compared to EFV-based regimens. However, cautious use of RPV is still recommended in those with preexisting psychiatric conditions.

RPV (trade name Edurant), at a dose of 25 mg orally once daily, is co-formulated with both TDF/FTC (trade name Complera) and TAF/FTC (trade name Odefsey). The combination of RPV with the INSTI dolutegravir (trade name Juluca) was recently approved as the first dual-therapy STR indicated for use in individuals with 6 months or more of virologic suppression based on data from the SWORD-1 and SWORD-2 trials (as a so-called *stable switch*). Additionally, clinical trials evaluating RPV as a component of the first dual-therapy long-acting injectable ART regimen (in combination with the novel INSTI cabotegravir) demonstrated efficacy in the ATLAS and FLAIR trials, and this combination (trade name Cabenuva) has been FDA-approved as the first once-montly injectable regimen; it is also approved only for stable-switch. RPV-based regimens should be avoided in patients with high pretreatment viral loads (>100,000 copies/mL) and low CD4 counts (<200 cells/mm^3) due to lower virologic efficacy noted in this population in clinical trials.

DOR (trade name Pifeltro), dosed 100 mg orally once daily, is a novel NNRTI that is co-formulated with TDF/3TC (trade name Delstrigo) and has demonstrated noninferiority to both EFV and ritonavir-boosted darunavir in the DRIVE-AHEAD and DRIVE-FORWARD trials. DOR has a unique resistance profile and has an interaction profile and administration requirements that are pharmacokinetically more appealing when compared to its counterpart, RPV.

ETV (trade name Intelence) is reserved for use in multidrug-resistant (MDR) HIV and is largely known for comprising part of the TRIO regimen during a time period where limited options existed for individuals with MDR HIV.

NNRTI administration requirements and interaction potential

When selecting an NNRTI-based regimen it is important to be mindful of administration requirements and drug interaction profiles due to the varying requirements among the individual agents.

EFV should be administered on an empty stomach to reduce untoward effects, as concentrations are increased when administered with food. Additionally, dosing at bedtime is recommended to limit CNS toxicities during the daytime.

Alternatively, RPV and ETV should be administered with food for optimal absorption and efficacy. RPV requires administration with a high-fat meal, including at least 390 kilocalories. NVP and DOR are the only NNRTIs that can be administered without regard to meals.

Rilpivirine is the only NNRTI that requires an acidic gastric pH for absorption; antacids and H_2-receptor antagonists must be appropriately timed for adequate absorption, and concomitant use with proton pump inhibitors is contraindicated.

NVP, EFV, and ETV are all inducers of cytochrome P450 (CYP)3A4, leading to potential for decreased levels and therapeutic failure of concomitant medications metabolized through this pathway, including select antidepressants, antipsychotics, anticoagulants, hepatitis C direct-acting antivirals, hormonal contraceptives, statins, and treatments for opioid use disorder.

NNRTI resistance mechanisms

The activity of first-generation NNRTIs can be completely diminished by a single-point mutation, most commonly K103N. For second-generation NNRTIs, rilpivirine resistance occurs most frequently through the single-point mutation E138K. Point mutations including V106A, Y188L, and M230L are associated with a 10-fold or greater reduced susceptibility to doravirine. ETV is considered to have a higher barrier resistance than all other NNRTIs; however, single-point mutations (i.e., Y181C or Y188L) in RT can decrease susceptibility to all members of the NNRTI class, including ETV.

Protease inhibitors and pharmacokinetic boosters

PIs prevent HIV aspartyl protease from cleaving polyproteins into their structural and enzymatic components, which results in immature and noninfectious viral particles. PIs are well-known for their high genetic barrier to resistance and low potential for transmitted resistance and have proved effective in treatment-experienced individuals with MDR HIV. However, the use of PI-based regimens as initial therapy has fallen out of favor due to a high toxicity profile and interaction potential, especially in an aging patient population with multiple comorbidities and potential for polypharmacy. The clinical role for PI-based regimens is most appreciated in individuals who cannot receive an INSTI- or NNRTI-based regimen due to concerns for poor adherence or resistance.

PIs are metabolized through CYP3A4 and are commonly administered in combination with a CYP3A4 inhibitor (also known as a PK booster), either cobicistat or ritonavir (RTV). The combination serves to prolong the half-life of the PI, increase virologic potency, and allow for once-daily dosing. Ritonavir (trade name Norvir) at a dose of 100 mg and cobicistat (trade name Tybost) at a dose of 150 mg are both utilized as PK boosters in combination with PIs. RTV was originally marketed as a PI at a dose of 600 mg twice daily. Due to pill burden, toxicity, and multiple drug–drug interactions, RTV is now exclusively utilized at a lower dose as a PK booster. Cobicistat has no antiviral activity. Cobicistat is also used as a booster for the INSTI elvitegravir, again to allow once-daily dosing. PIs and PK boosters are associated with multiple drug–drug interactions not limited to CYP3A4 inhibition, which can lead to toxicity from and/or therapeutic failure of concomitant medications. PK boosters are summarized in Table 98.3.

Older PIs (amprenavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir) require more frequent dosing and are associated with higher rates of toxicity. Preferred PIs, including atazanavir and darunavir, are the focus of this section. Their drug characteristics are summarized in Table 98.3.

Atazanavir (ATV) and darunavir (DRV)

Atazanavir (trade name Reyataz) has been studied unboosted at a dose of 400 mg orally once daily in treatment-naïve individuals and in combination with ritonavir 100 mg or cobicistat 150 mg at a dose

of 300 mg once daily for treatment-naïve and treatment-experienced individuals. Unboosted atazanavir was associated with more treatment failures and atazanavir resistance in clinical trials; therefore, boosted atazanavir is preferred.

Darunavir (trade name Prezista) was first approved for use in treatment-experienced individuals at a dose of 600 mg orally twice daily in combination with ritonavir 100 mg twice daily. This remains the recommended dosing regimen in those with one or more darunavir-associated resistance mutations and in pregnant women due to metabolic changes of pregnancy. Darunavir 800 mg once daily in combination with cobicistat 150 mg or ritonavir 100 mg can be utilized in all other individuals. The virologic benefit of darunavir has only been established when given concomitantly with RTV or cobicistat; therefore, unboosted DRV is not recommended.

FDC tablets are available for cobicistat-boosted darunavir (trade name Prezcobix) and cobicistat-boosted atazanavir (trade name Evotaz) to decrease pill burden. Cobicistat-boosted darunavir is combined with TAF/FTC to form the only PI-based STR (trade name Symtuza).

PIs and boosters have been associated with gastrointestinal adverse effects, including nausea, vomiting, and diarrhea. Many PIs have been associated with metabolic derangements, including dyslipidemia, insulin resistance, and fat maldistribution. Adverse effects that are specific to atazanavir include indirect hyperbilirubinemia with jaundice and scleral icterus, cholelithiasis, and nephrolithiasis. The structure of darunavir contains a sulfonamide moiety, and cross-allergenicity may occur in those with sulfonamide allergies. Stevens–Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported. Observational cohort studies have reported an association between darunavir, indinavir, fosamprenavir, and lopinavir/ritonavir and an increased risk of myocardial infarction. Cautious use or avoidance is recommended in those with high cardiovascular risk.

TABLE 98.3 **SUMMARY OF PREFERRED PROTEASE INHIBITORS AND BOOSTERS**

Generic Name (Abbreviation) *Trade Name*	**Adult Dosing, Formulations, Coformulations** *Trade Name* (Abbreviation)	**Metabolic Pathway, Dose Adjustments, Major Drug–drug Interactions**	**Resistance Pathways**	**Adverse Effects, Considerations for Use**
Protease Inhibitors				
Atazanavir (ATV) *Reyataz*	Dosing: *ARV-naïve:* 300 mg PO qd boosted with RTV 100 mg or COBI 150 mg PO qd, or 400 mg PO qd unboosted *With TDF or ARV-Experienced:* unboosted ATV not recommended Formulations: 150, 200, and 300 mg capsules 50 mg single packet oral powder FDC: *Evotaz* (ATV/c)	Hepatic through CYP3A4 Dose adjustment: Renal: Baseline CrCl <70 mL/min: avoid ATV/c with TDF Hepatic: Avoid boosted ATV Major DDIs: Inhibits CYP3A4 **Extensive DDIs** **Requires acid for absorption**, dose limitations of acid-reducing agents exist and must be appropriately timed **Contraindicated with strong inducers[a] and rifapentine** Administer rifabutin at a dose of 150 mg PO daily **DRV and ATV may affect levels of many medications** including certain anxiolytics, antidepressants, antipsychotics, alpha-adrenergic antagonists, anticoagulants, antifungals, antiplatelets, cardiac medications, contraceptives, corticosteroids, HCV direct-acting antivirals, treatments for opioid dependence, and statins The degree of interaction depends on specific PI and booster **Many contraindications exist**	I50L I84V Minor mutations at 10, 16, 20, 24, 32, 33, 34, 36, 46, 48, 53, 54, 60, 62, 64, 71, 73, 82, 85, 90, 93	Nausea, hyperbilirubinemia with jaundice/scleral icterus, nephrolithiasis **Requires food for absorption** Less adverse metabolic effects than other PIs; more favorable option than DRV if high cardiac risk Lower virologic efficacy when combined with ABC/3TC when HIV RNA >100,000 copies/mL

TABLE 98.3 CONTINUED

Generic Name (Abbreviation) *Trade Name*	Adult Dosing, Formulations, Coformulations *Trade Name* (Abbreviation)	Metabolic Pathway, Dose Adjustments, Major Drug–drug Interactions	Resistance Pathways	Adverse Effects, Considerations for Use
Darunavir (DRV) *Prezista*	Dosing: *ARV-naïve:* 800 mg PO qd boosted with RTV 100 mg or COBI 150 mg PO qd *DRV resistance mutations or during pregnancy:* 600 mg PO Q12H boosted with RTV 100 mg PO Q12H Formulations: 75, 160, 600, and 800 mg tablets 100 mg/mL oral suspension FDC: *Prezcobix* (DRV/c) STR: *Symtuza* (DRV/c/TAF/FTC)	Hepatic through CYP3A4 Dose adjustment: Renal: Baseline CrCl <70 mL/min: avoid DRV/c with TDF Hepatic: avoid boosted DRV in CTP C Major DDIs: Inhibits CYP3A4 Induces CYP2C9 **Extensive DDIs** **Contraindicated with strong inducers[a] and rifapentine** Administer rifabutin at a dose of 150 mg PO daily DRV and ATV may affect levels of many medications (see ATV for further information)	I50V V11I I54L L89V V32I L33F I47V I54M I76V I84V	Diarrhea, nausea, headache, hyperlipidemia **Requires food for absorption** **Increased CV events** associated with DRV in some cohort studies; **avoid if high CV risk**
Pharmacokinetic Enhancers/Boosters				
Cobicistat (COBI, c) *Tybost*	Dosing: 150 mg PO qd in combination with ATV, DRV, or EVG Formulations FDCs: *Evotaz* (ATV/c) *Prezcobix* (DRV/c) STRs: *Genvoya* (EVG/c/TAF/FTC) *Stribild* (EVG/c/TDF/FTC) *Symtuza* (DRV/c/TAF/FTC)	Hepatic through CYP3A4 Dose Adjustment: Renal: CrCl <70 mL/min: Not recommended when used with TDF Hepatic: not studied in CTP C Major DDIs: Inhibits CYP3A4, 2D6 and OAT1B1/B3 **Extensive DDIs**, increases levels of many medications leading to toxicity (see DDIs for DRV and ATV for classes that may be affected) Avoid with rifamycins	N/A	Not considered an active agent within a regimen; utilized as a CYP3A4 inhibitor to boost levels of PIs, EVG to allow for once-daily dosing Diarrhea, nausea, hyperlipidemia May artificially increase creatinine without decreasing renal function Requires food for absorption
Ritonavir (RTV, r) *Norvir*	Dosing: 100 mg PO qd or BID in combination with PI (refer to ATV and DRV for specific dosing recommendations) Formulations: 100 mg tablet 100 mg soft gel capsule 80mg/mL oral solution 100 mg single packet oral powder FDC: *Kaletra* (LPV/r)	Hepatic through CYP 3A4, 1A2, 2B6, 2D6 Dose Adjustment: Renal: N/A Hepatic: avoid in CTP C Major DDIs: Inhibits CYP3A4, 2D6 and P-pg Induces CYP 2B6, 1A2, 2C19, 2C9 and UGT1A1 **Extensive DDIs**, may increase or decrease levels of medications depending upon dominant metabolic pathway and concomitant PI Contraindicated with strong inducers Administer rifabutin 150 mg PO qd	M46L V82A I84V Minor mutations at 10, 20, 24, 32, 36, 54, 71, 73, 76, 77, 90	Not considered an active agent within a regimen; utilized as a CYP3A4 inhibitor to boost levels of PIs to allow for once-daily dosing Diarrhea, nausea, dyslipidemia Requires food for absorption

Abbreviations: ARV = antiretroviral; CrCl = creatinine clearance; CTP = Child-Turcotte-Pugh; CV = cardiovascular; CYP = cytochrome P450; DDI = drug–drug interaction; FDC = fixed-dose combination; P-gp = p-glycoprotein; STR = single-tablet regimen; UGT = uridine diphosphate-glucuronosyltransferase

[a]Examples of strong inducers include rifampin, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin

The PI class also includes amprenavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, and tipranavir. These agents are no longer in clinical use except in very rare instances (usually based on patient preference not to change from an older regimen). Given their extremely limited clinical use in the modern era, they have not been included in this table.

PI administration requirements and interaction potential

All PIs and boosters require food for adequate absorption and efficacy. Atazanavir also requires an acidic gastric pH for absorption and should be separated appropriately from acid-reducing medications. Drug–drug interactions with PIs and boosters are extensive, and each agent may differ significantly in their interaction profile.

In general, PIs and boosters may increase (or sometimes decrease) levels of many medications, including certain antidepressants, antipsychotics, anticoagulants, antimycobacterials, antiarrhythmics, hepatitis C direct-acting antivirals, hormonal contraceptives, statins, benzodiazepines, treatments for opioid dependence, and corticosteroids. Interactions can lead to serious toxicities. For example, concomitant use of boosted PIs and intranasal or inhaled corticosteroids can lead to significant increases in corticosteroid levels, systemic exposure, and Cushing's syndrome. Beclomethasone is the only inhaled/intranasal corticosteroid that can be safely coadministered due to limited CYP3A4 metabolism.

The nature of each interaction may also be influenced by the concomitant booster. While both ritonavir and cobicistat inhibit CYP3A4, ritonavir also induces CYP1A2, CYP2B6 CYP2C19, and CYP2C9, and this may lead to increased or decreased levels of concomitant medications depending on the dominant metabolic pathway. For example, warfarin is an anticoagulant that is metabolized through multiple CYP enzymes. Concomitant cobicistat and warfarin may increase warfarin concentrations due to CYP3A4 inhibition, leading to increased risk for bleeding. However, concomitant ritonavir and warfarin may decrease warfarin concentrations through CYP1A2 and CYP2C9 induction, leading to increased risk for thrombosis.

It is essential to consult drug–drug interaction resources, including the US DHHS HIV Guidelines and the University of Liverpool website (www.hiv-druginteractions.org) to evaluate the potential for drug–drug interactions prior to the addition or discontinuation of a boosted PI.

PI resistance mechanisms

Resistance to PIs occurs through the development of multiple minor mutations or single major mutations. Primary resistance to atazanavir occurs through the presence of I50L, I84V, and/or N88S. Two or more resistance mutations are often required to substantially impact virologic response to boosted darunavir; major darunavir mutations are I50V, I54M, L76V, and I84V. In the setting of multiple PI mutations, phenotypic testing can be performed to determine the clinical utility and predicted effectiveness of darunavir.

Integrase strand transfer inhibitors (INSTIs)

INSTIs exert their activity by blocking HIV integrase-mediated incorporation of HIV cDNA into the host DNA genome. First-generation INSTIs include raltegravir (RAL) and cobicistat-boosted elvitegravir (EVG/c). Second-generation INSTIs, including dolutegravir (DTG) and bictegravir (BIC), are easier to administer and have a higher genetic barrier to resistance when compared to the first-generation class. In head-to-head clinical trials, INSTIs have demonstrated either noninferiority or superiority to NNRTI- and PI-based regimens. Their high tolerability and virologic efficacy support their place as first-line treatment options worldwide. Table 98.4 presents a summary of the INSTIs.

Raltegravir (RAL)

Raltegravir (trade name Isentress) was the first INSTI to receive FDA approval in 2007 and has the most cumulative clinical data of the class. RAL is administered 400 mg orally twice daily in most individuals, 1,200 mg (two 600-mg tablets) once daily (trade name Isentress HD) in non-pregnant individuals, and 800 mg (two 400-mg tablets) twice daily with potent inducers such as rifampin. RAL is not available as a co-formulated product.

For the combined endpoint of virologic efficacy and tolerability, RAL-based regimens have demonstrated superiority to EFV- and PI-based regimens in treatment-naïve individuals (STARTMRK and ACTG A5257). Additionally, when compared to EFV-based regimens, RAL- and DTG-based regimens have demonstrated a faster reduction in viral load and greater proportion of viral suppression at delivery in women who presented for treatment late in pregnancy (IMPAACT 1081 and DolPHIN-2). Switch studies for RAL have yielded disparate results. In SWITCHMRK 1 and 2, switching from a PI-based regimen to a RAL-based regimen demonstrated improved lipid profiles but increased virologic failure rates, thus highlighting the low genetic barrier with first-generation INSTIs. In a second study with lower rates of individuals who had previously experienced virologic failure, a switch from a PI-based regimen to RAL met noninferiority criteria for virologic efficacy. RAL does not require dose adjustments in renal or mild to moderate hepatic impairment.

RAL in combination with a tenofovir pro-drug and FTC or 3TC remains a recommended treatment option as initial therapy for most individuals in the DHHS Guidelines. Additionally, RAL is currently the recommended INSTI in individuals who are trying to conceive. In clinical practice, however, RAL is not widely used mainly due to its low genetic barrier to resistance, lack of a co-formulated product, and high pill burden relative to other options within the class.

Cobicistat-boosted elvitegravir (EVG/c)

Elvitegravir was the second INSTI to gain FDA approval in 2012 and is the only agent within the class that requires boosting with cobicistat. The pharmacologic concepts of boosting with PIs can be applied to EVG/c, including the high potential for drug–drug interactions, with the caveat that EVG is never combined with RTV. EVG is administered 150 mg orally once daily in combination with cobicistat 150 mg and is only available as a co-formulated product with TDF/FTC (trade name Stribild) and TAF/FTC (trade name Genvoya).

EVG-based regimens have demonstrated noninferior virologic suppression rates when compared to EFV- and PI-based regimens in treatment-naïve individuals (GS-102 and GS-103) and superiority to a boosted ATV-based regimen in treatment-naïve women (WAVES). The STR containing EVG/c with TDF/FTC should not be initiated in patients with a creatinine clearance of <70 mL/min and should be discontinued once the creatinine clearance decreases below 50 mL/min. EVG/c with TAF/FTC can be administered without dose adjustment in those on chronic hemodialysis, but use is not recommended in those with creatinine clearances below 30 mL/min who are not receiving chronic HD. Dose adjustment is not required for either regimen in mild-moderate hepatic impairment.

TABLE 98.4 **SUMMARY OF INTEGRASE STRAND TRANSFER INHIBITORS (INSTIS)**

Generic Name (Abbreviation) *Trade Name* Generation	**Adult Dosing, Formulations, Coformulations** *Trade Name* (Abbreviation)	**Metabolism, Elimination, Dose Adjustments, Major Drug–drug Interactions**	**Resistance Mutations and Pathways**	**Adverse Effects, Considerations for Use**
Bictegravir (BIC) Second generation INSTI	Dosing: 50 mg PO qd Formulations: BIC is only available as part of a STR STR: *Biktarvy* (BIC/TAF/FTC)	Hepatic through CYP3A4 and UGT1A1-mediated glucuronidation Dose adjustment: Renal: CrCl <30 mL/min: avoid BIC/FTC/TAF Hepatic: avoid in CTP C Major DDIs: Inhibits OCT2 and MATE1 transporters **Contraindicated** with dofetilide May increase levels of metformin (monitor) Polyvalent and divalent cations reduce absorption of all INSTIs through chelation; must be appropriately timed **Avoid with strong inducers[a], rifabutin, and rifapentine**	Q148H/K/R plus 1 or more INSTI mutation	Headache, nausea, diarrhea, weight gain May artificially increase creatinine without decreasing renal function High barrier to resistance Small tablet size
Dolutegravir (DTG) *Tivicay* Second generation INSTI	Dosing: 50 mg PO qd *INSTI-Experienced with certain INSTI mutations, or if coadministered with rifampin (without INSTI resistance)*: 50 mg PO BID Formulations: 50 mg tablet STRs: *Dovato* (DTG/3TC) *Juluca* (DTG/RPV) *Triumeq* (DTG/ABC/3TC)	Hepatic through CYP3A4 and UGT1A1/3/9-mediated glucuronidation Dose adjustment: Renal: caution if CrCl <30 mL/min in those who require BID DTG Hepatic: avoid in CTP C Major DDIs: Inhibits OCT2 **Contraindicated with dofetilide** May increase levels of metformin (titrate carefully and monitor) Polyvalent and divalent cations reduce absorption of all INSTIs through chelation; must be appropriately timed Can be administered with certain strong inducers at a dose of 50 mg BID (carbamazepine, rifampin); avoid with other strong inducers[a] and rifapentine	Q148H/K/R plus 1 or more INSTI mutation	Headache, insomnia Weight gain Depression and suicidal ideation (rare) CK elevations and myopathy (rare) May artificially increase creatinine without decreasing renal function High barrier to resistance

(*continued*)

TABLE 98.4 CONTINUED

Generic Name (Abbreviation) *Trade Name* Generation	**Adult Dosing, Formulations, Coformulations** *Trade Name* (Abbreviation)	**Metabolism, Elimination, Dose Adjustments, Major Drug–drug Interactions**	**Resistance Mutations and Pathways**	**Adverse Effects, Considerations for Use**
Elvitegravir (EVG) First generation INSTI	Dosing: 150 mg PO qd with cobicistat Formulation: EVG is only available as part of STR STRs: *Genvoya* (EVG/c/TAF/FTC) *Stribild* (EVG/c/TDF/FTC)	Hepatic through CYP3A4 and UGT1A1/3-mediated glucuronidation Cobicistat inhibits CYP3A4; CYP2D6 Dose adjustment: Renal: Baseline CrCl <70 mL/min: avoid EVG/c with TDF; CrCl <50 mL/min: discontinue EVG/c with TDF Hepatic: avoid in CTP C Polyvalent and divalent cations reduce absorption of all INSTIs through chelation; must be appropriately timed **May affect levels of many medications** including certain anxiolytics, antidepressants, antipsychotics, alpha-adrenergic antagonists, anticoagulants, antifungals, antiplatelets, cardiac medications, contraceptives, corticosteroids, HCV Direct Acting Antivirals, treatments for opioid dependence, and statins **Many contraindications exist** **Avoid with strong inducers[a], rifabutin, and rifapentine**	Q148H/K/R N155H E92Q/G/V T66A/I/K	Nausea, diarrhea Depression and suicidal ideation (rare) **Requires food for absorption** Removed from preferred initial regimens due to more adverse effects and interactions than other INSTIs
Raltegravir (RAL) *Isentress* *Isentress HD* First generation INSTI	Dosing: 400 mg PO BID *Non-pregnant:* 1200 mg (two 600 mg tablets) PO qd *Concomitant rifampin without INSTI resistance:* 800 mg (two 400-mg tablets) PO BID Formulations: 400 and 600 mg tablet 25 and 100 mg chewable tablets 100 mg single packet for oral suspension	UGT1A1-mediated glucuronidation Dose adjustment: Renal: N/A Hepatic: N/A Major DDIs: Polyvalent and divalent cations reduce absorption of all INSTIs through chelation; must be appropriately timed May be administered with rifampin at a dose of 800 mg BID (avoid other strong inducers[a] and once-daily rifapentine)	Q148H/K/R N155H E92Q/G/V T66K Y143R/H/C	Rash (including SJS), headache, insomnia nausea, diarrhea CPK elevation, muscle weakness, and rhabdomyolysis Depression and suicidal ideation (rare) Highest pill burden of INSTI class Preferred INSTI in those trying to conceive

Abbreviations: CK = creatine kinase; CrCl = creatinine clearance; CTP = Child-Turcotte-Pugh; CYP = cytochrome P450; DDI = drug–drug interaction; MATE = multidrug and toxin extrusion protein; OCT = organic cation transporter; SJS = Stevens Johnson Syndrome; STR = single-tablet regimen; UGT = uridine diphosphate-glucuronosyltransferase

[a]Examples of strong inducers include rifampin, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin

EVG-based regimens are no longer recommended as initial therapy for most people with HIV due to a low genetic barrier and limitations in side-effect and interaction profiles when compared to RAL-, DTG-, and BIC-based regimens.

Dolutegravir (DTG)

Dolutegravir (trade name Tivicay), a second-generation INSTI, is administered 50 mg orally once daily or 50 mg twice daily in individuals with first-generation INSTI resistance or in combination with potent inducers, such as rifampin. DTG is co-formulated with ABC/3TC (trade name Triumeq), 3TC (trade name Dovato), and RPV (trade name Juluca).

DTG/3TC was the first dual-therapy regimen approved for use in treatment-naïve individuals with baseline HIV RNA levels of <500,000 copies/mL based on data from the GEMINI-1 and GEMINI-2 trials. However, it should not be used in individuals with HBV coinfection or without baseline HIV genotypic resistance testing demonstrating 3TC susceptibility.

DTG-based regimens have demonstrated noninferiority to RAL-based regimens (SPRING-2) and superiority to EVF- and PI-based regimens (SINGLE and FLAMINGO, ARIAS) in treatment-naïve individuals. In treatment-experienced individuals, DTG-based regimens have outperformed RAL-based regimens, with higher rates of virologic suppression and lower rates of virologic failure due to treatment-emergent INSTI resistance (SAILING). DTG has also demonstrated an effective role in heavily treatment-experienced individuals, including those with NRTI or first-generation INSTI resistance (VIKING). DTG does not require dose adjustment in renal or mild to moderate hepatic impairment. However, cautious use is recommended in individuals with a creatinine clearance <30 mL/min when twice-daily dolutegravir is indicated because there may be a loss of therapeutic effect.

Based on its robust clinical efficacy and tolerability, DTG is a component of multiple regimens recommended as initial therapy in most individuals with HIV.

Bictegravir (BIC)

Bictegravir, a novel second-generation INSTI, is structurally similar to dolutegravir and was approved by the FDA in 2018 as part of a once-daily STR including bictegravir 50 mg and TAF/FTC (trade name Biktarvy). Similar to EVG/c, BIC is only available as a component of a STR and not as a standalone product. The slight structural differences between BIC and DTG increase the in-vitro potency of BIC against select INSTI mutations; however, an improved resistance profile has not yet been proved clinically.

BIC in combination with TAF/FTC has demonstrated noninferior virologic suppression rates when compared to DTG-based regimens in treatment-naïve individuals and noninferiority to DTG- and PI-based regimens in treatment-experienced individuals. BIC in combination with TAF/FTC does not require dose adjustment in individuals with mild to moderate hepatic impairment. Use is currently not recommended in those with a creatinine clearance of <30 mL/min. BIC should not be used in those with first-generation INSTI resistance; DTG administered twice daily or a non–INSTI-based regimen is preferred in this scenario.

BIC in combination with TAF/FTC is a recommended initial regimen for most individuals with HIV and has several advantages over other INSTI-based regimens, including a high genetic barrier, limited drug–drug interactions, co-formulation with an NRTI backbone with HBV activity, appropriateness for use in rapid initiation of ART, and small tablet size.

INSTI adverse effects

Adverse effects that are linked to the INSTI class include headache, insomnia, rash, and rare neuropsychiatric side effects. Recently, INSTI-based regimens have been associated with the potential for increased weight gain in clinical trials when compared to NNRTI- or PI-based regimens. This effect has been most pronounced with DTG and BIC when combined with TAF and appears to disproportionately affect black and Hispanic women. As described previously with TAF, the clinical significance of and mechanistic explanation for this finding is currently unknown, including whether reversibility of weight gain is possible on discontinuation of therapy.

DTG, BIC, and cobicistat can inhibit tubular secretion of creatinine without affecting glomerular filtration rate. An increase in creatinine of 0.1 to 0.4 mg/dL is expected. RAL and DTG have been associated with rare elevations in creatine kinase and proximal myopathy.

Boosted EVG is the most poorly tolerated agent of the class, with a side-effect profile like that of boosted PIs, including nausea, diarrhea, and dyslipidemia.

INSTI administration requirements and interaction profile

RAL, BIC, and DTG can be administered without regard to meals, whereas boosted EVG requires food for adequate absorption. As EVG is co-formulated with cobicistat, it has the highest potential for drug–drug interactions and may increase levels of medications metabolized through CYP3A4, thus increasing risk for toxicity. A close evaluation of the medication profile should be performed prior to the initiation or discontinuation of boosted EVG. BIC and DTG are minor substrates of CYP3A4 and are inhibitors of the renal transporter organic cation transporter 2 (OCT2). When combined with medications that are renally eliminated through this pathway (metformin and dofetilide), this can result in increased exposure and potential for toxicity. RAL is metabolized by uridine diphosphate-glucuronosyltransferase (UGT) enzymes and has the fewest drug–drug interactions of the class.

The most commonly overlooked but clinically significant drug–drug interaction with the INSTI class is the potential for chelation and reduced INSTI absorption when coadministered with polyvalent and divalent cations. Antacids and cation-containing supplements must be appropriately timed or avoided in certain scenarios. The percentage decrease in bioavailability varies, depending on the INSTI and concomitant cation. For instance, the bioavailability of DTG and BIC is relatively unchanged when coadministered simultaneously with iron or calcium supplements with food. However, EVG/c and RAL should be administered at least 2 hours before or at least 6 hours after iron and calcium supplements.

When coadministered with rifampin, DTG should be administered at a dose of 50 mg twice daily, and RAL should be administered at a dose of 800 mg twice daily in individuals without INSTI resistance. BIC- and EVG-based regimens should not be coadministered with any rifamycins.

INSTI resistance mechanisms

Resistance to INSTIs can occur through primary single-point mutations or the combination of primary and accessory mutations. Primary single-point mutations in the integrase enzyme, such as Q148H/R/K, N155H, or E92Q/V, can reduce the activity of first-generation INSTIs. EVG and RAL commonly demonstrate cross-resistance, and EVG should not be used in those with prior RAL resistance. Lower rates of DTG susceptibility and antiviral activity have been shown when one or more additional INSTI mutations are present with Q148H/K/R. That said, several mutations are required to confer high-level resistance to DTG or BIC. For example, Q148H/R and G140S in combination with mutations L41I/M, E92Q, T97A, E138A/K, G140A, or N155H are associated with 5- to 20-fold reduced susceptibility to DTG. The combination of G140S and Q148H decreases bictegravir susceptibility 4.8-fold; with additional E138K, susceptibility is reduced even further.

Entry inhibitors

Entry inhibitors target various steps in the process of HIV entry into host CD4+ cells. Enfuvirtide (ENF), maraviroc (MVC), ibalizumab (IBA), and fostemsavir (FTR) are the antiretrovirals that make up this class. These agents are reserved for use in individuals with limited treatment options due to MDR HIV and are not recommended as a component of initial drug therapy.

Enfuvirtide (T-20; trade name Fuzeon), a fusion inhibitor, received FDA approval in 2003 as a salvage drug for treatment-experienced patients with advanced HIV. ENF blocks the conformational change in glycoprotein (gp) 41 required for membrane fusion and HIV entry into the CD4+ cell and is available as a 90 mg subcutaneous injection administered twice daily. Injection site reactions occur in 98% of patients and may manifest as pain, nodules, cysts, or pruritus. Additional adverse effects include nausea, vomiting, diarrhea, fatigue, and insomnia. Dose adjustment is not required for hepatic or renal impairment, and clinically significant drug interactions have not been reported. Resistance to ENF can occur with amino acid substitutions on viral gp41, usually at positions 36, 38, 40, and 43.

Maraviroc (trade name Selzentry) is an allosteric antagonist of the host cell coreceptor CCR5 and prevents the essential interaction between CCR5 and viral gp120 and the conformational change required for viral attachment, fusion, and entry. HIV strains may utilize different host coreceptors for entry, either CCR5, CXCR4, or both. CCR5 antagonists are only effective against R5 virus and not X4 or mixed R5/X4 virus. A phenotypic viral tropism assay must be performed prior to initiation of MVC to determine if the circulating virus is R5-tropic, X4-tropic, or dual/mixed R5/X4-tropic. Individuals may have low levels of X4-tropic virus that circulate below the detection limit of the tropism assay, which can lead to virologic escape and therapeutic failure. Selection of X4-tropic virus may have additional consequences, including a faster decline in CD4 count and progression to AIDS. MVC is administered 300 mg orally twice daily without regard to meals, and dose adjustment is required when given with concomitant CYP3A4 inducers or inhibitors. Side effects of MVC include rash, upper respiratory tract infection, and fever. Resistance to MVC can occur through amino acid substitution on viral gp120 or when selection of CXCR4-binding virus occurs.

Ibalizumab (trade name Trogarzo), a post-attachment inhibitor, is a humanized monoclonal antibody that binds to domain 2 of the CD4+ cell receptor, inducing a conformational change that blocks the interaction between gp120 and HIV co-receptors. Ibalizumab is administered as an intravenous infusion at a loading dose of 2,000 mg followed by a maintenance infusion of 800 mg every 2 weeks thereafter. Clinical experience with ibalizumab is limited to a single-arm, 40-participant study in adults harboring MDR HIV who were failing salvage therapy. When combined with an individually optimized background regimen including at least one fully active agent, 43% of individuals achieved a viral load of <50 copies/mL at week 25. Common side effects of IBA include diarrhea, dizziness, nausea, rash, and creatinine elevations. There are no known clinically significant drug–drug interactions with IBA, and renal or hepatic impairment is not expected to alter its pharmacokinetic parameters.

Fostemsavir (trade name Rukobia), a pro-drug of temsavir, is a gp120 attachment inhibitor. Once hydrolyzed to the active moiety, temsavir binds directly to the viral gp120 subunit near its CD4-binding site, causing a conformational change that inhibits viral attachment to the CD4+ cell. Fostemsavir is administered 600 mg orally twice daily without regard to meals. Results from the BRIGHTE study demonstrated efficacy of FTR in highly treatment-experienced patients failing their current regimen with only one or two antiretroviral classes remaining. When administered in combination with an optimized background regimen including at least one fully active agent, 60% of individuals achieved an HIV RNA <40 copies/mL at week 96. The most common adverse reaction observed in clinical trials was nausea. Fostemsavir is a substrate of CYP3A4 and should not be coadministered with strong CYP3A4

inducers, such as rifampin, carbamazepine, and phenytoin. Additionally, levels of ethinyl estradiol and statins may be increased when administered concomitantly with FTR. Dose adjustment is not required in renal or hepatic impairment. The presence of gp120 resistance-associated polymorphisms at sites S375, M426, M434, or M475 has been associated with a reduced virologic response to fostemsavir.

New and investigational medications

Cabotegravir + Rilpivirine intramuscular formulation

Cabotegravir, a new INSTI that is an analog of dolutegravir, has a long half-life that allows for once-monthly intramuscular dosing. Rilpivirine, an NNRTI, can also be formulated as a once-monthly nanosuspension. The combination of these two agents as a once-monthly injection has demonstrated success both in treatment-naïve (the LATTE and FLAIR trials) and patients already on therapy ("stable switch"; the ATLAS trial), provided that the patient does not have preexisting INSTI and rilpivirine resistance. This combination was recently approved in January 2021 as the first fully non-oral treatment option for patients.

Islatravir

Islatravir, also called MK-8591, is a nucleoside reverse transcriptase translocation inhibitor (NRTTI). It represents a new class of agents and has the potential for less frequent dosing due to its long half-life. It is now in clinical trials in combination with doravirine and lamivudine.

Other agents

There are a number of other agents in development, several of which represent new classes of agents and which will further strengthen the HIV armamentarium. Maturation inhibitors, CCR5 antagonists, capsid inhibitors, and several monoclonal antibodies are in development and represent exciting future directions for treatment.

Use of ART therapy

Guidelines for ART initiation

Treatment with ART is now recommended for all people living with HIV regardless of CD4 count and HIV viral load. These recommendations are supported by results from high-quality, randomized controlled trials (RCTs) that have demonstrated conclusively a mortality benefit to people living with HIV with initiation of ART and a dramatic reduction in transmission risk with treatment of people living with HIV.

Treatment guidelines have evolved over the years. With the advent of ART, treatment was focused largely on prevention of opportunistic disease. The benefits of treatment had to be balanced with the side effects, high pill burdens, drug toxicities, and risk of development of drug resistant viral strains all seen with earlier regimens. Initiation of treatment was therefore initially driven by CD4 count. Numerous large clinical trials and new drug development have led to evolution in treatment guidelines, shifting from the use of CD4 cutoffs to determine timing of treatment initiation to now recommending universal, lifelong treatment for all patients. The SMART trial, published in 2006, clearly demonstrated a mortality benefit with continuous ART therapy once initiated rather than intermittent, CD4-driven treatment. Prior to that, some clinicians favored a "drug conservation" approach (sometimes called "structured treatment interruptions") in which ART was used to "boost" patients' CD4 counts and then stopped to minimize toxicity; therapy was reinitiated once the CD4 count fell below 350 cells/mm^3. The SMART trial randomized patients to this approach versus continuous therapy and demonstrated lower mortality to continuous therapy. Several trials followed, demonstrating a mortality benefit to treatment initiation at higher and higher CD4 counts. This progression culminated in 2015 with the publication of the START and TEMPRANO trials, which both demonstrated a clear reduction in AIDS-related events, serious non–AIDS-related events, or death from any cause in patients started on ART even at high CD4 counts. Following this, all major guidelines-defining bodies have changed treatment recommendations to encourage treatment initiation as soon as patients are ready, regardless of CD4 count.

Early treatment initiation is not only beneficial to the individual. Treatment is also prevention, and numerous trials have demonstrated conclusively that people living with HIV who are treated with ART and have an undetectable HIV viral load (<200 copies/mL) cannot transmit HIV to others. Aggregate data from the HPTN 052, PARTNER, PARTNER-2, and Opposites Attract trials have demonstrated conclusively that transmission does not occur from patients living with HIV to their HIV-negative partners if the virus remain undetectable, often described as "undetectable = untransmittable." This concept, popularized as "U = U," has become a major public health and empowerment message for people living with HIV. The demonstration of this public health benefit across numerous trials was also a major factor in driving all treatment guidelines to recommend universal treatment of patients living with HIV.

A number of trials have also looked at "rapid start" protocols. Though this is defined slightly differently in different studies, it can be conceptually explained as either initiation of ART at time of diagnosis ("same day ART") or within a brief window after diagnosis, generally 7 days. These trials have demonstrated a shorter time to viral suppression, which is of benefit to decreasing risk of transmission. Data from lower- and middle-income countries also demonstrate higher rates of linkage-to-care, higher rates of people achieving viral suppression, and better health outcomes, including lower rates of severe illness and death. Data from higher income

countries, where diagnosis at higher CD4 counts is more common and more infrastructures may exist to aid in patient retention, are still accumulating. Though there is insufficient broad evidence for guidelines to recommend universal "rapid start" or "test-and-treat" for all patients in all settings, this is an area of active investigation and guideline development.

Selection of regimen for treatment-naïve patients

Treatment guidelines have evolved over the years based on a number of factors, and choice of a regimen may still be influenced by co-occurring medical conditions, patients' current (non-HIV) medications, pregnancy status or desire to become pregnant, medication cost and access to coverage, and transmitted resistance. In spite of these nuances, treatment has become increasingly straightforward, with first-line recommended regimens across both higher- and low/moderate-income countries favoring treatment with two classes of medications, generally two NRTIs paired with an INSTI. See Box 98.1 for recommended initial regimens for most people with HIV and Box 98.2 for recommended regimens for some people with HIV.

A treatment regimen selection should always include assessment of resistance, and all patients initiating therapy should have an HIV-1 genotype assay performed to look for baseline resistance. In most cases, patients can be initiated on therapy before results have returned from this assay, and adjustments can be made if necessary should concerning resistance mutations be present. Most treatment regimens for treatment-naïve patients recommend the use of tenofovir with emtricitabine.

Integrase inhibitors have repeatedly demonstrated superiority over other classes (including NNRTIs, PIs, and entry inhibitors) in terms of sustained viral suppression and/or tolerability. Therefore, all first-line regimens pair NRTIs with an integrase inhibitor.

BOX 98.1

Recommended initial regimens for most people with HIV

- Bictegravir/tenofovir alafenamide/emtricitabine (AI)
- Dolutegravir/abacavir/lamivudine—only for patients who are HLA-B*5701 negative (AI)
- Dolutegravir (DTG) plus tenofovir plus emtricitabine or lamivudine (AI)
- Raltegravir plus tenofovir plus emtricitabine or lamivudine (BI for tenofovir disoproxil fumarate, BII for tenofovir alafenamide)
- Dolutegravir plus lamivudine—except for patients with an HIV VL >500,000, or if resistance testing is unknown, or HBV co-infected (AI)

As per US Department of Health and Human Services (DHHS) guidelines.

BOX 98.2

Recommended initial regimens in certain clinical situations

- INSTI plus 2 NRTIs:
- EVG/c/tenofovir/FTC (BI for both TAF/FTC and TDF/FTC)
- Boosted PI plus 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV)
- (DRV/c or DRV/r) plus tenofovir/FTC (AI)
- (ATV/c or ATV/r) plus tenofovir/FTC (BI)
- (DRV/c or DRV/r) plus ABC/3TC—if HLA-B*5701 negative (BII)
- NNRTI plus 2 NRTIs:
- DOR/TDF/3TC (BI) or DOR plus TAF/FTC (BIII)
- EFV plus TDF/FTC (BI for EFV 600 mg/TDF/FTC or EFV 600 mg/TDF/3TC, BII for EFV 600 mg plus TAF/FTC)
- RPV/tenofovir/FTC (BI)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm^3
- Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:
- DTG plus 3TC (AI)
- DRV/r plus RAL BID (CI)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm^3
- DRV/r once daily plus 3TC (CI)

Abbreviations: INSTI = integrase strand transfer inhibitors, NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor.

Personalized pharmacotherapy

With the shift to life-long treatment for all, the tolerability and durability of ART is now even more essential. With numerous effective and acceptable options to choose from, initiating or adjusting ART should always be based on regimen- and patient-specific factors. The concept and application of "personalized pharmacotherapy," including selection of ART based on pre-ART characteristics, patient-specific factors and preferences, pregnancy considerations, and additional scenarios, is discussed next.

Pre-ART characteristics

Some regimens have been associated with an increased risk of virologic failure in the setting of high pretreatment HIV RNA levels or low pretreatment CD4 count. For example, RPV-based regimens should not be initiated in those with baseline CD4 counts of <200 cells/mm^3. Additionally, RPV-based regimens and the combination of ABC/3TC with EFV or ATV/r should not be initiated in those with pretreatment HIV RNA of >100,000 copies/mL. Dual therapy with DTG/3TC should not be initiated in those with pretreatment HIV RNA of >500,000 copies/mL due to limited data in this population.

Rapid ART

If rapid initiation of ART is desired, ABC-based regimens should be avoided where HLA-B*5701 results are not readily available. Additionally, NNRTI-based regimens and dual-therapy with DTG/3TC should not be initiated without baseline HIV genotypic resistance testing demonstrating 3TC susceptibility. Preferred regimens for rapid initiation or if poor adherence or resistance is anticipated include a second-generation INSTI (DTG or BIC) or boosted darunavir in combination with tenofovir/FTC as these regimens have a high genetic barrier to resistance and will also cover HBV coinfection.

Ease of administration

Options for STRs are listed in Table 98.5. For individuals who prefer a regimen that can be administered without regard to meals, BIC-, DTG-, RAL-, and DOR-based regimens are appropriate. Boosted regimens (EVG/c and boosted PIs) and RPV-based regimens require food for absorption, and EFV-based regimens must be administered on an empty stomach to avoid adverse effects. RPV and ATV also require an acidic environment for absorption and may not be an optimal selection in individuals who require long-term acid-reducing agents.

Polypharmacy

Boosted regimens (EVG/c and boosted PIs) have the highest potential for drug–drug interactions. Therefore, BIC-, DTG-, RAL-, and DOR-based regimens are optimal in individuals receiving multiple concomitant medications. A comprehensive medication list should be obtained, and drug interactions should be assessed prior to initiation or adjustment of ART.

Concomitant disease states

Cardiovascular disease

ABC, DRV/r, and LPV/r have been associated with potential for increased risk of myocardial infarction, and cautious use or avoidance is recommended in those with high cardiovascular risk.

If a boosted PI is required, an ATV-based regimen may be preferable to a DRV-based regimen. BIC-, DTG-, RAL-, RPV-, and DOR-based

TABLE 98.5 **SINGLE-TABLET REGIMENS**

Trade name (abbreviation)	**Components and dosing**
INSTI plus Two NRTIs	
Biktarvy (BIC/TAF/FTC)	Bictegravir 50 mg/tenofovir AF 25 mg/emtricitabine 200 mg: 1 PO qd
Genvoya (EVG/c/TAF/FTC)	Elvitegravir 150 mg/cobicistat 150 mg/tenofovir AF 10 mg/emtricitabine 200 mg: 1 PO qd with food
Stribild (EVG/c/TDF/FTC)	Elvitegravir 150 mg/cobicistat 150 mg/tenofovir DF 300 mg/emtricitabine 200 mg: 1 PO qd with food
Triumeq (DTG/ABC/3TC)	Dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg: 1 PO qd
INSTI plus One NRTI	
Dovato (DTG/3TC)	Dolutegravir 50 mg/lamivudine 300 mg: 1 PO qd
INSTI plus One NNRTI	
Juluca (DTG/RPV)	Dolutegravir 50 mg/rilpivirine 25 mg: 1 PO qd with food
Boosted PI plus Two NRTIs	
Symtuza (DRV/c/TAF/FTC)	Darunavir 800 mg/cobicistat 150 mg/tenofovir AF 10 mg/emtricitabine 200 mg: 1 PO qd with food
NNRTI plus Two NRTIs	
Atripla (EFV/TDF/FTC)	Efavirenz 600 mg/tenofovir DF 300 mg/emtricitabine 200 mg: 1 PO QHS on an empty stomach
Complera (RPV/TDF/FTC)	Rilpivirine 25 mg/tenofovir DF 300 mg/emtricitabine 200 mg: 1 PO qd with food
Delstrigo (DOR/TDF/3TC)	Doravirine 100 mg/tenofovir DF 300 mg/lamivudine 300 mg: 1 PO qd
Odefsey (RPV/TAF/FTC)	Rilpivirine 25 mg/tenofovir AF 25 mg/emtricitabine 200 mg: 1 PO qd with food
Symfi (EFV/TDF/3TC)	Efavirenz 600 mg/tenofovir DF 300 mg/lamivudine 300 mg: 1 PO QHS on an empty stomach
Symfi Lo (EFV/TDF/3TC)	Efavirenz 400 mg/tenofovir DF 300 mg/lamivudine 300 mg: 1 PO QHS on an empty stomach

Abbreviations: AF = alafenamide; DF = disoproxil fumarate; INSTI = integrase strand transfer inhibitors, NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor.

TABLE 98.6 **FIXED-DOSE COMBINATIONS**

Trade name (abbreviations)	**Components**	**Dosing**
Two NRTIs		
Cimduo (TDF/3TC)	Tenofovir DF 300 mg/lamivudine 300 mg	1 PO QD
Combivir (ZDV/3TC)	Zidovudine 300 mg/lamivudine 150 mg	1 PO BID
Descovy (TAF/FTC)	Tenofovir AF 25 mg/emtricitabine 200 mg	1 PO QD
Epzicom (ABC/3TC)	Abacavir 600 mg/lamivudine 300 mg	1 PO QD
Temixys (TDF/3TC)	Tenofovir DF 300 mg/lamivudine 300 mg	1 PO QD
Truvada (TDF/FTC)	Tenofovir DF 300 mg/emtricitabine 200 mg	1 PO QD
Protease inhibitor/booster		
Evotaz (ATV/c)	Atazanavir 300 mg/cobicistat 150 mg	1 PO QD with food
Prezcobix (DRV/c)	Darunavir 800 mg/cobicistat 150 mg	1 PO QD with food

Abbreviations: AF = alafenamide; DF = disoproxil fumarate; INSTI = integrase strand transfer inhibitors, NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor.

regimens may also be considered. For individuals receiving ABC-containing regimens, such as DTG/ABC/3TC, simplifying to DTG/3TC or DTG/RPV or switching to a tenofovir-based NRTI backbone may be appropriate. Certain antiretrovirals have also been associated with dyslipidemia, including EFV, EVG/c, and boosted PIs. TDF has been associated with lower lipid levels than TAF or ABC. BIC, DTG, RAL, DOR, and RPV are considered lipid neutral.

Renal disease

TDF and ATV have been associated with an increased risk for kidney toxicity. In individuals with chronic kidney disease (CrCl <60 mL/min), ABC- and TAF-based regimens are considered safer for use than TDF. TAF has been approved for use in patients with a CrCl of ≥15 mL/min and has been studied in a small population of patients on hemodialysis; however, its use has not been studied in those with a CrCl of <15 mL/min who are not yet on HD. NRTI-sparing regimens, such as DTG/3TC or DTG/RPV (only in stable switch) may also be considered. DTG, BIC, RPV, and cobicistat may artificially increase serum creatinine without reducing GFR. An increase of up to 0.4 mg/dL can be expected.

Osteoporosis

People living with HIV are at increased risk for low bone mineral density and bone fractures. Certain ARVs, including TDF, have been associated with progressive decline in bone mineral density, urinary phosphate wasting, and resultant osteomalacia. TAF and ABC have lesser impact on BMD than TDF and are preferred in postmenopausal women or those at high risk for osteoporosis. An NRTI-sparing regimen (DTG/3TC or DTG/RPV) could also be an optimal choice in this scenario.

Psychiatric illnesses

Certain regimens have been associated with adverse psychiatric effects and even suicidality, mainly EFV-based regimens and less frequently RPV-based regimens. INSTI-based regimens have also been implicated in causing mild to moderate adverse neuropsychiatric events, including insomnia and sleep disorders in retrospective cohort studies and case series. Certain ARVs, such as boosted PIs, EVG/c, and EFV, may increase or decrease levels of medications utilized for psychiatric illnesses. An appropriate assessment of potential for drug–drug interactions should be performed prior to initiation or discontinuation of any ARVs.

ART selection in pregnancy

All pregnant women with HIV should initiate on ART as soon as possible, regardless of their CD4 count or HIV viral load, both for their own health and to prevent maternal-to-child transmission of virus. To minimize risk of transmission, antiretrovirals should be given to women both prior to and following delivery, and they should be given to the neonate postnatally. Resistance testing should be sent prior to initiating therapy in pregnant women, but therapy should then be initiated *before results are available* because earlier viral suppression has been associated with lower risk of transmission to the fetus. Choice of treatment initiation regimen remains an area of active research. In general, recommendations for the use of ART in pregnant women are the same as those who are not pregnant; however, in some instances, recommendations have been modified based on concerns about drugs or due to limited experience with newer agents in pregnancy.

While a detailed discussion of antiretroviral choice during pregnancy is beyond the scope of this chapter, a few preferred regimens will be noted. Importantly, the DHHS panel recommends that women who are already on fully suppressive ART regimens when pregnancy occurs *should continue on those regimens* unless there are specific concerns about safety or inferior efficacy during pregnancy. If initiating therapy in a pregnant woman, the DHHS recommends a few preferred regimens based on currently available safety and pharmacokinetic data. All regimens pair a dual-NRTI backbone

with either an integrase inhibitor (DTG or RAL) or boosted PI (ATV/r or DRV/r).

For NRTI backbones, TDF is preferred over TAF due to limited available data on TAF use in pregnancy, and TDF/FTC and TDF/3TC are recommended equally, with a recommendation for caution in patients with renal insufficiency. ABC/3TC is also recommended as a preferred NRTI backbone combination in patients who are HLA-B*5701 negative and who do not have an HIV viral load of >100,000 if used in combination with EFV or ATV/r.

Preferred options for a third agent to be given in combination with a dual-NRTI backbone include INSTIs or a boosted PI. For INSTIs, DTG and RAL are recommended as preferred regimens, with the important caveat that the use of DTG at conception and in very early pregnancy has been associated with a small but potential increase in the risk of neural tube defects. Therefore, in patients planning pregnancy, DTG use should be discussed with the patient to ensure informed decision-making. Of note, RAL must be given as twice-daily dosing. Regarding other INSTIs, BIC does not have data on use in pregnancy and is therefore not recommended as a preferred agent, and EVG/c have only limited data, but these include a concern about inadequate drug levels of both EVG and cobicistat in the second and third trimesters, thus limiting usage in pregnancy. If considering a boosted PI during pregnancy (again, with a dual-NRTI backbone), either ATV/r or DRV/r are recommended during pregnancy based on extensive experience. DRV/r must be used twice daily in pregnancy due to inadequate levels with once-daily dosing, particularly during the third trimester.

Alternative regimens to consider in pregnancy include ZDV/3TC as an alternative dual-NRTI backbone, and LPV/r, EFV, or RPV in combination with a preferred dual-NRTI backbone as alternative third agents. Drugs with insufficient data in pregnancy and therefore not preferred include BIC, DOR, IBA, and TAF. The use of cobicistat is not recommended due to inadequate serum levels in the second and third trimesters. Finally, agents not recommended for initial ART in pregnancy include ETR, MVC, NVP, and T-20. Furthermore, these agents are also not recommended for treatment-experienced women in pregnancy except in special circumstances.

ART selection in patients with multidrug-resistant HIV

In contrast to treatment-naïve patients, management of patients with MDR HIV is complex. MDR-HIV can be seen in patients who have failed two or more standard ART regimens and rarely can be seen in newly diagnosed patients who acquired a resistant strain of virus. Treatment in these settings often require a nonstandard regimen. Ideally, three active agents should be selected based on resistance testing, and potency of the drugs is considered an important factor in determining the best regimen. In general, PIs and second-generation integrase inhibitors (dolutegravir and bictegravir) have the highest barriers to resistance and are useful as backbones when selecting a regimen.

Understanding a patient's full resistance history often requires review of prior resistance testing and/or sending a new resistance test. A number of different resistance tests exist; they fall into two broad categories—genotyping and phenotyping. *Genotypes* are obtained by amplifying and sequencing circulating HIV RNA and looking for mutations known to be associated with resistance (e.g., the M184V mutation associated with the reverse transcriptase genome is associated with lamivudine and emtricitabine resistance). An HIV-1 genotype can be obtained for NRTI, NNRTI, PI, and INSTI resistance. Separate testing may be required for INSTIs, and also for entry inhibitors. In patients with an undetectable HIV viral load, a *genotype archive* can be obtained as genotypic and phenotypic testing is not possible since there is no circulating HIV RNA to amplify. The genotype archive test amplifies cellular-associated integrated viral DNA in infected CD4-positive cells to look for known resistance mutations. This test can provide useful information in patients who are virologically suppressed on complex regimens who want to simplify their pill burden or who are having side effects to their current regimen. *Phenotypic tests* report viral growth in the presence of drug exposure. This test is more costly and takes significantly longer to result, but may be useful particularly in cases of complex resistance patterns in which the interaction of multiple mutations may be difficult to predict purely through interpretation of genotyping.

Individual regimens should be tailored to the unique resistance pattern seen in the patient. Clinicians should perform a careful review of all known resistance testing because older resistance tests may reveal archived resistance that may not be present on most recent testing due to low circulating levels. Clinicians should also review treatment history because clinical failure on an agent also raises concern for underlying resistance even if a resistance test was not obtained at the time. Once a composite of the patient's known resistance mutations can be constructed, the clinician should look at remaining active agents and try to construct a regimen that prioritizes durability and simplicity and which minimizes drug–drug interactions.

A number of studies have looked at salvage regimens for patients on failing regimens or those with complex resistance. These have been instructive in determining some best practices. Second-generation NNRTIs can sometimes can be used. The TRIO study followed patients with complex resistance history (virologic failure with three or more primary PI and NRTI mutations and three or fewer darunavir and NNRTI mutations) and demonstrated that a regimen of etravirine, raltegravir, and darunavir (dosed 600 mg BID) in these patients maintained durable viral suppression of 86% at 48 weeks. This regimen is now rarely used, however, largely because of the significant pill burden. Similarly to etravirine, doravirine, another second-generation NNRTI, has been shown to have efficacy even in the presence of mutations that affect other NNRTI agents.

In general, PIs have a high genetic barrier to resistance and therefore are often still active in patients with baseline resistance. Darunavir has the strongest evidence for usage in a salvage regimen, even in highly treatment-experienced patients. The POWER 1 and 2 studies compared provider-chosen regimens versus a regimen

with darunavir/ritonavir (dosed BID) in extensively treatment-experienced patients and demonstrated significantly better virologic suppression with darunavir/ritonavir. As mentioned previously, in patients with no known major darunavir mutations (I50V, I54M, L76V, and I84V), once-daily dosing is preferred but if known major resistance mutations are present, twice-daily dosing has demonstrated superiority.

A number of studies have looked at integrase inhibitors as well for patients with treatment resistance. Raltegravir and elvitegravir were studied, including raltegravir in the previously mentioned TRIO study and elvitegravir in the GSK 119 study, and demonstrated excellent outcomes even in patients with multiple NRTI and NNRTI mutations when treated with the combination EVG/c/TAF/FTC plus darunavir 800 mg once daily. This two-tablet once-daily regimen greatly simplified pill burden for many patients but was limited by the study parameters that specified no major darunavir mutations and no baseline integrase mutations. With the rollout of second-generation INSTIs (dolutegravir and bictegravir), construction of regimens for resistant virus has largely shifted to use of these agents. The SAILING trial demonstrated superiority of dolutegravir over raltegravir for highly treatment-resistance patients. The VIKING trials demonstrated sustained activity of dolutegravir even in the presence of multiple INSTI resistance mutations, with dolutegravir dosing increased to twice-daily. Evidence is emerging with bictegravir as well.

For highly treatment-resistant patients, use of alternative agents such as maraviroc, enfuvirtide, ibalizumab, or fostemsavir, should be considered.

Important resources exist to help clinicians create composite resistance profiles and understand predicted drug activity. The IAS-USA publishes a helpful and freely available online resource and "pocket card" detailing known resistance mutations (https://www.iasusa.org/resources/hiv-drug-resistance-mutations/), and the Stanford University HIV Drug Resistance Database allows clinicians to input composite resistance mutations on a simple online form to generate predictions of drug susceptibility (https://hivdb.stanford.edu).

Laboratory testing

A new diagnosis of HIV should be confirmed with laboratory testing. In general, in the United States, clinical laboratories are using fourth-generation enzyme-linked immunosorbent assay (ELISA) tests for HIV screening. These tests detect antibodies to both HIV-1 and HIV-2, as well as the p24 antigen, an early antigen in HIV infection. Fourth-generation testing is generally positive within 14 to 30 days from infection, and 99% would be positive at 44 days after infection. Confirmation testing is achieved through use of a different assay for HIV-1 or HIV-2 antibodies. For patients with a positive screening test but negative confirmatory antibody testing, HIV-1 polymerase chain reaction (PCR) testing is performed to capture patients who may be in the "window" period of antigen positivity before antibody formation.

For newly diagnosed patients with HIV, initial laboratory testing should include a CD4 cell count and HIV viral load to establish baseline values. In addition, patients should undergo resistance testing to assess for acquisition of resistant virus; approximately 15% of treatment-naïve patients will have acquired a virus with preexisting drug resistance. Baseline laboratory testing including a CBC and differential, basic metabolic panel (BMP), liver function testing (LFT: ALT, AST, total bilirubin), urinalysis, and a random or fasting lipid profile is important. Testing for coinfections is also recommended, including hepatitis B (hepatitis B core and surface antibody testing and hepatitis B surface antigen testing), hepatitis C, and tuberculosis (purified protein derivative [PPD] or interferon-γ release assays [IGRA]). Patients should also undergo testing for sexually transmitted infections, including syphilis antibody testing, and testing for gonorrhea and chlamydia at all potentially exposed sites (typically oral and rectal swabs and a urine sample for PCR testing); women should also have trichomonas testing. HLA B*5701 testing should be tested in any patients who will be initiating on abacavir-based regimens.

In patients with very low CD4 counts (generally <100) at treatment initiation, additional laboratory testing should be considered, including toxoplasma immunoglobulin G (IgG) testing and cytomegalovirus (CMV) IgG testing to assess for prior infection and to gauge risk of reactivation. G6PD enzyme assay testing should be considered in patients who require prophylaxis against *Pneumocystis*, particularly in those with a known sulfa allergy. In patients with CD4 counts of <50, consideration should be given to workup of occult opportunistic infections; this often includes checking mycobacterial blood cultures (for *Mycobacterium avium* complex and other nontuberculous mycobacteria), CMV viral load and an ophthalmologic exam to rule out CMV retinitis, and cryptococcal antigen testing in patients who live or have had travel to endemic areas.

All patients should be treated with antiretrovirals as soon as they are ready, and, in many cases, treatment may be initiated even prior to return of all laboratory testing through rapid-start protocols. Once patients initiate medications, repeat laboratory testing should be performed at 2 to 8 weeks after treatment initiation to ensure viral response and monitor for potential toxicities. This testing includes an HIV viral load, BMP, and LFTs. Once patients are stable on therapy, repeat laboratory testing should be performed every 3 to 6 months, again monitoring HIV viral load, BMP, and LFTs. Annual lipid testing and CBC with differential testing is recommended for all patients; yearly urinalysis is additionally recommended in patients on tenofovir therapy. CD4 monitoring recommendations have changed over the years and generally are more limited in nature once immune recovery is observed and as long as viral load suppression is maintained. Generally, patients should have a CD4 cell count checked at treatment initiation, then every 3 to 6 months for the first 2 years of therapy as long as the CD4 count remains <300. After 2 years of therapy, CD4 monitoring can be performed annually for patients with a CD4 count between 300 and 500, and is considered optional in patients with a CD4 count >500 as long as the HIV viral load remains suppressed.

It is not uncommon for patients with a low CD4 nadir to have a more muted immunologic response to therapy, and patients who initiate therapy at a CD4 count of <200 often do not recover a CD4 count of >500 even after years of therapy. There is no known benefit to changing ART in these patients and generally no

clinical consequence to a lower CD4 count in otherwise virologically suppressed patients.

With the advent of more sensitive testing for HIV viral loads, "blipping" has become a more common phenomenon. "Blips" are temporary increases in viral loads from undetectable to 50 to 1,000 copies/mL. Blips do not represent virologic failure and patients should generally be continued on their current regimen without changes. Blips should prompt a discussion with the patient about medication adherence, drug–drug interactions, and taking medications properly with or without food as indicated. The viral load should be repeated in 2 to 4 weeks to ensure that the blip has resolved and the patient is not progressing to virologic failure.

Virologic failure represents sustained elevation in viral load. This can occur in patients initiated on therapy who fail to suppress 24 to 48 weeks after treatment initiation, or in patients who were previously virologically suppressed and develop a persistent viremia. In the setting of virologic failure, patients should undergo resistance testing to determine if a new regimen should be initiated, and they should be assessed for and counseled on barriers to medication adherence.

Postexposure prophylaxis

Healthcare personnel, persons who inject drugs (PWID), victims of sexual assault, and those who engage in unprotected sex are at risk for HIV exposure. After initial exposure, HIV remains localized within dendritic cells of the skin and mucosa before systemic spread and development of chronic infection. Post-exposure prophylaxis (PEP) is the immediate administration of ART to an exposed individual to prevent systemic HIV infection.

PEP is characterized further into nonoccupational exposure prophylaxis (nPEP) and occupational exposure prophylaxis (oPEP). Nonoccupational exposure to HIV occurs most frequently through sexual contact without barrier protection, sexual assault, or intravenous drug use. Occupational exposure to HIV occurs through parenteral exposure, via percutaneous injury from a needle stick or sharp object, or direct contamination of mucous membranes or nonintact skin with potentially infectious sources. Sources that should be considered potentially infectious in the healthcare setting include blood, tissue, semen, vaginal secretions, cerebrospinal fluid, synovial fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. Saliva, sputum, sweat, tears, urine, feces, and vomitus are not considered infectious unless visibly bloody.

The estimated risk of HIV transmission is influenced by several factors, including the route of transmission, the inoculum of infectious virus, the viral load of the source patient, and the exposed individual's immunologic response. Estimated risk of transmission is 0.3% and 0.09% for parenteral and membrane exposures, respectively. Nonintact skin exposure is estimated to be even lower. Occupational HIV transmission has been associated with deep injuries, visible blood on the device, procedures involving inoculation into a vein or artery, and exposure to fluids from a source patient with terminal illness, likely reflective of the risk for transmission in the setting of a high viral load. For sexual exposures, highest per-act transmission risk occurs with receptive anal intercourse (0.5–3.38%) due to a higher density of lymphoid follicles in rectal mucosa and a higher potential for abrasions when compared to vaginal mucosa.

Guidelines for nPEP and oPEP were most recently updated in 2016 and 2013, respectively. As prospective RCTs have not been conducted, recommendations are based on efficacy studies in animal models, observational studies, epidemiologic studies, and expert consensus.

First-line regimens for PEP consist of triple-drug ART with tenofovir disoproxil fumarate and emtricitabine as the dual NRTI backbone in combination with twice-daily raltegravir or once-daily dolutegravir. Due to the potential risk for neural tube defects in the first trimester with dolutegravir therapy, raltegravir is currently the preferred INSTI early in pregnancy and in nonpregnant women of childbearing potential who are sexually active or who have been sexually assaulted and are not using effective birth control. Preferred and alternative regimens for PEP are listed in Box 98.3. For those with a CrCl of ≤59 mL/min, the alternative NRTI backbone, zidovudine in combination with lamivudine, should be prescribed and renally dosed as appropriate. Two-drug regimens are no longer recommended for PEP. Additionally, the use of nevirapine for PEP is contraindicated due to the risk of hepatotoxicity.

When therapy is indicated, PEP should be initiated as soon as possible and within 72 hours of exposure. Animal models demonstrate that prevention of HIV acquisition decreases substantially from 100% to 50% to 25% for therapy initiation at 24, 48, and 72 hours post-exposure, respectively. If the HIV status of the source patient is positive or unknown, therapy should be continued for a total of 28 days post exposure. In animal studies, all animals receiving PEP for 28 days remained uninfected; half of animals treated for 10 days remained uninfected; and no animals receiving 3 days were protected.

BOX 98.3

Combined recommendations for non-occupational and occupational post-exposure prophylaxis (PEP)

Preferred regimens
RAL or DTG + TDF/FTC
Alternative Regimens, INSTI-Based
EVG/c/TDF/FTC
RAL or DTG + AZT/3TC
Alternative Regimens, PI-Based
DRV/r + TDF/FTC or AZT/3TC
ATV/r +TDF/FTC or AZT/3TC
LPV/r + TDF/FTC or AZT/3TC
Alternative Regimens, NNRTI-Based
RPV + TDF/FTC or AZT/3TC

Abbreviations: INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

HIV testing of the source patient should be conducted, if possible, and once consent is obtained. If the HIV status of the source patient is negative, PEP can be safely discontinued. HIV testing of the exposed individual should occur at baseline, 4 to 6 weeks, 3 months, and 4 to 6 months after exposure. Additional laboratory testing of the exposed individual should include screening for bacterial sexually transmitted infections, pregnancy, and hepatitis B virus and hepatitis C virus infection, if indicated. Follow-up should occur within 72 hours of exposure to provide additional counseling; ensure continued PEP is indicated; assess adherence, access, and tolerability; and manage side effects. Minimal laboratory testing to evaluate the safety of PEP includes serum creatinine and hepatic function tests at baseline and upon completion of therapy.

For individuals who report behaviors or situations that may result in an ongoing risk for HIV acquisition, risk reduction counseling and intervention services should be performed. If indicated, pre-exposure prophylaxis (PrEP) should be considered at the conclusion of their 28-day PEP course. PWID should be offered medication-assisted treatment, if appropriate, and counseled on safe injecting and sexual practices, including referral to syringe exchange programs where available.

Pre-exposure prophylaxis

PrEP is the administration of antiretrovirals to an HIV-negative patient who is at high risk for acquiring HIV infection. A number of trials have demonstrated efficacy in prevention of HIV acquisition in patients taking PrEP. Effective prevention of HIV transmission has been demonstrated in men who have sex with men (MSM) in the iPrEX study, serodiscordant couples in the PartnersPrEP study, heterosexual individuals (both men and women) in the TDF2 study, and PWID in the Bangkok Tenofovir study. Studies of single-drug TDF, the oral combination of TDF/FTC, and the oral combination of TAF/FTC have shown efficacy. In the United States, Truvada (TDF/FTC) and Descovy (TAF/FTC) are the only agents currently FDA-approved for use for PrEP. TDF/FTC is approved for all higher risk individuals; TAF/FTC is approved for MSM and transgender women who have sex with men (this was the population studied in the DISCOVER trial that demonstrated noninferiority of TAF/FTC to TDF/FTC as PrEP). In general, patient compliance in PrEP trials was not ideal; however, patients who adhered to their medication appeared to significantly reduce their risk of infection.

Concerns do exist with PrEP, especially in those patients who might still become infected with HIV despite taking PrEP. PrEP is not a full three-drug ART treatment regimen and therefore viral resistance may develop to the PrEP drugs should infection occur. A negative HIV status must be confirmed prior to PrEP initiation, and patients should undergo HIV testing frequently throughout therapy as a new positive result should prompt immediate full three-drug ART therapy. Patients who are unwilling or unable to undergo frequent monitoring may pose a risk to themselves (potential for development of a resistant HIV virus) and to the community (potential to transmit a resistant HIV infection).

Other considerations must be made prior to starting PrEP as well. A patient's hepatitis B status should be assessed, as should their baseline renal function. Willingness of patients to undergo interval lab testing should be evaluated (including both HIV testing, test of renal function, and testing for other sexually transmitted infections). Women taking PrEP who may become or recently became pregnant should have risks and benefits to the fetus clearly discussed. Ideally, uninfected women taking PrEP who become pregnant should abstain from further high-risk sexual contact to fully minimize their risk of contracting HIV during their pregnancy. Since tenofovir is a primary medication in this regimen, renal function should be monitored at baseline and periodically.

Immune reconstitution inflammatory syndrome

Patients with HIV who are initiated on ART at a low baseline CD4 count (usually <100 cells/mm^3) may be at risk for IRIS. In this patient population, hosts may be unable to mount an appropriate immune inflammatory defense response, and OIs may exist in the absence of significant symptoms. As the immune system is restored with ART treatment, these subclinical infections can stimulate an aggressive inflammatory reaction. This reaction usually involves infected organ systems and is generally more common and profound in patients with disseminated OIs and high titers of pathogen. Autoimmune IRIS reactions that are unrelated to a known OI have also been described.

IRIS is a clinical diagnosis that may be difficult to discern from a true new infection or drug reaction. IRIS is broadly divided into two types, *paradoxical IRIS* describes a paradoxical worsening of a treated, known OI, while *unmasking IRIS* describes the unmasking of a previously subclinical untreated infection. Both forms of IRIS are commonly seen and can co-occur (i.e., patients can have multiple OIs present, with a clinical worsening of known disease and the unmasking of a second OI). Diagnosis of IRIS involves workup for potential undiagnosed disease and treatment of any diagnosed diseases. Once IRIS is considered the most likely possibility, nonsteroidal anti-inflammatory drugs or corticosteroid medications may be considered depending on severity.

Though initiation of ART in a patient with a known OI may increase the risk of IRIS, studies have demonstrated that, in most cases, IRIS can be managed and a mortality benefit exists to starting ART promptly (generally within 2 weeks of initiating treatment of the OI). Exceptions to this "treat early" approach are cryptococcal meningitis and tuberculous meningitis. For patients with cryptococcal meningitis, trials in low- and moderate-income countries have demonstrated a mortality benefit to delayed ART initiation after 5 weeks of therapy. For tuberculous meningitis, one trial demonstrated an increase in grade 4 adverse events with early ART initiation. Aside from these specific diagnoses however, the evidence strongly supports prompt initiation of ART within 2 weeks of initiating treatment of an OI.

Suggested reading

AIDS Info. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. 2020. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0

Centers for Disease Control (CDC). Preexposure prophylaxis for the prevention of HIV infection in the United State—2017 Update Clinical Practice Guideline. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

Centers for Disease Control (CDC). Updated US Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. September 25, 2013. https://stacks.cdc.gov/view/cdc/20711

Centers for Disease Control (CDC). Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016. April 2016. http://stacks.cdc.gov/view/cdc/38856

Stanford University. HIV drug resistance database. https://hivdb.stanford.edu/

Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2018;320(4):379–396.

Günthard HF, Calvez V, Paredes R, et al. Human immunodeficiency virus drug resistance: 2018 recommendations of the International Antiviral Society–USA Panel. *Clin Infec Dis*. 2018.

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Immune reconstitution inflammatory syndrome

Suzaan Marais and Graeme Meintjes

Introduction

In the majority of patients with advanced HIV disease, treatment with antiretroviral therapy (ART) results in a decreased HIV viral load, increased CD4 count, improved immunologic function, and subsequently, reduced opportunistic infections (OIs) and mortality. During the early stages of immune recovery on ART, a subset of patients may experience clinical deterioration due to the immune reconstitution inflammatory syndrome (IRIS); this can be as high as 25% of patients in cohorts with advanced immunosuppression at the start of ART. IRIS typically occurs during the initial 3 months of ART (when there is rapid reversal of the immunosuppressed state) as the result of a dysregulated immune response directed at infective or, less commonly, noninfective antigens. The majority of IRIS cases are associated with mycobacterial, fungal, or viral infections. However, IRIS may also be associated with other diseases (Table 99.1). Selected significant IRIS manifestations are discussed in further sections. Cutaneous IRIS manifestations are common and are highlighted in Table 99.1.

Two forms of infective IRIS are recognized: (1) paradoxical IRIS (p-IRIS), in which an OI is diagnosed and treated appropriately prior to starting ART with the subsequent development of recurrent, worsening, or new symptoms and signs after starting ART; and (2) unmasking IRIS (u-IRIS), in which a previously present but clinically undetected and therefore untreated OI becomes apparent after starting ART, typically with an unusually exaggerated inflammatory presentation (Figure 99.1). In both scenarios the spectrum of IRIS manifestations vary considerably; these may be localized or involve multiple organ systems, and systemic inflammatory signs may be prominent. IRIS may be mild and self-limiting, lasting days to weeks, or infrequently persist for years. In a small proportion of cases IRIS may be life-threatening or fatal, particularly in forms that involve the central nervous system (CNS) and those that result in airway compromise, organ failure, or organ rupture (Table 99.2). Risk factors associated with IRIS include a low CD4 count (particularly <50 cells/mm^3), high HIV viral load (particularly >5 $\log_{10}$), high pathogen load related to the OI, a rapid decline in HIV viral load and/or rise in CD4 count on ART, and short interval between initiation of OI treatment and ART. As no confirmatory tests exist, the diagnosis of p-IRIS relies on identifying the characteristic sequence of clinical events and exclusion of other possible causes for clinical deterioration, such as drug reaction or toxicity, failure of treatment for the OI (due to poor adherence, drug malabsorption, or antimicrobial drug resistance), or an alternative/additional infection or malignancy. U-IRIS is diagnosed using standard diagnostic tests for the underlying infection.

General principles in infective IRIS prevention and management

Prior to starting ART, thorough screening for OIs and, when diagnosed, initiation of appropriate treatment will prevent some cases of u-IRIS. A short interval between OI treatment and ART initiation is a strong risk

TABLE 99.1 **INFECTIOUS CAUSES AND NONINFECTIVE MANIFESTATIONS OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)**

Infections	Other conditions
Mycobacteria	**Autoimmune**
Tuberculosis	Systemic lupus erythematosus (SLE), lupus-like disease
Nontuberculous mycobacteria, especially *Mycobacterium avium* complex	Thyroid disease
Leprosy	Rheumatoid arthritis
Bacille Calmette–Guérin	Guillain–Barré syndrome
Fungi	Reiter's syndrome
Cryptococcus	Polymyositis
Pneumocystis	Relapsing polychondritis
Histoplasma	Alopecia
Candida	Cerebral vasculitis
Trichophyton rubrum	Idiopathic thrombocytopenic purpura
Penicillium marneffei	Poststreptococcal glomerulonephritis
Coccidioides	Vitiligo
Viruses	Nephrotic syndrome
Herpes simplex virus[a]	Autoimmune hepatitis
Herpes zoster virus[a]	Thrombotic thrombocytopenic purpura
Cytomegalovirus	**Other inflammatory conditions**
JC polyomavirus	Sarcoidosis
Hepatitis B and C virus	Foreign-body reaction
Molluscum contagiosum[a]	Folliculitis[a]
Human papilloma virus[a]	Lymphoid interstitial pneumonitis
Polyoma BK virus	Photodermatitis
HIV encephalitis	Peyronie's disease
Parvovirus B19	Dermatofibromata
Human T lymphotropic virus type-2	Dyshidrosis
Epstein–Barr virus	Gouty arthritis
Protozoa	**Malignancy**
Toxoplasma	Kaposi's sarcoma
Microsporidia	
Leishmania	
Cryptosporidia	
Helminths	
Schistosoma	
Strongyloides	
Bacteria	
Bartonella	
Proprionibacteria[a]	
Klebsiella	
Arthropods	
Sarcoptes scabiei	

[a] Common causes and manifestations of cutaneous IRIS.

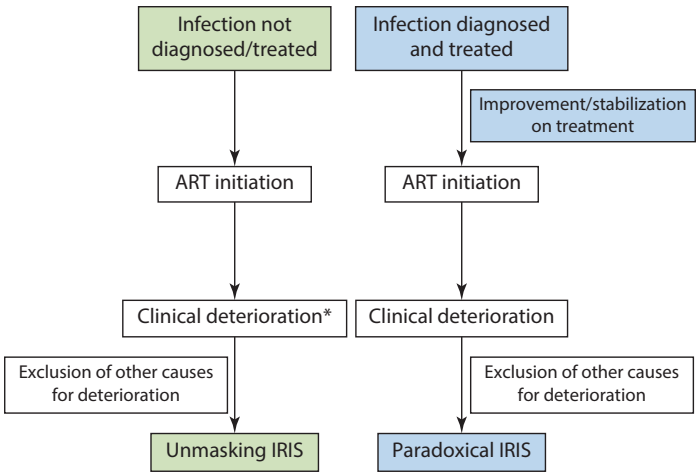

FIGURE 99.1 Schematic representation of the typical sequence of events associated with the two forms of infective immune reconstitution inflammatory syndrome (IRIS): unmasking (green) and paradoxical (blue). *, Characterized by heightened inflammatory features; ART, antiretroviral therapy.

TABLE 99.2 CAUSES AND MANIFESTATIONS OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) REPORTED THAT ARE POTENTIALLY LIFE-THREATENING

Causes	Manifestations
Neurologic manifestations	
Tuberculosis	Meningitis, intracerebral space-occupying lesions, spinal epidural abscess
Nontuberculous mycobacteria	Meningoencephalitis, brain abscess
JC virus	Progressive multifocal leukoencephalopathy
Cytomegalovirus	Encephalitis, vasculitis, ventriculitis
Herpes simplex virus	Encephalitis
Herpes zoster virus	Meningoencephalitis, vasculitis
Candida	Meningitis, vasculitis
Parvovirus B19	Encephalitis
BK virus	Meningoencephalitis
Toxoplasma	Encephalitis
Autoimmune reaction	Demyelinating central nervous system disease, cerebral vasculitis, Guillain–Barré syndrome
HIV itself the target of IRIS	Encephalitis
Cryptococcus	Meningitis, intracerebral space-occupying lesions, cerebellitis
Coccidioides	Meningitis
Extraneural manifestations	
Kaposi's sarcoma	Pneumonitis, airway and gastrointestinal tract involvement
Tuberculosis	Splenic rupture, bowel perforation, airway compression by lymph nodes, pericardial effusion, and acute renal failure
Nontuberculous mycobacteria	Airway compression by lymph nodes, alveolitis
Hepatitis B and C virus	Fulminant liver failure, progression of liver cirrhosis
Bacille Calmette–Guérin	Disseminated disease
Pneumocystis	Pneumonitis

factor for p-IRIS. However, delaying ART comes at the cost of remaining vulnerable to HIV disease progression, additional OIs, and mortality, particularly in severely immunosuppressed patients. The optimal time for starting ART depends on the underlying OI and will be discussed in relevant upcoming sections.

A key component of management is optimal therapy of the OI. Anti-inflammatory therapy should be considered to alleviate symptoms and reduce inflammation particularly in more severe cases. Nonsteroidal anti-inflammatory drugs (NSAIDs) may provide symptomatic relief in patients with mild IRIS manifestations. Corticosteroids are the most frequently used anti-inflammatory drugs in cases of IRIS related to mycobacterial and fungal infections, particularly in severe cases, and are the only treatment modality for which supportive clinical trial data exist. However, corticosteroids should generally only be considered when the diagnosis of IRIS has been made with certainty, having excluded alternative causes for clinical deterioration. Corticosteroids should normally not be used in patients with Kaposi's sarcoma (KS) as they may worsen this condition. There are isolated case reports of clinical response when other immunomodulatory drugs such as thalidomide and adalimumab were used to treat IRIS, but such approaches remain experimental. ART should not be interrupted in IRIS cases as this may increase vulnerability to other OIs and predispose to ART drug resistance. IRIS may also recur after ART reinitiation. ART interruption may be considered, however, as a last resort for patients with life-threatening IRIS, particularly those nonresponsive to corticosteroid therapy.

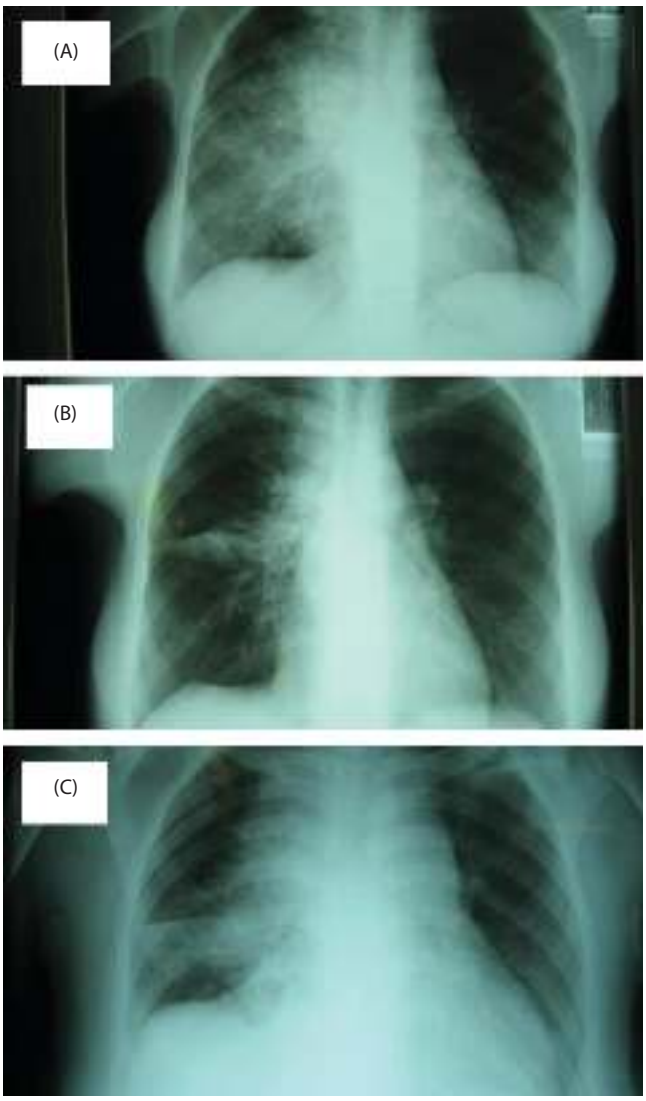

FIGURE 99.2 Chest radiograph sequence in a patient with paradoxical tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS): (A) at time of TB diagnosis, (B) improvement on TB treatment prior to antiretroviral therapy (ART), (C) worsening of pulmonary infiltrate and mediastinal lymph node enlargement at the time of IRIS presentation.

Pathogen-specific IRIS manifestations

Tuberculosis

Tuberculosis (TB)-IRIS is the most frequent form of IRIS in countries where TB/HIV coinfection rates are high. P-TB-IRIS occurs in 8% to 54% of patients who start ART while on TB treatment, typically 1 to 3 weeks, but up to 3 months, after starting ART. Presenting features relate to inflammation at previously recognized and/or new TB disease sites. Common symptoms and signs include fever, cough, tachycardia, lymphadenitis, pulmonary infiltrates (Figure 99.2), serous effusions, and tender hepatomegaly. Other manifestations include abscesses and osteitis. Neurologic TB-IRIS occurs in a substantial proportion of p-TB-IRIS cases (12% in one series) and presents as meningitis (Figure 99.3), intracranial tuberculomata, radiculomyelitis, spinal epidural abscesses, or brain abscesses. Although p-TB-IRIS is usually a self-limiting condition with an attributable mortality of 2%, neurologic forms are frequently fatal. The average symptom duration for p-TB-IRIS is 2 to 3 months, but in a minority TB-IRIS it is prolonged, lasting for months to years. Of particular importance in making the diagnosis is the exclusion of drug-resistant TB, which may present indistinguishably from p-TB-IRIS associated with drug-susceptible TB. Superficial and fluctuant lymph nodes can be aspirated and large deep collections, such as psoas abscesses, may be drained under ultrasound guidance to provide symptomatic relief and to obtain a specimen to rule out drug-resistant TB. The use of anti-inflammatory drug treatment depends on disease severity. Corticosteroid treatment (at a starting dose of 1–2 mg/kg/d of prednisone, or its equivalent, for 2–4 weeks and thereafter tapered based on individual clinical response) is indicated for life-threatening forms and may provide symptomatic relief for other cases with significant symptoms. The only randomized controlled trial (RCT) to assess treatment for any form of IRIS compared prednisone with placebo for the treatment of p-TB-IRIS, excluding patients with immediately life-threatening TB-IRIS. Patients in the prednisone arm received 1.5 mg/kg/d for 2 weeks followed by 0.75 mg/kg/d for a further 2 weeks. Prednisone was associated with a significant reduction in number of days hospitalized and also resulted in more rapid symptom and radiologic improvement.

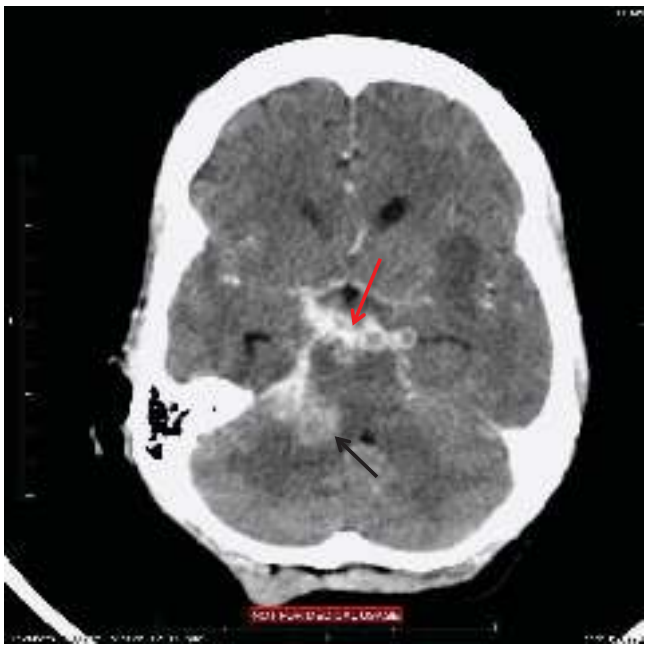

FIGURE 99.3 CT brain findings in a patient who developed tuberculosis (TB) meningitis-immune reconstitution inflammatory syndrome (IRIS). Post-contrast imaging shows marked basal meningeal enhancement (*red arrow*) and multiple ring-enhancing lesions (*red and black arrow*) at IRIS presentation.

Evidence from three RCTs suggests that the optimal time to start ART in severely immunosuppressed TB patients (CD4 <50 cells/mm^3) is 2 to 4 weeks after TB treatment initiation. Starting ART at this time point (compared with 8–12 weeks) was associated with a survival benefit in one trial and a reduction in AIDS progression and mortality as a combined end point in the others, even though earlier ART increased the incidence of TB-IRIS two- to fivefold. Thus ART cannot be deferred for IRIS prevention in patients with very low CD4 counts. However, in such patients there is evidence for a strategy to prevent TBV-IRIS: an RCT demonstrated that in patients with HIV-associated TB and CD4 counts of ≤100 cells/mm^3, a 4-week course of prednisone (40 mg/d for 2 weeks followed by 20 mg/d for 2 weeks) reduced the incidence of TB-IRIS by 30% and was well tolerated. TB meningitis (TBM) patients are at higher risk of developing life-threatening neurologic TB-IRIS, and early ART was associated with more severe adverse events in an RCT of ART timing in TBM patients. Hence certain guidelines recommend deferring ART until 4 to 6 weeks after TB treatment initiation in TBM patients.

U-TB-IRIS is diagnosed in patients who present with unusually inflammatory or accelerated features of TB during the first 3 months of ART. Examples include unmasking pulmonary TB-IRIS presenting with rapid onset of respiratory symptoms and respiratory distress mimicking bacterial pneumonia, and suppurative lymphadenitis. A high index of suspicion for TB should be maintained in TB-endemic settings in all patients who present with clinical deterioration after starting ART. When diagnosed, standard TB treatment should be initiated.

Cryptococcosis

Cryptococcal IRIS most commonly presents with meningitis. Paradoxical cryptococcal meningitis (p-CM)-IRIS occurs in up to 30% of CM patients who commence ART, although it has been reported less frequently in recent cohorts. Other CNS manifestations include intracranial cryptococcomas or abscesses, cerebellitis, and spinal cord abscesses. Extra-CNS manifestations such as fever, lymphadenitis, soft tissue and skin lesions, cavitating or nodular pulmonary disease, and chorioretinitis have also been described. The majority of cases present 1 to 2 months after ART initiation, although a minority may present after more than a year on ART. P-CM-IRIS is associated with raised intracranial pressure (ICP) in up to 75% of cases and an increased inflammatory response with higher protein and white cell concentrations in cerebrospinal fluid (CSF) when compared to those from the pre-ART CM event. Diagnostic workup for p-CM-IRIS is directed at excluding other neuroinflammatory etiologies and cryptococcal relapse as causes for deterioration by CSF analysis. A cryptococcal relapse is indicated by a positive cryptococcal CSF culture after >3 months of antifungal therapy or an increase in quantitative culture from pre-ART culture. Amphotericin B plus flucytosine (where available) or fluconazole (induction phase doses of 800 mg/d) should be restarted pending fungal culture results in patients with severe deterioration. If the CSF is sterile, maintenance doses of fluconazole may be resumed. Intensive management of raised ICP with daily lumbar puncture, when required, is critical in the management of p-CM-IRIS. Although no clinical trial data exist, prednisone (1 mg/kg/d, or equivalent, tapered over 2–6 weeks) should be considered in patients with ongoing symptoms or life-threatening neurologic impairment, but ideally only after cryptococcal relapse has been excluded.

Starting ART early (within 1–2 weeks from CM diagnosis versus 4–5 weeks) is associated with increased mortality in CM patients, and ART should be deferred until 4 to 6 weeks of antifungal treatment have been received.

Unmasking cryptococcal IRIS presents during the initial months of ART with manifestations such as meningitis with a particularly high CSF white cell count (for example >50 cells × 10^6/L) or a raised opening pressure refractory to treatment, suppurative lymphadenitis, rapidly expanding CNS lesions (cryptococcomas), and cavitating or necrotic pneumonitis. A clear distinction between CM cases first diagnosed after ART that are related to immune reconstitution and those that are related to persistent immunosuppression may be difficult; therefore, these two groups are collectively referred to as "ART-associated CM." In resource-limited settings, currently, at least a third of all new CM cases are diagnosed in patients on ART. An important preventative strategy for ART-associated CM in high-burden settings involves screening patients with CD4 counts of <100 or <200 cells/mm^3 for subclinical cryptococcal infection prior to ART using blood cryptococcal antigen test. A positive test is highly predictive of subsequent ART-associated CM, and such patients should have meningitis excluded. If meningitis is excluded on CSF analysis they should be treated preemptively with fluconazole at a starting dose of 800 or 1,200 mg/d.

JC virus

Reactivation of the JC virus results in progressive multifocal leukoencephalopathy (PML), a demyelinating disease of the brain, usually diagnosed in patients with CD4 counts of <100 cells/mm^3. Both u-PML-IRIS and p-PML-IRIS are described, and both are associated with significant mortality. The majority of cases present within 3 months of ART initiation, but u-PML-IRIS may develop after >6 months on ART. Clinical deterioration during PML-IRIS is usually acute and may be transient, unlike the course of PML in patients not on ART. In >50% of PML-IRIS cases there is gadolinium enhancement on MRI, which is not observed outside the context of IRIS. The diagnosis cannot rely on detecting JC virus from CSF by polymerase chain reaction (PCR) as partial containment of viral replication by the recovering immune system can result in false-negative results, which is found in approximately 40% of PML cases receiving ART compared to approximately 5% of ART-naïve PML cases. Brain biopsy may be required to exclude other causes for deterioration (e.g., lymphoma). The treatment of PML-IRIS is particularly difficult as there is limited evidence regarding effective antiviral therapy for JC virus. Interruption of ART for 2 to 3 weeks has been associated with favorable outcome in isolated cases, but this is associated with risks, and PML-IRIS may recur when ART is resumed. The role of corticosteroids is controversial, given that there is no specific treatment for the underlying JC virus infection, but may be indicated in patients with severe neurologic deterioration and those with edema on brain imaging.

Cytomegalovirus

Cytomegalovirus (CMV)-IRIS usually presents with eye involvement. This can manifest as a first episode of retinitis after starting ART. More commonly though, CMV-IRIS presents as immune recovery uveitis (IRU), which usually occurs in patients diagnosed with CMV retinitis prior to ART who subsequently experience an increase in CD4 count on ART. IRU can also be unmasked by ART. Rarely, CMV-IRIS may affect other organs such as the colon, esophagus, or brain. The cumulative incidence of p-CMV-IRU is 38%, and patients with the greatest retinal involvement (>30% of the retinal surface) during the pre-ART retinitis episode are at highest risk for IRU. CMV-IRU is distinguished clinically from typical CMV retinitis by the abundance of intraocular inflammatory cells and inactive CMV retinitis in the former. The spectrum of IRU inflammation ranges from asymptomatic vitreitis to persistent uveitis with cystoid macular edema (CME) and epiretinal membrane formation. Worsening retinitis due to active CMV infection and persistent visual symptoms due to vitreous debris relating to previous CMV retinitis as well as new OIs should be considered in the differential diagnosis. The treatment of CMV-IRU varies according to disease severity. Cases with mild CME and visual acuity more than 20/30 can be observed without treatment. In more severe cases, periorbital or intravitreal corticosteroid injections usually result in decreased inflammation, but these treatments are not always associated with improved vision.

Hepatitis B and C viruses

ART initiation is frequently complicated by liver enzyme elevation (LEE). Patients coinfected with hepatitis B (HBV) or hepatitis C virus (HCV) are at increased risk because they are predisposed to drug-induced liver injury but also because of enhanced immune responses directed at the hepatitis virus. Hepatitis-IRIS is poorly defined, but significant LEE (rise of alanine aminotransferase [ALT] >5 × upper limit of normal, or >3 × of baseline if abnormal prior to ART), particularly within 3 months of starting ART, should prompt consideration of the diagnosis. Rarely, hepatitis-IRIS has been associated with severe hepatic dysfunction resulting in fulminant hepatic failure or life-threatening progression of cirrhosis. The diagnosis of hepatitis-IRIS is challenging as the most important differential diagnosis is drug-induced liver injury. Risk factors for hepatic flares on ART in HBV coinfection include high HBV DNA and ALT levels before ART. There are no evidence-based guidelines for managing hepatitis-IRIS. It has been suggested that HBV or HCV should be treated prior to ART initiation to minimize the risk of hepatitis-IRIS in high-risk cases (e.g., those with underlying liver cirrhosis). A pragmatic approach to a patient with chronic viral hepatitis with significant LEE on ART includes the following: (1) stop hepatotoxic non-ART drugs; (2) exclude alternative causes, as far as possible; (3) alter ART (if necessary) to exclude drugs with the highest risk for hepatotoxicity (especially nevirapine) and maintain patients coinfected with HBV on an effective ART regimen that contains two drugs also active against HBV (e.g., tenofovir and either lamivudine or emtricitabine); (4) monitor liver function tests and clinical status closely and consider liver biopsy if no improvement; and (5) interrupt ART if hepatic failure occurs and restart once liver enzymes are normalizing. In HBV coinfected patients, preferably two HBV active drugs should be continued during ART interruption to prevent viral rebound. None of the HIV drugs is effective against HCV, and treatment with anti-HCV therapy should be considered during ART interruption in affected patients. Corticosteroids and other immunosuppressive drugs should be avoided in hepatitis-IRIS as they may result in increased viral replication and hepatic deterioration.

Kaposi's sarcoma

KS is caused by the KS-associated herpesvirus (KSHV) and is the most common malignancy in HIV-infected persons. Although starting ART is associated with the resolution or improvement of KS lesions in most patients, p-KS-IRIS occurs in approximately 14% of patients with KS at a median time of 7 weeks on ART. U-KS-IRIS has also been reported. KS-IRIS cases present with new lesions or inflammation or enlargement of existing skin lesions. Lymphedema and oral, gastrointestinal, airway, and lung involvement are other manifestations. KS-IRIS is frequently fatal in settings with limited access to chemotherapy, with mortality of 48% reported for p-KS-IRIS in an African cohort. Pre-ART risk factors for p-KS-IRIS include more extensive KS disease, high plasma HIV-1 viral load (>5 $\log_{10}$), detectable plasma KSHV DNA, and not receiving KS treatment (chemotherapy). P-KS-IRIS might be prevented by administering chemotherapy, particularly in severe cases, prior to

ART. Treatment of KS-IRIS similarly includes systemic chemotherapy and/or localized radiotherapy. Corticosteroids may result in rapid progression of existing or new KS lesions and are therefore not used for KS-IRIS.

IRIS unrelated to HIV infection

IRIS is best described in the context of ART treatment of HIV infection, but it is also recognized in persons recovering from other causes of immune suppression, such as patients who interrupt immune suppressive drugs (e.g., tumor necrosis factor [TNF] inhibitors, natalizumab, and drugs used in solid organ/stem cell transplants). Further discussion is beyond the scope of this chapter, and the reader is referred to the review by Sun et al. (see Suggested reading).

IRIS pathogenesis

Central to the pathogenesis of most forms of ART-related IRIS is the rapid recovery of immune function in the presence of large amounts of infective antigen. Several components of the immune system have been implicated including activated antigen-specific CD4 and CD8 T lymphocytes, macrophages and monocytes, neutrophils, natural killer (NK) cells, and proinflammatory cytokines and chemokines. The hallmark of the tissue pathology associated with mycobacterial and fungal IRIS is granuloma formation, sometimes with suppuration. Viral forms of IRIS are characterized by CD8 T-cell infiltrates.

Conclusion

IRIS may complicate ART initiation in up to 25% of patients in cohorts starting ART with advanced immunosuppression. This is because the major determinant of IRIS is progression to advanced HIV disease that places individuals at risk of OIs. In resource-poor settings many patients still enter HIV care with advanced HIV and remain at risk for IRIS. Because there is no confirmatory test for IRIS, it is a clinical diagnosis and other causes of deterioration should be excluded before making the diagnosis of IRIS. In most cases ART is continued, treatment for the underlying infection should be optimized, and, for mycobacterial and fungal forms of IRIS, corticosteroids can be considered when symptoms are significant. There is RCT evidence to support the use of steroids for treatment and prevention of p-TB-IRIS, but in other forms of IRIS their use as treatment is based on anecdotal evidence of benefit.

Suggested reading

Barber DL, Andrade BB, Sereti I, et al. Immune reconstitution inflammatory syndrome: The trouble with immunity when you had none. *Nat Rev Microbiol*. 2012;10:150–156.

Crane M, Matthews G, Lewin SR. Hepatitis virus immune restoration disease of the liver. *Curr Opin HIV AIDS*. 2008;3:446–452.

Dhasmana DJ, Dheda K, Ravn P, Wilkinson RJ, Meintjes G. Immune reconstitution inflammatory syndrome in HIV-infected patients receiving antiretroviral therapy: Pathogenesis, clinical manifestations and management. *Drugs*. 2008;68:191–208.

French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS*. 2004;18:1615–1627.

Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. *Lancet Infect Dis*. 2010;10:791–802.

Letang E, Lewis JJ, Bower M, et al. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: Higher incidence and mortality in Africa than in the UK. *AIDS*, 2013;27:1603–1613.

Meintjes G, Rabie H, Wilkinson RJ, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome and unmasking of tuberculosis by antiretroviral therapy. *Clin Chest Med*. 2009;30:797–810.

Meintjes G, Scriven J, Marais S. Management of the immune reconstitution inflammatory syndrome. *Curr HIV/AIDS Rep*. 2012;9:238–250.

Meintjes G, Stek C, Blumenthal L, et al.; PredART Trial Team. Prednisone for the prevention of paradoxical tuberculosis-associated IRIS. *N Engl J Med*. 2018 Nov 15;379(20):1915–1925.

Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. 2010;24:2381–2390.

Namale PE, Abdullahi LH, Fine S, Kamkuemah M, Wilkinson RJ, Meintjes G. Paradoxical TB-IRIS in HIV-infected adults: A systematic review and meta-analysis. Future Microbiol. 2015;10(6):1077–1099.

Sun HY, Singh N. Immune reconstitution inflammatory syndrome in non-HIV immunocompromised patients. *Curr Opin Infect Dis*. 2009;22:394–402.

Tan K, Roda R, Ostrow L, et al. PML-IRIS in patients with HIV infection: Clinical manifestations and treatment with steroids. *Neurology*. 2009;72:1458–1464.

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Opportunistic infections in HIV

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Timely recognition and treatment of HIV-associated opportunistic infections (OIs) remains an important skill for practicing physicians worldwide. Whereas the overall incidence of these infections has fallen sharply since the advent of combination antiretroviral therapy (*aka* highly active antiretroviral therapy or HAART), OIs remain the most serious threat to well-being and survival among HIV-infected individuals with advanced immunosuppression. Despite improved access to screening globally, morbidity from OIs is often the first indication of previously undiagnosed HIV infection. Thus, familiarity of healthcare personnel with the presenting signs, symptoms, and treatment of OIs is key to improving HIV-related clinical outcomes at both the individual and community levels.

Fortunately, with most OIs, the likelihood of symptomatic disease correlates with CD4 count (Figure 100.1). Periodic CD4 measurements are, therefore, an integral part of OI surveillance, prevention and treatment. This chapter offers a clinical overview of the most frequently encountered OIs. Current concepts and approaches to management are also discussed.

Mucocutaneous infections

The largest threat to oral health in HIV-infected patients is oral candidiasis or "thrush." While not pathognomonic, the development of thrush in a young, otherwise healthy adult without known risk factors such as diabetes mellitus or recent antibiotic or inhaled steroid use should raise concern for undiagnosed HIV infection. Thrush typically presents as white, loosely adherent deposits on the dorsum of the tongue, but frequently extends posteriorly to involve the palate and oropharynx. Severe cases are associated with oral discomfort, dysgeusia, and nausea. Candidal angular cheilitis is also seen in HIV-infected patients but is rarer than thrush in this population. Clinically, it is indistinguishable from other causes of cheilitis, manifesting as painful, bleeding sores at the corners of the mouth. Treatment of both conditions consists of either oral or topical antifungal therapy (Table 100.1).

Seborrhea dermatitis is another common complication of HIV infection and presents as a greasy, flaky, and faintly erythematous rash with a predilection for the face. Areas rich in sebaceous glands—the hairline, eyebrows, nose, and nasolabial folds—are prime targets. The role of *Malassezia furfur* infection in pathogenesis remains uncertain. Topical antifungal and corticosteroid agents are used to treat this condition (Table 100.1).

Recurrent or multidermatomal cutaneous herpes zoster infections are sometimes the only outward indication of waning cell-mediated immunity in HIV-infected adults. Lancinating pain and paresthesias in the soon-to-be involved dermatome are followed days later by the sudden outcropping of vesicles on an erythematous base. Use of oral acyclovir or related agents (valacyclovir or famciclovir) within 72 hours improves symptoms, speeds up crusting, and may reduce the risk of postherpetic neuralgia (Table 100.1).

Painful, burning vesicular lesions in the perineum or perirectal region are most often due to herpes simplex virus (HSV) reactivation. Mucocutaneous HSV infections are more frequent at CD4 counts of ≤500

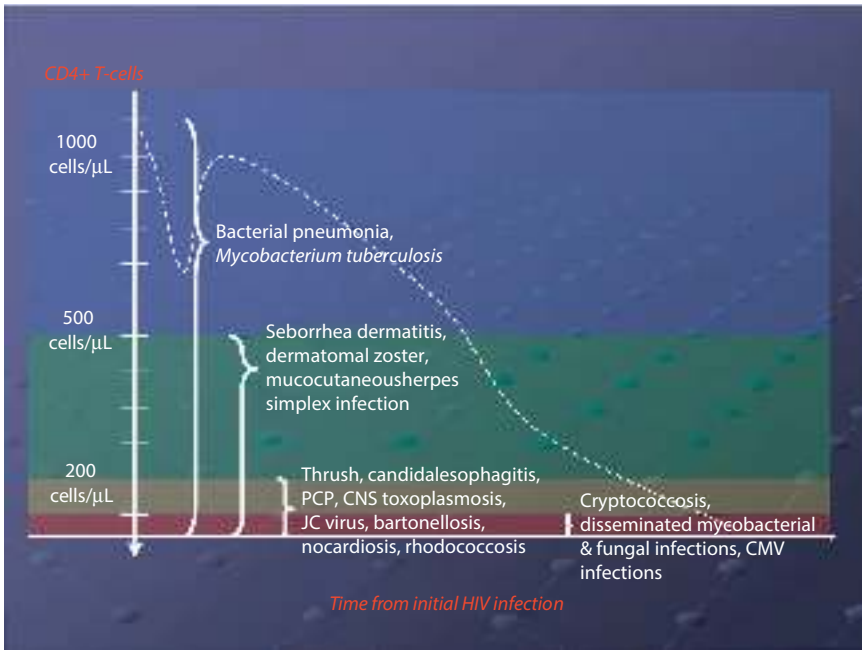

FIGURE 100.1 Spectrum of opportunistic infections in untreated HIV infection and the CD4 T-cell count ranges in which they manifest. CMV, cytomegalovirus; CNS, central nervous system; PCP, *Pneumocystis jirovecii* pneumonia.

cells/mm^3. Oral acyclovir, valacyclovir, and famciclovir are all effective in reducing the severity and duration of symptoms. They are also effective prophylactically (Table 100.1).

Skin lesions due to molluscum contagiosum, like the aforementioned OIs, also tend to be more frequent and severe in HIV-infected individuals. Molluscum contagiosum is caused by a poxvirus that causes characteristically firm, umbilicated, and sometimes pedunculated skin lesions (Figure 100.2). Intertriginous areas of the body, namely the axillae, perineum, antecubital, and popliteal fossae, are preferentially involved. Transmission requires intimate physical contact with an infected person. No specific chemotherapy exists; however, effective ART can hasten lesion regression. Alternatively, lesions can be removed by cryotherapy, curettage, or laser cautery (Table 100.1).

Oral hairy leukoplakia, caused by Epstein–Barr virus infection of lingual squamous epithelium, manifests as painless, white, tightly adherent, vertical ridges on the lateral aspect of the tongue. Lesions can be subtle so close inspection of the entire surface of the tongue and sublingual mucosa is warranted. Robust immune recovery through HAART is the most effective treatment for this condition (Table 100.1).

Pulmonary infections

Globally, *Mycobacterium tuberculosis* and *Pneumocystis jirovecii* remain the two most frequently identified causes of pneumonia in HIV-infected patients. They are also major causes of both morbidity and mortality in this population. Thus, the initial evaluation and management of lower respiratory tract infections in HIV-positive persons rests on the following principles: (1) prompt administration of empiric antibiotics against community- or hospital-acquired pneumonia pathogens, (2) immediate respiratory isolation of individuals presenting with either symptoms or chest imaging findings concerning for pulmonary tuberculosis (MTB), and (3) early administration of empiric treatments for *P. jirovecii* pneumonia (PJP) in individuals presenting with evidence of advanced HIV disease *plus* either acute respiratory failure and/or radiographic findings suspicious for PJP (discussed later).

The evaluation of pneumonia in HIV-infected individuals with low CD4 counts often requires CT scans of the chest in addition to chest x-rays (CXR). This is particularly true in cases where CXR findings—coupled with clinical inferences drawn from the history, physical exam, laboratory findings, and most recent CD4 count—do not comport with one specific cause of pneumonia. Given the myriad of possibilities in patients with AIDS (Table 100.2), cross-sectional imaging can be used to refine the initial differential diagnosis pending results of more definitive microbiologic and histopathologic tests.

Pneumocystis jirovecii pneumonia

Low-grade fever, dry cough, and progressive dyspnea are the cardinal symptoms of PJP. Risk factors include CD4 counts of ≤200 cells/mm^3, CD4 percentage of ≤14, prior PJP, or thrush at the time of presentation. Radiographically, PJP usually presents as symmetric, perihilar, interstitial, or alveolar infiltrates (Figure 100.3). However, excluding PJP purely on the basis of CXR findings can be risky. For example, follow-up CTs sometimes uncover classic PJP findings where prior CXRs had either been clear or suggestive of a bacterial process. Furthermore, a number of "atypical" radiographic

TABLE 100.1 **MANAGEMENT OF MUCOCUTANEOUS OPPORTUNISTIC INFECTIONS**

Condition/pathogen	First-line treatment	Notes
Thrush or candidal angular cheilitis	Fluconazole, 100 mg PO qd for 7–14 days	Alternative therapies include: Clotrimazole troches, 10 mg PO 5 × daily; nystatin solution, swish and swallow QID; or. In the event of azole resistance: amphotericin B suspension, 100 mg/mL PO QID; amphotericin B deoxycholate, 0.3–0.7 mg/kg IV qd; liposomal or lipid complex amphotericin, 3–5 mg/kg; voriconazole, 200 mg PO qd; or caspofungin 50 mg IV qd for 7–14 days.
Seborrhea dermatitis	Face: imidazole cream (ketoconazole 2% or clotrimazole 1%) plus hydrocortisone 1.0%–2.5% or desonide 0.05% cream BID Scalp/body: antidandruff shampoo (e.g., Selsun Blue or Head and Shoulders) plus triamcinolone 0.1% cream (body) or solution (scalp)	Severe cases may require addition of oral ketoconazole, 200–400 mg qd for 2–4 weeks.
Varicella-zoster virus	Acyclovir, 800 mg PO 5 × daily; famciclovir, 500 mg PO TID; or valacyclovir, 1000 mg PO TID for 7–10 days	(1) Trigeminal or disseminated cutaneous zoster; attendant meningoencephalitis; or evidence of visceral involvement (i.e., elevated transaminases and/or pancreatic enzymes) all merit IV acyclovir, 10 mg/kg q8h, until clinical resolution (minimum 14–21 days). (2) In the event of acyclovir resistance: foscarnet, 40–60 mg/kg IV q8h, or cidofovir plus IV hydration and oral probenecid to mitigate renal toxicity.
Herpes simplex virus	Acyclovir, 400 mg PO TID; famciclovir, 500 mg PO BID; or valacyclovir, 1000 mg PO BID for 7–14 days	In the event of acyclovir resistance: foscarnet, 40–60 mg/kg IV q8h, or cidofovir plus IV hydration and oral probenecid to mitigate renal toxicity.
Molluscum contagiosum	Laser, cryotherapy, and curettage plus HAART	
Oral hairy leukoplakia (OHL)	HAART	(1) OHL is pathognomonic of underlying HIV infection. (2) Rarely warrants specific therapy; but oral acyclovir 800 mg PO 5 × daily and podophyllin have been used with variable success in severe cases.

Abbreviations: PO = orally; QID = four times per day; qd = every day; BID = twice per day; TID = three times per day; HAART = highly active antiretroviral treatment; IV = intravenously.

findings—including cystic, apical, nodular, and cavitary infiltrates—have also been described in cytologically proven cases of PJP.

In managing suspected cases of PJP, it is imperative that prompt initiation of therapy always take precedence over making a definitive cytological diagnosis. Delays in PJP-specific therapy are the biggest threat to survival once the patient has sought medical care. And, contrary to notions held by some clinicians, treatment does not significantly reduce the yield of stainable pneumocystis organisms detectable in respiratory secretions within the first few days of therapy.

Intravenous (IV) trimethoprim-sulfamethoxazole (TMP-SMX) is the first-line agent for treating *severe* PJP (Table 100.3). In patients with sulfa allergies, IV pentamidine should be used instead. Pentamidine-related toxicities (e.g. acute pancreatitis, hypoglycemia, and renal failure) are, however, common and should be aggressively sought when using this drug. Adjunctive steroids have been shown to improve survival in individuals presenting with a PaO_2 of ≤70 mm Hg or alveolar–arterial (A-a) gradients of >35 mm Hg. Nonetheless, overall mortality rates, even in the post-HAART era, approach 30% and remain as high as 60% to 80% in ventilated patients.

In *mild to moderate* PJP, double-strength *oral* TMP–SMX is the drug of choice. Other effective oral regimens are available for individuals with sulfa allergies, including clindamycin plus primaquine, dapsone plus trimethoprim, and atovaquone (Table 100.3).

A definitive diagnosis of PJP is achieved with the identification of pneumocystis organisms in either sputum, bronchoalveolar lavage, or lung biopsy specimens. A variety of stains are commercially available, of which direct fluorescent antibodies to *P. jirovecii* organisms are the most sensitive and specific. Pneumocystis-specific polymerase chain reaction (PCR) of bronchoalveolar lavage fluid is also used for diagnosis, though it may not be able to distinguish between colonization and infection. Notably, in cases where the clinical index of suspicion for PJP as the sole cause of symptoms and radiological findings is high, elevated serum (1-3)-β-d-glucan levels may obviate the need for bronchoscopy or lung biopsy.

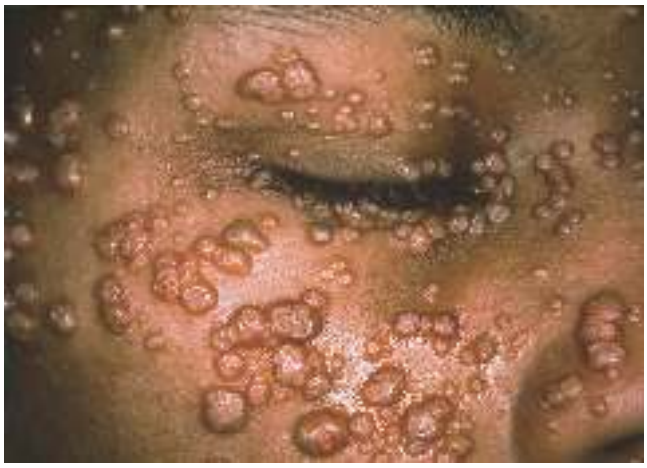

FIGURE 100.2 Molluscum contagiosum. Numerous flesh-colored umbilicated papules appeared on the face of a 33-year-old man with a 3 -year history of AIDS and a CD4 cell count of 60 cells/μL. Prominent lesions along the margin of the eyelids prevented him from closing his eyes completely.

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N Engl J Med. 1998 Mar 26;338(13):888. Northwestern University, Chicago, Illinois.

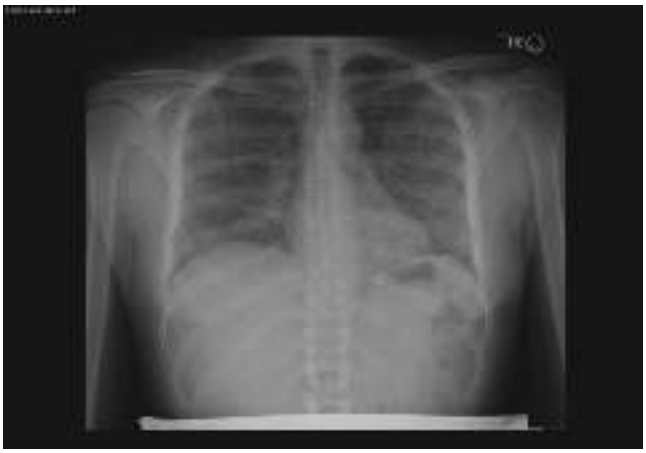

FIGURE 100.3 Pneumocystis jirovecii pneumonia (PJP). Bilateral interstitial infiltrates on chest x-ray in a 39-year-old woman with AIDS and CD4 count of 33 cells/mm^3.

TABLE 100.2 **ETIOLOGIC CORRELATES OF RADIOLOGIC FINDINGS IN HIV-INFECTED PATIENTS WITH PNEUMONIA**

Chest x-ray or computed tomography findings	Common pathogens
(1) Focal/lobar asymmetric consolidation *without* intrathoracic lymphadenopathy	*Streptococcus pneumoniae, Moraxella catarrhalis, Haemophilus influenzae; Mycobacterium tuberculosis* in individuals with primary infection or CD4 counts >350 cells/mm^3.
(2) Diffuse interstitial or alveolar infiltrates *without* intrathoracic lymphadenopathy	*Pneumocystis jirovecii*, respiratory viruses (e.g., influenza virus and respiratory syncytial virus), *Mycoplasma pneumoniae.*
(3) Reticulonodular and/or cavitating nodular infiltrates *without* intrathoracic lymphadenopathy (*acute presentations*)	*Mycoplasma pneumoniae, Staphylococcus aureus*, *Klebsiella pneumoniae, Pseudomonas aeruginosa.*
(4) Reticulonodular and/or cavitating nodular infiltrates *plus* intrathoracic lymphadenopathy (*indolent presentations*)	*Mycobacterium tuberculosis, Nocardia asteroides, Aspergillus fumigatus*, *Rhodococcus equi, pulmonary Kaposi's Sarcoma (due to Human herpesvirus 8).*

Clinical improvement in severe cases of PJP is typically protracted and can take as long as a week. Only patients failing to show improvement beyond this time period are deemed treatment failures. We advocate the following approach to such cases: (1) starting adjunctive corticosteroid therapy in situations where the initial PaO_2 or A-a gradient had suggested otherwise, (2) switching to *IV* TMP-SMX (or IV pentamidine in patients allergic to sulfa) if either *oral* TMP-SMX or a second-line agent had been used initially, and/or (3) repeating bronchoscopy to obtain additional bronchoalveolar lavage samples (as well as transbronchial lung tissue specimens if not previously obtained). These can then be used to identify pathogens that may have been missed during the initial round of testing.

Mycobacterial infections

Unlike PCP, the risk of active *Mycobacterium tuberculosis* (MTB) infection in HIV-infected individuals is high even at normal CD4 counts. However, lower lobe, noncavitary, and extrapulmonary disease are more frequent at CD4 counts of ≤350 cells/mm^3. Chemotherapy recommendations are identical to seronegative patients with pulmonary MTB except clinicians have to be mindful of higher rates of treatment failure and drug resistance in HIV-positive patients. Furthermore, dose adjustments of HAART and/or anti-tuberculous agents are frequently necessary to avoid adverse drug interactions in patients being treated for both infections concurrently (Table 100.3).

The leading nontuberculous mycobacterial pulmonary pathogen in HIV-positive patients is *Mycobacterium avium* complex (MAC). Such cases are distinct from *disseminated* MAC (discussed later) in which severe CD4 lymphopenia and mycobacteremia are the rule. In the post-HAART era, the majority of cases of pulmonary MAC manifest within weeks of initiating HAART, leading some to posit an immunologic mechanism. Combination therapy comprising clarithromycin or azithromycin, ethambutol, and rifabutin is the treatment regimen of choice (Table 100.3).

Rarer mycobacterial causes of pneumonia in HIV-infected patients are *Mycobacterium kansasii* and the so-called *rapid-grower*

TABLE 100.3 **MANAGEMENT OF PULMONARY OPPORTUNISTIC INFECTIONS**

Pathogen	First-line treatment	Notes
Pneumocystis jirovecii	Mild to moderate disease: TMP–SMX-DS, 2 tabs PO TID; dapsone, 100 mg PO qd, plus TMP, 5 mg/kg PO q8h; clindamycin, 450 mg PO or 600 mg IV q8h, plus primaquine, 15 mg qd; or atovaquone, 1500 mg qd for 21 d Severe disease: TMP–SMX, 15 mg/kg IV (TMP component) qd in 3–4 divided doses, or, in patients with sulfa allergy, pentamidine, 4 mg/kg IV qd, plus prednisone (40 mg BID × 5 d; 20 mg BID × 5 d; 20 mg qd × 11 d) for 21 d	(1) Caution must be taken with the use of primaquine or dapsone in patients at risk for G6PD deficiency because of the risk of hemolytic anemia. Such individuals should be tested for G6PD deficiency in anticipation of exposure to these drugs. (2) May discontinue *secondary* prophylaxis after CD4 >200 cells/mm^3 for >3 mo.
M. *tuberculosis*	Isoniazid, 5 mg/kg/d, plus rifampin, 600 mg PO qd, plus pyrazinamide, 15–30 mg/kg PO qd, plus ethambutol, 15–25 mg/kg/d as initial therapy	Clinically significant drug-drug interactions between rifampin and antiretroviral medications (e.g. protease and integrase inhibitors) have been reported and should be researched thoroughly prior to adding rifampin to any antiretroviral regimen. Rifabutin, 150–300 mg PO qd, may be used in lieu of rifampin in such cases.
M. *avium* complex	Clarithromycin, 500 mg PO BID, or azithromycin, 600 mg qd, plus ethambutol, 15–25 mg/kg/d, plus rifabutin, 300 mg PO qd for a minimum of 12 mo	In patients on efavirenz, azithromycin is preferred over clarithromycin as part of the 3-drug regimen because efavirenz lowers the serum levels of the latter.
M. *kansasii*	Isoniazid, 5 mg/kg/d, plus rifampin, 600 mg PO qd, plus ethambutol, 25 mg/kg/d (× 2 months then 15 mg/kg) for 15–18 mo	If patient is taking a protease inhibitor, replace rifampin with rifabutin, 150–300 mg PO qd, because rifampin significantly lowers serum levels of protease inhibitors.
M. *abscessus*	Amikacin plus either cefoxitin or imipenem plus macrolide for 4–8 wk, followed by macrolide plus second agent for 6–12 mo	Monitor for inducible macrolide resistance.
M. *fortuitum*	Amikacin or tobramycin plus 2 of cefoxitin or imipenem or levofloxacin for 2–6 wk followed by 2 oral agents for 12 mo	
Histoplasma capsulatum (pulmonary and non-CNS disseminated disease)	Mild-to-moderate disease: itraconazole, 200 mg PO TID for 3 d, followed by itraconazole, 200 mg BID for 12 wk Severe illness: amphotericin B deoxycholate, 0.7 mg/kg IV qd, or liposomal or lipid complex amphotericin, 3–5 mg/kg, until clinically improved followed by itraconazole, 200 mg q12h for 12 wk	
Coccidioides immitis (pulmonary and non-CNS disseminated disease)	Mild-to-moderate disease: fluconazole, 400–800 mg PO qd Severe illness: amphotericin B deoxycholate, 0.5–1.0 mg/kg IV qd, followed by fluconazole, 400–800 mg PO qd	Lifelong suppression with fluconazole, 400 mg PO qd, is recommended, even with CD4 >200 cells/mm^3 on HAART.
Blastomycosis dermatitidis (pulmonary and non-CNS disseminated disease)	Amphotericin B deoxycholate, 0.7–1.0 mg/kg IV qd, or liposomal amphotericin, 3–5 mg/kg, until clinically improved, followed by itraconazole, 200 mg for 12 wk	
Aspergillus fumigatus (pulmonary and non-CNS disseminated disease)	Voriconazole, 6 mg/kg IV × 1, followed by either 4 mg/kg IV or 100–200 mg PO BID for 2–3 wk; oral voriconazole for suppression	(1) Alternatives to voriconazole: amphotericin B deoxycholate; liposomal or lipid complex amphotericin 3–5 mg/kg; or caspofungin +/− voriconazole (2) Also note: when using voriconazole with efavirenz, voriconazole dose should be increased to 400 mg q12h and decrease the efavirenz to 300 mg QD.
Nocardia asteroides (pulmonary and non-CNS disseminated disease)	TMP-SMX (15 mg/kg/d TMP; 75 mg/kg/d SMX) × 3 wk followed by 10 mg/kg/d TMP component PO	In severe cases: add amikacin or imipenem or third-generation cephalosporin when limited by aminoglycoside toxicity.
Rhodococcus equi (pulmonary and *non-CNS* disseminated disease)	Erythromycin or imipenem, 0.5 g IV q6h, plus rifampin, 600 mg PO qd for 2 wk, followed by oral clarithromycin or azithromycin plus rifampin for suppression	Alternative agents: ciprofloxacin or linezolid.

Abbreviations: TMP–SMX = trimethroprim-sulfamethoxazole; DS = double strength; PO = orally; TID = three times a day; IV = intravenously; qd = every day; BID = twice a day; CNS = central nervous system; G6PD = glucose-6-phosphate dehydrogenase; HAART = highly active antiretroviral therapy.

mycobacteria; namely *M. abscessus, M. fortuitum*, and *M. chelonae*. *M. kansasii* lung infections often mimic pulmonary MTB clinically as well as radiographically (see Table 100.3 for treatment recommendations).

Endemic mycoses

Pulmonary coccidioidomycosis, histoplasmosis, and blastomycosis primarily affect individuals with CD4 counts of ≤250 cells/mm^3. Rates of infection are higher in endemic areas. In the case of coccidioidomycosis, this comprises the San Joaquin valley (i.e., central and southern parts of California), southern Arizona, southwestern New Mexico, and west Texas. Histoplasmosis and blastomycosis, on the other hand, are both endemic to the Ohio and Mississippi River basins. However, blastomycosis is also found in northwestern New York as well as in the south-central and southeastern regions of the United States.

Previous or current residence in these regions is the main risk factor for all of these infections. In patients with higher CD4 counts, focal alveolar or nodular/cavitary infiltrates with or without intrathoracic lymphadenopathy are the common radiographic finding. Diffuse reticulonodular infiltrates, indicative of hematogenous dissemination, are, however, more common in individuals with very advanced immunodeficiency (i.e., CD4 counts ≤100 cells/mm^3). Life-threatening infections require induction chemotherapy with amphotericin-B-based drugs followed by maintenance treatment with oral triazoles (Table 100.3).

Pulmonary aspergillosis

Severe CD4 lymphopenia is one of several risk factors associated with pulmonary aspergillosis; others include neutropenia, recent exposure to corticosteroids, and marijuana use. Two distinct clinical syndromes have been described: isolated tracheobronchitis and pneumonitis. Symptoms in both cases include fever, productive cough, chest pain, and hemoptysis. Wheezing is more indicative of tracheobronchial involvement. Bronchoscopy in such cases reveals airway-obstructing mycelia and mucous balls. However, airway invasion can also occur, resulting in the formation of pseudomembranes and ulcerations. Radiographically, a variety of patterns have been observed with parenchymal disease, including subpleural focal opacities, diffuse reticulonodular infiltrates, and cavitary apical lesions. Treatment comprises voriconazole and/or amphotericin B-based drugs (Table 100.3).

Filamentous bacteria

Pulmonary nocardiosis and rhodococcosis are rare complications of AIDS in the post-HAART era. *Nocardia* and *Rhodococcus* are gram-positive, weakly acid-fast, filamentous bacteria. Both are associated with indolent to subacute lower respiratory infections. Radiographic features include nodular/cavitary pulmonary infiltrates with or without abscess formation. Concurrent mediastinal lymphadenopathy is also common. Disseminated disease with a predilection for brain and skin lesions has been observed with these organisms. Unlike nocardia, where blood cultures rarely turn positive, the yield of standard blood cultures approaches 50% in rhodococcal infections. The diagnosis of pulmonary nocardiosis, on the other hand, typically requires detection of branching, filamentous, acid-fast organisms either in sputa, bronchoalveolar lavage, or lung biopsy specimens. Chemotherapy is protracted in both diseases, and relapse is common in the absence of durable immune recovery from HAART (Table 100.3).

Gastrointestinal infections

Infections of the esophagus

Candidal esophagitis is a very common AIDS-defining OI. It manifests at CD4 counts of ≤200 cells/mm^3 and presents primarily as dysphagia and/or odynophagia. These symptoms are sometimes accompanied by chest pain or fever. In rare instances esophageal perforation can occur, usually as a complication of delayed or inadequate treatment. Triazoles are the mainstay of therapy (Table 100.4). Azole resistance may occur, particularly with recurrent episodes and in patients with very advanced HIV disease. In such cases, amphotericin-B-based therapies or echinocandins are usually effective (Table 100.4).

Rarely, herpes simplex virus (HSV) or cytomegalovirus (CMV) may infect the esophagus, causing symptoms indistinguishable from those encountered with candidal disease. Patients with the former are, however, usually more immunodeficient (i.e., CD4 counts ≤100 cells/mm^3). In patients presenting with esophageal symptoms but without evidence of thrush, it is customary to institute empiric candidal treatment and only pursue alternate causes (through endoscopically guided biopsy) with treatment failures (Table 100.4).

Diarrheal illness

Patients on HAART, particularly protease inhibitor-containing regimens, often experience treatment-related diarrhea. However, protracted symptoms or evidence of intestinal inflammation or invasion (i.e., fever, hematochezia, or abdominal pain) mandates an infectious workup.

Common community-acquired enteric pathogens, such as norovirus, *Salmonella*, *Campylobacter*, *Shigella*, *Yersinia*, and *Giardia*, are the usual culprits in individuals with CD4 counts >200 cells/mm^3. Invasive salmonellosis, campylobacteriosis, and shigellosis are, however, more frequent relative to the general population. Consequently, antibiotic treatment for these infections, whereas discretionary in otherwise healthy, HIV-seronegative persons, is recommended when these infections occur in the context of HIV disease (Table 100.4).

Patients with CD4 counts of ≤100 cells/mm^3 may experience severe, protracted watery diarrhea as a result of *Cryptosporidium, Microsporidia, Cyclospora*, or *Isospora* intestinal infections. Although much less frequent in the post-HAART era, effective chemotherapeutic agents against these organisms (with the exception of *Isospora* and *Cyclospora*) are sorely lacking. Antispasmodics and immune reconstitution via HAART are the mainstays of management (Table 100.4).

Symptomatic gastrointestinal CMV infections present most often in the large bowel. CMV colitis typically occurs at CD4 counts of ≤100 cells/mm^3 and presents as fever, bloody diarrhea, and abdominal pain. Treatment comprises 2 to 3 weeks of induction

TABLE 100.4 **MANAGEMENT OF OPPORTUNISTIC INFECTIONS OF THE DIGESTIVE TRACT**

Condition/pathogen	First-line treatment	Notes
Candidal esophagitis	Fluconazole, 200–400 mg PO qd for 14–21 d	In the event of azole resistance: amphotericin B suspension, 100 mg/mL PO QID; amphotericin B deoxycholate, 0.3–0.7 mg/kg IV qd; liposomal or lipid complex amphotericin, 3–5 mg/kg; voriconazole, 200 mg PO BID; or caspofungin, 50 mg IV qd, micafungin 150 mg IV qd, or anidulafungin 100 mg IV x 1 then 50 mg IV qd for 14–21 d.
Herpes simplex esophagitis	Acyclovir, 5 mg/kg IV, followed by acyclovir, 400 mg PO TID; famciclovir, 500 mg PO BID; or valacyclovir, 1000 mg PO BID for 7–14 d once patient is tolerating oral therapy	In the event of acyclovir resistance: foscarnet, 40–60 mg/kg IV q8h, or cidofovir, IV plus IV hydration, and oral probenecid to mitigate renal toxicity.
Cytomegalovirus esophagitis	Ganciclovir, 5–6 mg/kg/d IV, or valganciclovir, 900 mg PO BID, once patient tolerating oral therapy, for 2–3 wk followed by half-dose valganciclovir for chronic suppression	In the event of ganciclovir resistance: foscarnet, 90 mg/kg IV q12h, or cidofovir, IV plus IV hydration, and oral probenecid to mitigate renal toxicity.
Salmonellosis	Ciprofloxacin, 500–750 mg BID, or levofloxacin, 500 mg qd for 7–14 d	(1) Relapse is common and may necessitate chronic suppression; therefore, treat for 4–6 weeks in patients with CD4 count ≤200 cells/mm^3 or bacteremia. (2) Fluoroquinolone resistance is increasing, in which case azithromycin should be used.
Shigellosis	Ciprofloxacin, 500 mg BID, or levofloxacin, 500 mg qd for 3 d	(1) Treat for up to 14 d in patients with CD4 count ≤200 cells/mm^3 or bacteremia. (2) Alternative agent: azithromycin.
Campylobacteriosis	Ciprofloxacin, 500 mg BID, or azithromycin, 500 mg qd for 3 d	(1) Treat for up to 14 d in patients with CD4 count ≤200 cells/mm^3 or bacteremia. (2) Fluoroquinolone resistance is increasing rapidly, particularly in Southeast Asia.
Cryptosporidiosis	HAART *plus* antispasmodic +/− nitazoxanide 500 mg PO q12h for 14 d	
Microsporidiosis	Albendazole, 400 mg q12h for 3 wk	The most common cause of diarrheal illness, *Enterocytozoon bieneusi*, is the least susceptible species to albendazole.
Cyclosporidiosis	TMP–SMX-DS q6h for 10 d then 1 tab 3×/wk	Alternative agent: ciprofloxacin.
Isosporosis	TMP–SMX-DS q6h for 10 d then 1 tab 3×/wk	Alternative agents: ciprofloxacin, pyrimethamine plus folinic acid.

Abbreviations: PO = orally; qd = every day; QID = four times a day; IV = intravenously; BID = twice a day; TID = three times a day; HAART = highly active antiretroviral therapy; TMP–SMX-DS = trimethoprim–sulfamethoxazole-double strength.

therapy with IV ganciclovir or oral valganciclovir with half the induction dose as maintenance therapy thereafter (Table 100.4).

HIV cholangiopathy

Some intestinal pathogens (primarily *Cryptosporidium parvum* but also *Microsporidia*, CMV, and *Cyclospora*) are also able to infect the biliary tract, giving rise to a syndrome known collectively as *HIV cholangiopathy*. Typically a complication of very advanced HIV disease (CD4 counts ≤100 cells/mm^3), HIV cholangiopathy presents as right upper quadrant discomfort (rarely accompanied by fever or jaundice) and serum alkaline phosphatase elevation. Endoscopic retrograde cholangiopancreatography (ERCP) findings include papillary stenosis, biliary stricture, and/or biliary obstruction. Symptoms, while usually refractory to antimicrobial therapy, are often relieved by biliary stenting and sphincterotomy. Ursodeoxycholic acid (300 mg orally TID) is effective for symptom relief in patients with lesions not amenable to endoscopic intervention.

Neurologic infections

Meningitis

Cryptococcus neoformans is the most commonly identified cause of meningitis among HIV-infected patients. *C. gattii* has been

implicated in the Pacific Northwest of the US, Australia, and subtropical regions and is managed the same way as *C. neoformans*. Patients present subacutely with headache, fever, and lethargy. Other manifestations of increasing intracranial pressure (the most feared complication of this disease) include nausea, emesis, blindness, obtundation, and coma. Delays in therapy can be fatal. Management is three-pronged: (1) prompt initiation of induction antifungal therapy with an amphotericin-B-based drug *plus* 5-flucytosine for 14 days (Table 100.5), (2) serial lumbar punctures to alleviate excess intracranial pressure. and (3) consolidation as well as maintenance therapy with oral fluconazole. Similar clinical presentations, including a propensity for elevated intracranial pressure, are seen with MTB, histoplasma, and coccidioides meningitis (see Table 100.5 for treatment recommendations).

Encephalitis

Progressive multifocal leukoencephalopathy (PML) is caused by reactivation of previously latent JC virus infection within the brain parenchyma. Although much less frequent in the post-HAART era, PML remains one of the most disheartening complications of advanced HIV disease (i.e., CD4 counts ≤200 cells/mm^3). No effective antiviral therapies have been identified for this highly debilitating and often lethal disorder. Immune recovery through HAART remains the only recourse. Patients present with nonenhancing, periventricular, subcortical white matter lesions devoid of mass effect or surrounding edema. Lesions are more likely to enhance in patients who develop symptoms in the context of HAART (i.e., as part of an immune recovery inflammatory syndrome [IRIS]). Symptoms in either case include progressive focal motor-sensory deficits; visual field cuts; cerebellar findings such as ataxia, dysmetria, and vertigo; and seizures.

CMV meningoencephalitis is a marker of very advanced HIV immunodeficiency (≤100 cells/mm^3). Rapid cognitive deterioration marked by fever and headache is the usual presentation. The classic, almost pathognomonic, finding on MRI is a symmetric, T2-bright ventriculitis with extension to the adjacent periventricular white matter. However, nonspecific white matter changes are more common. Progressive cognitive decline in the face of antiviral treatment is common. Combination therapy comprising IV ganciclovir and foscarnet may improve outcomes (Table 100.5).

Varicella-zoster virus (VZV) brain infections are typically observed at CD4 counts of ≤200 cells/mm^3. Several variants have been described including focal as well as diffuse meningoencephalitis, cerebritis, and CNS vasculitis. Patients present with fever, encephalopathy, and/or focal motor-sensory deficits that typically follow, but may also precede, a dermatomal zoster outbreak. Treatment comprises IV acyclovir for a minimum of 2 to 3 weeks (Table 100.5).

Brain abscess

The most common cause of space-occupying brain lesions in HIV-infected patients with CD4 counts of ≤200 cells/mm^3 is toxoplasmosis (Figure 100.4). Patients present with headache, fever, confusion, and sometimes seizure. CNS toxoplasmosis is rare in toxoplasma-seronegative patients. In cases where primary CNS lymphoma is deemed less likely (i.e., patients seropositive for toxoplasma with multiple ring-enhancing brain lesions on MRI), an empiric trial of toxoplasma antibiotics (Table 100.5) is instituted in lieu of brain biopsy. Individuals who fail to improve after 10 to 14 days of treatment are subjected to stereotactic brain biopsy for a definitive histopathologic diagnosis.

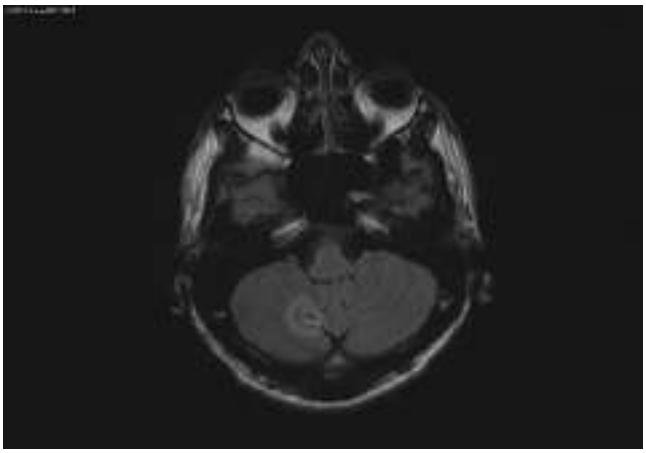

FIGURE 100.4 Cerebral toxoplasmosis. MRI reveals a 2.5 cm ring-enhancing lesion in the right cerebellar hemisphere.

Rarer causes of brain abscess in HIV-positive individuals include MTB, *Cryptococcus*, *Aspergillus*, the endemic mycoses, *Nocardia*, and *Rhodococcus* infections (see Table 100.5 for treatment recommendations). Concomitant pulmonary involvement, whereas rare with toxoplasmic brain infections, is a frequent finding with all these other pathogens.

Retinitis

CMV is the main infective threat to vision in patients with AIDS. Thus, acute blurry vision, photopsia, and/or scotomata in a patient with ≤100 cells/mm^3 merits emergent evaluation for CMV retinitis. Left untreated, symptoms quickly progress to blindness within days to weeks. Mechanisms for decreased visual acuity in CMV retinitis include retinal detachment (a consequence of large, peripheral lesions), involvement of the macula, and extension of lesions to the optic nerve. Funduscopically, CMV retinitis appears as multiple pale, yellow exudates against a red background. Retinal hemorrhages are also a common finding. Ganciclovir-impregnated retinal implants combined with oral valganciclovir is first-line therapy (Table 100.5).

VZV is a less common cause of acute retinal necrosis (ARN) in patients with HIV. Like CMV retinitis, permanent visual loss rapidly ensues if left untreated. Unlike the latter, however, VZV-related ARN can occur at any CD4 count. Progressive outer retinal necrosis (PORN), on the other hand, is a variant of VZV retinitis that targets individuals with very low CD4 counts, typically ≤100 cells/mm^3. (More recently, HSV and CMV have been implicated in isolated cases of PORN; however, VZV is generally thought to be the culprit in the majority of cases.) The lesions expand and coalesce in the periphery of the retina; thus, visual loss in VZV-related

TABLE 100.5 **MANAGEMENT OF NEUROLOGIC OPPORTUNISTIC INFECTIONS**

Pathogen/condition	First-line treatment	Notes
Cryptococcus neoformans	Amphotericin B, 0.7 mg/kg IV qd, plus 5-flucytosine (5-FC), 25 mg/kg q6h, or liposomal or lipid complex amphotericin, 4 mg/kg, plus 5-flucytosine, 25 mg/kg q6h for 2 wk, followed by 10 wk of fluconazole, 400 mg PO qd, followed by chronic suppression with fluconazole, 200 mg PO qd	Note: monitor 5-FC serum levels—peak and trough levels >80 mg/L and 40 mg/L, respectively, are associated with significant bone marrow toxicity.
M. *tuberculosis*	Isoniazid, 5 mg/kg/d, plus rifampin, 600 mg PO qd, plus pyrazinamide, 15–30 mg/kg PO qd, plus ethambutol 15–25 mg/kg/d for a minimum of 12 mo	Clinically significant drug-drug interactions between rifampin and antiretroviral medications (e.g. protease and integrase inhibitors) have been reported and should be researched thoroughly prior to adding rifampin to any antiretroviral regimen. Rifabutin, 150–300 mg PO qd, may be used in lieu of rifampin in such cases.
Histoplasma capsulatum meningoencephalitis	Amphotericin B deoxycholate, 0.7 mg/kg IV qd; liposomal or lipid complex amphotericin, 3–5 mg/kg, until clinically improved followed by itraconazole, 200 mg for 12–16 wk. Chronic suppression with 200 mg qd thereafter	Blood cultures, and even DuPont fungal isolators, are often negative in systemic histoplasma infections. However, a urinary histoplasma antigen-based test is >90% sensitive in patients with AIDS.
Coccidioides immitis meningoencephalitis	Fluconazole 400–800 mg IV or PO qd	Lifelong suppression with fluconazole, 400 mg PO qd, is recommended, even with CD4 >200 cells/mm^3 on HAART.
Blastomycosis dermatitidis meningoencephalitis	Amphotericin B deoxycholate, 0.7–1.0 mg/kg IV qd, or liposomal amphotericin, 3–5 mg/kg, until clinically improved, followed by itraconazole, 200 mg for 12 wk	
JC virus (progressive multifocal leukoencephalopathy)	HAART	
Varicella-zoster virus	Meningoencephalitis: acyclovir, 10 mg/kg IV for 14–21 d Acute retinal necrosis: intravenous acyclovir as above followed by chronic suppression with valacyclovir or famciclovir	In the event of acyclovir resistance: foscarnet 40–60 mg/kg IV q8h or cidofovir IV plus IV hydration and oral probenecid to mitigate renal toxicity.
Cytomegalovirus	Meningoencephalitis/polyradiculitis: ganciclovir, 5–6 mg/kg/d IV, or valganciclovir, 900 mg PO BID, +/− IV foscarnet, 90–120 mg/kg/d, until clinical improvement Retinitis: as above plus sustained-release ganciclovir intraocular implant q6–9 mo	(1) Lifelong chronic suppression with valganciclovir is recommended. (2) Under supervision of a qualified ophthalmologist, may discontinue maintenance therapy after maximal improvement and CD4 count has been >150 cells/mm^3 for >6 mo.
Toxoplasma gondii brain abscess	Pyrimethamine, 200 mg PO 1×, then 50–75 mg qd plus sulfadiazine, 1.0–1.5 g PO QID, plus folinic acid, 10–20 mg PO qd for 6 wk, followed by half-dose of all 3 drugs as chronic suppression	(1) Primary CNS lymphoma is the other leading cause of brain mass in this population but is more often unifocal, >4 cm, and distinguishable from cerebral toxoplasmosis on single-photon emission computed tomography and positron emission tomography. (2) In patients with sulfa allergy: replace sulfadiazine with clindamycin, dapsone, or atovaquone.
Aspergillus fumigatus	Voriconazole, 6 mg/kg IV 1×, followed by either 4 mg/kg IV or 100–200 mg PO BID for 2–3 wk; oral voriconazole for suppression	Less preferred agents: (1) amphotericin B deoxycholate; (2) liposomal or lipid complex amphotericin, 3–5 mg/kg; or (3) caspofungin +/− voriconazole.
Nocardia asteroides	TMP-SMX (15 mg/kg/d TMP; 75 mg/kg/d SMX) plus ceftriaxone, 2 g IV qd × 6 wk, followed by reduced doses of both drugs IV for 6–12 mo	In sulfa-allergic patients: substitute TMP–SMX with amikacin.
Rhodococcus equi	Erythromycin, 0.5 g IV q6h, plus imipenem, 0.5 g IV q6h, plus rifampin, 600 mg PO qd for 2 wk, followed by oral clarithromycin or azithromycin plus rifampin for suppression	Alternative agents: ciprofloxacin and linezolid.

TABLE 100.6 **MANAGEMENT OF DISSEMINATED INFECTIONS**

Pathogen/condition	First-line treatment	Notes
M. *avium* complex	Clarithromycin, 500 mg PO BID, or azithromycin, 600 mg qd, plus ethambutol, 15–25 mg/kg/d, plus rifampin, 600 mg PO qd, for a minimum of 12 mo	(1) In patients on efavirenz, azithromycin is preferred over clarithromycin as part of the 3-drug regimen; because efavirenz lowers drug levels of the latter. (2) If patient is taking a protease inhibitor, replace rifampin with rifabutin, 150–300 mg PO qd, because rifampin significantly lowers serum levels of protease inhibitors.
Histoplasma capsulatum	Mild to moderate disease: itraconazole, 200 mg PO TID for 3 d, followed by itraconazole, 200 mg BID for 12 wk Severe illness: amphotericin B deoxycholate, 0.7 mg/kg IV qd; amphotericin liposomal or lipid complex, 3–5 mg/kg, until clinically improved followed by itraconazole, 200 mg for 12 wk	
Talaromycosis	Amphotericin B deoxycholate, 0.6 mg/kg IV qd for 2 wk, followed by itraconazole, 200 mg q12h for 10 wk and then 100 mg PO q12h for suppression	
Bartonellosis	Erythromycin, 500 mg PO q6h for 12 wk minimum and until CD4 count >200 cells/mm^3	(1) Doxycycline with or without rifampin is preferred for CNS involvement. (2) Alternative agents for non-CNS disease: clarithromycin, 500 mg PO BID; azithromycin, 600 mg PO qd; or ciprofloxacin, 500 mg PO BID.

PORN occurs primarily as a result of retinal detachment. Treatment for VZV-related ARN consists of IV acyclovir for 2 to 3 weeks followed by oral valacyclovir (Table 100.5). VZV-related PORN, however, carries a worse prognosis primarily because it is more often refractory to antiviral therapy. One approach has been to administer ganciclovir and foscarnet intravenously along with intravitreal injections of ganciclovir and/or foscarnet.

Disseminated infections

Mycobacterium avium complex

Patients with disseminated MAC characteristically present with high, spiking fevers; progressive weight loss; and sometimes diarrhea. Elevated alkaline phosphatase levels (present in approximately 50% of cases) and enlarged para-aortic lymph nodes are also observed. Treatment consists of clarithromycin (or azithromycin), weight-based ethambutol, and rifabutin (Table 100.6).

Histoplasmosis

Disseminated histoplasmosis is a rare but potentially lethal complication of HIV infection. Presentations can either be indolent (i.e. manifesting as progressive fever, weight loss, and pancytopenia) or fulminant. The latter cases often manifest as an Addisonian crisis, a direct consequence of the propensity for histoplasma organisms to infiltrate and damage adrenal tissue. Treatment comprises amphotericin B-based chemotherapy followed by prolonged suppression with oral itraconazole (Table 100.6).

Talaromycosis *Talaromyces (formerly Penicillium) marneffei* is a dimorphic fungal pathogen that converts to a yeast at human body temperature. Disseminated talaromycosis is the third most common OI (after cryptococcal and MTB infection) in HIV-infected patients residing in Southeast Asia. Patients at highest risk have CD4 counts of ≤50 cells/mm^3. Usual symptoms include fever, weight loss, dry cough, lymphadenopathy, hepatosplenomegaly, and a rash similar to the umbilicated lesions of molluscum contagiosum. Serum alkaline phosphatase levels are often elevated. Blood cultures turn positive within 5 to 7 days of incubation. Treatment is similar to that of disseminated histoplasmosis (Table 100.6).

Bartonellosis

Patients present with fever, rash, and abdominal and/or bone pain. Risk factors include CD4 count of ≤200 cells/mm^3 and prior cat contact (*Bartonella henselae*) or human body louse infestation (*B. quintana*). Mucocutaneous manifestations, known as bacillary angiomatosis, are variable in appearance but classically present as enlarging violaceous plaques or nodules that mimic Kaposi's sarcoma. Bartonella osteomyelitis, a complication of *B. quintana* infection, is rare and involves the long bones and sometimes underlies cellulitic plaques.

B. henselae infections are uniquely associated with hepatosplenic peliosis which comprises cystic blood-filled, endothelium-lined spaces that appear as focal, hypodense lesions on CT (Figure 100.5). Application of Warthin–Starry stain to tissue specimens reveals pleomorphic microorganisms. In the absence of diagnostic tissue samples, confirmation of bartonellosis rests on culture and serology. Blood cultures and subsequent chocolate or heart infusion agar subcultures, however, have to be held for a minimum of 21 days.

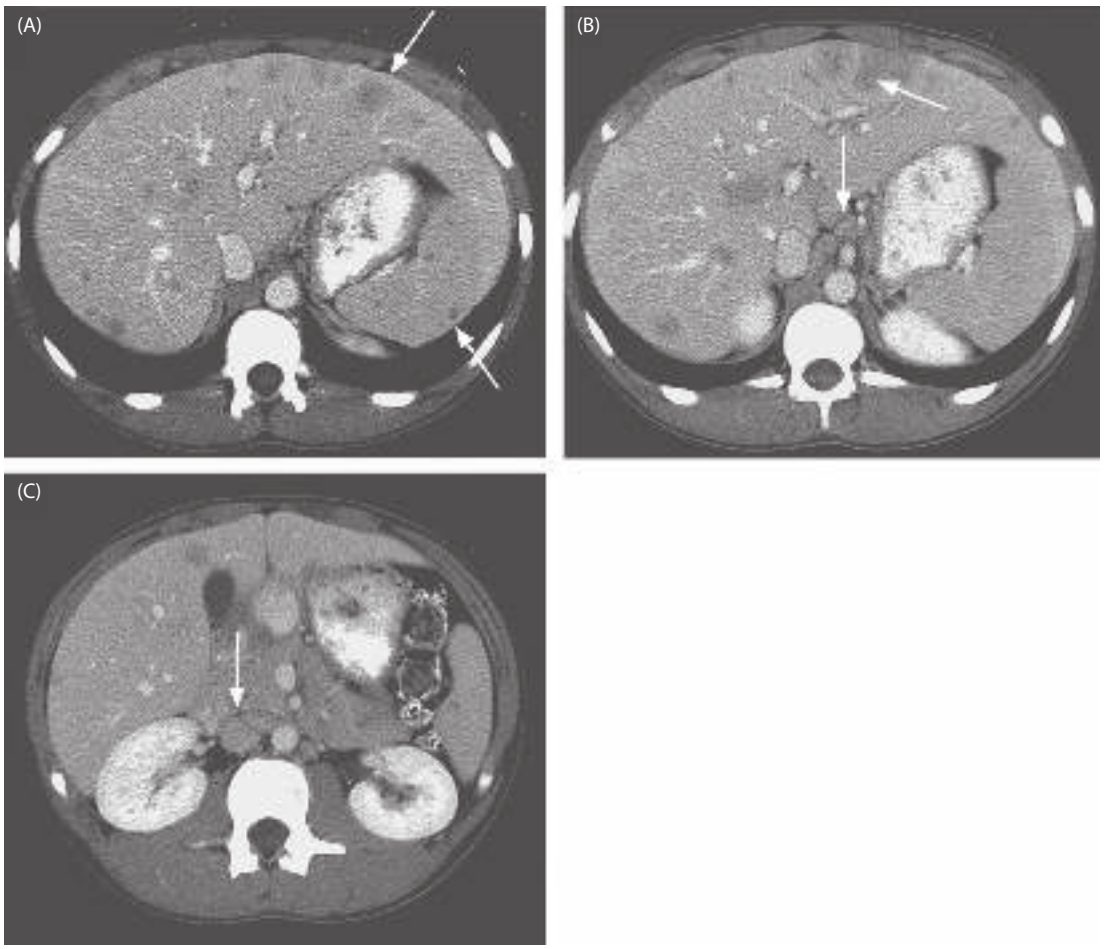

FIGURE 100.5 *Bartonella henselae* hepatosplenic peliosis. CT of the abdomen with intravenous contrast reveals multiple low-density lesions with central septations and surrounding halos (*arrows*) in the liver and spleen. An image obtained slightly below the image shown in Panel A (Panel B) shows larger lesions as well as lymphadenopathy around the celiac axis (*arrows*). An image obtained below the image shown in Panel B (Panel C) shows additional lymphadenopathy in the peri-pancreatic and periportal regions (*arrow*).

Reproduced with permission from Stephen Pelton, MD. Pelton SI, Kim JY, Kradin RL. Case records of the Massachusetts General Hospital. Case 27–2006. Department of Pediatric Infectious Disease, Boston Medical Center, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

Prolonged treatment with an oral macrolide is the treatment of choice (Table 100.6).

Suggested reading

Brooks JT, Kaplan JE, Holmes KK, et al. HIV-associated opportunistic infections—going, going, but not gone: The continued need for prevention and treatment guidelines. *Clin Infect Dis*. 2009;48:609–611.

Buchacz K, Baker RK, Palella FJ Jr, et al. AIDS-defining opportunistic illnesses in US patients, 1994–2007: A cohort study. *AIDS*. 2010;24(10):1549–1559.

Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. https://aidsinfo.nih.gov/guidelines

Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853–860.

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Prophylaxis of opportunistic infections in HIV disease

Brandi Manning, Robert L. Bettiker, and Jeffrey M. Jacobson

Introduction

The AIDS epidemic presented as severe manifestations of various opportunistic infections (OIs) in hosts whose immune systems were compromised. Individuals with AIDS succumbed to pneumocystic pneumonia, toxoplasmosis, disseminated *Mycobacterium* infection, and several other OIs and malignancies. Now, with the availability of potent, well-tolerated, and convenient antiretroviral therapy (ART), HIV-positive persons can be largely unaffected by these OIs as long as they remain well-adherent to ART. Nevertheless, OIs remain a common presenting feature at the time of initial diagnosis. Barriers to care and medication adherence can also allow HIV to progress, leaving patients susceptible to OI. For these reasons and others, prophylaxis for OI in HIV positive patients remains an important topic and cornerstone of providing care for this patient population.

Prophylaxis is commonly divided into two categories: primary and secondary. Primary prophylaxis serves the purpose of hopefully preventing an initial infection from occurring. Secondary prophylaxis, on the other hand, is given to patients who have been treated for an OI and are now vulnerable to relapse, recurrence, or repeat infection. Whether it is primary or secondary, any chemical prophylaxis prescribed should have a clear clinical benefit to the patient with regards to reduced morbidity and mortality without significant risk of adverse events or cost. Prophylaxis should always be presented to patients as an option, keeping risk and benefit in mind for shared decision-making.

Pneumocystis

Primary prophylaxis

Prior to the initiation of ART and primary prophylaxis, the incidence of *Pneumocystis jirovecii* infection was as high as 70% to 80% in patients with AIDS but has since decreased to less than one case per 100 person-years in the United States and Western Europe. Primary prophylaxis should be initiated in all HIV patients with a CD4 count of <200 cells/mm^3 or CD4% below 14%. Prophylaxis can also be considered for those patients with a CD4 count up to 250 cells/mm^3 who cannot have frequent close monitoring of CD4 counts. The preferred regimen for prophylaxis is one trimethoprim-sulfamethoxazole (TMP-SMX) double-strength tablet daily. Alternate dosing options of a single-strength daily tablet or a double-strength tablet three times weekly are also acceptable if the preferred regimen is not tolerated due to sensitivity. TMP-SMX is the most efficacious choice and adds protection for *Toxoplasma* and other bacterial infections. Adverse effects of rash, hepatitis, hyperkalemia, gastrointestinal upset, and fever are not uncommon. Nevertheless, if adverse events occur, continuing this preferred regimen with symptomatic care and alternative dosing may be considered. If

TABLE 101.1 **PRIMARY PROPHYLAXIS AGAINST *PNEUMOCYSTIS JIROVECII***

Agent	Notes	Discontinuation
Trimethoprim-sulfamethoxazole (TMP-SMX)	Double-strength daily dosing is the preferred regimen	CD4 ≥200 cells/mm^3 for >3 months *or*
	Mild adverse effects are common and decreased dosing should be attempted if necessary	CD4 ≥100 cells/mm^3 *and* the viral load is suppressed for >3 months
Dapsone	Contraindicated in G6PD deficiency and severe sulfa allergy	
Atovaquone	Cost-prohibitive and liquid only	
Aerosolized pentamidine	Via Respirgard II only	

a life-threatening reaction occurs, such as toxic epidermal necrolysis, TMP-SMX should be permanently discontinued.

If an alternate agent cannot be avoided, options include dapsone, atovaquone, or aerosolized pentamidine. Patients receiving dapsone should be screened for G6PD deficiency prior to initiation. Dapsone and atovaquone have similar prophylactic efficacy but atovaquone can be cost-prohibitive and is only manufactured in liquid formulation, making dapsone a more appealing option for most patients. Potential adverse effects of dapsone include rash, agranulocytosis, methemoglobinemia, and hepatic dysfunction. Dapsone should not be given to any patient who has a history of severe reaction to TMP-SMX. Aerosolized pentamidine is another—albeit rarely used—option, although this regimen will not offer protection against extrapulmonary pneumocystosis nor against toxoplasmosis and can also be expensive. Inhaled pentamidine distributes selectively to the lower lung fields, leaving the upper portions susceptible to pneumocystic infection. It is not recommended that clindamycin and primaquine be used for prophylaxis.

Women desiring pregnancy should be counseled to wait on pregnancy if possible until the CD4 count exceeds 200 cells/mm^3. If prophylaxis must be given during pregnancy, folate supplementation should be given with TMP-SMX during the first trimester.

Primary pneumocystic prophylaxis (Table 101.1) can be safely discontinued once patients on ART have a CD4 count of at least 200 cells/mm^3 for more than 3 months or if the CD4 count is >100 cells/mm^3 and the viral load is suppressed for more than 3 months.

Secondary prophylaxis

Secondary pneumocystic prophylaxis (Table 101.2) should be given to any HIV-positive patient diagnosed with a pneumocystic infection and started immediately upon completion of the treatment course, which is typically 21 days. The drug of choice for secondary prophylaxis remains TMP-SMX, just as for primary prophylaxis. Likewise, it should be continued until the CD4 count reaches >200 cells/mm^3 for 3 months or after 3 to 6 months of undetectable viral load with CD4 count >100 cells/mm^3.

Primary and secondary prophylaxis should be restarted if a patient's CD4 count drops to <100 cells/mm^3 regardless of the viral load or if the CD4 count is 100 to 200 cells/mm^3 with a detectable viral load. If a patient should acquire a pneumocystic infection with a CD4 count >200 cells/mm^3 and already on ART, lifelong prophylaxis should be considered.

Toxoplasmosis

Toxoplasma gondii is a protozoan that can cause encephalitis in HIV-positive patients as a reactivation of latent cysts in tissue. It can also cause disseminated disease as a primary infection. Prior to ART, one-third of *Toxoplasma* seropositive individuals with severe HIV developed toxoplasmosis within a year's time if not on chemoprophylaxis. The seroprevalence of *T. gondii* antibodies (IgG) is 11% in the United States and much higher in other parts of the world.

TABLE 101.2 **SECONDARY AND TERTIARY PROPHYLAXIS AGAINST *PNEUMOCYSTIS JIROVECII***

Agent	Notes	Discontinuation
Trimethoprim-sulfamethoxazole (TMP-SMX)	Start immediately after completing treatment for infection	CD4 ≥200 cells/mm^3 for > 3 months *or*
	Double-strength daily dosing is the preferred regimen	CD4 ≥100 cells/mm^3 *and* the viral load is suppressed for >3 months
Dapsone	Contraindicated in G6PD deficiency and severe sulfa allergy	
Atovaquone	Cost-prohibitive and liquid only	
Aerosolized pentamidine	Via Respirgard II only	

TABLE 101.3 **PRIMARY PROPHYLAXIS AGAINST *TOXOPLASMA GONDII***

Agent	Notes	Discontinuation
Trimethoprim-sulfamethoxazole (TMP-SMX)	Double-strength daily dosing is the preferred regimen	CD4 ≥200 cells/mm^3 for >3 months *or*
	Mild adverse effects are common and decreased dosing should be attempted if necessary	CD4 ≥100 cells/mm^3 *and* the viral load is suppressed for >3 months
Dapsone	Contraindicated in G6PD deficiency and severe sulfa allergy	
Atovaquone	Cost prohibitive and liquid only	

Primary prophylaxis

All HIV-positive patients should be assessed for IgG *T. gondii* antibodies at the time of diagnosis. In HIV-positive patients with CD4 counts <100 cells/mm^3 who are seropositive for *T. gondii* IgG, or when antibody levels are unknown, primary prophylaxis should be given (Table 101.3). The preferred regimen is one TMP-SMX DS tablet daily. As with Pneumocystis, alternate dosing options of a single-strength daily tablet or double-strength tablet three times weekly are also acceptable if the preferred regimen is not tolerated due to sensitivity. If an alternative agent cannot be avoided due to a life-threatening reaction, the options include dapsone and atovaquone with dapsone being the more affordable and preferable option for most patients who do not have G6PD deficiency.

If a seronegative patient is placed on an alternative pneumocystic prophylaxis regimen that does not cover toxoplasmosis, they should be retested if the CD4 count falls below 100 cells/mm^3.

As with Pneumocystis, toxoplasmosis prophylaxis can be discontinued once HIV-positive patients are taking ART and the CD4 count is >200 cells/mm^3 for 3 months. If the CD4 count is >100 cells/ mm^3 and the viral load is suppressed for >3 months, it is reasonable to stop primary prophylaxis. If, however, at any point the CD4 count falls below 100 cells/mm^3 again, primary prophylaxis should be resumed.

Secondary prophylaxis

Secondary prophylaxis (Table 101.4) against toxoplasmosis applies to patients who have successfully completed treatment for *Toxoplasma* encephalitis and are then appropriate for maintenance therapy. Unlike primary prophylaxis, the preferred regimen for secondary prophylaxis is pyrimethamine and sulfadiazine plus leucovorin. This will also provide protection against Pneumocystis. Twice-daily dosing of sulfadiazine (as opposed to four times daily dosing for treatment) is effective for prophylaxis. Higher dose clindamycin is an alternative option as a substitute for those unable to tolerate sulfadiazine. Atovaquone can be used as well (with or without pyrimethamine or sulfadiazine) and will also offer protection against Pneumocystis. Although not officially in the guidelines, there are data to suggest that TMP-SMX for secondary prophylaxis may be a valid option.

Secondary toxoplasma prophylaxis can be discontinued once the patient is symptom free, has a CD4 count of >200 cells/mm^3, and has been on ART for at least 6 months. Clinicians may also consider follow-up imaging for resolution of brain lesions prior to discontinuation. If the CD4 count declines below 200 cells/mm^3, secondary prophylaxis should be resumed. Unlike primary prophylaxis, there are insufficient data to withhold secondary prophylaxis in situations when the CD4 count is >100 but <200 cells/mm^3 and the viral load is suppressed.

TABLE 101.4 **SECONDARY PROPHYLAXIS AGAINST TOXOPLASMA GONDII**

Agent	Notes	Discontinuation
Pyrimethamine, sulfadiazine, and leucovorin	Start immediately after completing treatment for infection	Once patient is symptom free *and*
	This preferred regimen also protects against Pneumocystis	CD4 ≥ 200 cells/mm3 *and* has been on antiretroviral therapy (ART) for at least 6 months
Atovaquone and pyrimethamine	Used in patients who cannot tolerate sulfa	Consider repeat imaging prior to discontinuation
	Add sulfadiazine or inhaled pentamidine for Pneumocystis protection	
Clindamycin	High dose for use in patients who cannot tolerate sulfa	
	More affordable than atovaquone	

Invasive mycoses: Cryptococcosis, histoplasmosis, coccidioidomycosis

Cryptococcosis

Cryptococcus neoformans (and the geographically restricted *C. gattii*) is a yeast that caused disease in approximately 1 in 12 HIV infected individuals in developed countries prior to the institution of ART. Persons with CD4 counts of <100 cells/mm^3 are at greatest risk for disseminated disease. Cryptococcosis most often presents as subacute to acute meningitis, but can infect any organ.

Prophylaxis with fluconazole can decrease the risk of cryptococcosis in patients with CD4 counts of <100 cells/mm^3, but it is not often done due to the lack of survival benefit from the treatment, relatively low incidence of the disease, and cost.

Treatment of *C. neoformans* meningitis and other disseminated disease involves induction, consolidation, and maintenance (secondary prophylaxis) phases. Maintenance therapy with fluconazole 200 mg/d should continue for 1 year and can then be discontinued as long as the CD4 count is >100 cells/mm^3 and the HIV viral load has been undetectable for >3 months. Secondary prophylaxis with fluconazole should be reinitiated if the CD4 count falls below 100 cells/mm^3 again.

Histoplasmosis

Histoplasma capsulatum is a dimorphic fungus endemic in the Ohio and Mississippi River valleys, southeastern US, Puerto Rico, and Latin America. In these areas, histoplasmosis may occur in up to 5% of HIV-infected individuals, especially those with CD4 counts of <150 cells/mm^3. Infection is controlled via cellular immunity, and disease may represent a new infection or reactivation of a latent infection acquired years earlier. Histoplasmosis may present with fever, fatigue, weight loss, and hepatosplenomegaly. End-organ disease most commonly occurs in the lung, skin, and central nervous system (CNS). Gastrointestinal disease may present as diarrhea or as a mass mimicking a malignant tumor.

Primary prophylaxis (Table 101.5) should be considered in anyone with a CD4 count of <150 cells/mm^3 and is at risk due to occupational exposure or to living in an hyperendemic area (>10 cases of histoplasmosis/100 patient-years). Itraconazole 200 mg/d is the preferred regimen, although fluconazole 400 mg/d may have some efficacy. The newer azoles—voriconazole, posaconazole, and isovuconazonium—have not been evaluated for prophylaxis. Itraconazole requires acidic stomach conditions to be absorbed.

Prophylaxis may be discontinued in patients on ART once the CD4 count rises above 150 cells/mm^3 for 6 months. It should be restarted if the CD4 count falls below 150 again.

TABLE 101.5 **PRIMARY PROPHYLAXIS AGAINST HISTOPLASMOSIS IN ENDEMIC REGIONS**

Agent	Notes	Discontinuation
Itraconazole	Daily dosing of 200 mg is the preferred option	CD4 >150 cells/mm^3 *and* on highly active antiretroviral therapy (HAART) for 6 months
	Must be taken on an acidic stomach	
Fluconazole	Daily dosing of 400 mg is the second option	

Coccidioidomycosis

Coccidioides spp. are dimorphic fungi endemic in southwestern United States. Similar to *Histoplasma*, waning cellular immunity may allow disease to develop from either new or latent infections. Coccidioidomycosis may present as diffuse or focal pneumonia, meningitis, arthritis, or osteomyelitis. HIV-infected individuals exposed to this fungus are at increased risk of developing disease when the CD4 count falls below 250 cells/mm^3.

Primary prophylaxis for individuals at risk for coccidioidomycosis who are antibody negative for *Coccidioides* is *not recommended*. Serologic testing every 6 to 12 months in an individual at risk for the disease (living in an endemic area and CD4 <250) is reasonable. A newly positive test represents an infection, and, if there is no evidence of active disease, prophylaxis with fluconazole 400 mg/d can be started. Fluconazole can be discontinued once the CD4 count rises above 250 cells/mm^3 and HIV has been suppressed with ART.

Patients who had focal pulmonary disease should remain on antifungal therapy for at least 6 months. Twelve months or more of secondary prophylaxis (Table 101.6) is recommended for those who

TABLE 101.6 **PRIMARY AND SECONDARY PROPHYLAXIS AGAINST COCCIDIOIDOMYCOSIS IN ENDEMIC REGIONS**

Agent	Notes	Discontinuation
Fluconazole	400 mg/d for patients with CD4 <250 cells/mm3 and positive serologies against Coccidioides spp.	CD4 >250 cells/mm^3 *and* undetectable HIV viral load
Fluconazole	400 mg/d as secondary prophylaxis after treatment of mild disease	After 6 months *and* CD4 >250 cells/mm^3 *and* undetectable HIV viral load
Fluconazole or Itraconazole	400 mg/d fluconazole or 200 mg twice daily itraconazole	After 12 months *and* CD4 >250 cells/mm^3 *and* undetectable HIV viral load
	Secondary prophylaxis after treatment of diffuse pneumonia or systemic (non-central nervous system [CNS]) disease	
Fluconazole	400 mg/d as secondary prophylaxis after CNS disease	Lifelong therapy

had diffuse pulmonary disease or extrathoracic (other than CNS) disease. CD4 counts should be >250 cells/mm^3 and the viral load suppressed prior to discontinuation. Since relapse of CNS disease is common even in individuals without HIV, lifelong secondary prophylaxis is the norm for those with meningitis.

Cytomegalovirus

Cytomegalovirus (CMV) is a β-herpesvirus causing a latent infection in roughly half of adults by age 40. Patients with severe cellular immunosuppression (e.g., patients with a CD4 count <50 cells/mm^3) are at risk of end-organ disease, usually by reactivation of the virus but also through new infections. Retinitis is the most common manifestation of CMV disease in individuals with HIV/AIDS, but CMV can also cause esophagitis, colitis, pneumonitis, and CNS disease (encephalitis, ventriculitis, lumbar radiculopathy).

Prior to ART, roughly one in three persons with HIV would develop CMV retinitis before dying. In that era, daily oral ganciclovir (no longer available) was shown to prevent retinitis, but CMV prophylaxis never was the standard of care due to cost, toxicity, and the high number needed to treat to prevent the disease. With the institution of ART, the incidence of CMV retinitis decreased by >95%. A more recent prophylaxis trial with oral valganciclovir in individuals at risk of disease failed to show a benefit, and CMV primary prophylaxis is currently *not recommended*.

Patients who have had CMV retinitis treated and controlled should be placed on maintenance therapy to prevent relapse. Therapies may be administered orally, parenterally, or intravitreally, and the choice should be made with the consultation of an HIV expert and an ophthalmologist (Table 101.7). Other end-organ disease need not be secondarily prophylaxed, unless there is evidence of retinitis or a relapse. Intravitreal prophylaxis will not prevent systemic disease or disease in the contralateral eye.

Secondary prophylaxis may be discontinued safely once three conditions have all been met: (1) after 3 to 6 months of prophylaxis, (2) when all retinal lesions are deemed inactive, and (3) CD4 count has risen to >100 cells/mm^3 for 3 to 6 months. Relapses can occur at any CD4 count; patients should have periodic retinal exams.

TABLE 101.7 **OPTIONS FOR SECONDARY PROPHYLAXIS AGAINST CYTOMEGALOVIRUS**

Route of administration	Agent
Oral	Valganciclovir
Parenteral	Ganciclovir
	Foscarnet
	Ganciclovir plus foscarnet
	Cidofovir
Intravitreal	Ganciclovir
	Foscarnet
	Cidofovir
	Fomivirsen (not available in the United States)

Tuberculosis

Mycobacterium tuberculosis kills well over 1 million persons worldwide every year and is a leading cause of death among persons with HIV. Tuberculosis (TB) is acquired through inhalation of infectious droplets and is often contained by cellular immunity. Persons may have latent TB infection (LTBI) for decades. Persons with HIV have a high risk of reactivating their LTBI, and there appears to be no CD4 cell count threshold associated with TB disease. Nevertheless, the lower the CD4 count the higher the risk.

All persons with HIV should be screened for LTBI upon presentation to medical care (as all patients with TB should be screened for HIV). Two types of screens are currently used: the Mantoux tuberculin skin test (TST) and the interferon-γ release assay (IGRA) blood test. Either is acceptable, although the sensitivity of both decreases with increased immune suppression. Only one test need be performed; administering both tests is currently not recommended.

Individuals with HIV testing positive either via the TST (skin induration >5 mm) or IGRA should have active TB ruled out. At a minimum, a chest x-ray should be obtained looking for active pulmonary disease. If there is no evidence of active TB, then the LTBI should be treated. Nine months of daily isoniazid plus pyridoxine remain the mainstay of LTBI therapy, although compliance tends to decrease in the last months of therapy. Three months of isoniazid plus rifapentine (and pyridoxine) given once weekly under directly observed therapy (DOT) appears to be as safe and efficacious as 9 months of isoniazid. Other alternative regimens are listed in Table 101.8.

Patients should be monitored every few weeks for adherence and toxicity. Medications should be discontinued if liver enzymes rise above five times the upper limits of normal. Patients should be cautioned to avoid alcohol, and clinicians should watch for drug interactions.

Once LTBI or active TB has been treated, reinfection occurs rarely in the United States. Secondary prophylaxis is not needed.

Disseminated mycobacterium avium complex

Organisms belonging to the *Mycobacterium avium* complex (MAC) can be found throughout the environment. HIV-infected individuals

TABLE 101.8 **LATENT TUBERCULOSIS TREATMENT IN PERSONS LIVING WITH HIV**

Agent	Duration
Isoniazid 300 mg/d plus pyridoxine 25–50 mg/d	9 months
Rifapentine (750 mg for 32–50 kg, 900 mg for >50 kg) weekly *plus* isoniazid 900 mg weekly plus pyridoxine 50mg weekly	12 weeks
Rifampin 600 mg/d	4 months

are at high risk of MAC disease, either localized (e.g., lymphadenitis) or disseminated, when the CD4 cells fall to <50 cells/mm^3. Disseminated disease often presents with fever, weight loss, or diarrhea. Patients with low CD4 counts and symptoms of MAC should have active disease ruled out prior to prophylaxis initiation.

MAC prophylaxis is currently not recommended in patients on suppressive ART. It is likewise not recommended in persons initiating ART regardless of CD4 count. Prophylaxis is only indicated in individuals with a CD4 count <50 cells/mm^3 whose viral load is not suppressed while on HAART. Medications include azithromycin 1,200 weekly or clarithromycin 500 mg twice daily. Rifabutin is an alternative for those who cannot tolerate the macrolides, but drug interactions can make administration difficult. Primary prophylaxis can be stopped once viral suppression has been achieved with ART.

For patients with MAC disease, full therapy against this mycobacterium should be continued for at least 1 year as secondary prophylaxis or maintenance therapy. Secondary prophylaxis can be discontinued after 12 months as long as the patient has no evidence of MAC disease, is on ART, and the CD4 count is > 100 cells/mm^3 for 6 months.

Vaccinations

Persons living with HIV who are older than age 13 should receive vaccinations against *Streptococcus pneumonia*. If never previously vaccinated, administer 1 dose of 13-valent pneumococcal conjugate vaccine (PCV13) followed at least 8 weeks later by 1 dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23). Patients should receive a second dose of PPSV23 at least 5 years later and again at age 65 as long as the previous dose was given more than 5 years before. If the patient has already received the PPSV23 prior to receiving the PCV13, then defer administration of PCV13 at least 1 year after the PPSV23. Of note, administering the PPSV23 once the CD4 count is at least 200 cells/mm^3 will increase efficacy.

If not previously vaccinated and immune to hepatitis B, all persons living with HIV should complete the vaccine series with a three-dose series of single-antigen hepatitis B vaccine or combined hepatitis B and hepatitis A vaccine if the patient is also at risk for hepatitis A. Risk factors for hepatitis A in HIV-positive patients include MSM, injection drug use, and chronic liver disease. Patients should be assessed for immunity after completing the hepatitis B vaccine series, and nonresponders should repeat the series once there is a sustained increase in CD4 count.

All persons living with HIV should be offered the inactivated influenza vaccine annually. The live-attenuated vaccine is contraindicated in this patient population. Follow Advisory Committee on Immunization Practices (ACIP) guidelines for further details regarding age appropriate vaccinations.

Suggested reading

Mocroft, et al. Is it safe to discontinue primary *Pneumocystis jirovecii* pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? Results from: Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE). *CID*. 2010 Nov 1;51(9):1114.

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

Section 13

Nosocomial infection

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Percutaneous injury

Risks and management

David Kuhar and Krista Powell

Healthcare personnel (HCP) are at risk of occupational exposure to bloodborne pathogens such as hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV from needlesticks and injuries from sharp objects. Risk factors for transmission of bloodborne pathogens as a result of occupational exposure are related to the source patient (e.g., titer and infectivity of the virus in his or her blood or body fluid), the injury (e.g., quantity of blood or body fluid transferred during the exposure), and the recipient individual (e.g., immunologic status).

Percutaneous exposures are the most common mechanism for transmission of bloodborne pathogens in healthcare settings. Hospital-based HCP in the United States have previously been estimated to sustain an average of 384,325 (range: 311,091–463,922) percutaneous injuries annually. Data from several surveillance systems have demonstrated that the majority of reported injuries occur in the acute care setting, particularly medical floors, operating rooms, and intensive care units.

Prevention of bloodborne pathogen transmission through exposure prevention requires a diversified approach following the occupational health and safety hierarchy of controls. Measures include the development of improved engineering controls (e.g., safer medical devices), work practices (e.g., technique changes to reduce handling of sharp objects), and infection control measures, including use of personal protective equipment. Another important pre-exposure strategy to prevent infection includes HBV immunization.

Although preventing exposures is the primary means of preventing bloodborne pathogen infection, appropriate post-exposure management is an important element of workplace safety. The Occupational Health and Safety Administration's bloodborne pathogens standard requires employers to develop written exposure control plans to protect all employees at risk of exposure to blood or other potentially infectious materials and to provide job-related post-exposure evaluation and follow-up to all employees. Healthcare organizations should have a system that includes written protocols for prompt confidential reporting, evaluation, counseling, treatment, and follow-up of any occupational exposures that may place HCP at risk for acquiring bloodborne infection. Each incident of occupational exposure to blood or body fluid that may contain HBV, HCV, or HIV should be evaluated as rapidly as possible and should include testing of the source patient for the appropriate bloodborne pathogens, testing of the exposed person for prior infection, and prompt administration of prophylactic agents when indicated.

Initial exposure management and evaluation

Wounds should be washed with soap and water. There is no evidence that the use of antiseptics for wound care or expressing fluid by squeezing the wound further reduces the risk of bloodborne pathogen transmission. However, the use of antiseptics is not contraindicated. The exposure should be evaluated for potential to transmit HBV, HCV, and HIV based on the type of potentially contaminated source body substance involved and the route and severity of the exposure. Blood, fluid containing visible blood, or other potentially infectious fluid (including semen; vaginal secretions; and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids) or tissue can be infectious for bloodborne pathogens.

The person whose blood or body fluid is the source of a percutaneous injury should be evaluated for HBV, HCV, and HIV infection. Information available in the medical record at the time of exposure (e.g., laboratory test results, admitting diagnosis, or past medical history) or from the source individual may help determine the likelihood of bloodborne virus infection. If the HBV, HCV, and/or HIV infection status of the source is unknown, the source person should be informed of the incident and tested for evidence of bloodborne virus infection as soon as possible, including preferably using a nucleic acid test for HCV. Procedures should be followed for testing source persons, including obtaining informed consent, in accordance with applicable state and local laws. If the exposure source's infectious status cannot be determined (e.g., unknown source patient), decisions about post-exposure management should be made on a case-by-case basis after considering the type of exposure and the clinical and/or epidemiologic likelihood of infection with HBV, HCV, or HIV.

Bloodborne pathogens

Hepatitis B virus infection

HBV infection is a well-recognized occupational risk for HCP. The risk of HBV infection is primarily related to the degree of contact with blood and also to the hepatitis B e antigen (HBeAg) status of the source patient. In studies of unvaccinated HCP who sustained injuries from needles contaminated with blood containing HBV, the risk of developing clinical hepatitis from exposure to hepatitis B surface antigen (HBsAg)- and HBeAg-positive blood was 22% to 31%, and the risk of developing serologic evidence of HBV infection, 37% to 62%. By comparison, the risk of developing clinical hepatitis from a needle contaminated with HBsAg-positive, HBeAg-negative blood was 1% to 6%, and the risk of developing serologic evidence of HBV infection, 23% to 37%.

All HCP at risk for contact with contaminated blood or body fluids should be vaccinated against HBV. Pre-vaccination serologic testing for previous infection is not performed for the majority of persons being vaccinated because of occupational risk unless the hospital or healthcare organization considers testing cost-effective. Regardless of vaccination history, testing is cost-effective for high-risk HCP populations, including those born in geographic regions with high (≥8%) and intermediate (2–7%) HBsAg prevalence, unvaccinated US-born HCP whose parents were born in regions of high HBsAg prevalence, HIV-positive HCP, HCP who have disclosed having engaged or currently engaging in high-risk substance abuse or sexual behaviors, and HCP who require immunosuppressive therapy or who are on hemodialysis. These HCP should be tested for HBsAg and antibodies to hepatitis B core antigen (anti-HBc)/antibody to HBsAG (anti-HBs) to determine infection status. Hepatitis B vaccine can be administered at the same time as other vaccines. Vaccination options include a two-dose series (administered at time zero and 1 month) and a three-dose series (administered at time zero, 1 month, and 6 months). Two doses of Heplisav-B (HepB-CpG) administered <4 weeks apart should be repeated. Both doses of the two-dose series should consist of HepB-CpG. If the three-dose series is interrupted after the first dose, the second dose should be administered as soon as possible. The second and third doses should be separated by at least 2 months. If only the third dose is delayed, it should be administered when convenient. To determine the need for revaccination and to guide post-exposure prophylaxis, post-vaccination serologic testing should be performed for all HCP at risk for occupational exposure to blood or body fluids 1 to 2 months after completion of the vaccination series for a protective concentration of anti-HBs (≥10 mIU/mL). Persons who do not respond to the primary vaccine series should complete a second vaccine series or be evaluated to determine if they are HBsAg positive. Revaccinated persons should be retested at the completion of the second vaccine series.

HCP with previous documentation of a complete vaccine series, but no documentation of anti-HBs of ≥10mIU/mLmay be at risk for HBV infection. Some experts suggest that they undergo anti-HBs testing upon hire or matriculation. Vaccinated HCP without previous anti-HBs testing who sustain an occupational exposure should be tested for anti-HBs as soon as possible after the exposure. Completely vaccinated HCP with anti-HBs <10mIU/mL should receive additional vaccination. For HCP who received two doses of HepB-CpG, revaccination may consist of a second complete HepB vaccine series followed by anti-HBs testing 1 to 2 months after the final dose. Alternatively, revaccination may consist of administration of an additional single HepB vaccine dose followed by anti-HBs testing 1 to 2 months later (and, if anti-HBs remains <10 mIU/mL, completion of the second HepB vaccine series followed again by anti-HBs testing 1–2 months after the final dose). For HCP who received the three-dose series, revaccination may consist of an additional dose of HepB vaccine, followed by anti-HBs testing 1 to 2 months later. HCP whose anti-HBs remain <10mIU/mL could receive two additional vaccine doses (to complete a second vaccine series), followed by repeat anti-HBs testing 1 to 2 months after the last dose.

Primary nonresponders to vaccination who are HBsAg negative should be considered susceptible to HBV infection and counseled regarding the need to obtain hepatitis B immunoglobulin (HBIG) prophylaxis for any known or probable exposure to HBsAg-positive

TABLE 102.1 **RECOMMENDED POST-EXPOSURE PROPHYLAXIS FOR PERCUTANEOUS EXPOSURE TO HEPATITIS B VIRUS (HBV), UNITED STATES**

Vaccination and antibody response status of exposed person[a]	**Treatment when source is found to be:** HBsAg[b] positive	HBsAg negative	Source not tested or status unknown
Unvaccinated/incompletely vaccinated or vaccine refusers	HBIG[c] × 1 and complete HB vaccine series[d]	Complete HB vaccine series	Complete HB vaccine series
Previously vaccinated			
Known responder[e]	No treatment	No treatment	No treatment
Known nonresponder[e]			
After complete series	HBIG × 1 and initiate revaccination	Initiate revaccination	If known high-risk source, treat as if source were HBsAg positive
After two complete series	HBIG × 2 (separated by 1 month)	No treatment	If known high-risk source, treat as if source were HBsAg positive

[a] Persons who have previously been infected with HBV are immune to reinfection and do not require post-exposure prophylaxis.
[b] Hepatitis B surface antigen.
[c] Hepatitis B immunoglobulin; dose 0.06 mL/kg intramuscularly.
[d] Hepatitis B vaccine series. Healthcare personnel should be tested 1 to 2 months after completion of the vaccination series for anti-HBs.
[e] A seroprotective (adequate) level of anti-HBs after completion of a vaccination series is defined as anti-HBs ≥10 mIU/mL; a response <10 mIU/mL is inadequate and is not a reliable indicator of protection.
[f] Antibody to HBsAg.

blood (Table 102.1). Any blood or body fluid exposure of an unvaccinated susceptible person should lead to initiation of the hepatitis B vaccine series.

For percutaneous exposures to HBV-infected blood, the decision to provide prophylaxis must take into account several factors, including the HBsAg status of the source and the hepatitis B vaccination and vaccine-response status of the exposed person. The hepatitis B vaccination status and the vaccine-response status (if known) of the exposed person should be reviewed. Table 102.1 summarizes prophylaxis recommendations for percutaneous exposure to blood according to the HBsAg status of the exposure source and the vaccination and vaccine-response status of the exposed person. When HBIG is indicated, it should be administered as soon as possible after exposure (preferably within 24 hours). The effectiveness of HBIG when administered >7 days after exposure is unknown. Hepatitis B vaccine, when indicated, should also be given as soon as possible (preferably within 24 hours) and can be given simultaneously with HBIG (though it should be administered intramuscularly at a separate site, with vaccine always given in the deltoid muscle). For exposed persons who are in the process of being vaccinated but have not completed the vaccination series, vaccination should be completed as scheduled and HBIG added. HBV testing should be performed on any exposed person who has an illness compatible with hepatitis.

Hepatitis C virus infection

HCV is not transmitted efficiently through occupational exposures to blood. The average incidence of anti-HCV seroconversion after accidental percutaneous exposure from an HCV-positive source is 1.8% (range, 0–7%). The risk for transmission after exposure to fluids or tissues other than HCV-infected blood has not been quantified but is thought to be low.

HCP who provide care to persons exposed to HCV in the occupational setting should be knowledgeable regarding the risk for HCV infection and appropriate counseling, testing, and medical follow-up. Immunoglobulin and antiviral agents are not recommended for post-exposure prophylaxis (PEP) after exposure to HCV. For the person exposed to a source with HCV viremia or for whom HCV infection status is unknown, testing for anti-HCV should be performed within 48 hours of exposure. A reflex HCV RNA test should be performed if anti-HCV testing is positive. If anti-HCV testing is negative, or if reflex HCV RNA is negative after positive anti-HCV testing, then HCV RNA testing should be repeated ≥3 weeks after exposure. If RNA testing is negative, many experts recommend testing for anti-HCV at 4 to 6 months post-exposure; a reflex HCV RNA test should be performed if anti-HCV testing is positive. All persons with current HCV infection as evidenced by a positive HCV RNA test should be referred for evaluation by a practitioner with expertise in liver disease and HCV treatment. Spontaneous clearance of infection may occur up to 6 months after exposure, so persons with positive HCV RNA testing <6 months after exposure should be tested again ≥6 months after exposure to determine infection status.

Human immunodeficiency virus infection

In 2014, the US Centers for Disease Control and Prevention (CDC) updated the 2005 risk estimate of HIV transmission after a percutaneous exposure to HIV-infected blood. Based on a meta-analysis and systematic review of 21 published studies, estimated average risk is approximately 0.23% (95% confidence interval: 0%, 0.46%). Fourteen of the 21 studies reported no transmissions. These and other studies suggest that infection risk is increased by factors that increase the "effective" viral dose, such as exposure to a larger quantity of blood (e.g., a device visibly contaminated with the patient's

blood, a procedure that involved a needle placed directly in a vein or artery, a deep injury) and a source patient with a high viral load.

After exposure, timely receipt of HIV post-exposure prophylaxis can reduce the risk for HIV transmission. HCP exposed to HIV should be evaluated as soon as possible (within hours) after their exposure and should be tested for HIV at baseline (i.e., to establish infection status at the time of exposure). Whenever possible and according to applicable state and local laws, the HIV status of the exposure source patient should be determined to guide appropriate use of HIV PEP. Administration of PEP should not be delayed while waiting for test results. If the source patient is determined to be HIV-negative, PEP should be discontinued and no follow-up HIV testing for the exposed provider is indicated.

After exposure to HIV, PEP should be initiated as soon as possible. PEP should be administered for 4 weeks, if tolerated. The drug regimen selected for HIV PEP should have a favorable side-effect profile as well as a convenient dosing schedule to facilitate both adherence to the regimen and completion of 4 weeks of PEP. Given the complexity of choosing and administering HIV PEP, whenever possible, consultation with an infectious diseases specialist or another physician who is an expert in the administration of antiretroviral agents is recommended. Such consultation should not, however, delay timely initiation of PEP.

Box 102.1 lists the preferred regimen for HIV PEP, alternative regimens, medications to be used only in consultation with an expert, and medications that are not recommended for use as PEP. A regimen containing three (or more) antiretroviral drugs is now recommended routinely for all occupational exposures to HIV. Tenofovir (TDF) plus emtricitabine (FTC) plus raltegravir (RAL) is recommended as the preferred regimen for occupational exposures

BOX 102.1

Recommended HIV post-exposure prophylaxis (PEP) regimens

Preferred HIV PEP regimen

Raltegravir (Isentress; RAL) 400 mg PO twice daily
Plus
Truvada,1 PO once daily
(Tenofovir DF [Viread; TDF] 300 mg + emtricitabine [Emtriva; FTC] 200 mg)

Alternative regimens

(May combine one drug or drug pair from the left column with one pair of nucleoside/nucleotide reverse transcriptase inhibitors from the right column. Prescribers unfamiliar with these agents/regimens should consult physicians familiar with the agents and their toxicities.)[a]

Raltegravir (Isentress; RAL) Tenofovir DF (Viread; TDF) + emtricitabine (Emtriva; FTC); available as Truvada
Darunavir (Prezista; DRV) + ritonavir (Norvir; RTV) Tenofovir DF (Viread; TDF) + lamivudine (Epivir; 3TC)
Etravirine (Intelence; ETR) Zidovudine (Retrovir; ZDV; AZT) + lamivudine (Epivir; 3TC); available as Combivir
Rilpivirine (Edurant; RPV) Zidovudine (Retrovir; ZDV; AZT) + emtricitabine (Emtriva; FTC)
Atazanavir (Reyataz; ATV) + ritonavir (Norvir; RTV)
Lopinavir/ritonavir (Kaletra; LPV/RTV)
The following alternative is a complete fixed-dose combination regimen and no additional antiretrovirals are needed: Stribild (elvitegravir, cobicistat, tenofovir DF, emtricitabine)

Alternative antiretroviral agents for use as PEP *only* with expert consultation

Abacavir (Ziagen; ABC)[b]
Efavirenz (Sustiva; EFV)
Enfuvirtide (Fuzeon; T20)
Fosamprenavir (Lexiva; FOSAPV)
Maraviroc (Selzentry; MVC)
Saquinavir (Invirase; SQV)
Stavudine (Zerit; d4T)

Antiretroviral agents generally not recommended for use as PEP

Didanosine (Videx EC; ddI)
Nelfinavir (Viracept; NFV)
Tipranavir (Aptivus; TPV)

Antiretroviral agents contraindicated as PEP

Nevirapine (Viramune; NVP)

[a] The alternative regimens are listed in order of preference; however, other alternatives may be reasonable based on patient and clinician preference.

[b] Abacavir hypersensitivity reaction can be fatal and is associated with the HLA -B*5701 allele. HCP considered for treatment with abacavir should first undergo screening for the HLA -B*5701 allele.

to HIV. This regimen is tolerable, potent, conveniently administered, and has been associated with minimal drug interactions. Tenofovir, a component of Truvada, is not indicated for HCP with an estimated creatinine clearance (eCrCl) of <60 mL/min. Some experts recommend using antiretroviral drugs for PEP after occupational exposure that were approved for use after the release of the US Public Health Service (USPHS) 2013 guidelines for the management of occupational exposure to HIV and recommendations for PEP. For example, tenofovir alafenamide (TAF) has been used instead of TDF in PEP regimens. The once-daily integrase strand transfer inhibitor, dolutegravir (DTG), has been used instead of twice-daily RAL as part of occupational PEP regimens, however, concerns have been raised about use of DTG during the perinatal period. Because many antiretroviral agents can have adverse effects in pregnancy or have insufficient data, they may not be recommended for use in pregnancy. When prescribing PEP, anticipating and preemptively treating side effects (e.g., nausea, diarrhea, etc.) commonly associated with taking antiretroviral agents is encouraged. (Findings from

TABLE 102.2 **PRACTICE RECOMMENDATIONS FOR HEALTHCARE FACILITIES (HCFS) IMPLEMENTING GUIDANCE FOR MANAGEMENT OF OCCUPATIONAL EXPOSURES TO BLOODBORNE PATHOGENS (BBPS)**

Practice recommendation	Implementation checklist
Establish a BBP management policy	All institutions where HCP may experience exposures should have a written policy for management of exposures
	The policy should be reviewed periodically to ensure it is up to date
Implement management policies	HCFs should provide appropriate training to all personnel on the prevention of and response to occupational exposures
	HCFs should establish hepatitis B vaccination programs
	HCFs should establish exposure-reporting systems
	HCFs should have personnel who can manage an exposure readily available at all hours of the day
	HCFs should have ready access to post-exposure prophylaxis (PEP) for use by exposed personnel as necessary
Establish laboratory capacity for BBP testing	HCFs should provide prompt processing of specimens from exposed and source persons to guide management of occupational exposures
	Testing should be performed with appropriate counseling and consent
Select and use appropriate PEP regimens	HCFs should develop a policy for the selection and use of PEP antiretroviral regimens for HIV exposures within their institution
	Hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) should be available for timely administration
	HCFs should have access to resources with expertise in the selection and use of PEP
Provide access to counseling for exposed healthcare personnel (HCP)	HCFs should provide counseling for healthcare personnel (HCP) who may need help to deal with the emotional impact of an exposure and who should be instructed to use precautions to prevent secondary transmission during the follow-up period
	HCFs should provide medication adherence counseling to assist HCP complete HIV PEP as necessary
Monitor for adverse effects of PEP	HCP taking antiretroviral PEP should be monitored periodically for adverse events through clinical evaluation, including blood testing, at baseline and 2 weeks post-exposure
Monitor for seroconversion	HCF should develop a system to encourage exposed HCP to return for follow-up testing
Monitor exposure management programs	HCFs should develop a system to monitor reporting and management of occupational exposures to ensure timely and appropriate response
	Evaluate:
	Exposure reports for completeness and accuracy
	Access to care (i.e., the time of exposure to the time of evaluation)
	Laboratory result reporting time
	Review:
	Exposures to ensure that HCP exposed to sources not infected with BBPs do not receive PEP or PEP is stopped
	Monitor:
	Completion rates of HBV vaccination and HIV PEP
	Completion of exposure follow-up

an African observational study suggesting that perinatal exposure to DTG-containing antiretroviral regimens was associated with neural tube defects have prompted recommendations that HCP prescribing PEP should avoid use of DTG for non-pregnant women of childbearing potential who are sexually active or who have been sexually assaulted and who are not using an effective birth control method and pregnant women early in pregnancy, since the risk of an unborn infant developing a neural tube defect is during the first 28 days. See: https://stacks.cdc.gov/view/cdc/38856 "Update: Interim Statement Regarding Potential Fetal Harm from Exposure to Dolutegravir—Implications for HIV Post-exposure Prophylaxis (PEP)."

Re-evaluation of the exposed person should be performed within 72 hours post-exposure, especially as additional information about the exposure or source person becomes available. HCP with occupational exposure to HIV should receive follow-up counseling regarding precautions to prevent secondary transmission during the follow-up period, post-exposure testing, and medical evaluation regardless of whether they receive PEP. HIV testing should be performed for 6 months post-exposure (e.g., at 6 weeks, 12 weeks, and 6 months). Use of fourth-generation combination HIV p24 antigen–HIV antibody immunoassays allow for earlier detection of HIV infection. If the clinician is certain that a fourth-generation combination HIV p24 antigen–HIV antibody test is being utilized, then HIV testing could be performed at baseline, 6 weeks, and concluded at 4 months post-exposure. If PEP is used, the HCP should be monitored for drug toxicity by medical evaluation and by checking, at a minimum, CBCs and renal and hepatic function tests at baseline and again 2 weeks after starting PEP. The scope of post-exposure blood testing should be based on medical conditions in the exposed person and the anticipated toxicities of the drugs included in the PEP regimen. Further testing may be indicated if abnormalities were detected. HIV testing should be performed on any exposed person who has an illness compatible with HIV seroconversion.

Guidance for healthcare facilities

In Table 102.2, specific practice recommendations for the management of occupational bloodborne pathogen exposures are outlined to assist healthcare institutions with the implementation of established exposure management guidelines. All recommendations given are valid as of February 2019.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Suggested reading

Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention; Shefer A, et al. Immunization of healthcare personnel: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(RR-7):1–45.

Department of Labor Occupational Safety and Health Administration. Occupational exposure to blood-borne pathogens: Final rule. *Fed Reg*. 1991;56:C29–CFR Part 1910.1030:64175.

Kuhar DK, Henderson DK, Struble KA, et al. Updated US Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *Infect Control Hosp Epidemiol*. 2013;34(9):875–892.

Naggie S, Holland DP, Sulkowski MS, Thomas DL. Hepatitis C virus postexposure prophylaxis in the healthcare worker: Why direct-acting antivirals don't change a thing. *Clin Infect Dis*. 2016;64(1):92–99.

Patel P, Borkowf CB, Brooks JT, et al. Estimating per-act HIV transmission risk: A systematic review. *AIDS* 2014;28(10):1509–1519.

Panlilio AL, Orelien JG, Srivastava PU, et al. Estimate of the annual number of percutaneous injuries among hospital-based healthcare workers in the United States, 1997–1998. *Infect Control Hosp Epidemiol*. 2004;25:556–562.

Schillie S, Harris A, Link-Gelles R, Romero J, Ward J, Nelson N. Recommendations of the Advisory Committee on Immunization Practices for use of a hepatitis B vaccine with a novel adjuvant. *MMWR Morb Mortal Wkly Rep*. 2018;67(15):455–458.

Schillie S, Murphy TV, Sawyer M, et al. CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering post-exposure management. *MMWR Recomm Rep*. 2013;62(RR-10):1–19.

Schillie S, Vellozi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2018;67(1):1–31.

US Department of Health and Human Services. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. December 2018. https://aidsinfo.nih.gov/guidelines/html/3/perinatal/224/whats-new-in-the-guidelines

103

Hospital-acquired fever

Susan K. Seo and Arthur E. Brown

Fever is a common clinical problem in hospitalized patients. Although the development of fever in a hospitalized patient may be the clinical expression of a community-acquired infection that has completed its incubation period, this chapter focuses on the possible causes of new-onset fever occurring at least 48 hours after hospital admission. The reader, however, should keep other diagnoses in mind and inquire about the patient's history of travel, pet and animal exposure, hobbies (e.g., gardening, whitewater rafting, and other adventure sports), sexual activity, dietary preferences, occupational exposures, recent immunizations, drug (including corticosteroids) and herbal ingestion within the past month, recent contact with febrile or ill individuals, and other epidemiologic factors such as season of the year.

Nosocomial fever occurs in 2% to 31% of medical inpatients. The wide range in prevalence rates has been attributed to differences in definition of fever, methods of temperature measurement, study population (e.g., general medical patients, geriatric patients), and healthcare setting (e.g., county, university, or Veterans Affairs hospital). Hospital-acquired fever may be due to an infectious and/or noninfectious cause, either happening alone or concurrently. An etiology can be identified after appropriate workup in 73% to 88% of patients. It is not uncommon for length of stay and resource utilization to be increased due to the management of the febrile episode.

Not surprisingly, nosocomial infections account for 56% to 74% of causes of fever in hospitalized patients, with the most common infectious causes being bloodstream infections, upper and lower respiratory tract infections, and urinary tract infections (Box 103.1). There has been a steady increase in the rates of nosocomial infections due to multidrug-resistant organisms (MDROs). Knowledge of local surveillance data, including antibiotic resistance patterns, and patient risk factors for acquisition of MDROs is important as one considers choice of empiric antimicrobial therapy. Noninfectious causes comprise 14% to 31%. These are usually related to some form of vascular disruption (e.g., myocardial infarction, pulmonary embolism), inflammatory (e.g., gout) or collagen vascular disease (e.g., lupus), endocrine disorder (e.g., adrenal insufficiency), malignancy, or drug (Box 103.2). In some instances, the only identifiable factor may be an invasive procedure (e.g., surgery, bronchoscopy) performed within 24 hours of fever onset.

A comprehensive review of the patient's history and a full physical exam should be performed to find clues to the source(s) of fever. Disorders of immune function, valvular heart disease, history of previous placement of prosthetic devices (e.g., orthopedic), prior illness and treatment including for MDROs, drug allergies, and history of transplantation should be reviewed with the patient. Attention should also be paid to risk factors for hospital-acquired fever such as recent surgical, endoscopic, or interventional radiologic procedures; recent urinary and respiratory tract instrumentation; intravascular devices; drug therapy; blood transfusions; and immobilization. The physical examination should be complete but focus on vital signs; general appearance; signs of toxicity; skin rash; presence of genital, mucosal, and/or conjunctival lesions; presence of cardiac murmur or rub; new crackles; decreased breath sounds; egophony and/or pleural friction rub on lung auscultation; abdominal tenderness; hepatosplenomegaly; costovertebral angle tenderness; arthritis; spinal tenderness; meningismus; and/or neurologic dysfunction.

Obviously, the postoperative patient will have special attention given to the operative site and wounds. Consultation with the surgeon regarding the operative findings, technical difficulties, and complications is essential. Similarly, conferring with the endoscopist after bronchoscopy, endoscopic retrograde

BOX 103.1

Infectious causes of hospital-acquired fever

Bloodstream
- Intravascular device-related (e.g., triple-lumen central venous catheter, Hickman, Broviac, Port)
- Sepsis due to bacterial or fungal organisms

Central nervous system
- Epidural abscess
- Meningitis

Gastrointestinal
- Cholangitis
- Diverticulitis
- Intra-abdominal abscess
- Pseudomembranous colitis

Respiratory tract
- Aspiration pneumonia
- Empyema
- Hospital-acquired pneumonia
- Sinusitis
- Ventilator-associated pneumonia

Skin and soft tissue
- Cellulitis
- Myonecrosis
- Necrotizing fasciitis

Surgical site (incisional, deep space, or abscess)

Urinary tract
- Catheter-related
- Post instrumentation (e.g., cystoscopy)

Other
- Endocarditis
- Prosthetic device infection
- Suppurative thrombophlebitis
- Transfusion-related (bacterial, fungal, viral, parasitic)

BOX 103.2

Examples of noninfectious causes of hospital-acquired fever

Biologic agents (e.g., vaccines, cytokines)/drugs
- Alcohol or drug withdrawal
- Drug fever
- Drug overdose (e.g., anticholinergic agents)
- Neuroleptic malignant syndrome

Cardiac causes
- Myocardial infarction
- Pericarditis

Collagen vascular diseases
- Vasculitis

Endocrine disorders
- Adrenal insufficiency
- Thyroid storm

Factitious fever

Inflammatory diseases
- Gout, pseudogout
- Nonviral hepatitis

Intra-abdominal conditions
- Acalculous cholecystitis
- Acute pancreatitis
- Mesenteric ischemia
- Upper or lower gastrointestinal bleeding

Malignancy
- Tumor fever

Neurologic conditions
- Intracranial or subarachnoid hemorrhage
- Seizures
- Stroke
- Subdural hematoma

Procedure-related
- Benign postoperative fever
- Endobronchial intubation
- Transfusion reaction

Thromboembolic disease
- Deep venous thrombosis
- Pulmonary embolus
- Superficial thrombophlebitis

Vascular conditions
- Sickle cell crisis

cholangiopancreatography, colonoscopy, or cystoscopy may reveal information regarding the etiology of post-endoscopic fever in such a patient. The patient with cancer may receive a significant amount of blood products over time and may develop transfusion-related infections (see Chapter 104, "Transfusion-related infection"). Infections found in the alcoholic, drug abusing, thermally injured, diabetic, elderly, or immunocompromised patient require special consideration (see chapters covering these topics). The immunocompromised patient with cancer in particular may have a variety of possible infectious etiologies to consider (see Chapter 85, "Infections in patients with neoplastic disease").

The investigation of hospital-acquired fever should take into consideration possible foci of infection. The initial evaluation typically includes a CBC, urinalysis, chest radiograph, and cultures of blood, urine, and, if indicated, sputum. Adequate sputum for microbiologic evaluation should contain few epithelial cells and numerous polymorphonuclear neutrophils if the patient is not neutropenic. However, obtaining a good specimen, particularly in critically ill and/or neutropenic patients, might be difficult. Appropriate cultures of wound sites and drainage are also important. It is essential to obtain fresh material from the drainage site rather than the material that has been dwelling in the collection apparatus. In the patient with diarrhea, stool specimens should be obtained and tested for *Clostridium difficile*. When a rash is present, a biopsy of the skin should be obtained for both histologic and microbiologic

examination. Vascular access devices are suspect. If possible, these should be removed and the tips sent for culture.

It is important that the specimens are obtained correctly and are transported to the microbiology laboratory quickly. This aids in the recovery of fastidious organisms, particularly anaerobic bacteria. Examination of the Gram-stained specimen is useful in judging the adequacy of the specimen and aids in the presumptive etiologic diagnosis. There is also increasing adoption of rapid diagnostics (e.g., peptide nucleic acid fluorescence in situ hybridization [PNA FISH], matrix-assisted laser desorption ionization-time of flight [MALDI-TOF] mass spectrometry, and multiplexed nucleic acid amplification tests) by clinical microbiology laboratories, as these technologies expedite time to organism identification and, when combined with antimicrobial stewardship, improve time to appropriate therapy. Procalcitonin is a serum biomarker that rises with systemic inflammation, especially from bacterial origin, but false-positive and false-negative results can occur, necessitating careful interpretation within the clinical context. Certainly, decisions regarding antimicrobial therapy should not be solely based on procalcitonin levels. In addition, the degree to which procalcitonin rises varies among pathogens, and it is unclear how to interpret results in patients with renal failure, immunocompromised patients, post-surgical patients, and others under severe physiologic stress. That being said, procalcitonin-based algorithms in non–critically ill patients with suspected or proven respiratory infections or critically ill patients with suspected sepsis have been shown to be useful, particularly in guiding early discontinuation of antibiotic therapy.

Further radiographic studies may be needed depending on the clinical situation. Appropriate CT scans should be conducted to locate a deep (i.e., pelvic) source of fever in a postoperative patient who underwent abdominal surgery. Ultrasonographic studies help in evaluating the liver and spleen and the vascular system. Sometimes, gallium scans or indium-labeled white blood cell scans may assist in locating occult foci of infection. Once located, radiographically guided drainage or open drainage of the abscess can be achieved.

In summary, determining the cause of fever in hospitalized patients can be very challenging. Although infection is common, the clinician needs to be aware that hospital-acquired fever may constitute a variety of other conditions.

Suggested reading

Arbo MJ, Fine MJ, Hanusa BH, Sefcik T, Kapoor WN. Fever of nosocomial origin: Etiology, risk factors, and outcomes. *Am J Med*. 1993;95:505–512.

Filice GA, Weiler MD, Hughes RA, Gerding DN. Nosocomial febrile illnesses in patients on an internal medicine service. *Arch Intern Med*. 1989;149:319–324.

Gutfilen B, Lopes de Souza SA, Martins FPP, et al. Use of 99mTc-mononuclear leukocyte scintigraphy in nosocomial fever. *Acta Radiol*. 2006;47:699–704.

Hedrick TL, Sawyer RG. Health-care-associated infections and prevention. *Surg Clin North Am*. 2005;85:1137–1152.

Kaul DR, Flanders SA, Beck JM, Saint S. Brief report: Incidence, etiology, risk factors, and outcome of hospital-acquired fever. A systematic, evidence-based review. *J Gen Intern Med*. 2006;21:1184–1187.

Kaye KS, Pogue JM. Infections caused by resistant gram-negative bacteria: Epidemiology and management. *Pharmacotherapy*. 2015;35:949–962. doi:10.1002/phar.1636.

Messacar K, Parker SK, Todd JK, Dominguez SR. Implementation of rapid molecular infectious disease diagnostics: The role of diagnostic and antimicrobial stewardship. *J Clin Microbiol*. 2017;55:715–723. doi:10.1128/JCM.02264-16. Epub 2016 Dec 28.

Moon SY, Park KH, Lee MS, Son JS. Hospital-acquired fever in oriental medical hospitals. *BMC Health Serv Res*. 2018;18:88. doi:10.1186/s12913-018-2896-1.

Rhee C. Using procalcitonin to guide antibiotic therapy. *Open Forum Infect Dis*. 2016;4:ofw249. doi:10.1093/ofid/ofw249. eCollection 2017 Winter.

Sager R, Kutz A, Mueller B, Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. *BMC Med*. 2017;15:15. doi:10.1186/s12916-017-0795-7.

Trivalle C, Chassagne P, Bouaniche M, et al. Nosocomial febrile illness in the elderly. *Arch Intern Med*. 1998;158:1560–1565.

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Transfusion-related infection

William R. Jarvis and Virginia R. Roth

The transfusion of blood and blood components is associated with a very low but ever-present risk of infection. It is estimated that 1 in every 2000 units of blood may carry an infectious agent and that about 4 in 10 000 recipients develop a chronic disease or die as a result of receiving contaminated blood. A wide variety of viral, bacterial, and parasitic agents have been associated with blood transfusion (Box 104.1). Concerns have also been raised about the potential for transmission of Creutzfeldt–Jakob disease (CJD) and its new variant (vCJD) through blood products. However, no human episodes of CJD or vCJD have been definitively linked to blood or blood component transfusion to date, and case–control studies have not found blood transfusion to be a risk factor for CJD. The risk of viral transmission has been markedly reduced with improved screening, particularly using nucleic acid testing (NAT). The risk is now estimated to be 1 in 2 million units for human immunodeficiency virus (HIV) or hepatitis C virus (HCV) and approximately 1 in 200 000 units for hepatitis B virus (HBV). Because the risk of viral or parasitic infection is very low and blood is screened for HCV, HBV, HIV, and human T-cell lymphoma/leukemia virus (HTLV) 1, the remainder of this chapter focuses on bacterial complications of blood transfusion, which can be diagnosed and treated.

Although the rate of bacterial contamination of blood products is unknown, the rate of bacterial infection associated with blood products is estimated to be similar to that of viral infection. The Bacterial Contamination of Blood Products (BaCON) study, a collaboration among the Centers for Disease Control and Prevention (CDC), American Red Cross, American Association of Blood Banks (AABB), and Department of Defense, conducted active surveillance for transfusion-transmitted bacteremia between 1998 and 2000. There were 34 bacteremic episodes and 9 deaths. The rate of transfusion-transmitted bacteremia (events per 106 units) was 9.98 for single-donor platelets, 10.64 for pooled platelets, and 0.21 for red blood cell units; for fatal reactions, the rates were 1.94, 2.22, and 0.13, respectively. The fatality rate associated with transfusion-related sepsis has been estimated to be 1 in 6 million transfused units. Transfusion-transmitted bacterial sepsis is the second most common cause of transfusion-related fatality (after clerical error). Between October 1995 and September 2004, 85 (13%) of 665 transfusion fatalities reported to the Food and Drug Administration were due to bacteria; 58/85 (68%) were due to gram-negative bacteria. In 2008, there were approximately 24 million blood components transfused. During FY2008, there were 46 FDA-reported transfusion-related fatalities, with subsequent reports of 44 in FY2009, 40 in FY2010, and 30 in FY2011. Of these, 5 (11%), 2 (5%), and 4 (13%) in FY 2009, FY2010, and FY2011, respectively, were traced to microbial infection. In FY2010 and FY2011, *Babesia*, *Staphylococcus aureus*, *Escherichia coli*, *Morganella morganii*, and *Klebsiella pneumoniae* accounted for all the fatalities. However, more common nonfatal episodes of transfusion reaction, which may result from bacterial contamination of blood or blood components, often are assumed to be an immune response to transfused leukocytes and are not fully investigated for contamination.

BOX 104.1

Infections transmissible by blood transfusion

Viruses
- Hepatitis
- Hepatitis A virus (HAV)
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Hepatitis D virus (HDV)
- Hepatitis E virus (HEV)
- Hepatitis G virus (HGV)
- Cytomegalovirus (CMV)
- Epstein–Barr virus (EBV)
- Nonhepatitis
- HIV-1 and -2
- HTLV-1 and -2
- Human herpesvirus 8 (HHV-8)[a]
- Parvovirus B19
- Colorado tick fever virus
- West Nile virus
- Dengue virus
- Severe acute respiratory syndrome (SARS) virus variant
  - Creutzfeld–Jakob disease (vCJD)
- Chikungunya virus
- Avian influenza virus[a]

Bacteria
- *Yersinia*
- *Pseudomonas*
- *Staphylococcus*
- Other gram-positive or gram-negative bacteria
- *Rickettsia*
- Spirochetes
- Syphilis
- Recurrent fever
- Lyme disease[a]
- Ehrlichia[a]

Protozoa
- *Plasmodium* spp. (malaria)
- *Babesia microti*
- *Babesia* spp.
- *Trypanosoma cruzi* (Chagas disease)
- *Toxoplasma* spp.
- *Leishmania* spp.
- Nematode (loasis, other microfilaria)
- *Treponema pallidum* (syphilis)

Abbreviations: HIV = human immunodeficiency virus; HTLV = human T-cell lymphoma/leukemia virus.

[a] Potential risk only, no reported case.

Whole blood and erythrocytes

After collection, whole blood may be maintained at room temperature for ≤8 hours before being stored at 1°C to 6°C (33.8°F to 42.8°F) up to 35 to 42 days, depending on the additives used (Table 104.1). Erythrocytes may be prepared from whole blood at any point during the normal storage period of the whole blood. Then, the erythrocytes may be stored at 1°C to 6°C up to the expiration date of the whole blood unit from which they were prepared. The growth of psychrophilic organisms, such as *Yersinia enterocolitica* or *Pseudomonas* species, is favored by these storage conditions, accounting for most erythrocyte transfusion-related sepsis episodes (Table 104.2). These episodes tend to occur with units that have been stored for >14 to 25 days, which reflects a growth lag of about 7 to 14 days followed by exponential growth of the organism; levels of 10^9 organisms/mL are reached by 38 days, and 315 ng of endotoxin/mL (approximately 4000 EU/mL) by 28 to 34 days. Transfusion of such units can lead to both septic and endotoxic shock.

Platelets

Each year, approximately 9 million platelet-unit concentrates are transfused in the United States. Platelets are stored in oxygen-permeable containers with agitation at 20°C to 24°C (68°F to 75.2°F) for ≤5 days. The most common transfusion-associated infection reported in the United States is bacterial contamination of platelet components. Bacterial contamination is estimated to occur at the incidence rate of 1:1000 to 1:3000 platelet units. Platelet transfusion-related sepsis usually involves common skin organisms, e.g., *Staphylococcus epidermidis, S. aureus*, or other aerobic bacteria that can grow rapidly at room temperature (Table 104.2). Sepsis episodes related to platelet transfusion also tend to occur with units

TABLE 104.1 **BLOOD COMPONENT STORAGE CONDITIONS AND ESTIMATED BACTERIAL CONTAMINATION RATES**

Component	Storage conditions	Estimated contamination rate
Whole blood	≤8 h at room temp	0.03%
CPDA-1	≤35 d at 1°C–6°C	
CPD plus AS	≤45 d at 1°C–6°C	
Packed red blood cells	≤35 d at 1°C–6°C	≤0.5%
CPDA-1	≤45 d at 1°C–6°C	
CPD plus AS		
Platelets	≤5 d at 20°C–24°C	Single donor, ≤2.5% Pooled, ≤10%
Plasma	Frozen, stored ≤18°C	≤0.1%
	For use, thawed and stored ≤24 h at 1°–6°C	

Abbreviations: CPDA = citrate-phosphate-dextrose-adenine (additives); CPD = citrate-phosphate-dextrose; AS = adenine saline (additives).

TABLE 104.2 **REPORTED EPISODES OF TRANSFUSION-ASSOCIATED SEPSIS**

		Duration in days from collection to transfusion	
PATHOGEN	**PERCENTAGE**	**MEDIAN**	**RANGE**
Erythrocytes			
Yersinia enterocolitica	49.0	24	7–41
Pseudomonas fluorescens	23.5	24	16–32
Serratia liquefaciens	7.8	21	17–26
Treponema pallidum	2.0	≤1	–
Pseudomonas putida	2.0	–	–
Other species	15.7	23	20–26
Platelets			
Staphylococcus epidermidis	33.3	4	3–5
Salmonella choleraesuis	11.7	≤1	–
Serratia marcescens	8.3	2	1–3
Staphylococcus aureus	5.0	5	3–6
Bacillus cereus	5.0	–	–
Streptococcus viridans group	3.3	3	1–6
Salmonella enteritidis	3.3	5	3–5
Other species	23.3	4	2–6

that are late in the storage period (around 4 to 5 days), when there may be a higher titer of organisms than early in the storage period. In addition, sepsis episodes occur more frequently with pooled platelet units than with single-donor apheresis units. A pooled platelet unit is prepared by combining 6 to 10 random donor platelet concentrates up to 4 hours before transfusion. In contrast, an apheresis unit is prepared by separating platelets from the whole blood of a single donor and returning other blood components to the donor. The higher rate of sepsis associated with pooled platelets primarily is seen because, on average, pooled platelets are stored longer than apheresis platelets. With pooled platelets, there also is a higher risk of contamination associated with the exposure to multiple donors or with the manipulation of the concentrates. In March 2004, an AABB standard was introduced that required routine quality control testing for bacterial contamination of apheresis platelet products. On January 31, 2011, a new AABB Standard, 5.1.5.1.1, specified that bacterial detection methods for PLT components shall use assays either approved by the Food and Drug Administration (FDA) or validated to provide sensitivity equivalent to these FDA-approved methods. These were implemented in many US and Canadian blood centers and have reduced the risk of platelet-associated bacterial infection.

Plasma and plasma-derived products

Plasma is either collected by apheresis or prepared from whole blood and is stored at below −18°C (−0.4°F) within 6 hours of collection. It can be thawed in a water bath using a plastic overwrap or in a microwave and subsequently stored at 1°C to 6°C up to 24 hours before transfusion. The survival of bacteria is not supported by these storage conditions. However, equipment may carry contamination; for example, one reported episode of sepsis associated with a plasma transfusion was attributed to a contaminated water bath used for thawing the unit.

Contamination of plasma-derived products also is thought to be rare. They are prepared from plasma stored under very stringent conditions, and many of the products also undergo viral inactivation procedures. However, contamination may still occur, as demonstrated by outbreaks of hepatitis C virus infections associated with the administration of contaminated intravenous immunoglobulin or hepatitis A virus associated with plasma-derived products.

Sources of contamination

Contamination of blood or blood components may occur intrinsically if a donor is bacteremic or viremic at the time of donation; it may also occur extrinsically from the skin during phlebotomy or from containers and other equipment used during processing and storage. The infecting organism may reflect the source of contamination. With *Y. enterocolitica*-contaminated erythrocytes, the implicated source is often an asymptomatic episode of gastrointestinal (GI) illness within the previous month. Because the GI illness is usually mild, the donor may not recall or may neglect to report the episode during prescreening.

Clinical management

Although these contamination episodes are rare, it is important to consider the possibility of blood and blood component contamination when a patient develops a fever during or soon after a transfusion (Figure 104.1). If bacteremia cannot be ruled out, the transfusion should be stopped immediately. Any residual blood product or administration set should immediately be quarantined and refrigerated. A Gram-stain and/or acridine orange-stain smear of the blood product should be performed. Stain and/or culture of blood component segments usually are negative, even when the unit itself is positive; this may reflect low-level contamination of the unit at the time of donation. Cultures of the blood product in the bag, the patient's blood before antimicrobials are begun, and any intravenous solution used during transfusion should be obtained promptly. Information about the donor should be reviewed completely. If organisms are recovered from the recipient and blood product, molecular typing of patient and donor isolates may prove causality.

After appropriate cultures are obtained, broad-spectrum empiric antimicrobial therapy should be started. Empiric treatment of suspected sepsis associated with blood products must be based on the component. Because most reported sepsis episodes associated with erythrocyte transfusion have been caused by *Y. enterocolitica* or *Pseudomonas* species, particularly *Pseudomonas fluorescens*, initial therapy may include trimethoprim–sulfamethoxazole or an antipseudomonal β-lactam plus an aminoglycoside. Because infectious complications associated with platelets usually are caused by

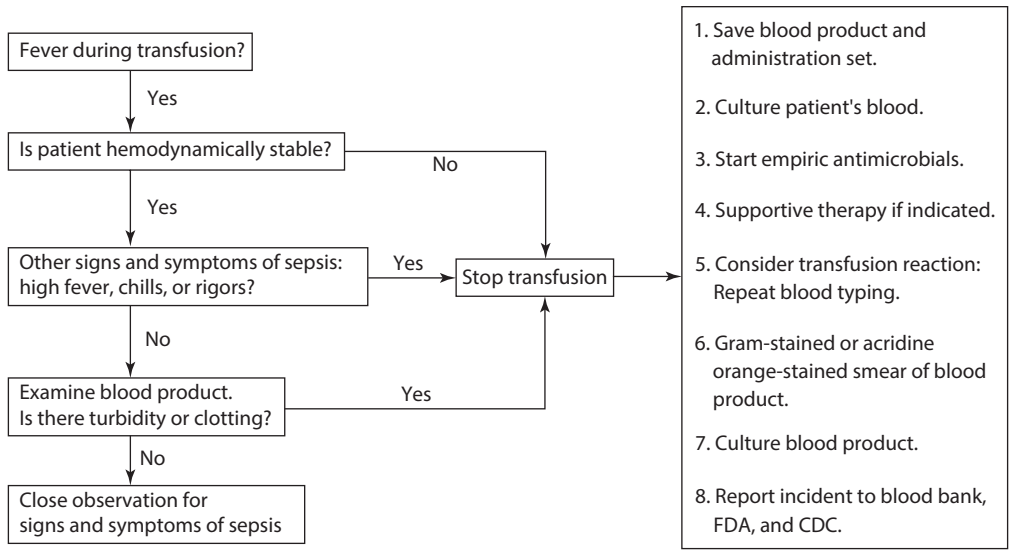

FIGURE 104.1 Management of Fever During Transfusion

aerobic bacteria, e.g., coagulase-negative staphylococci or *S. aureus* and occasionally gram-negative organisms, initial empiric therapy may include a penicillinase-resistant penicillin and an aminoglycoside. Empiric therapy should be narrowed as soon as an infecting pathogen is identified and antimicrobial susceptibility results are available.

Prevention

Sensitive, rapid diagnostic tests for detecting bacterial contamination are not yet available. Therefore, minimizing the risk of transfusion-associated sepsis depends on appropriate donor screening, donor site inspection and preparation, and proper handling of the blood components (Box 104.2). Detection of infectious complications associated with blood products may be increased by educating the medical and blood bank staff about the signs and symptoms of patients with transfusion reactions, the importance of immediately reporting transfusion reactions to the blood bank, promptly culturing the blood of the recipient, promptly performing stains and culture of the blood component, and ensuring quarantined refrigerated storage of the unit and administration set until contamination has been excluded.

BOX 104.2

Prevention of transfusion-associated sepsis

Donors

Screen for infectious diseases (health questionnaire); inquire about travel, behaviors, dental work, signs and symptoms of recent illness

Phlebotomy

Inspect site; avoid dimpled areas of the skin
Prepare site properly
Use aseptic techniques

Bag and component preparation

Use aseptic techniques
Perform proper cleaning and disinfection of processing equipment; use plastic overwraps in water baths for thawing
Use appropriate storage conditions
Visually inspect contents before transfusion

Suggested reading

Blajchman MA. Bacterial contamination and proliferation during the storage of cellular blood products. *Vox Sang*. 1998;74 (suppl 2):155–159.

Brecher ME, Jacobs MR, Katz LM, et al.; AABB Bacterial Contamination Task Force. Survey of methods used to detect bacterial contamination of platelet products in the United States in 2011. *Transfusion*. 2013;53:911–918.

Eder AF, Kennedy JM, Dy BA, et al.; American Red Cross Regional Blood Centers. Bacterial screening of apheresis platelets and the residual risk of septic transfusion reactions: the American Red Cross experience (2004–2006). *Transfusion*. 2007;47:1134–1142.

Goodnough LT, Brecher ME, Kanter MH, et al. Transfusion medicine: blood transfusion. *N Engl J Med*. 1999;340:438–447.

Gubernot DM, Nakhasi HL, Mied PA, et al. Transfusion-transmitted babesiosis in the United States: summary of a workshop. *Transfusion*. 2009;49:2759–2771.

Kuehnert MJ, Roth VR, Haley NR, et al. Transfusion-transmitted bacterial infection in the United States, 1998 through 2000. *Transfusion*. 2001;41:1493–1499.

Pealer LN, Marfin AA, Petersen LR, et al. Transmission of West Nile virus through blood transfusion in the United States in 2002. *N Engl J Med*. 2003;349:1236–1245.

Ramirez-Arcos S, Jenkins C, Dion J, et al. Canadian experience with detection of bacterial contamination in apheresis platelets. *Transfusion*. 2007;47:421–429.

Roth VR, Kuehnert MJ, Haley NR, et al. Evaluation of a reporting system for bacterial contamination of blood components in the United States. *Transfusion*. 2001;41:1486–1492.

Schreiber GB, Busch MP, Kleinmann SH, et al. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med*. 1996;334: 1685–1690.

Wagner SJ, Friedman LI, Dodd RY. Transfusion-associated bacterial sepsis. *Clin Microbiol Rev*. 1994;7:290–302. www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM300764.pdf (accessed July 17, 2014).

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Intravascular catheter-related infection

Johny Fares, Alexandre E. Malek, and Issam I. Raad

Introduction

Central venous catheters (CVC) are essential in securing vascular access for fluids, medications, blood products, total parenteral nutrition (TPN), and hemodialysis. They are employed for both inpatients and outpatients. Central line-associated bloodstream infections (CLABSI) are major healthcare-associated infections, especially in high-risk patients. According to the US Centers for Disease Control and Prevention (CDC), the incidence of CLABSIs has dropped by around 50% between 2008 and 2016. However, according to the National Healthcare Safety Network (NHSN), these infections are still associated with a high mortality rate of 12% to 25% and the high healthcare cost of $45,814 per CLABSI in the United States.

Pathogenesis

Colonization is universal after insertion of a CVC, occurring as early as 1 day after insertion, and is independent of catheter-related infection. Electron microscopy studies of catheter surfaces show that adherent microorganisms can be found in either a free-floating form or a sessile form embedded in a biofilm.

The process of adherence results from the interaction of three factors: intrinsic properties of the catheter, host-derived proteins, and microbial factors. The surface irregularities and charge difference of the catheter facilitate bacterial adherence. Some microorganisms adhere better to polyvinyl chloride, silicone, and polyethylene surfaces than to Teflon polymers and polyurethane. In addition, thrombogenesis is more commonly seen with certain catheter materials that are associated with higher risk of colonization and catheter-related infections. Host factors consisting of plasma proteins such as fibrinogen, fibronectin, laminin, and thrombospondin result in the formation of a thrombin sheath on the internal and external surfaces of the catheter. Then, colonizing microorganisms adhere via secretion of extracellular, polysaccharide-rich material, or glycocalyx, leading to a biofilm formation on the external surface of short-term catheters and internal surface of long-term catheters (dwell time of at least 30 days). This biofilm enables bacteria to adhere to the catheter and resist antibiotics, making their eradication difficult.

Microorganisms colonize vascular catheters through different sources. For short-term catheters, the skin of the site of insertion is the major source for colonization; bacterial skin flora migrate along the external surface of the catheter. The hub of the vascular device is the most common source of colonization for long-term catheters, with microorganisms introduced from the hands of medical personnel. In this case, colonizing bacteria migrate along the internal surface of the catheter. Hematogenous seeding from a secondary source of infection and contamination of the infusate or additives, such as contaminated heparin flush, are rare causes of colonization and infection of vascular devices.

Other CLABSI risk factors: femoral catheterization has higher rates of infections and thrombotic complications than subclavian catheterization and, compared to gauze dressing, transparent occlusive dressing is associated with significantly increased rates of insertion site colonization, local catheter-related infection, and CLABSI when CVCs remain for >3 days.

The causative microorganisms associated with CLABSI are primarily gram-positive bacteria, followed by gram-negative bacteria and *Candida* spp. Skin flora such as *Staphylococcus epidermidis* and *S. aureus* remain the predominant source of CLABSI, followed by *Enterococcus faecalis*, *Klebsiella* spp. (*pneumoniae/oxytoca*), *Enterococcus faecium,* and *Escherichia coli.* Microorganisms that contaminate the hands of medical personnel, such as *Pseudomonas, Acinetobacter, Stenotrophomonas maltophilia*, and *Candida* are also common causative organisms. Emerging pathogens such as *Achromobacter*, rapidly growing mycobacteria (*M. chelonae* and *M. fortuitum*), and fungal elements such as *Fusarium, Malassezia furfur*, and *Rhodotorula* spp. have been described in *specific* conditions (i.e., hyperalimentation, interleukin-2 therapy).

Organisms such as *E. coli*, *Enterococcus faecium*, and *Streptococci viridans* are more commonly seen in oncology patients as compared to non-oncology patients. This predominance is attributed to the mucosal barrier injury seen in cancer patients, leading to the translocation of these organisms from the gastrointestinal tract.

Clinical manifestations and diagnosis

The clinical presentation of CLABSI consists of nonspecific systemic signs and local manifestations at the skin insertion site.

The systemic features include fever and chills, which may be accompanied by hypotension, hyperventilation, altered mental status, and nonspecific gastrointestinal manifestations such as nausea, vomiting, abdominal pain, and diarrhea. Deep-seated infections such as endocarditis, osteomyelitis, retinitis, and organ abscess may complicate CLABSI caused by virulent organisms such as *S. aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*. Local manifestations are neither sensitive nor specific. On one hand, they may be absent, especially in immunocompromised patients. On the other hand, peripherally inserted central catheter (PICC) lines may produce sterile exit site inflammation (26%).

The CDC and the Infectious Diseases Society of America (IDSA) definitions of intravascular catheter-related bloodstream infections (CRBSI) are summarized in Table 105.1.

The CLABSI definition may lack specificity. For example, in some cancer patients, particularly those with compromised mucosal barrier, some laboratory-confirmed bloodstream infections (LCBI) that are labeled CLABSI may have resulted from bacteria translocation from the gastrointestinal tract. To distinguish LCBI related to central lines from those due to unapparent sources, the CDC developed a new definition termed mucosal barrier injury LCBI (MBI-LCBI) whereby a recognized intestinal organism is cultured from the blood of patients with clues to mucosal barrier injury such as gastrointestinal graft-versus-host disease, diarrhea, or neutropenia.

CRBSI as defined by the IDSA more specifically identifies the CVC as the source of the bacteremia.

Preventive strategies

CVCs should only be used when medically necessary and should be removed as soon as possible. The subclavian site is preferred for non-tunneled CVC. Femoral sites should be avoided in adult patients.

TABLE 105.1 **DIAGNOSIS OF CENTRAL LINE-ASSOCIATED BLOODSTREAM INFECTION (CLABSI) ACCORDING TO THE CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) DEFINITION AND INFECTIOUS DISEASES SOCIETY OF AMERICA (IDSA) 2009 GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF INTRAVASCULAR CATHETER-RELATED INFECTIONS**

CDC definition of central line-associated bloodstream infections (CLABSIs)[a]	IDSA 2009 definition of intravascular catheter-related bloodstream infection (CRBSI)
Patient has a CVC that was in place for >2 days and CVC was present on the date of the LCBI or the day before. In addition, the LCBI must not be related to an infection at another site and must meet one of the following criteria: • A recognized pathogen cultured from one or more blood cultures • A common skin contaminant cultured from *two* or more blood cultures drawn on separate occasions within 2 days of each other and at least *one* of the following clinical signs or symptoms: fever (>38°C/100°F), chills, or hypotension *and* signs and symptoms • For patient ≤1 year of age, a common skin contaminant is cultured from two or more blood cultures drawn on separate occasions within 2 days of each other and the patient has at least one of the following clinical signs or symptoms: fever (>38°C/100°F core), hypothermia (<36°C/97°F core), apnea, or bradycardia	• **Diagnostic method sparing the catheter**: A definite CRBSI requires one of the following to be present: • The same organism is cultured from two simultaneous quantitative blood cultures drawn from the catheter and peripheral site with a CVC/peripheral colony count ratio ≥3:1 • The differential time to positivity of at least 2 hours (microbial growth from blood drawn from a catheter is detected at least 2 hours before microbial growth from blood drawn from the peripheral site) • **Diagnostic method implicating catheter removal**: A definite CRBSI requires that the same organism is cultured from at least one percutaneous blood culture and from a culture of the catheter tip (in semiquantitative catheter culture ≥15 CFU per catheter segment, or in quantitative catheter culture ≥10^2 CFU per catheter segment)

[a] CDC definition of CLABSI does not require catheter removal.
Abbreviations: CVC = central venous catheter, LCBI = laboratory-confirmed bloodstream infection.

Guidelines for the prevention of intravascular catheter-related infections emphasize the importance of educating and training healthcare personnel who insert and maintain catheters. Hand hygiene with soap and water or alcohol-based rubs should be performed before and after inserting, replacing, accessing, or dressing a CVC. The use of maximal sterile barrier precautions that includes the use of a cap, mask, sterile gown, and a sterile full body drape is recommended for CVC insertion.

Skin cleansing using chlorhexidine preparation before CVC insertion reduces the risk of CVC colonization and CLABSI. Alternatively, tincture of iodine or 70% alcohol could be used when chlorhexidine is contraindicated.

Dressing choice may vary: sterile, transparent dressing allows visual monitoring of the CVC and requires less frequent changes than sterile gauze. The use of chlorhexidine-impregnated dressing is recommended in patients >2 months of age, for short-term catheters. Regular monitoring of CVC by visual inspection or by palpation through the dressing is recommended.

Antimicrobial-coated catheters have also been introduced to reduce the incidence of CLABSIs. They are recommended by the CDC for prevention of catheter-related infections for CVCs that are expected to remain in place for >5 days if rates of CLABSI remain elevated despite the implementation of aseptic techniques including maximal sterile barrier precautions. CVCs coated with minocycline and rifampicin (M-R) were found to be the most successful in doing so. They provide an antimicrobial protection for several weeks (28–50 days) and were shown to decrease the incidence of CLABSI in cancer patients with no increase in the rate of resistance of staphylococcal species against minocycline and rifampicin. Chlorhexidine-/silver sulfadiazine-coated catheters could also be used. However, they provide a shorter duration of protection and a 12-fold lower reduction in CLABSI incidence compared to the M-R coated catheters.

Antimicrobial catheter lock and flush solutions are recommended by CDC in patients who have long-term catheters and a history of multiple CRBSIs. Catheter lock solution technique consists of flushing the catheter lumen and then filling it with 1 to 3 mL of a combination of an anticoagulant plus an antimicrobial agent. The lock dwell time in the lumen of the CVC may vary from 2 to 12 hours depending on the solution. Initially, heparin was widely used as an antithrombotic agent to maintain catheter patency, but it has been shown to enhance staphylococcal biofilm formation at the concentration of 1,000 U/mL used in catheter locks. Currently, other chelators, such as citrate and ethylenediamine-tetraacetic acid (EDTA) are widely used as a component of catheter lock solutions due to their very potent anticoagulant effect, their ability to prevent the biofilm formation, and their synergistic antimicrobial activity. A minocycline-EDTA combination was shown to be very effective in preventing CLABSIs in patients with long-term CVCs, especially in cancer patients and hemodialysis patients. Nitroglycerin-citrate-ethanol (NiCE) lock solution is also effective in reducing the rate of CLABSI as shown by multiple in vitro and in vivo studies. With the emergence of resistant microorganisms, such non-antibiotic antimicrobial lock solutions are preferred over antibiotic lock solutions as CLABSI prophylaxis. In addition, many studies showed that they are superior to the antibiotic lock solutions in preventing CLABSIs. For example, Minocycline and EDTA (M-EDTA) solution was superior to vancomycin–heparin lock solution, both in an in vitro biofilm model and an animal model.

The CDC does not recommend routine catheter exchange and guidewire exchange as CLABSI preventive measures. However, the guidewire may be used to (1) replace a malfunctioning catheter, (2) convert an existing catheter to a different type, and (3) salvage the vascular access as an alternative strategy in patients with limited venous access along with the use of systemic antimicrobial therapy.

A summary of the preventive strategies are listed in Box 105.1.

Therapy

After confirming that the catheter is the source of the bloodstream infection, treatment of CLABSI involves catheter management (removing, exchanging, or salvaging the line) and systemic antimicrobial therapy. A summary of therapies are listed in Table 105.2.

Catheter management

Catheter removal is the most popular approach in the management of catheter-related infections. The IDSA recommends the removal of long-term catheters (indwelling for ≥14 days) in patients with

BOX 105.1

Measures for the prevention of central line-associated bloodstream infection (CLABSI)

- **Traditional measures:**
- Education of healthcare personnel on vigilant catheter insertion and care
- Use the subclavian vein as the preferred insertion site for nontunneled CVCs and avoiding femoral insertions
- Hand hygiene
- Use of maximal sterile barrier precautions during CVC insertion (includes the use of a cap, mask, sterile gown, and a sterile full body drape)
- Skin cleansing using chlorhexidine before CVC insertion
- Skilled infusion therapy team
- Removal of unnecessary CVCs
- **Novel technology:**

Strongly recommended or well-supported evidence:

- Antimicrobial coating of catheters particularly if the catheter is expected to remain in place >5 days
- Prophylactic antimicrobial catheter lock solutions particularly in patients who have long-term catheters and a history of multiple CLABSI
- Chlorhexidine bathing
- Topical antibiotics at the insertion site, only for hemodialysis patients

Abbreviation: CVC = central venous catheter.

TABLE 105.2 **MANAGEMENT OF CATHETER-RELATED INFECTIONS**

Microorganism	Duration of systemic therapy	Catheter management
Coagulase-negative staphylococci		Catheter removal or salvage
CVC removed	5–7 d	
CVC retained	10–14 d	
Staphylococcus aureus		Catheter removal
Uncomplicated	14 d	
Complicated If catheter retained	4-6 wk 4 wk	
Gram-positive bacilli	7 d	Catheter removal. Could attempt salvage
Enterococcus	7-14 d	Catheter removal. Could attempt salvage
Gram-negative rods	7–14 d	Catheter removal. Could attempt salvage depending on the causative organism.
***Candida* species**		Catheter removal
Uncomplicated	14 d	
Complicated	6 wk	
Mycobacterium	14 d	Catheter removal

Abbreviation: CVC = central venous catheter.

complicated CRBSI (severe sepsis, suppurative thrombophlebitis, endocarditis); in cases of persistent bloodstream infection after >72 hours of antimicrobial therapy to which the infecting microbes are susceptible; or if the causative organism is *S. aureus, P. aeruginosa*, a fungus, or a mycobacterium. Short-term catheters (indwelling <14 days) should be removed if the causative organism is a gram-negative bacilli, *S. aureus*, enterococci, fungi, or mycobacteria.

However, catheter removal and replacement is costly, and it is associated with many complications in high-risk patients (e.g., cancer patients and hemodialysis patients, who are often thrombocytopenic and have limited vascular access). Catheter salvage, when possible, can reduce the risks and cost associated with catheter removal. In fact, IDSA guidelines recommend catheter salvage in patients with uncomplicated long-term catheter-related bloodstream infections who have limited vascular access that is critical for their survival.

Antimicrobial lock therapy is an effective alternative. It consists of locking a highly concentrated antibiotic-based solution into the infected line for several hours daily. Many lock solutions have been tried. Some were found to be ineffective, such as vancomycin-based lock solutions that were associated with high risk of failure, especially with *S. aureus*. New lock solutions, such as ethanol (25%)-minocycline-EDTA combination, show very promising results in vitro and clinically and have been shown to eradicate multidrug-resistant (MDR) organisms (i.e., methicillin-resistant *S. aureus* [MRSA], ESBL gram-negative organisms) and *Candida* spp.

Catheter exchange over a guidewire is also an available alternative for the management of the CVC in CRBSI. Using an antibiotic-coated catheter for such an exchange could improve the overall outcome of CLABSI. Multiple studies showed that catheter exchange over guidewire using minocycline-rifampicin–coated CVC may improve the overall response rate and prevent cross-contamination during the exchange procedure.

Systemic therapy

The choice and duration of antibiotic therapy depend on many factors such as the causative organism and its antibiotic susceptibility, presence or absence of any deep-seated infections, and the management of the catheter itself. Most of the CLABSIs will be treated for a period of 5 to 14 days, depending on the isolated microorganisms. However, in cases of complicated CLABSI (i.e., septic thrombophlebitis, endocarditis, or metastatic infection) or if the CLABSI persists beyond 72 hours of initiation of appropriate antimicrobial therapy, the vascular catheter should be removed and the infection should be treated with parenteral antibiotics for at least 4 weeks.

When determining the duration of antimicrobial therapy, the first day on which blood cultures are negative is counted as day 1.

Coagulase-negative staphylococci

Coagulase-negative staphylococcus (CoNS) is the most common causative organism of CLABSI. However, due to the high contamination rate of blood cultures by this organism, a single positive blood culture growing CoNS is not enough to prove a true bloodstream infection. The IDSA recommends obtaining additional blood cultures from the CVC and peripheral vein to prove that it is a true CoNS bloodstream infection rather than a contamination. Once proved, the usual management is catheter removal and systemic therapy. Because most CoNS are nosocomially acquired and are resistant to penicillins, the choice of a glycopeptide (i.e., vancomycin) is recommended pending susceptibility. Antibiotic therapy is then tailored according to the susceptibility testing. Methicillin-susceptible CoNS are treated with nafcillin or oxacillin (first-generation cephalosporins are a good alternative), whereas methicillin-resistant CoNS are treated with vancomycin. Daptomycin or quinupristin-dalfopristin could be used as alternative antimicrobial agents. Duration of therapy is usually 5 to 7 days if the catheter is removed and there is no complications. If the catheter is retained, treatment should be for 10 to 14 days, and the catheter should be treated with an antibiotic lock solution. For patients with an endovascular implant or orthopedic hardware, the catheter is usually removed and a systemic therapy of at least 14 days is recommended. However, if the catheter is retained in this group of patients, 14 to 21 days of antimicrobial therapy is recommended. Note that *Staphylococcus lugdunensis* CRBSI could lead to serious complications such as endocarditis and thus should be managed in same way as *S. aureus* CRBSI.

Staphylococcus aureus

According to the CDC vital signs report, the rate of CLABSI caused by *S. aureus* in the ICU was reduced by 73% between 2006 and 2011. However, *S. aureus* CLABSI is still common and is associated with high rates of deep-seated infection such as osteomyelitis, septic phlebitis, and endocarditis. Management usually consists of line removal and systemic antibiotic therapy. Failure to remove the catheter is associated with persistent bacteremia, relapse, and increased mortality. The CVC should be removed unless there are major contraindications, in which case the patient should either receive an antibiotic lock therapy or have his or her CVC exchanged over a guidewire with an antimicrobial-impregnated CVC, along with 4 weeks of systemic antimicrobial therapy. For methicillin-sensitive *S. aureus*, nafcillin or a first-generation cephalosporin is the first choice. Vancomycin, daptomycin, or quinupristin-dalfopristin could be used for the treatment of MRSA. Strains resistant to linezolid have been reported.

A14 days course of intravenous therapy is enough if the CVC is removed, no deep-seated infection is present, follow-up blood cultures after 48 to 96 hours of the initiation of the antibiotic therapy are negative, and the patient defervesced within 48 to 72 hours of therapy. If fever or bacteremia persists for >72 hours or if the patient has another prosthetic device or there is evidence of endocarditis, suppurative thrombophlebitis, or metastatic infection, the intravenous therapy duration should be expanded to at least 4 to 6 weeks.

Echocardiography should be performed for all patients with *S. aureus* CLABSI, starting with transthoracic echocardiography (TTE) and proceeding to transesophageal echocardiography (TEE) if a vegetation is identified on TTE. However, TTE is not enough to rule out infective endocarditis, particularly for those with persistent fever or bacteremia beyond 72 hours of initiation of antimicrobial therapy.

Gram-positive bacilli

Vancomycin remains the antibiotic of choice in the treatment of CLABSI caused by gram-positive bacilli such as *Bacillus* and *Corynebacterium* species. Removal of the catheter is recommended.

Enterococcus

CRBSI caused by enterococcus is usually managed with catheter removal and systemic antibiotic therapy. However, catheter salvage using an antibiotic lock therapy is an alternative as long as there are no associated complications (i.e. deep-seated infections, persistent bacteremia, catheter site inflammation signs). The duration of systemic therapy for uncomplicated CRBSI is 7 to 14 days, independently of the catheter management. The choice of antibiotic depends on the susceptibility of the organism; ampicillin for susceptible enterococci and vancomycin for resistant organisms.

Gram-negative bacilli

Over the past decade, the incidence of CLABSI caused by gram-negative rods has increased, especially in cancer patients. The most common gram-negative organisms associated with CLABSI are *Klebsiella pneumoniae, Enterobacter* spp., *P. aeruginosa, Acinetobacter* spp., and *Stenotrophomonas maltophilia*. Management involves catheter removal and systemic antibiotic therapy for 7 to 14 days. Salvaging the catheter with an antibiotic lock solution could be attempted in cases of uncomplicated CLABSI. High-risk patients (i.e., previous history of MDR bacteremia, neutropenia, and previous antibiotic therapy) should be started on empiric antibiotic therapy that covers MDR gram-negative organisms; these include fourth-generation cephalosporin, β-lactam/β-lactamase inhibitors, or carbapenem with or without aminoglycoside. A combination of two antibiotics as empiric therapy for high-risk patients is an alternative. Trimethoprim-sulfamethoxazole is the drug of choice for *S. maltophilia* CLABSI.

Candida

IDSA guidelines recommend removing the CVC and treating for 14 days after the first negative blood culture in uncomplicated cases of *Candida* infection. Endophthalmitis (15% of untreated cases) merits 6 weeks of therapy. Fluconazole or echinocandin (caspofungin, micafungin, or anidulafungin) should be considered in documented cases of catheter-related candidemia. If the rates of fluconazole-resistant *C. glabrata* and *C. krusei* in the hospital are high, or the patient was exposed to azoles in the previous 3 months, an echinocandin is the drug of choice.

Mycobacterial disease

Catheter removal is recommended and surgical intervention may be needed in long-term catheters infected with *M. chelonae* or *M. fortuitum*. A 14-day course of antimicrobials is suggested. However, a longer duration of therapy is required in complicated cases.

Suggested reading

Bleyer AJ, Mason L, Russell G, Raad II, Sherertz RJ. A randomized, controlled trial of a new vascular catheter flush solution (minocycline-EDTA) in temporary hemodialysis access. *Infect Control Hosp Epidemiol*. 2005;26(6):520–524.

Campos RP, do Nascimento MM, Chula DC, Riella MC. Minocycline-EDTA lock solution prevents catheter-related bacteremia in hemodialysis. *J Am Soc Nephrol*. 2011;22(10):1939–1945.

Centers for Disease Control and Prevention (CDC). Vital signs: Central line-associated blood stream infections--United States, 2001, 2008, and 2009. *MMWR Morb Mortal Wkly Rep*. 2011;60(8):243–248.

Chaftari AM, Hachem R, Jiang Y, et al. Changing epidemiology of catheter-related bloodstream infections in cancer patients. *Infect Control Hosp Epidemiol* 2018, 39:727–729.

Chaftari A-M, Hachem R, Szvalb A, et al. Correction for Chaftari et al., "A novel nonantibiotic nitroglycerin-based catheter lock solution for prevention of intraluminal central venous catheter infections in cancer patients." *Antimicrob Agents Chemother*. 2017;61(8):e01324–17.

Chatzinikolaou I, Zipf TF, Hanna H, et al. Minocycline-ethylenediaminetetraacetate lock solution for the prevention of

implantable port infections in children with cancer. *Clin Infect Dis*. 2003;36(1):116–119.

Darouiche RO, Berger DH, Khardori N, et al. Comparison of antimicrobial impregnation with tunneling of long-term central venous catheters: a randomized controlled trial. *Ann Surg*. 2005;242(2):193–200.

Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: Data summary for 2006 through 2008, issued December 2009. *Am J Infect Control*. 2009;37:783–805.

Estes R, Theusch J, Beck A, Pitrak D, Mullane KM. Activity of daptomycin with or without 25% ethanol compared to combinations of minocycline, EDTA, and 25% ethanol against methicillin-resistant Staphylococcus aureus isolates embedded in biofilm. *Antimicrob Agents Chemother*. 2013;57(4):1998–2000.

Falagas ME, Fragoulis K, Bliziotis IA, Chatzinikolaou I. Rifampicin-impregnated central venous catheters: A meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2007;59:359–369.

Hajjej Z, Nasri M, Sellami W, Gharsallah H, Labben I, Ferjani M. Incidence, risk factors and microbiology of central vascular catheter-related bloodstream infection in an intensive care unit. *J Infect Chemother*. 2014;20:163–168.

Holland TL, Arnold C, Fowler VG. Clinical management of Staphylococcus aureus bacteremia: A review. *JAMA*. 2014;312(13): 1330–1341.

Jamal MA, Rosenblatt J, Jiang Y, Hachem R, Chaftari A-M, Raad II. Prevention of transmission of multidrug-resistant organisms during catheter exchange using antimicrobial catheters. *Antimicrob Agents Chemother*. 2014;58(9):5291–5296.

Kaasch AJ, Fowler VG, Rieg S, et al. Use of a simple criteria set for guiding echocardiography in nosocomial Staphylococcus aureus bacteremia. *Clin Infect Dis*. 2011;53(1):1–9.

Krishnasami Z, Carlton D, Bimbo L, et al. Management of hemodialysis catheter-related bacteremia with an adjunctive antibiotic lock solution. *Kidney Int*. 2002;61(3):1136–1142.

Lai NM, Chaiyakunapruk N, Lai NA, O'Riordan E, Pau WSC, Saint S. Catheter impregnation, coating or bonding for reducing central venous catheter-related infections in adults. *Cochrane Database Syst Rev*. 2016;3:CD007878.

Logghe C, Van Ossel C, D'Hoore W, Ezzedine H, Wauters G, Haxhe JJ. Evaluation of chlorhexidine and silver-sulfadiazine impregnated central venous catheters for the prevention of bloodstream infection in leukaemic patients: A randomized controlled trial. *J Hosp Infect*. 1997;37(2):145–156.

Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.

Nachnani GH, Lessin LS, Motomiya T, Jensen WN, Bodey GP. Scanning electron microscopy of thrombogenesis on vascular catheter surfaces. *N Engl J Med*. 1972;286:139–140.

O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2002;51:1–29.

O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, Raad II. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis.* 2011;52(9):e162–e193.

Raad I, Buzaid A, Rhyne J, et al. Minocycline and ethylenediaminetetraacetate for the prevention of recurrent vascular catheter infections. *Clin Infect Dis*. 1997;25(1):149–151.

Raad I, Chaftari A-M, Zakhour R, et al. Successful salvage of central venous catheters in patients with catheter-related or central line-associated bloodstream infections by using a catheter lock solution consisting of minocycline, EDTA, and 25% ethanol. *Antimicrob Agents Chemother*. 2016;60(6):3426–3432.

Raad I, Hanna H, Dvorak T, Chaiban G, Hachem R. Optimal antimicrobial catheter lock solution, using different combinations of minocycline, EDTA, and 25-percent ethanol, rapidly eradicates organisms embedded in biofilm. *Antimicrob Agents Chemother*. 2007;51:78–83.

Raad I, Hanna H, Jiang Y, et al. Comparative activities of daptomycin, linezolid, and tigecycline against catheter-related methicillin-resistant Staphylococcus bacteremic isolates embedded in biofilm. *Antimicrob Agents Chemother*. 2007;51: 1656–1660.

Raad I, Hanna H, Maki D. Intravascular catheter-related infections: Advances in diagnosis, prevention, and management. *Lancet Infect Dis*. 2007;7:645–657.

Raad I, Reitzel R, Jiang Y, Chemaly RF, Dvorak T, Hachem R. Anti-adherence activity and antimicrobial durability of anti-infective-coated catheters against multidrug-resistant bacteria. *J Antimicrob Chemother*. 2008;62(4):746–750.

Raad I, Rosenblatt J, Reitzel R, Jiang Y, Dvorak T, Hachem R. Chelator-based catheter lock solutions in eradicating organisms in biofilm. *Antimicrob Agents Chemother*. 2013;57(1):586–588.

Raad II, Fang X, Keutgen XM, Jiang Y, Sherertz R, Hachem R. The role of chelators in preventing biofilm formation and catheter-related bloodstream infections. *Curr Opin Infect Dis*. 2008;21(4):385–392.

Ramos ER, Reitzel R, Jiang Y, et al. Clinical effectiveness and risk of emerging resistance associated with prolonged use of antibiotic-impregnated catheters: More than 0.5 million catheter days and 7 years of clinical experience. *Crit Care Med*. 2011;39(2):245–251.

Rasmussen RV, Høst U, Arpi M, et al. Prevalence of infective endocarditis in patients with Staphylococcus aureus bacteraemia: The value of screening with echocardiography. *Eur J Echocardiogr*. 2011;12(6):414–420.

Reitzel RA, Rosenblatt J, Hirsh-Ginsberg C, et al. In vitro assessment of the antimicrobial efficacy of optimized nitroglycerin-citrate-ethanol as a nonantibiotic, antimicrobial catheter lock solution for prevention of central line-associated bloodstream infections. *Antimicrob Agents Chemother*. 2016;60(9):5175–5181.

Rosenblatt J, Reitzel R, Dvorak T, Jiang Y, Hachem RY, Raad II. Glyceryl trinitrate complements citrate and ethanol in a novel antimicrobial catheter lock solution to eradicate biofilm organisms. *Antimicrob Agents Chemother*. 2013;57(8):3555–3560.

See I, Freifeld AG, Magill SS. Causative organisms and associated antimicrobial resistance in healthcare-associated, central line-associated bloodstream infections from oncology settings, 2009–2012. *Clin Infect Dis*. 2016;62(10):1203–1209.

Stillman RM, Soliman F, Garcia L, Sawyer PN. Etiology of catheter-associated sepsis. Correlation with thrombogenicity. *Arch Surg*. 1977;112:1497–1499.

Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.

Zinkernagel AS, Zinkernagel MS, Elzi M V, et al. Significance of staphylococcus lugdunensis bacteremia: Report of 28 cases and review of the literature. *Infection*. 2008;36(4):314–321.

106

Infections associated with urinary catheters

Lindsay E. Nicolle

Urinary tract infections (UTIs) are a common and clinically important outcome of the use of urinary catheters. Urinary catheters may be (1) short-term (<30 days) indwelling urethral catheters, (2) long-term (>30 days) indwelling urethral or suprapubic catheters, or (3) used for intermittent catheterization. UTI with a catheter in situ is usually asymptomatic and referred to as *catheter-associated asymptomatic bacteriuria* (CA-ASB). Symptomatic infection is referred to as *catheter-acquired urinary infection* (CA-UTI). Different types of catheter are indicated for different populations and have different risks for the occurrence of infection (Table 106.1).

Pathogenesis

Acquisition of urinary infection with catheter use is virtually always through ascending infection (Box 106.1). For indwelling urethral catheters, bacteria usually ascend into the bladder on the biofilm that forms on the external and internal surfaces of the catheter tubing but may also ascend through reflux of contaminated urine up the drainage tubing. Disruption of the closed drainage system from the bladder to the drainage bag may also introduce bacteria, and there is a high incidence of new bacteriuria which develops within 24 hours following such a break in the system. Bacteria introduced at the time of catheterization account for <5% of infections.

Bacteriuria is a predictable consequence when an indwelling catheter remains in situ for a long enough time. The likelihood of developing bacteriuria is 3% to 7% per day while the catheter remains in situ. The determinants of symptomatic infection are not well described, but trauma to the mucosa or catheter obstruction may precipitate CA-UTI.

With intermittent catheterization, organisms are repeatedly introduced into the bladder at catheterization. Individuals managed with intermittent catheterization usually have a neurogenic bladder with incomplete bladder emptying so organisms, once introduced, may persist in the bladder. The organisms that cause bacteriuria are usually present as colonizing bacteria in the periurethral area but may also be introduced by contamination of the catheter or on the hands of the individual performing catheterization.

Bacteriology

Urinary infection identified in the setting of urethral catheterization is considered complicated UTI. *Escherichia coli* remains an important pathogen in these infections, but other organisms are also frequently isolated. These include other Enterobacteriaceae such as *Klebsiella pneumoniae*, *Citrobacter* spp., *Enterobacter* spp., and *Serratia marcescens*. For long-term indwelling catheters, in particular, infections with urease-producing organisms such as *Proteus mirabilis*, *Morganella morganii*, or *Providencia stuartii* are common. *Pseudomonas aeruginosa* and other gram-negative nonfermenters such as *Acinetobacter* spp. may be isolated, as well as gram-positive organisms, particularly enterococci and coagulase-negative staphylococci.

TABLE 106.1 **TYPES OF CATHETER USE AND FREQUENCY OF URINARY INFECTION IN CATHETERIZED POPULATIONS**

Catheter	Usual population	Infection rate
Indwelling urethral		
Short-term	Acute-care facility	5% per day
	Output monitoring	Women > men
	Postsurgical	
	Acute retention	
Long-term	Long-term care:	100% prevalence
	5–10% of residents	
	Chronic retention—men	
	Healing of pressure ulcer	
Intermittent catheter	Neurogenic bladder	1–3% per
	Spinal cord injury	catheterization
	Multiple sclerosis	
	Other impaired bladder emptying	

Candida albicans and other yeast species also occur, usually isolated from subjects receiving antimicrobials. The high frequency of recurrent infection and repeated courses of antimicrobials promote the emergence of more resistant organisms.

Polymicrobial bacteriuria is characteristic of infection in subjects with long-term indwelling catheters but may also occur with other types of catheterization. Long-term indwelling catheters or short-term catheters in situ for more than a few days are covered with a bacterial biofilm on both interior and external surfaces. This biofilm is composed of microorganisms, bacterial extracellular glycopolysaccharides, and protein and minerals incorporated from the urine. There is a complex microbial flora with multiple organisms growing in the biofilm; usually two to five organisms are present in a mature biofilm. The biofilm is an environment within which microorganisms are relatively protected from both antimicrobials and the host inflammatory and immune response. Urine specimens obtained for culture through the biofilm-laden catheter are contaminated by organisms present in the biofilm which may not be present in bladder urine. The number, type, and quantity of organisms isolated from these specimens may differ from a specimen of simultaneous bladder urine.

BOX 106.1

Methods by which organisms gain access to the bladder in catheter-acquired urinary infection

Ascending infection

- Introduced when the catheter is placed in the bladder
- Ascending from periurethral area on biofilm on mucous sheath on external catheter surface
- Ascending from interior drainage bag or tubing on biofilm
- Intraluminal from drainage bag with urine reflux
- Introduced with breaks in closed drainage

Other (uncommon)

- Hematogenous from another body site

Morbidity and mortality

Most catheter-acquired urinary infections are asymptomatic. However, catheterized subjects are at risk for increased morbidity from symptomatic UTI. Pyelonephritis, fever, and bacteremia may require hospitalization or result in extended hospitalization when nosocomially acquired. Local complications including prostatitis and epididymitis, purulent urethritis, urolithiasis, and urethral abscesses may occur. Crystalline biofilm formed by urease-producing organisms, principally *P. mirabilis*, is the most common cause of catheter obstruction. Acute urinary infection in subjects with spinal cord injury or other neurologic diseases may present as increased lower limb spasticity or autonomic hyperreflexia. Urinary infection in residents with chronic indwelling urethral catheters is the most frequent cause of bacteremia in long-term care facilities, with these residents experiencing three times the incidence of fever as bacteriuric long-term care facility residents without an indwelling catheter. Occasionally, acute urosepsis occurs, but mortality directly attributable to urinary infection is uncommon relative to the high frequency of bacteriuria.

Diagnosis

A diagnosis of urinary infection in a catheterized patient requires microbiologic confirmation. Clinical findings will then determine whether infection is symptomatic or asymptomatic. Culture of an appropriately collected urine specimen is essential. The specimen must be collected before antimicrobial treatment is initiated. It may be obtained directly at the time catheterization is initiated, by intermittent catheterization, from a newly placed catheter in subjects with long-term indwelling urethral catheters, or by aspiration from the catheter port of a short-term indwelling catheter. Quantitative criteria for the microbiologic diagnosis of urinary infection are shown in Table 106.2. Lower quantitative counts in subjects with indwelling catheters often reflect contamination from catheter biofilm rather than bladder bacteriuria.

A diagnosis of symptomatic urinary infection requires a positive urine culture. However, a positive urine culture is common in catheterized patients at any time. Patients with short-term indwelling catheters have an increasing prevalence of bacteriuria the longer the catheter remains in situ; those maintained on intermittent catheterization have a prevalence of about 50% at any time. Virtually all individuals with chronic long-term indwelling catheters are persistently bacteriuric. Thus, although a positive urine culture is necessary for diagnosis of urinary infection, it is not sufficient to identify symptomatic infection—clinical symptoms must also be present.

TABLE 106.2 **MICROBIOLOGIC DIAGNOSIS OF URINARY INFECTION IN SUBJECTS WITH CATHETER**

Clinical presentation	Quantitative count of bacteria
Asymptomatic	$\geq 10^5$ CFU/mL single specimen
Symptomatic	
In and out catheter	$\geq 10^2$ CFU/mL[a]
Indwelling catheter	$\geq 10^5$ CFU/mL

[a] Including subjects with intermittent catheterization.
Abbreviation: CFU = colony-forming unit.

Clinical presentations consistent with urinary infection are listed in Box 106.2. Localizing genitourinary symptoms or signs such as flank pain and tenderness, fever with an obstructed catheter, acute hematuria, or recent catheter trauma support a diagnosis of symptomatic urinary infection with a high degree of confidence. However, most patients with indwelling catheters and symptomatic urinary infection will not have localizing genitourinary symptoms. A frequent clinical scenario is fever and a positive urine culture without localizing findings to the genitourinary tract or another potential site of infection. Catheterized patients often present with fever alone as a manifestation of urinary infection, but other potential sources must always be considered. In one study of subjects with long-term indwelling catheters, only 33% of such episodes were confirmed to be due to a urinary source. Thus, in the absence of localizing genitourinary findings or bacteremia with the urinary isolate, symptomatic urinary infection is a diagnosis of exclusion.

BOX 106.2

Clinical presentations of acute urinary infection in subjects with bladder catheters

Asymptomatic
Symptomatic
Systemic
- Acute pyelonephritis
- Fever with catheter obstruction
- Fever with acute hematuria
- Bacteremia with urinary isolate
- Increased lower leg spasms or autonomic hyperreflexia in spinal cord injury
- Fever without genitourinary localizing findings and no alternate source (≤50% urinary source)

Local[a]
- Urethritis
- Epididymitis
- Urethral abscess
- Bladder or kidney stones
- Catheter obstruction
- Prostatitis
- Scrotal abscess

[a] Local complications are primarily seen with long-term indwelling urethral catheters.

Pyuria is a universal accompaniment of bacteriuria in individuals with indwelling catheters and is also present in most bacteriuric patients who use intermittent catheterization. Pyuria may also be present in the absence of bacteriuria due to irritation of the bladder by the catheter. The presence of pyuria or level of pyuria associated with bacteriuria has not been shown to have any prognostic clinical significance. Thus, pyuria is insufficient to make a diagnosis of urinary infection, and the presence of pyuria is not, by itself, an indication of symptomatic infection.

Treatment

Treatment of asymptomatic bacteriuria is not indicated for subjects managed by intermittent catheterization or with an indwelling urethral catheter. For subjects with long-term indwelling catheters, antimicrobial treatment of CA-ASB does not decrease the frequency of subsequent symptomatic episodes but leads to recurrent bacteriuria with more resistant bacteria. As previously noted, pyuria by itself or with bacteriuria is not an indication for treatment in an individual who is asymptomatic. For women, if catheter-acquired bacteriuria persists for 48 hours after removing a short-term indwelling catheter, treatment may be indicated. This clinical question has not been addressed for men, and no definitive recommendation can be given.

When symptomatic infection is diagnosed clinically, a urine specimen for culture should be obtained in every case before initiation of antimicrobial therapy. For individuals with catheters in situ for ≥2 weeks, the catheter should be replaced and a specimen for culture obtained from the newly placed catheter before initiating antimicrobial therapy. This allows collection of a urine specimen that is representative of bladder organisms without biofilm contamination. Replacing the catheter immediately prior to antimicrobial therapy has also been shown to shorten the time to defervescence and decrease the likelihood of symptomatic relapse in short-term follow-up. It is assumed that these beneficial effects result from removal of the biofilm with its high concentration of organisms. For short-term indwelling catheters where mature biofilm formation is less likely, catheter replacement prior to initiating antimicrobial therapy is not recommended.

Oral antimicrobials appropriate for treatment of urinary infection are listed in Table 106.3, and parenteral antimicrobials are listed in Table 106.4. Parenteral therapy should be initiated in patients who are hemodynamically unstable, are vomiting or otherwise unable to take oral medications, have impaired gastrointestinal absorption, or have a high likelihood of being infected with an organism resistant to oral agents.

If symptoms are mild but persistent, antimicrobial therapy should not be initiated until the urine culture results are available. This allows for selection of antimicrobial therapy specific for the infecting organism. Empiric antimicrobial therapy should be initiated pending urine culture results when a patient is significantly ill with fever or other systemic symptoms or when the patient has other severe symptoms attributable to urinary infection.

TABLE 106.3 **ORAL ANTIMICROBIALS FOR TREATMENT OF URINARY TRACT INFECTION IN CATHETERIZED PATIENTS WITH NORMAL RENAL FUNCTION**

Antimicrobial	Dosage
Penicillins	
Amoxicillin	500 mg TID
Amoxicillin-clavulanic acid	500/125 mg TID or 875/125 mg BID
Cephalosporins	
Cephalexin	500 mg QID
Cefaclor	500 mg QID
Cefadroxil	1 g OD or BID
Cefuroxime axetil	250 mg BID
Cefixime	400 mg OD
Cefpodoxime proxetil	100–400 mg BID
Fluoroquinolones[a]	
Norfloxacin	400 mg BID
Ciprofloxacin	250–500 mg BID
Ofloxacin	200–400 mg BID
Levofloxacin	250–500 mg OD
Other	
Nitrofurantoin	50–100 mg QID
Trimethoprim	100 mg BID
Trimethoprim–sulfamethoxazole	160/800 mg BID

[a] Recommended for oral empiric therapy.

TABLE 106.4 **PARENTERAL ANTIMICROBIALS FOR TREATMENT OF URINARY TRACT INFECTION IN INDIVIDUALS WITH NORMAL RENAL FUNCTION**

Antimicrobial	Dosage
Aminoglycoside	
Amikacin[a]	5 mg/kg q8h or 15 mg/kg q24h
Gentamicin[a]	1–1.5 mg/kg q8h or 4–5 mg/kg q24h
Tobramycin[a]	1–1.5 mg/kg q8h or 4–5 mg/kg q24h
Penicillin	
Ampicillin	1–2 g q6h
Piperacillin	3 g q4h
Piperacillin/tazobactam	4 g/500 mg q8h
Ticarcillin/clavulanic acid	50 mg/kg q6h
Cephalosporins	
Cefazolin	1–2 g q8h
Ceftriaxone	1–2 g q24h
Cefotetan	1 g q12h
Cefotaxime	1–2 g BID or TID
Cefepime	2 g q12h
Ceftazidime	0.5–2 g q8h
Ceftazidime-avibactam	2g/500 mg q8h
Ceftolozane-tazobactam	1.5g q8h
Other	
Aztreonam	1 g q6h
Imipenem/cilastatin	500 mg q6h
Ertapenem	1g q24h
Meropenem	500 mg q8h
Doripenem	500 mg q8h
Vancomycin	500 mg q6h or 1 g q12h

[a] Recommended for initial empiric therapy with ampicillin if renal function is normal.

The selection of initial empiric therapy should consider recent antimicrobial therapy prescribed to the patient; bacteriology and susceptibilities of previous urine cultures from the patient, when available; and resistance patterns of endemic flora in an institution in addition to patient tolerance. An aminoglycoside, with or without ampicillin for enterococci, is usually appropriate for initial empiric parenteral therapy. In the presence of moderate to severe renal failure, an extended-spectrum β-lactam antimicrobial or fluoroquinolone may be preferred rather than an aminoglycoside. When there is a concern about resistant organisms, alternative empiric therapy with coverage specific for the expected susceptibilities should be selected. Once urine culture and susceptibility results from the pretherapy urine specimen are available, usually 48 to 72 hours after initiation of therapy, the antimicrobial regimen can be reassessed and, if appropriate, changed to alternative specific therapy. This should include a change to oral therapy, whenever possible, for patients in whom parenteral therapy was initiated.

If the patient continues to require an indwelling catheter, the treatment duration should be for as short a period as possible (5–7 days). Longer courses of therapy will promote the emergence of organisms of increasing resistance, potentially increasing the difficulty in treating future episodes of symptomatic infection. If the catheter is removed, 7 to 14 days of therapy should be given. For subjects managed with intermittent catheterization, 7 days is recommended for lower tract symptoms and 10 to 14 days for systemic infection.

Prevention

The most effective means of preventing catheter-associated infection is not to use a catheter or, if there is a clear clinical indication for use, to limit the duration of catheterization to as short a period as possible (Box 106.3). When feasible, alternate strategies to

BOX 106.3

Prevention of catheter-acquired urinary tract infection

Effective

- Restrict indications for catheter use
- Limit duration of catheter use
- Daily review of continuing need for catheter
- Aseptic insertion (for indwelling catheter)
- Maintain closed drainage system
- Antibiotics first 4 days (not recommended)[a]
- Antibiotics at removal (not recommended)[a]

Not effective

- Bladder irrigation with antimicrobial
- Periurethral care with soap or disinfectant
- Routine catheter replacement
- Disinfectant in drainage bag
- Coating of catheter with antimicrobial substances[b]
- Antimicrobial prophylaxis

[a] Not recommended because of emerging antimicrobial resistance.

[b] Nitrofurazone coating may decrease symptomatic infection but has increased adverse effects.

manage voiding, such as a condom catheter for men, should be used. For short-term indwelling catheters, the maintenance of a closed drainage system is important in delaying acquisition of infection. Antimicrobial therapy given during the first 3 days of catheterization or at the time of catheter removal is associated with a decreased frequency of infection. However, these antimicrobial strategies are not recommended because they are associated with an increased frequency of reinfection with more resistant organisms. Other interventions that have been systematically evaluated, such as daily periurethral cleaning with either soap or a disinfectant and addition of disinfectants to the drainage bag, are not effective in decreasing the frequency of symptomatic infection.

It is not clear that any interventions will decrease the frequency of bacteriuria in subjects with chronic indwelling urethral catheters. Preventive strategies in these patients must focus on limiting symptomatic infection through early identification of catheter obstruction and prevention of catheter trauma to the genitourinary mucosa. Routine replacement of chronic indwelling catheters is not recommended. The catheter should be replaced only if there is obstruction or other catheter malfunction or prior to treatment of symptomatic urinary infection.

For spinal cord-injured patients managed with intermittent catheterization, use of prophylactic antimicrobials may decrease the frequency of infection in the early postinjury period but is not effective in the long term as infection with organisms of increased antimicrobial resistance occurs. Thus, prophylactic antimicrobials are not recommended in patients using intermittent catheterization. Maintenance of bladder volumes of <500 mL in these subjects may decrease the frequency of symptomatic infection. For nursing home patients, rates of infection with intermittent catheterization are similar if either a clean or sterile catheter technique is used. Thus, clean technique is recommended because it is less costly.

Antimicrobial therapy should be given to subjects with asymptomatic bacteriuria before an invasive genitourinary procedure, such as transurethral prostatic resection or stone extraction, where there is a high likelihood of mucosal trauma. Antimicrobial therapy is initiated before the surgical procedure and is conceptually "prophylaxis" to prevent bacteremia and sepsis rather than treatment of asymptomatic bacteriuria. Antimicrobial therapy is not indicated before a chronic indwelling urethral catheter change because this is not a high-risk procedure.

UTI in catheterized patients is primarily a technologic problem of biofilm formation on inert devices. Thus, substantive progress in preventing these infections will require technologic development of devices resistant to biofilm formation. Many antimicrobial-coated or -impregnated urinary catheters have been developed, and some of these are widely used. Nitrofurazone-coated catheters may be associated with a small decrease in the incidence of symptomatic infection in hospitalized patients with short-term catheters but there is an increased frequency of adverse effects with these catheters. Silver alloy catheters have not consistently been shown to improve outcomes. Catheters using other biomaterials or coatings are under further development, but none of these has yet been documented to decrease morbidity.

Suggested reading

Batura D, Gopal Rao G, Foran M, Brempony F. Changes observed in urine microbiology following replacement of long-term urinary catheters: need to modify UTI guidelines in the UK? *Int Urol Nephrol*. 2018;50:25–28.

Chant C, Smith DM, Marshall JC, Friedrich JO. Relationship of catheter-associated urinary tract infection to mortality and length of stay in critically ill patients: A systematic review and meta-analysis of observational studies. *Crit Care Med*. 2011;39:1167–1173.

Chenoweth CE, Gould CV, Saint S. Diagnosis, management, and prevention of catheter-associated urinary tract infections. *Infect Dis Clin North Am*. 2014;28:105–120.

Cope M, Cevallos ME, Cadle RM, et al. Inappropriate treatment of catheter associated asymptomatic bacteriuria in a tertiary care hospital. *Clin Infect Dis*. 2009;48:1182–1188.

Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA, Healthcare Infection Control Practices Advisory Committee (HICPAC). Guideline for prevention of catheter-associated urinary tract infections 2009. www.cdc.gov/hicpac/cauti/001_cauti.html

Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:625–663.

Kizilbash QF, Peterson NJ, Chen GJ, Naik AD, Trautner BW. Bacteremia and mortality with urinary catheter-associated bacteriuria. *Infect Control Hosp Epidemiol*. 2013; 34:1153–1159.

Meddings J, Rogers AM, May M, Saint S. Systematic review and meta-analysis: Reminder systems to reduce catheter-associated urinary tract infections and urinary catheter use in hospitalized patients. *Clin Infect Dis*. 2010;51:550–560.

Pichard R, Lam T, MacLennan G, et al. Antimicrobial catheters for reduction of symptomatic urinary tract infection in adults requiring short-term catheterization in hospital: A multicenter randomized controlled trial. *Lancet*. 2012;380:1927–1935.

Siddiq DM, Darouiche RO. New strategies to prevent catheter-associated urinary tract infections. *Nat Rev Urol*. 2012;17:305–314.

Tambyah PA, Maki DG. Catheter-associated urinary tract infection is rarely symptomatic. *Arch Intern Med*. 2000;160:678–687.

Section 14

Infections related to surgery and trauma

107

Postoperative wound infection

E. Patchen Dellinger

Postoperative wound infection or surgical site infection (SSI) is the archetypal surgical infection because it follows a surgical procedure and requires surgical intervention for resolution. As with many infections, best results are obtained by prompt diagnosis and treatment, which is facilitated by understanding the risk factors. The most obvious factor influencing risk of infection is the density of bacterial contamination of the incision. This was recognized several decades ago in the wound classification system that divides all surgical wounds into the following four categories: clean, clean-contaminated, contaminated, and dirty. Clean wounds result from an elective procedure without break in technique that does not involve any area of the body other than skin normally colonized by resident bacteria. Clean-contaminated wounds result from a procedure such as elective bowel resection that intentionally opens the gastrointestinal (GI) tract or other colonized region such as the female genital tract but does not result in grossly visible spill of contents during the procedure. Contaminated procedures are those with gross spill from the GI tract or trauma and emergency procedures in which a wound has been created without normal antisepsis and sterile technique. A dirty wound is one that results from an operation in an area of active infection or previous bowel injury and leak. Among these categories, infection risk ranges historically, before modern understanding and practice of perioperative antibiotic prophylaxis, from 2% for clean wounds to 30% to 40% for dirty wounds when the skin is closed primarily.

Studies done many decades ago demonstrate that essentially all surgical incisions, even in clean operations, have some bacteria in the wound at the end of the procedure. Clinicians have recognized that the nature of host defenses and the extent to which the operative procedure or preexisting disease impairs these defenses also influences the risk of wound infection. Modern wound classifications that include underlying risk as well as the risk of bacterial contamination predict infection more accurately. The first widely used system, developed by the National Research Council in 1964, divided all surgical wounds by inherent risk of contamination into clean, clean-contaminated, contaminated, and dirty. The next version assigned 1 point each for wound classification of contaminated or dirty, an operation lasting longer than the 75th percentile for that procedure, and an American Society of Anesthesiology (ASA) physical status classification of 3 or 4. In this system, the risk of postoperative wound infection for patients with risk points of 0, 1, 2, or 3 is 1.5%, 2.9%, 6.8%, and 13.0%, respectively. These data reflect modern use of perioperative prophylactic antibiotics, as discussed in Chapter 112, "Surgical prophylaxis." Efforts at the Centers for Disease Control and Prevention (CDC) and the National Healthcare Safety Network (NHSN), which is now the most prominent national surveillance system, have worked to develop more precise procedure-specific risk predictions for SSIs. They now report infection rates at participating hospitals in terms of Standardized Infection Ratios (SIR), which express the rate for a given hospital and given procedure as a ratio of observed divided by expected SSI rate. To report SIR, NHSN looks at data for 39 different specific procedure categories and applies between 1 to 11 specific risk factors taken from the list in Table 107.1 associated with each procedure category to calculate the expected SSI rate.

TABLE 107.1 **POTENTIAL RISK FACTORS USED BY THE NATIONAL HEALTHCARE SAFETY NETWORK (NHSN) FOR ESTIMATING SURGICAL SITE INFECTION (SSI) RISK FOR DIFFERENT PROCEDURE CATEGORIES**

ASA score	Wound class
BMI	Age
Closure technique	Gender
Oncology hospital	Medical school affiliation
Procedure duration	Hospital bed size
Anesthesia type	Emergency
Trauma	Scope
Diabetes	Spinal level

Diagnosis

The diagnosis of postoperative wound infection is obvious when the wound opens and discharges pus. However, the diagnosis is ideally made earlier and prompt therapeutic intervention undertaken. It is rare for a postoperative wound infection to be clinically evident before the fourth or fifth postoperative day. The sole exceptions to this are infections caused by β-hemolytic streptococci or by histotoxic *Clostridium* species and, more rarely, wound toxic shock. These infections can be clinically evident within fewer than 24 hours, and, although they are rare, they tend to be devastating. The wound of any patient with severe systemic signs of infection during the first few days after an operation should be inspected for signs of infection (Figure 107.1). Streptococcal infections are marked by local signs of inflammation and at times an exudate containing white blood cells (WBCs) and gram-positive cocci. Clostridial infections lack signs of inflammation and produce a thin exudate lacking WBCs because of the action of clostridial exotoxins, but gram-positive rods without spore formation are evident on Gram smear. Wound toxic shock due to toxin production by staphylococci or streptococci is a rare complication of SSI and represents <1% of all SSI. Most of these cases present within 48 hours of an operation. The earliest signs are fever, diarrhea, and vomiting. Profuse watery diarrhea, erythroderma, and hypotension are also characteristic. Initially, local signs of wound infection are often absent. Drainage and irrigation of the wound in combination with a systemic antistaphylococcal antibiotic is recommended. Although most wound infections are diagnosed between 5 and 15 days after the procedure, in some cases, diagnosis may be delayed considerably. This is more likely with wounds with a significant amount of tissue overlying the area such as abdominal wounds in morbidly obese patients and wound infections under chest wall musculature following a posterolateral thoracotomy.

Because most patients have some fever in the first several days after a major operative procedure such as abdominal exploration or thoracotomy, fever is not a specific sign of postoperative infection (Figure 107.2). It is tempting for the surgeon to continue prophylactic antibiotics or to restart antibiotics if the patient shows early postoperative fever, but this impulse should be resisted because these infections will not resolve without opening the wound. When antibiotics are given without a commitment to open the wound, the most likely results are a delay in diagnosis and definitive treatment, a consequent increase in morbidity, and risk of additional complication such as wound dehiscence or herniation. A few surgical wounds exhibit erythema adjacent to the incision, either concentrated around skin sutures or staples or diffusely. In the absence of marked induration and/or drainage, this erythema usually does not indicate wound infection. The average clinician will be sorely tempted to prescribe antibiotics for a patient with such a wound, but most resolve without any specific treatment, and no data suggest that administration of antibiotics in such a situation will prevent the need to open the wound for a real infection.

Therapy

Incisional drainage

The primary treatment for a wound infection is to open the wound and evacuate the infected material. Antibiotics are used as adjunctive treatment only for patients who exhibit signs of significant systemic response to the infection or in whom there is evidence of invasive soft tissue infection beyond the boundaries of the surgical incision. The evidence for infection may be most prominent in a portion of the incision, but in most cases, the entire incision will be involved under the skin and will have to be opened. If necrotic tissue is found in the wound, some preliminary debridement may be helpful, but small shreds of involved tissue will separate by themselves over time if the wound is left open and subjected to gauze dressing changes two to three times daily, decreasing in frequency as the wound clears. The importance of dressing changes is greater if the wound is deep, as in patients with severe obesity or in posterolateral thoracotomy wounds in muscular patients. If the wound is undermined, it is important to place the dressing so that gauze is in contact with all areas of the wound, but the dressings should not be put in forcefully or under pressure because this causes pain, inhibits drainage of exudate, and stimulates excess scar formation and slows wound closure, which occurs through the normal mechanism of contracture of granulation tissue.

When an incision is opened initially, it should be inspected by a physician who understands the procedure and the underlying anatomy. If the procedure was a celiotomy or a thoracotomy, the integrity of the closure of the abdominal or chest wall should be verified and evidence sought for purulent fluids originating deep to the abdominal or chest wall. In some cases, the incisional infection is not the primary event but is a signal of more severe and more extensive infection at a deeper level (see Chapters 55 and 57, "Abdominal abscess" and "Peritonitis," respectively).

Antibiotics

At the time of diagnosis and opening of the wound, empiric antibiotic administration should only occur when there are signs of a significant systemic reaction with temperature >38°C/100.4°F), elevated

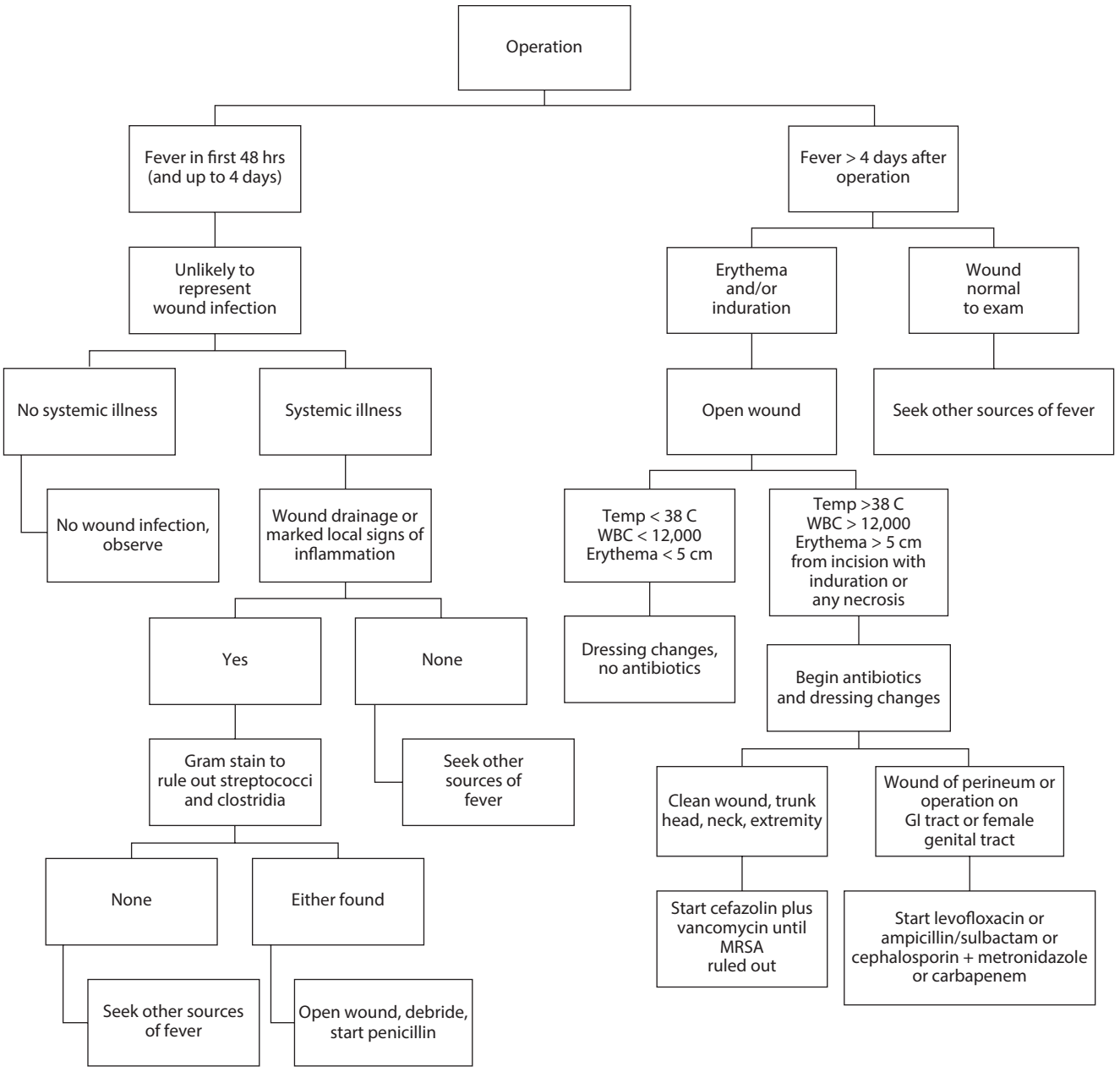

FIGURE 107.1

pulse rate, or absolute WBC count >12,000; when inspection of the wound reveals invasive infection in the subcutaneous space or at the fascial level; or when surrounding erythema and induration extend >5 cm from the line of incision. The agent chosen should be guided by Gram smear of the wound exudate and the nature of the procedure. Infections following clean operations that have not entered the GI tract and that involve the head and neck, trunk, or extremities tend to be caused by *Staphylococcus aureus* or, less commonly, streptococcal species. If Gram smear confirms gram-positive cocci and if antibiotics will be given, treatment is appropriate with an initial parenteral dose of cefazolin or oxacillin, 1 g intravenously (IV). For patients allergic to penicillin and cephalosporins, clindamycin, 900 mg, or vancomycin, 1 g IV, is acceptable. If the patient can take oral fluids and is not thought to have bacteremia, subsequent treatment can be with oral cephalexin or cephradine, 500 mg, or clindamycin, 450 mg four times daily. As community-acquired methicillin-resistant *S. aureus* (CA-MRSA) increase in frequency, consideration should be given to initiating treatment with sulfamethoxazole/trimethoprim, 800/160 mg orally (PO) every 12 hours; doxycycline, 100 mg PO every 12 hours; or vancomycin, 1 g IV every 12 hours; or linezolid, daptomycin, telavancin, or ceftaroline, until susceptibility data are available. Antibiotic treatment should be continued only as long as systemic signs of infection or local cellulitis continue to be present, usually 3 days or less.

For infections that follow operations in the axilla, gram-negative enteric bacilli are more commonly causative, and after operations on

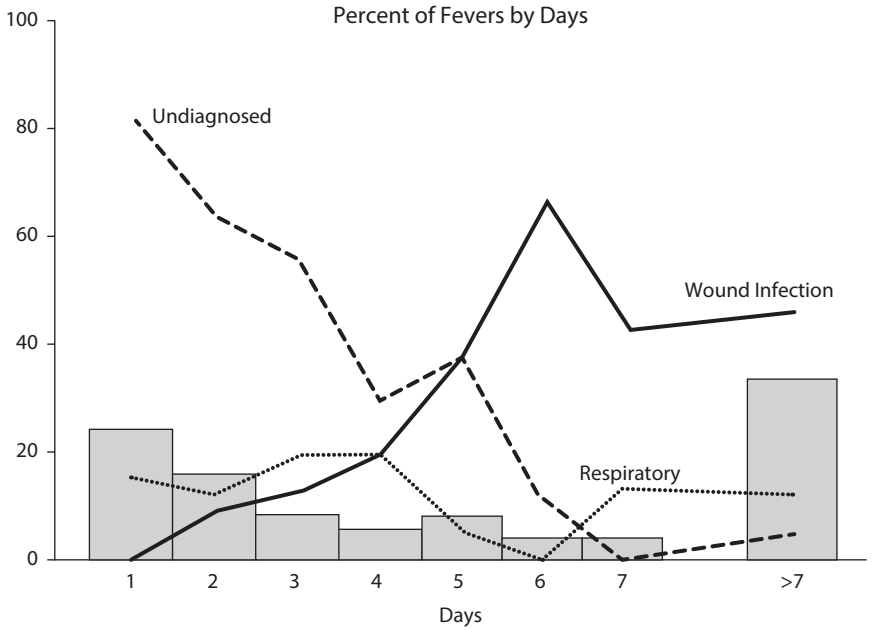

FIGURE 107.2 Bars represent the percent of all postoperative fevers occurring on the indicated day following an operative procedure. Lines indicate the percentage of fevers occurring on each day attributable to the cause indicated. (From Dellinger EP. Approach to the patient with postoperative fever. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases*, 3rd edn. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:817–823).

the perineum or involving the GI tract or the female genital tract both facultative and obligate anaerobic bacilli and cocci are often involved. In these cases, if antibiotic treatment is thought necessary, initial treatment can be a cephalosporin or a fluoroquinolone combined with metronidazole. Patients allergic to penicillin and cephalosporins can receive levofloxacin, 500 mg IV every 12 hours, combined with metronidazole, 1 g IV every 12 hours. Again, the treatment should usually be for 3 days or less. If the patient is able to take oral agents, switching to an oral regimen of levofloxacin, 500 mg every 24 hours, combined with metronidazole, 500 mg every 6 hours, should be considered.

In the rare patient who has an invasive wound infection caused either by β-hemolytic streptococci or by a histotoxic *Clostridium* spp. diagnosed in the first 48 hours after operation, aggressive antimicrobial therapy is necessary in addition to opening the wound and inspecting it in the operating room under general anesthesia, with the option of aggressive soft tissue debridement if evidence of spreading soft tissue invasion and necrosis is found. Penicillin G, 4 million units IV every 4 hours, is appropriate if the diagnosis of streptococcal or clostridial infection is firm. If in doubt, cefazolin or vancomycin provides treatment for staphylococcal infections in addition to streptococcal and clostridial infections, but the addition of metronidazole for anaerobic coverage may be prudent. CA-MRSA have been reported to cause necrotizing soft tissue infections, so initial treatment of these infections with gram-positive cocci should include the use of vancomycin, 1 g IV every 12 hours.

Wound closure

The most reliable method for handling an infected wound that has been opened is to continue dressing changes and allow the wound to close spontaneously by secondary intention. In straightforward wound infections, this results in a very satisfactory result in most cases. In a minority of wounds, the incision can be reclosed, usually with tapes, after the incision has cleared up and is lined by healthy granulation tissue. The failures that occur at this time are as often caused by the geometry of the wound as they are by the bacterial content.

Suggested reading

Burke JF. Identification of the source of staphylococci contaminating the surgical wound during operation. *Ann Surg*. 1963;158:898–904.

Centers for Disease Control and Prevention. The NHSN Standardized Infection Ratio (SIR) [Internet]. 2018 [cited 16 September 2018]. https://www.cdc.gov/nhsn/pdfs/ps-analysis-resources/nhsn-sir-guide.pdf

Culver DH, Horan TC, Gaynes RP, et al. Surgical wound infection rates by wound class, operative procedure, and patient risk index. National Nosocomial Infections Surveillance System. *Am J Med*. 1991; 91(3B):152S–157S.

Dellinger EP. Approach to the patient with postoperative fever. In Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious diseases*, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004: 817–823.

Dellinger EP. Surgical infections. In Mulholland MW, Lillemoe KD, Doherty GM, Maier RV, Upchurch GR Jr, eds. *Greenfield's surgery: Scientific principles and practice*, 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008: 132–146.

Garibaldi RA, Brodine S, Matsumiya S, et al. Evidence for the non-infectious etiology of early postoperative fever. *Infect Control*. 1985;6:273–277.

Horan TC, Gaynes RP, Martone WJ, et al. CDC definitions of nosocomial surgical site infections, 1992: A modification of CDC definitions of surgical wound infections. *Am J Infect Control*. 1992;20:271–274.

Miller LG, Perdreau-Remington F, Rieg G, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles. *N Engl J Med*. 2005;352:1445–1453.

Mu Y, Edwards JR, Horan TC, Berrios-Torres SI, Fridkin SK. Improving risk-adjusted measures of surgical site infection for the national healthcare safety network. *Infect Control Hosp Epidemiol*. 2011;32:970–986.

National Academy of Sciences, National Research Council, et al. Postoperative wound infections: The influence of ultraviolet irradiation on the operating room and of various other factors. *Ann Surg*. 1964;160(Suppl 2):1.

Paydar KZ, Hansen SL, Charlebois ED, Harris HW, Young DM. Inappropriate antibiotic use in soft tissue infections. *Arch Surg*. 2006;141:850–854; discussion 855–856.

Saeed MJ, Dubberke ER, Fraser VJ, Olsen MA. Procedure-specific surgical site infection incidence varies widely within certain National Healthcare Safety Network surgery groups. *Am J Infect Control*. 2015;43(6):617–623.

Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59–10–52.

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Trauma-related infection

Mark A. Malangoni

Infection is a serious complication of trauma, particularly among patients who have a greater severity of injury or suboptimal host defenses. Although exsanguination and central nervous system injury are the most common causes of mortality in the first 48 hours following injury, patients who die later often succumb to infectious complications or their consequences.

Trauma-related infection represents either infection at an original site of injury or infection that occurs as a direct result of injury. Examples of the former are an infected laceration or osteomyelitis at the site of an open fracture. The latter includes empyema after a penetrating wound to the chest and an intra-abdominal abscess that follows repair of a gunshot wound to the colon. Infection also can occur at sites remote from the area of injury; however, these infections usually are indirectly related to the immediate injury and will not be discussed further.

Similar to other infections, trauma-related infections occur when there is an imbalance in the normal relationship between microorganisms, the local environment, and innate or acquired host defenses. These infections can occur either from the introduction of small numbers of highly pathogenic bacteria or following contamination from a large inoculum of less pathogenic organisms. Common pathogens is various areas of the body are listed in Table 108.1.

Injury can lead to infection by (1) direct contamination of a sterile site with exogenous microorganisms; (2) disruption of the natural epithelial barriers of the gastrointestinal, respiratory, or gynecologic tracts, with contamination from endogenous microorganisms; (3) impairment of local antimicrobial clearance mechanisms by direct damage to tissues and the introduction of foreign bodies, hematomas, or seromas which act as adjuvants to promote infection; and (4) weakened systemic host defenses through secondary mechanisms that are either preexisting or secondary to the consequence of injury.

Various preexisting conditions may also contribute directly to the development of trauma-related infections through detrimental effects on local or systemic defense mechanisms. Examples include diabetes mellitus, obesity, malnutrition, advanced age, alcoholism, and single or multiple organ system dysfunction. Hyperglycemia, hypoxemia, and hypothermia also increase the likelihood of developing a trauma-related infection. Importantly, the adequacy of the blood supply to the injured area can affect the propensity to develop infection, and impaired perfusion because of preexisting disease or perturbations due to the injury per se increases the risk of developing an infection.

Necessary invasive and diagnostic interventions such as the placement of endotracheal tubes, intravascular catheters, and urinary catheters provide microorganisms with a portal of entry to sterile body sites, bypassing normal defenses. This can result in infection at the site of entry or may cause a distant infection following hematogenous dissemination of pathogens. Improper treatment can also predispose to infection by impairing the clearance of bacteria.

Efforts to prevent infection should begin immediately after injury. The general principles of initial management of injury include meticulous examination of external wounds to determine the extent and severity of injury. Bleeding should be controlled by application of direct pressure or by identification and ligation of major bleeding points. Control of bleeding, evacuation of hematomas, debridement of all devitalized soft tissues, removal of foreign material, and identification of bony fractures are essential to proper wound management. The injury site should be irrigated with a physiologic solution such as 0.9% normal saline. Wounds

TABLE 108.1 **POTENTIAL PATHOGENS BASED ON ANATOMIC LOCATIONS**

Skin	*Staphylococcus epidermidis* *Staphylococcus aureus* *Clostridium* species *Bacteroides species (non-fragilis)*
Oropharynx	*Staphylococcus epidermidis* *Staphylococcus aureus* β-hemolytic streptococci *Streptococcus pneumoniae* Anaerobic streptococci *Candida albicans* *Bacteroides species (non-fragilis)*
Upper gastrointestinal tract	Enterococci *Candida albicans* Enterobacteriaceae (e.g., Escherichia coli, Klebsiella, Enterobacter)
Distal gastrointestinal tract	Enterobacteriaceae Enterococci *Bacteroides fragilis* *Clostridia* species

should be covered with a sterile dressing, preferably moistened with 0.9% normal saline, as soon as possible in order to prevent further contamination and tissue desiccation; however, this process should not impede definitive care or transfer to a trauma center when indicated.

In traumatic wounds associated with fractures, there is a direct relationship between the risk of infection and the severity of related soft tissue injury. Early immobilization of fractures reduces additional soft tissue damage, limits hematoma formation, and can help decrease the risk of infection by preventing dissemination of contaminating bacteria when an open fracture is present. Fracture immobilization also helps promote restoration of normal homeostasis.

After appropriate cleansing, debridement, and hemostasis are completed, wound closure should be addressed. In general, simpler techniques are preferred over more elaborate ones. Traumatic wounds with a low risk for infection should undergo primary closure. Soft tissue injuries at increased risk for infection include those that have devitalized or ischemic tissue, are located at or near areas of heavy colonization such as the groin or perineum, have a delay of 6 hours or more to definitive care, or are complicated by the presence of associated diseases or conditions that compromise clearance of contaminating organisms. Crush injury, high-velocity and shotgun injuries, coexisting thermal injury, and irregular or stellate wound configurations are other indicators of high-risk wounds. Wounds that are heavily contaminated or at high risk for infection should not be closed primarily. In these situations, it is more prudent to repeat cleansing and debridement of the site of injury and delay closure until it can be done safely. Unless the wound environment is sufficient to allow for closure with a low risk of infection, wounds should be allowed to heal by secondary intention or have delayed primary closure. Although this may seem inconvenient for the patient, it often avoids substantial consequences associated with infection.

Stab wounds and low-velocity gunshot wounds can usually be irrigated and closed primarily as long as there has not been significant exogenous or endogenous contamination. When intestinal injury is present, there is an increased concentration of microorganisms contaminating the site of injury, particularly at the exit site, and these wounds should be left open. High-velocity missile track and shotgun wounds should not be closed primarily and are best managed by debridement and irrigation of entrance and exit sites, followed by coverage with sterile dressings. Complex wounds with extensive areas of devitalized soft-tissue are best managed by debridement and irrigation with dressing care. Exposed soft tissue can be managed with wet-to-dry dressing changes using 0.9% normal saline to promote a healthy granulating bed that can be covered later either with a split-thickness skin graft or with full-thickness skin or can be allowed to heal by secondary intention. Although it may be tempting to use antiseptic or antimicrobial-containing agents for irrigation, these substances offer no advantage in the early treatment of wounds and may impair healing. When wounds that are healing by secondary intention begin to granulate and contract, it may be appropriate to switch to hydrocolloid gels or alginates, which are associated with less discomfort and a less frequent need for dressing changes. Negative pressure wound therapy has been demonstrated to be useful for treatment of large open wounds once contamination has been minimized as it accelerates wound contraction and reduces the time to healing. It also has the advantages of requiring less frequent dressing changes and improved patient comfort.

Antibiotic therapy is not a substitute for sound clinical judgment, excellent local wound care, aseptic technique, and careful handling of tissues. For uncomplicated minor wounds with minimal contamination and a low risk of infection, antibiotic therapy is unnecessary. Empiric antibiotic therapy is beneficial when there is heavy bacterial contamination, an open fracture, involvement of a joint space, major soft tissue injury, or delay of initial management for >6 hours, as well as for patients with impaired local or systemic host defenses. Initial cultures of contaminated wound sites usually add little to treatment decisions. Tetanus toxoid and tetanus immunoglobulin should be administered in accordance with established guidelines for contaminated wounds.

Empiric antibiotic therapy should be directed primarily against gram-positive bacteria in most soft tissue wounds. When contamination with anaerobes and gram-negative enteric bacteria is suspected, such as with a farm-related injury or a human bite, the antimicrobial spectrum must include agents effective against these organisms. Treatment should be continued only for 24 hours in wounds with a minor or moderate degree of contamination; a longer duration of treatment is recommended when contamination is greater. Recommended antibiotic choices are listed in Table 108.2.

The high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the community and among patients or those who reside in long-term care facilities mandates a reassessment of the approach to the treatment of patients who are potentially contaminated or infected with these organisms. When MRSA is

TABLE 108.2 **ANTIBIOTIC THERAPY FOR TRAUMATIC WOUNDS**[a]

Clean lacerations	No antibiotics recommended
Heavily contaminated lacerations or wounds at risk for infection	Cefazolin, 1–2 g IV q8h Amoxicillin-clavulanate, 500 mg PO q12h, or 250 mg PO q8h For penicillin-allergic patients, use ciprofloxacin 400 mg IV or 500 mg PO q12h plus metronidazole 500 mg IV or PO q6h or Moxifloxacin 400 mg IV or PO q24h
Farm injuries and human bites; soil contamination; delays in care of heavily contaminated wounds	Piperacillin-tazobactam, 3.375 g IV q6h, or amoxicillin-clavulanate, 500 mg PO q12h, or 250 mg q8h (see Chapter 23, "Human and animal bites") For penicillin-allergic patients, use ciprofloxacin 400 mg IV or 500 mg PO q12h plus metronidazole 500 mg IV or PO q6h, or moxifloxacin 400 mg IV or PO q24h
Penetrating abdominal injury[b]	Cefotetan, 2 g IV q8h, or piperacillin-tazobactam, 3.375 g IV q6h For penicillin-allergic patients, use ciprofloxacin 400 mg IV q12h plus metronidazole 500 mg IV q6h, or moxifloxacin 400 mg IV q24h

[a] Local infection data and resistance patterns may require additional coverage when methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected (see text).
[b] Doses should be repeated for every 10 units of blood loss.

suspected, empiric therapy should be chosen based on whether this is considered a community-acquired or healthcare-acquired strain. Healthcare-acquired strains usually require treatment with vancomycin, linezolid, daptomycin, telavancin, or clindamycin whereas community-acquired MRSA is often susceptible to trimethoprim-sulfamethoxazole and tetracyclines in addition to the preceding agents. Cultures should be done at the time of drainage or debridement in patients who develop an infection in order to identify the antimicrobial susceptibility profile of these organisms and to direct therapy.

The occurence of intra-abdominal infection after penetrating abdominal trauma is a paradigm that defines risk factors for trauma-related infection in a single body cavity. Increased patient age, number and degree of organ injuries, units of blood products transfused, delays in treatment, and presence of severe contamination, such as with colon injury, identify patients at high risk for infection after penetrating abdominal trauma. These factors are indicators of diminished physiologic reserve, impairments that result from the systemic effects of injury, detrimental effects of hemorrhagic shock and transfusion, and the contribution of heavy bacterial contamination to the risk of infection. Because these risk factors cannot be completely defined before operation, empiric treatment with a broad-spectrum antimicrobial agent effective against gram-negative facultative organisms and anaerobes is indicated (Table 108.2). Patients with a low risk of infection need only a single dose of antibiotic, but those at greater risk, such as with colon injury, should be treated for 24 hours. Treatment >24 hours has repeatedly been demonstrated to be of no added value.

Fewer than 2% of patients operated for blunt abdominal injury are found to have contamination from injury to the gastrointestinal tract. In this circumstance, cefazolin alone is adequate empiric treatment. Metronidazole should be added when bowel injury is suspected or confirmed. Antimicrobials can be discontinued immediately if no hollow viscus injury is found.

Damage control laparotomy has gained utility in the management of patients with abdominal injury accompanied by hypothermia, metabolic acidosis, and excessive blood loss. Following correction of all deficits in the intensive care unit, these patients are usually reoperated within 24 to 48 hours. There is no evidence to support continuation of antibiotics in this situation.

Bullets or pellets that penetrate the gastrointestinal tract and lodge in soft tissues can result in soft tissue infections through a combination of direct tissue injury and bacterial contamination. In this situation, the contaminating foreign material should be removed, debridement done, and definitive closure delayed.

Intra-abdominal infection following penetrating trauma is a serious healthcare-acquired infection and often involves antimicrobial-resistant organisms. Recommended intravenous treatment regimens include either a carbapenem or piperacillin-tazobactam alone or cefepime in combination with metronidazole. Ciprofloxacin plus metronidazole or moxifloxacin alone are useful alternatives for patients who are allergic to β-lactams. Vancomycin or linezolid should be added when MRSA is suspected. Cultures must be done to identify pathogens and delineate their antimicrobial sensitivity profile, and therapy is adjusted based on culture results.

Approximately 3% to 5% of patients who incur a hemothorax will develop empyema. The main risk factors for this complication are retained hemothorax and prolonged tube thoracostomy use. While there is inconclusive evidence for the use of prophylactic antimicrobials for hemothorax, there is strong evidence that evacuation of retained hemothorax within 72 hours reduces the incidence of posttraumatic empyema.

Suggested reading

Goldberg SR, Anand RJ, Como JJ, et al. Prophylactic antibiotic use in penetrating abdominal trauma: An Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg*. 2012;73: S321–S325.

Moore FO, Duane TM, Hu, CKC, et al. Presumptive antibiotic use in tube thoracostomy for traumatic hemopneumothorax: An Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg*.2012; 73: S341–S344.

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Infected implants

Gordon Dickinson

This chapter addresses infections associated with artificial devices of a specialized nature. The rate of infection is generally low, but, collectively, there are millions of these devices implanted yearly, so the infections are not rare. Optimal treatment requires participation of surgical specialists experienced in the management of these difficult infections, especially for pseudophakic endophthalmitis, in which the mainstay of therapy is intraocular injections.

Intraocular lens-associated infections (pseudophakic endophthalmitis)

Pseudophakic endophthalmitis is thought to occur as a consequence of contamination with flora of conjunctival sac or lid margin at the time of surgery. There have been reports of infections arising from contamination of lenses and neutralizing and storage solutions.

The differential diagnosis of endophthalmitis following cataract extraction includes sterile inflammation as well as bacterial and fungal infection. The most common presenting signs and symptoms include pain in the involved eye, decreased visual acuity, red eye, lid edema, hypopyon, and absent or poor red reflex. A single bacterial strain is usually isolated; the most common pathogen is a coagulase-negative staphylococcus (approximately 50% in one large series) followed by *Staphylococcus aureus*. Virtually any microorganism can be implicated. Delayed-onset pseudophakic endophthalmitis has been reported after uncomplicated initial cataract surgery. This entity presents ≥1 months after surgery and is manifest by waxing and waning ocular inflammation. The leading cause of delayed-onset pseudophakic endophthalmitis is *Cutibacterium acnes* (formerly *Propionibacterium acnes)*. Diagnostic evaluation requires aqueous and vitreous samples for Gram stain and culture. Vitrectomy may have therapeutic as well as diagnostic value.

Patients should be seen by an ophthalmologist immediately. Antimicrobials administered intraocularly and topically are the mainstay of treatment for this localized infection. Because of unpredictable antibiotic penetration, systemic antibiotic are of secondary importance and generally unnecessary. (See also Chapter 15, “Endophthalmitis”).

Cochlear implants

Cochlear device implantation is available to adults and children as young as 1 year of age to correct severe hearing loss. The device consists of a subcutaneous receiver, a lead wire that passes through the middle ear, and fibers that contact the cochlear nerve. An external component with microphone and transmitter is positioned adjacent to the receiver. Infections, reported to occur in 1.5% to 4% of cases, may be classified as surgical wound infection, otitis media, or meningitis. Surgical wound infections generally arise in

the immediate postoperative period and are manifest by tenderness, erythema, and swelling. Meningitis may occur in the postoperative period, but also may be encountered in the months following implantation. Otitis media in an ear with a cochlear device may also occur either in the postoperative period or long afterward. Symptoms suggestive of a surgical wound infection or otitis media deserve immediate attention, with collection of a specimen for culture if possible and prompt initiation of antibiotics to minimize the infection and preserve the device. Many infections can be managed medically without removal of the device, although wound dehiscence over the receiver or progression of symptoms generally mandate device removal. Meningitis, encountered more frequently in children, may be associated with or without otitis media. The pathogens are typical of otitis-associated meningitis seen in children without cochlear implants. Because *Streptococcus pneumoniae* is a leading cause, empiric antibiotic therapy should include antimicrobials appropriate for this pathogen. Once an infection obviously involves the cochlear implant, it is difficult to salvage the device, a very serious matter because reimplantation may not be feasible. Prior to implantation of a cochlear device, both 13 valent conjugated polysaccharide and 23 valent polysaccharide pneumococcal vaccines should be administered according to current guidelines.

Breast implant–associated infections

Breast prosthesis implantation, for augmentation or reconstruction post-mastectomy, is a common procedure. In 2018, in the United States, an estimated 313,735 augmentation mammoplasty procedures were performed. Prostheses approved by the US Food and Drug Administration (FDA) consist of a silicone rubber shell filled with either saline or silicone polymer gel (in 2018, an estimated 88% were of the latter type). They are implanted in a subglandular or submuscular pocket through inframammary, periareolar, transaxillary, transareolar, or transumbilical approaches. Infection rates following augmentation mammoplasty range from 1.1% to 2.5% and are much higher following reconstruction. Vascular compromise of the soft tissue in mastectomy and longer operative times are thought to contribute to the overall higher incidence of infections in breast reconstruction. Intraoperative breakdown of sterile technique, contaminated supplies, and hematogenous seeding are all possible sources of implant-associated infection. Endogenous flora of human breast tissue is similar to skin flora and accounts for most infections. The most common pathogens are *Staphylococcus* spp. including *S. aureus* and *S. epidermidis,* followed by a broad spectrum of gram-positive and -negative organisms including *Serratia marcescens*, *Pseudomonas aeruginosa*, *Escherichia coli*, Group B streptococcus, *Enterobacter*, and *M. morganii*. Fungal infection is rare. A combination of patient comorbidities and surgical techniques are the major risk determinants. The signs and symptoms are variable, but common findings are malaise, fever, tenderness, induration, breast erythema, asymmetry, and ultrasonographic evidence of periprosthetic fluid accumulation. Severe sepsis can develop, and there are case reports of toxic shock syndrome occurring in the early postoperative period.

Clusters as well as sporadic infections caused by *Mycobacterium abscessus* and *M. fortuitum* have been reported. The source of the pathogen is usually not identified, but inadequate equipment sterilization is suspected. Local signs and symptoms are similar to other bacterial infections, with a more subtle or delayed onset and a lack of improvement on standard antibiotic therapy. Gram stain of the fluid usually reveals no organisms but many polymorphonuclear leukocytes. Stain for acid-fast bacilli is sometimes positive. A definitive diagnosis is established by culture of the organism.

Although oral fluoroquinolones have been suggested as treatment for early, subtle symptoms, breast implant–associated infections are treated with systemic antibiotics. As methicillin-resistant *S. aureus* and methicillin-resistant coagulase-negative staphylococci have become increasingly common, empiric regimens should include vancomycin along with coverage for gram-negative organisms such as imipenem. Subsequent adjustment is made according to culture results. Duration of the therapy will depend on the causative organism, severity of infection, and clinical response; it usually ranges from 10 to 14 days. Agents with potential activity for most atypical mycobacteria include amikacin, cefoxitin, fluoroquinolones, clarithromycin, azithromycin, doxycycline, and imipenem, but susceptibility studies should be obtained, and a combination of two or more effective agents is recommended to prevent development of resistance. Infections caused by mycobacteria require months of therapy. Although early aggressive antibiotic treatment of infections can sometimes preserve the implant, continued, severe, or systemic symptoms require implant removal with capsule debridement and postsurgical drain placement. Rarely will the contralateral implant have to be removed. Surgical replacement is possible once all symptoms resolve; most surgeons prefer to wait for 6 months to allow tissue recovery.

Penile implant–associated infection

Infection is a major complication for implantation of penile prostheses, occurring in an estimated 3% of cases. Most penile prosthesis–associated infections likely originate at the time of the implantation. Common sources of infection include skin, colorectal and perianal flora, urine, and operating room environment. Infection can present within days after surgery to several weeks or months post implantation. *S. epidermidis* is isolated in >50% of cases; other bacteria include *S. aureus* and gram-negative enteric bacteria such as *E. coli*, *P. aeruginosa, Klebsiella* spp. and *Proteus* spp. Gonococcal and fungal infections have been reported. Signs and symptoms of infections include new-onset pain, swelling, tenderness, erythema, induration, fluctuance, erosion, and extrusion of prosthesis. Infections caused by *S. epidermidis* are often subtle and may present with dysfunction of the prosthesis or pain upon manipulation of the device.

Empiric antibiotic therapy treatment should be directed at both gram-positive bacteria and gram-negative coliform bacteria pending isolation of the causative pathogen. There is universal consensus that if a penile implant–associated infection occurs, the implant and all associated foreign material should be removed. There are, however, diverging views about surgical management. The preferred approach is a two-stage operation with the infection-associated device removed, the wound allowed to heal, and then replacement 4 to 6 months later. Although this approach is usually successful, the penis may be shortened by scarring. For selected patients, surgeons may elect to remove the infection-associated device, debride the wound, and implant a new device in a single-stage operation. For uncomplicated infections with the device out, a 10- to 14-day course of systemic antibiotics is given, whereas for complicated infections or when the device is immediately replaced, antibiotic therapy should be continued for at least a week or more after all signs of infection have resolved.

Suggested reading

Darouiche RO. Treatment of infections associated with surgical implants. *N Engl J Med*. 2004;350:1422–1429.

Latani T. Breast implant infections: an update. *Infect Dis Clin North Am*. 2018;32:877–884.

Lopategui DM, Balise RR, Bouzoubas LA, et al. The impact of immediate salvage surgery on corporeal length preservation in patients presenting with penile implant infections. *J Urol*. 2018;200:171–177.

Mulcahy J. Current approach to the treatment of penile implant infections. *Ther Adv Urol*. 2010;2:69–75.

Rubin LG, Papsin B, et al. Cochlear implants in children: Surgical site infections and prevention and treatment of acute otitis media and meningitis. *Pediatrics*. 2010;126:381–391.

Wiechman K, Levine S, Wilson S, et al. Antibiotic selection for the treatment of infectious complications of implant-based breast reconstruction. *Ann Plast Surg*. 2013;71:140–143.

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Infection in the burn-injured patient

Roger W. Yurt and Rafael Gerardo Magaña

The diagnosis of infection in the patient with major burn injury is especially problematic because the signs of infection are the same as those of the response to injury.

The tissue injury that occurs with a major burn and the associated inflammatory response to it cause one of the greatest perturbations of homeostasis that occurs in any disease state. Thus the greatest challenge in developing a differential diagnosis in the burn-injured patient is to distinguish between the injury state and infection. That the manifestation of infection may be blunted by diminished immune response further complicates evaluation of the patient while also contributing to an increased susceptibility to infection.

The challenge posed in the clinical and laboratory evaluation of the burn-injured patient is summarized in the outline of injury-related changes in Table 110.1.

Injury pathophysiology and susceptibility to infection

The initial approach to the burn-injured patient is oriented toward limiting the progression of the injury by stabilization of the patient and maintenance of blood flow to the wound. The zone of coagulative necrosis consists of tissue that has been irreversibly damaged, whereas the surrounding zone of stasis contains areas of potentially reversible injury. Adjacent areas, known as the hyperemic zone, may also evolve to become necrotic if the blood flow is not maintained. For this reason, the primary goal of early burn therapy is to ensure adequate delivery of oxygen, nutrients, and circulating cells to the wound. In addition to prevention of progression of the injury, immediate burn care focuses on maintenance of a viable tissue interface at which both specific and nonspecific defenses against infection can be mounted.

The depth of burn injury is categorized as partial or full thickness. Full-thickness injuries will heal only by contraction, ingrowth of surrounding epidermis, or grafting of tissue because all epidermis in the wound has been destroyed. These wounds are leathery and dry, contain thrombosed vessels, and are insensate. Partial thickness wounds contain residual epidermis, which can close the wound if blood flow is maintained and infection does not supervene.

Partial thickness wounds are red and moist, and pain is elicited by touch. Deep partial-thickness wounds contain only epithelial elements associated with organelles of the skin. They take longer to heal (2 to 3 weeks) than superficial partial-thickness wounds, and there is a greater functional and cosmetic deformity if they are allowed to heal primarily. These wounds are difficult to differentiate by clinical evaluation from superficial partial-thickness injuries, which usually heal within 10 days to 2 weeks.

The dynamic aspect of burn wounds is dramatically seen when partial-thickness wounds convert to full-thickness wounds during a difficult resuscitation of a patient. Although this is rarely seen with current methods of resuscitation, resuscitation that is delayed or performed on patients at extremes of age occasionally will show this progression.

TABLE 110.1 CLINICAL AND LABORATORY SIGNS RELATED TO INJURY THAT COMPLICATE THE EVALUATION OF THE PATIENT WITH BURN INJURY

Sign	Abnormality
General condition	Lethargy-electrolyte imbalance
	Analgesic effects
	Hyperventilation
	Pain, topical agents
	Tachycardia
	Pain, volume depletion, hypermetabolism
Fluid balance	Hypovolemia
	Initial injury
	Delayed-evaporative loss
Fluid composition	Hypernatremia
	Free water loss
	Inadequate fluid replacement
	Hyponatremia
	Excessive free water
	Effects of topical silver nitrate
	Hyperglycemia
	Stress
Temperature	Hypothermia
	Heat loss to the environment
	Large fluid requirement
	Hyperthermia
	Hypermetabolism
	Endotoxin from the wound
Neutrophil response	Neutrophilia
	Acute
	5–7 days after injury
	Neutropenia
	2–3 days after injury

Any agent that causes cellular death can lead to a deeper wound. With this in mind, caustic topical agents and vasopressors are avoided, the wound is not allowed to desiccate, and the patient is kept warm.

Both mortality and susceptibility to infection correlate directly with the extent of the surface area injury. Distribution of surface area varies with age, so a chart is used to plot accurately the extent and depth of surface area burned. The rule of nines may be used to estimate the extent of injury as follows: torso, back and front, each 18%; each leg 18%; each arm 9%; and head 9%. Calculation of the extent of injury is helpful in estimating fluid requirements and prognosis. Patients with greater than 25% to 30% total body surface area burn exhibit the pathophysiologic features already described.

Prevention of infection

Current data do not support the general use of prophylactic systemic antibiotics in the inpatient population. Frequent evaluation of the wound and surrounding tissue allows early and appropriate therapy of cellulitis while sparing a majority of patients exposure to unnecessary antibiotics. However, some practitioners give systemic antibiotics (cephalexin) to outpatients with burns because it is not possible to observe closely and ensure appropriate care of the wound. The use of systemic antibiotics in these patients is individualized such that those who are likely to follow up with their care and recognize changes in their wounds are not given antibiotics. The one time that prophylactic systemic antibiotics are used in inpatients is at the time of surgical manipulation because this may cause bacteremia. Antibiotics are administered immediately before and during burn wound excision. The choice of antibiotics is dictated by knowledge of the current flora in the burn center or, more specifically, by the burn wound flora of the individual patient.

The mainstay of prevention of burn wound infection is aggressive removal of the necrotic tissue and closure of the wound with autograft. In the interim, topical antimicrobial prophylaxis will decrease the incidence of conversion of partial-thickness to full-thickness wound by local infection, and these agents may prolong the sterility of the full-thickness burn wound. Silver sulfadiazine is the most commonly used topical agent and is a soothing cream with good activity against gram-negative organisms. Because it does not penetrate the wound, it is used only as a prophylactic antimicrobial. Bacterial resistance to silver sulfadiazine has been reported, and it has been reported to cause neutropenia. Silver nitrate in a 0.5% solution is an effective topical agent when used before wound colonization. This agent does not penetrate the eschar, and therefore its broad-spectrum gram-negative effectiveness is diminished once bacterial proliferation has occurred in the eschar. Additional disadvantages of this agent include the need for continuous occlusive dressings, which limits the evaluation of wounds and restricts range of motion. The black discoloration of the wound, as well as the environment, contributes to the decrease in the use of silver nitrate. Mafenide acetate (Sulfamylon) cream has a broad spectrum of activity against staphylococci. A significant advantage of this agent is that it penetrates burn eschar and therefore is effective in the colonized wound. The disadvantages of Sulfamylon are a transient burning sensation, an accentuation of postinjury hyperventilation, and inhibition of carbonic anhydrase activity.

Recent experience with a new silver-impregnated dressing that does not have to be changed daily suggests that this agent is a good alternative for prophylaxis against infection in partial-thickness wounds.

The goal of burn therapy is to prevent burn wound infection by permanent closure of the wound as rapidly as possible. Early removal of necrotic tissue and wound closure has the advantages of removal of eschar before colonization, which typically occurs 5 to 7 days after injury, and of reduction of the overall extent of injury. A drawback of early excisional therapy is the possibility that burned tissue that may heal if left alone over a 2- to 3-week period may be unnecessarily excised.

Advances in resuscitation have led to the ability to salvage an increasing number of patients from the shock phase immediately

after injury and have resulted in a greater number of patients surviving to the time (3 to 4 days after the injury) when the effects of inhalation injury become clinically prominent. In patients without inhalation injury but with large burns, postinjury hyperventilation and subsequent decreases in tidal volume may lead to atelectasis and subsequent pneumonia. Diminished mucociliary function and destruction of the airways by inhalation of products of combustion lead to airway obstruction and infection.

Frequent diagnostic and therapeutic bronchoscopies are necessary in this group of patients. Attempts at specific prophylaxis of the sequelae of inhalation injury, such as nebulization of antibiotics and treatment with steroids, have failed to show any benefit.

Nosocomial infections are of even greater concern in the burn intensive care setting than other units because of the large open colonized wounds. Cross-contamination is avoided by use of gowns, gloves, and masks by nurses, medical staff, and visitors. The patient is not touched except with a gloved hand, and each patient is restricted to his or her own monitoring and diagnostic equipment. If adequate nursing care can be provided, it is preferable to isolate patients who have large open wounds in individual rooms. Cohort patient care has been shown to be effective in reducing endemic infections.

Diagnosis and treatment of infections

Wound infection

Because the full-thickness burn wound is at high risk for infection, routine clinical and laboratory surveillance of the wound is an absolute necessity. Daily observation of the wound for discoloration, softening or maceration of the eschar, or the development of cellulitis provides early detection of wound-associated infection. Although surface cultures of the burn wound provide insight into the organisms that are colonizing the wound, evaluation of a biopsy of the burn wound is the only way to obtain accurate assessment of the status of the wound. Systematic evaluation of burn wounds with quantitative culture of biopsies of all areas of wound change documents the clinical diagnosis of wound infection and provides identification and antimicrobial sensitivity of the involved organism. Routine biopsy of full-thickness burn wounds on an every-other-day schedule provides evidence of advancing wound infection and serves as a basis for initiating therapy. Arapid fixation technique allows histologic diagnosis of invasive infection within 3 hours, whereas quantitative counts and identification of the organism are available in 24 hours.

This combined use of histologic and culture techniques provides early diagnosis as well as the identity of the organism and its sensitivity to antimicrobials. When the findings are consistent with invasive infection (greater than or equal to 10^5 organisms/g of tissue), aggressive surgical therapy is instituted to excise the involved wound. In preparation for surgery or in patients who require stabilization before general anesthesia is given, a penetrating topical agent is used (Sulfamylon). The choice of antibiotic is based on previous biopsy sensitivity data or data accumulated on sensitivities of the current flora in the patient population.

A growing number of patients present with primary nonsuppurative gram-positive infections. These infections are often caused by methicillin-resistant *Staphylococcus aureus* (personal observation), and whether diminished neutrophil response or a change in the nature or the virulence of such organisms may explain this phenomenon is unknown.

Pulmonary infection

From a practical standpoint, inhalation injury is diagnosed by history, physical examination, and bronchoscopy. A history of exposure to fire in a closed space along with findings of carbonaceous sputum, singed nasal vibrissae, and facial burns are associated with a high incidence of inhalation injury. In the burn patient, pulmonary complications after injury are not uncommon and may increase the mortality rate of ventilator-associated pneumonia (VAP), which may increase from 40% to 77% in the presence of significant inhalation injury. Bronchoscopy reveals upper airway edema and erythema, whereas bronchorrhea, carbon in the bronchi, and mucosal slough suggest lower airway and parenchymal injury.

Carboxyhemoglobin levels may be elevated, but with a half-life of 45 minutes on 100% oxygen the level may be normal. Chest x-ray studies are of little value in making the diagnosis of inhalation injury because they are often normal for the first 72 hours after injury. Xenon ventilation–perfusion lung scan reveals trapping of xenon in the ventilation phase and is supportive of a diagnosis of small airway obstruction secondary to injury of the distal airways and parenchyma. Although hematogenous pneumonia is less common than in the past, it remains a significant problem in the patient with burns. When it occurs, the source (most commonly the wound or suppurative vein) must be defined and eradicated. Prophylactic antibiotics are not used for either bronchopneumonia or hematogenous pneumonia; specific therapy is based on knowledge of previous endobronchial culture, and sensitivity is substantiated by repeat cultures at the time of diagnosis. Diagnosing pneumonia in this population may be difficult. Different clinical scores have been developed to this end; however, they are of little value because they have low specificity and sensitivity when compared with specimens obtained via bronchoalveolar lavage. A culture with 10^4 organisms/mL is generally considered to be significant enough to warrant antibiotic therapy. Bronchoalveolar lavage with negative results also reduces the usage of unnecessary antibiotics.

Suppurative thrombophlebitis

Suppurative thrombophlebitis is mentioned in particular in relation to the patient with burn injury because it is the most common cause of repeatedly positive blood cultures in the presence of appropriate antibiotics in this population. These findings alone should lead to a presumptive diagnosis of a suppurative process in a previously cannulated vein. The process may be insidious, with only minimal clinical findings. Because of this complication, venous cannulation should be minimized, but when it is necessary catheters should be changed on a regular basis. In some centers this is done as often as every 3 days. Treatment consists of surgical excision of the entire involved vein to the level of normal bleeding vessel. In this setting the differential diagnosis should include endocarditis.

Chondritis/suppurative chondritis

Burn wounds that involve the ear are of particular concern, because its cartilage has no intrinsic blood supply and thus has the potential to develop chondritis and subsequent suppurative chondritis. Because the ear is covered only by skin and has no subcutaneous tissue, the cartilage is at risk for infection when there is a full-thickness burn causing local necrosis. This often leads to loss of tissue and permanent deformity and, in some cases, loss of the ear.

Damaged skin acts as a portal of entry. In addition, local edema may predispose to thrombosis of central vessels. *Pseudomonas* and *Staphylococcus* are the most common pathogens involved in this pathology.

Sulfamylon is of benefit in this condition because it can penetrate eschar to the level of cartilage and prevent bacterial invasion. Pressure-related damage to the ear must be avoided. Therefore, the ear should be dressed in topical only or topical and one layer of nonadherent gauze. To avoid pressure on the ear, a pillow for the head should not be allowed.

Once suppurative chondritis ensues, surgical intervention is mandatory and consists of drainage and debridement of all nonviable tissue. This can be accomplished by making an incision on the helical rim of the ear (bivalving), with subsequent drainage and excision of nonviable tissue. The ear is then dressed with an antibacterial solution, changed on a twice-daily schedule, and allowed to heal by secondary intention. Special attention should be given to avoid any form of compression to keep the dressings in place, because this may increase the extent of necrosis.

Suggested reading

Darling GE, Keresteci MA, Ibanes D, et al. Pulmonary complications in inhalation injuries with associated cutaneous burn. *J Trauma*. 1996;40:83–89.

Fagon JY, Chastre J, Hance AJ, et al. Evaluation of clinical judgment in the identification and treatment of nosocomial pneumonia in ventilated patients. *Chest*. 1993;103:547–553.

Greenhalgh DG, Saffle JR, Holmes JH 4th, et al American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res*. 2007;28:776–790.

Johnson WG, Seidenfeld JJ, Gomez P, et al. Bacteriologic diagnosis of nosocomial pneumonia following prolonged mechanical ventilation. *Am Rev Respir Dis*. 1988;137: 259–264.

Meduri GU. Diagnosis and differential diagnosis of ventilator-associated pneumonia. *Clin Chest Med*. 1995;16:61–93.

Peck MD, Weber J, McManus A, Sheridan R, Heimbach D. Surveillance of burn wound infections: a proposal for definitions. *J Burn Care Rehabil*. 1998;19:386–389.

Shirani KZ, Pruitt BA, Mason AD. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg*. 1987;205:82–87.

Wahl WL, Ahrns KS, Brandt MM, et al. Bronchioalveolar lavage in diagnosis of ventilator-associated pneumonia in patients with burns. *J Burn Care Rehabil*. 2005;26:57–61.

Yurt RW. Burns. In: Mandell GL, Gennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 6th edn. New York: Churchill Livingstone; 2005.

Yurt RW, Howell JD, Greenwald BM. Burns, electrical injuries, and smoke inhalation. In: Nichols DG, ed. *Rogers' Textbook of Pediatric Intensive Care*. Philadelphia, PA. Lippincott Williams & Wilkins; 2008:414–426.

Section 15

Prevention of infection

111

Nonsurgical antimicrobial prophylaxis

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Prevention

Chemoprophylaxis is the use of an antimicrobial agent to prevent infection. Chemoprophylaxis is often administered after exposure to a virulent pathogen or before a procedure associated with risk of infection. Chronic chemoprophylaxis is sometimes administered to persons with underlying conditions that predispose to recurrent or severe infection. Antibiotics can also be used as preemptive therapy (sometimes referred to as *secondary prophylaxis*) to prevent clinical disease in persons infected with a microorganism such as *Mycobacterium tuberculosis*. Immunization, another excellent means of preventing infection, is discussed in Chapter 113. For information on prophylaxis of bacterial endocarditis, see Chapter 17, "Endocarditis"; for information on prophylaxis in persons infected with the human immunodeficiency virus (HIV), see Chapter 101, "Prophylaxis of opportunistic infections in HIV disease"; for malaria prophylaxis, see Chapter 199, "Malaria"; for prophylaxis related to transplant recipients and neutropenic patients, see Chapter 88, "Infections in transplant recipients," and Chapter 84, "Infections in the neutropenic patient"; and for surgical prophylaxis, see Chapter 112, "Surgical prophylaxis."

Several concepts are important in determining whether chemoprophylaxis is appropriate for a particular situation. In general, prophylaxis is recommended when the risk of infection is high or the consequences significant. The nature of the pathogen, type of exposure, and immunocompetence of the host are important determinants of the need for prophylaxis. The antimicrobial agent should eliminate or reduce the probability of infection or, if infection occurs, reduce the associated morbidity. The ideal agent is inexpensive, orally administered in most circumstances, and has few adverse effects. The benefit conferred by prophylaxis must be weighed against the risks of antimicrobial use, including alteration of the normal microbiota and selection for antimicrobial resistance. The ongoing crisis of antibiotic-resistant bacteria underscores the importance of rational and not indiscriminate use of antimicrobial agents.

The efficacy of chemoprophylaxis is well established in situations such as perioperative antibiotic administration, exposure to invasive meningococcal disease, prevention of recurrent rheumatic fever, and prevention of tuberculosis. Chemoprophylaxis is accepted in other situations lacking supporting data. When the risk of infection is low, as with bacterial endocarditis following dental procedures, randomized clinical trials of prophylaxis are not feasible. However, the consequences of infection may be catastrophic, providing a compelling argument for chemoprophylaxis despite the low risk of infection. When prophylaxis is advocated without data confirming efficacy, there should be a scientific rationale to support the use of a particular antimicrobial agent.

Table 111.1 lists the situations in which antimicrobial prophylaxis is indicated after exposure to certain pathogens. Because the duration of exposure is usually brief, the duration of chemoprophylaxis is

TABLE 111.1 **PROPHYLAXIS FOLLOWING SELECTED EXPOSURES**

Exposure	Pathogen	Prophylaxis[a]	Comments
Meningitis and meningococcal bacteremia	*Neisseria meningitidis* (see Chapters 141, "Meningococcus and miscellaneous neisseriae" and 74, "Bacterial meningitis")	Rifampin, 600 mg (5 mg/kg for children <1 mo and 10 mg/kg for children ≥1 mo) q12h for 4 doses (not recommended for pregnant women); Ciprofloxacin, 500 mg (single dose) (non-pregnant or lactating adults only—unless no acceptable alternative therapy available—and if not resistant to ciprofloxacin); Ceftriaxone, 250 mg IM 1 dose (125 mg for children <15 yr).	Recommended for close contacts only, including household members, child-care center contacts and anyone directly exposed to oral secretions (through kissing, mouth-mouth resuscitation, or intubation/endotracheal tube management). Only healthcare workers who managed an airway or were otherwise exposed to respiratory secretions of a patient with meningococcal disease require prophylaxis. For travellers on a prolonged flight (≥8 hours), prophylaxis should be considered for passengers seated directly next to an index patient or anyone who had direct contact with respiratory secretions of an index patient during the flight. Prophylaxis is not recommended for close contacts of patients with noninvasive disease (e.g. pneumonia, conjunctivitis, or nasopharyngeal carriage). Significant increased risk of meningococcal disease associated with use of eculizumab, a terminal complement inhibitor. Consider penicillin prophylaxis for the duration of eculizumab treatment.
Meningitis	*Haemophilus influenzae*	Rifampin, 20 mg/kg for individuals ≥1 mo (max dose 600 mg) (10 mg/kg for children <1 mo) daily for 4 d.	Recommended for all index patients (unless treated with cefotaxime or ceftriaxone) and household contacts (except pregnant women) in households with 1) children <4 years who are not fully vaccinated or 2) immunocompromised members <18 years regardless of vaccination status. Index patients aged <2 years treated with any antibiotic other than cefotaxime or ceftriaxone should receive rifampin prophylaxis prior to hospital discharge. In childcare centers, prophylaxis is recommended when two or more cases of invasive Hib disease occur in <60 days and unimmunized or underimmunized children attend the center; all attendees and childcare providers, regardless of age or vaccine status, should receive prophylaxis in this scenario. There are currently no guidelines for prophylaxis for close contacts of patients with nontypable (non type b) *Haemophilus influenza*.
Perinatal group B streptococcus (GBS)	Group B streptococcus	Penicillin G, 5 million units IV initial dose then 2.5 to 3 million q4h, or ampicillin, 2 g IV initial dose then 1 g IV q4h, until delivery. If penicillin or cephalosporin allergic but no history of anaphylaxis, angioedema, respiratory distress or urticaria use cefazolin, 2 g IV initial dose then 1 g IV q8h until delivery. If penicillin or cephalosporin allergic with a history of anaphylaxis, angioedema or respiratory distress and (1) isolate susceptible to clindamycin and erythromycin, use clindamycin, 900 mg IV q8h until delivery, or (2) isolate not susceptible to clindamycin or erythromycin use vancomycin, 1 g IV q12h until delivery.	Women should be screened with vaginal and rectal swabs at 35–37 wk of gestation and intrapartum prophylaxis given if GBS isolated. Prophylaxis should also be given if (1) GBS bacteriuria during any trimester of current pregnancy (with exception of circumstance where cesarean delivery is performed prior to onset of labor and with intact amniotic membranes) (2) previous infant with invasive GBS disease or (3) with unknown GBS status and intrapartum temperature ≥38°C or ≥18 h of ruptured membranes or delivery <37 wk of gestation or intrapartum nucleic acid amplification test (NAAT) positive for GBS.

TABLE 111.1 **CONTINUED**

Exposure	Pathogen	Prophylaxis[a]	Comments
Human bite	*Streptococcus viridans*, other streptococci, oral anaerobes, *Staphylococcus epidermidis, Corynebacterium* sp., *Staphylococcus aureus*, *Eikenella corrodens*	Amoxicillin–clavulanic acid, 875/125 mg BID or 500/125 mg TID for 5 d. For penicillin allergy, consider clindamycin, 300 mg QID, plus ciprofloxacin or levofloxacin.	Cleaning, irrigation, and debridement of human bite wounds are critical interventions to prevent infection. Risk of infection depends on the depth of the wound, extent of tissue damage, and the etiologic pathogen. *Eikenella* is resistant to clindamycin, nafcillin/oxacillin, first-generation cephalosporins, metronidazole, erythromycin and TMP-SMX. Clenched-fist and other hand injuries are at increased risk for deep infection; x-rays recommended.
Cat bite	*Pasteurella multocida*, *S. aureus*, streptococci	Amoxicillin–clavulanic acid, 875/125 mg BID or 500/125 mg TID for 3–5 d. For penicillin allergy, consider doxycycline, 100 mg BID, or cefuroxime axetil, 500 mg BID. If culture positive for only *P. multocida* can narrow treatment to Penicillin G IV or Penicillin VK PO.	The decision whether to give preemptive early antimicrobial therapy following dog or cat bite should be based on host immune competence and wound severity based on the latest IDSA guidelines. Antibiotics are recommended for patients who (1) are asplenic; (2) are immunocompromised; (3) have advanced liver disease; (4) have moderate to severe injuries, especially to the hand or face; (5) have preexisting or resultant edema of the injury site; (6) have injuries that may have penetrated the periosteum or joint capsule.
Dog bite	*S. viridans*, oral anaerobes, *S. aureus*, *P. multocida, P. canis, Capnocytophaga* sp.	Amoxicillin–clavulanic acid, 875/125 mg BID or 500/125 mg TID for 3–5 d For penicillin allergy, consider clindamycin, 300 mg QID, plus either ciprofloxacin, 500 mg BID, or TMP–SMX, 1 double-strength tablet BID	
Sexual assault	*Trichomonas vaginalis*, *Chlamydia trachomatis*, *Treponema pallidum*, *Neisseria gonorrhoeae* HIV (recommendations below in table)	Ceftriaxone, 250 mg IM single dose, plus azithromycin, 1 g single dose, plus metronidazole, 2 g single dose or tinidazole 2 g single dose. Assess risk for HIV in assailant and evaluate survivor for the need for treatment with nonoccupational HIV postexposure prophylaxis (nPEP)	See nPEP guidelines below for detailed discussion of evaluation and treatment in the setting of possible HIV exposure.
Nonoccupational HIV exposure (sexual, injection-drug use, or other exposure)	HIV	Preferred regimen for healthy adults and adolescents: Emtricitabine/tenofovir disoproxil fumarate (TDF/FTC) 300/200 mg plus dolutegravir 50 mg or raltegravir 400 mg BID. If within the first trimester of pregnancy or may become pregnant within the next 28 days, raltegravir preferred. Alternative regimen for adults and adolescents: TDF/FTC plus darunavir 800 mg and ritonavir 100 mg once daily. TDF/FTC contraindicated if CrCl <60 mL/min; expert consult recommended to advise on alternative regimen. First dose should be administered on site as soon as possible after negative rapid HIV test result or immediately after non-rapid HIV test sent. A 28-day prescription should be provided.	Rapid HIV Ag/Ab testing preferable; ideally wait for result prior to offering nPEP. If rapid HIV test is positive, nPEP should NOT be given. If only non-rapid testing available, start nPEP immediately and arrange follow up in 1-2 days for HIV test results. The National Clinician's Post Exposure Prophylaxis Hotline (PEP line), 1-888-448-4911, is a resource available to help clinicians with nPEP decisions. Additional STI testing should be performed and preemptively treated as indicated. For prophylaxis following occupational HIV exposure, see Chapter 104, Percutaneous injury: risks and prevention

(*continued*)

TABLE 111.1 CONTINUED

Exposure	Pathogen	Prophylaxis[a]	Comments
Sexual contacts	*T. pallidum*	Benzathine penicillin G, 2.4 million units IM	Treat if exposed within the previous 90 days. If >90 days after exposure, treat if serologic test results not available and follow-up is uncertain. Doxycycline is an alternative in nonpregnant patients allergic to penicillin.
	N. gonorrhoeae	Ceftriaxone, 250 mg IM single dose plus Azithromycin 1 g single dose.	Dual therapy now routinely recommended for gonococcal infectious due to worsening antimicrobial resistance.
	C. trachomatis	Azithromycin, 1 g single dose, or doxycycline, 100 mg BID for 7 d	Use azithromycin in pregnant women
	T. vaginalis	Metronidazole, 2 g single dose or tinidazole, 2 g single dose. Alternative regimen: metronidazole 500 mg BID for 7 days.	Treatment of sex partners is crucial to achieve cure and prevent reinfection.
Influenza	Influenza A and B	Oseltamivir (≥3 months)or inhaled zanamivir (≥5 years) once daily used after exposure to influenza or as pre-exposure prophylaxis for the duration of the influenza outbreak in the community in high-risk population. Start as soon as possible after exposure, ideally within 48 hours.	Postexposure chemoprophylaxis can be considered for the following groups of asymptomatic adults and children ≥3 months: (1) Those for whom vaccination is contraindicated, unavailable, or expected to have low effectiveness and who are at very high risk of developing complications from influenza and (2) Those who are unvaccinated and are household contacts of a person at very high risk of complications from influenza. Patient education and close follow up for early empiric antiviral initiation can also be considered. Chemoprophylaxis should not be a substitute for vaccination. Historically, amantadine and rimantadine have been used for prophylaxis for influenza A. However, resistance is now widespread. NAI resistance remains uncommon, but has occurred, most notably during the 2008-2009 season when an oseltamivir-resistant H1N1 virus strain was predominant.
Whooping cough	*Bordetella pertussis*	Azithromycin, 500 mg single dose on day 1 then 250 mg/d on days 2–5, or erythromycin, 500 mg QID for 14 d. Clarithromycin, 500 mg BID for 7 d or TMP–SMX, 160/800 mg BID for 7 d, are alternative regimen options.	Postexposure prophylaxis (PEP) recommended for: (1) all household contacts of a pertussis case, regardless of vaccine status and (2) people at high risk of developing severe illness or those who have close contact with people at high risk of developing severe illness. PEP ideally should be provided within 21 days of exposure. Use pediatric dosing for children.
Lyme disease	*Borrelia burgdorferi*	Doxycycline 200 mg single dose	Antimicrobial prophylaxis following tick bite is not recommended in most situations. However doxycycline is recommended (1) within 72 h of the removal of an adult or nymph *Ixodes scapularis* tick and (2) if the tick has been attached >36 h and (3) if the exposure occurred in a region where prevalence of *B. burgdorferi* in ticks is greater than 20%.

TABLE 111.1 CONTINUED

Exposure	Pathogen	Prophylaxis[a]	Comments
Anthrax	*Bacillus anthracis*	Ciprofloxacin, 500 mg BID, or doxycycline, 100 mg bid for 60 d; alternatives include levofloxacin, 500 mg daily, amoxicillin, 1,000 mg TID or Pen VK 500 mg Q6h (for penicillin susceptible strains), and clindamycin 30 mg/kg/day divided q8h (max 900 mg per dose). Two monoclonal antibodies, raxibacumab and obiltoxaximab, are options when alternative therapies are not available or not appropriate.	Inhalational anthrax is considered one of the major threats associated with bioterrorism. Post-event emergency use of anthrax vaccine was approved by the FDA in 2015 for exposed adults 18 through 65 years of age. Vaccine does not replace need for PEP. Use pediatric dosing for children.
Plague	*Yersinia pestis*	Doxycycline, 100 mg BID, or ciprofloxacin, 500 mg BID, for 7 d.	Incubation period for pneumonic plague is short (2–3 d); for established infection, streptomycin IM or gentamicin IM/IV remain the agents of choice. Use pediatric dosing for children.
Tularemia	*Francisella tularensis*	Doxycycline, 100 mg BID for 14 d, or ciprofloxacin, 500 mg BID	Prophylaxis recommended only in cases of laboratory inhalation or percutaneous exposure.

Abbreviation: TMP-SMX = trimethoprim–sulfamethoxazole.
[a] All regimens are administered orally unless otherwise specified.

short, which helps limit adverse reactions, minimizes the potential for resistance, and limits cost. Table 111.1 includes chemoprophylaxis for human, dog, and cat bites. It is important to remember that, aside from antibiotics, immunization (rabies and tetanus vaccines), irrigation, and debridement are crucial in the management of both animal and human bites. Table 111.1 also includes microorganisms that have gained notoriety as possible agents of biologic warfare or terrorism and infections that are sexually transmitted. Significant evidence supports the use of tenofovir-emtricitabine for the prevention of HIV infection in high-risk populations prior to exposure (pre-exposure prophylaxis or PrEP). This approach requires strict adherence, regular HIV and sexually transmitted disease testing, frequent monitoring, and carries the potential risk of developing HIV drug resistance. Pre-exposure prophylaxis should be used in combination with other methods to prevent HIV. See Chapter 101 for more information regarding PrEP guidelines.

Persons with an underlying predisposition to infection may benefit from prophylactic antimicrobial agents (Table 111.2). In contrast to short-term prophylaxis administered after exposures, chronic prophylaxis is often required. Because of the duration of antibiotic administration, the complications of chemoprophylaxis, including alteration of the microbiota and antibiotic resistance, are major considerations. Given these concerns, the decision to prescribe chronic chemoprophylaxis should be made on a case-by-case basis and should always involve a risk versus benefit conversation with the patient and/or family.

Chemoprophylaxis for *M. tuberculosis* is used to prevent acquisition of infection in high-risk groups following exposure to a patient with contagious tuberculosis disease. More commonly, preemptive therapy is given to those latently infected as demonstrated by a positive tuberculin or purified protein derivative (PPD) skin test or a positive interferon-γ release assay (IGRA) to prevent the development of tuberculosis disease. The regimens for chemoprophylaxis or treatment of latent *M. tuberculosis* infection are listed in Table 111.3. Prior to initiating prophylaxis for latent infection, the clinician should rule out active disease with a chest radiograph. In the setting of suspected infection with multidrug-resistant *M. tuberculosis*, the decision to provide chemoprophylaxis and the choice of regimen should be made by experienced healthcare professionals.

Chemoprophylaxis has been advocated for other situations, but, at this time, there is debate about the optimal role (Table 111.4). Although data are limited, it is likely that cost–benefit analyses may not favor routine prophylaxis in some of these settings or that the benefits of prophylaxis in the short term would be outweighed by long-term consequences, such as the development of antibiotic-resistant organisms.

TABLE 111.2 CHRONIC PROPHYLAXIS IN SPECIFIC CLINICAL SETTINGS

Underlying condition or recurrent infections	Pathogens	Prophylaxis[a]	Comments
Acute rheumatic fever (prevention of recurrences)	*Streptococcus pyogenes*	Penicillin G, 1.2 million units IM every 34 wk or penicillin V, 250 mg BID; alternatives include erythromycin, 250 mg BID or sulfadiazine, 1 g daily (0.5 g if weight ≤27 kg)	Risk diminishes with increasing age and time since initial attack; optimal duration unknown but continue prophylaxis at least until the early 20s or for 5 yr after most recent attack; some authorities advocate lifelong prophylaxis, especially after rheumatic carditis; 3-wk dosing of penicillin is recommended in particularly high risk populations, including those who have recurrent acute rheumatic fever while on an every-4-week regimen.
Asplenia, including sickle cell disease	Predominantly *S. pneumoniae;* also *H. influenzae Neisseria meningitidis*	Penicillin V, 250 mg BID (125 mg BID for children ≤5 yr), or amoxicillin 500 mg BID; prophylaxis generally continued at least 1 year after splenectomy; for children with sickle cell disease, prophylaxis continued at least until aged 5 yr. Alternative option instead of daily prophylaxis is to self-administer amoxicillin-clavulanate at onset of any febrile illness while seeking medical attention	Efficacy of chemoprophylaxis clearly established for children with sickle cell disease; chemoprophylaxis generally not recommended for adults (lower risk). Worsening antibiotic resistance rates diminish attractiveness of antibiotic prophylaxis and increases the importance of vaccination.
Lymphedema with recurrent cellulitis	*S. pyogenes*	Penicillin VK, 250 mg BID. In penicillin-allergic patients, use macrolides	Given only to patients with frequent episodes of erysipelas; efficacy is limited in patients with significant underlying disease and high BMI. Important to differentiate stasis dermatitis (non-infectious condition) from cellulitis.
Spontaneous bacterial peritonitis (SBP)	*Escherichia coli*, other *Enterobacteriaceae, Streptococcus* and *staphylococcus* sp. *enterococcus* sp.	Ciprofloxacin 500 mg daily, or TMP–SMX, 1 double-strength tablet daily. Patients with Child-Pugh class B or C cirrhosis and active gastrointestinal bleeding should receive Ceftriaxone 1 gm IV daily with eventual step down to oral options as above.	Used in persons with ascites protein concentration of ≤1 g/dL, with active variceal bleeding, and in persons with previous SBP.

Abbreviation: TMP-SMX = trimethoprim–sulfamethoxazole.
[a] All regimens are administered orally unless otherwise specified.

TABLE 111.3 REGIMENS FOR CHEMOPROPHYLAXIS[a] OR PREEMPTIVE THERAPY FOR *M. TUBERCULOSIS*

Drug(s)	Regimen	Duration	Comments
Isoniazid (INH)	300 mg (10–15 mg/kg children) daily or 900 mg (20–30 mg/kg children) twice weekly	6–9 months	9-month regimen preferred as more effective. 6-month regimen more cost-effective and has better compliance, but should NOT be used for HIV-infected patients, patients with evidence of healed TB on CXR and children Intermittent regimens provided by directly observed therapy (DOT).
Isoniazid and rifapentine (RPT)	900 mg INH and 900 mg RPT weekly	3 months	Alternative to INH with advantage of shorter duration, fewer doses, and higher rates of treatment completion. Can be self-administered or given by DOT. Use weight-based dosing for those under 50 kg, children 2–11 years. Not recommended for children under 2 years, pregnant women, or HIV-infected persons on antiretroviral medications with clinically significant or unknown drug interactions with RPT.
Rifampin (RIF)	600 mg daily	4 months	Use for those intolerant of INH or if exposed to INH resistant tuberculosis. Weight-based dosing in children. Not recommended for HIV-infected persons on antiretroviral medications with clinically significant or unknown drug interactions with RIF.

Abbreviations: TB = tuberculosis; CXR = chest x-ray; TNF-α = tumor necrosis factor-α.
[a] Chemoprophylaxis recommended for certain high-risk patients including children <5 years during the "window period" after exposure to active tuberculosis and before follow-up testing at 8–10 weeks, regardless of negative initial test result. Depending on intensity of exposure and rate of skin test conversion among others exposed, full course treatment should be considered in exposed persons with HIV infection, those on immunosuppressive therapy (including following transplantation) or in persons taking TNF-α antagonists.

TABLE 111.4 **CONTROVERSIAL AREAS REGARDING THE USE OF PROPHYLACTIC ANTIBIOTICS**[A]

Condition	Comments
Prosthetic device prophylaxis	Routine chemoprophylaxis before dental work, or other procedures that cause transient bacteremia in patients with prosthetic joints or vascular prostheses, is usually not warranted; prosthetic joint infections caused by oral microbiota, including α-streptococci, are uncommon, with a rate approaching that of endocarditis in patients with mitral valve prolapse without regurgitation, for which chemoprophylaxis is not recommended; coronary stents do not appear to be prone to infection
Recurrent urinary tract infection (UTI)	For selected patients with more than three infections yearly; consider prophylaxis for 6–12 mo. Prophylactic antibiotic choice should be tailored individually based on prior urinary bacterial isolates identity and susceptibility. Anatomic and functional causes of recurrent UTI should be investigated and treated as indicated.
Chronic bronchitis, bronchiectasis	May be useful in selected patients with frequent exacerbations (>4/yr); some authorities prefer antibiotics at first sign of infection. Azithromycin daily for 1 yr has been shown to decrease frequency of exacerbations and improve quality of life in patients with chronic obstructive pulmonary disease; hearing loss noted in some subjects. Consider inhaled antipseudomonal antibiotic in patients with chronic bronchiectasis.
IV catheter-associated infections	Antibiotic or ethanol "lock" therapy has been shown to prevent central venous catheter-associated bloodstream infections in some high-risk patients including those with recurrent catheter infections but data remains limited.
Pancreatitis	In severe pancreatitis with necrosis, antibacterial (as well as antifungal) prophylaxis has been suggested. However, even if antimicrobials appear to decrease mortality, in pancreatic necrosis they do not prevent infections

Abbreviations: UTI = urinary tract infection; IV = intravenous.
[a] See also Chapter 68, "Infection of native and prosthetic joints."

Suggested reading

Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365(8):689–698.

Centers for Disease Control and Prevention (CDC). Update of recommendations for use of once-weekly isoniazid-rifapentine regimen to treat latent mycobacterium tuberculosis infection. *MMWR Morb Mortal Wkly Rep*. 2018;67(25):723–726.

Centers for Disease Control and Prevention (CDC). High risk for invasive meningococcal disease among patients receiving eculizumab (Soliris) despite receipt of meningococcal vaccine. *MMWR Morb Mortal Wkly Rep*. 2017;66(27):734–737.

Centers for Disease Control and Prevention (CDC). Announcement. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV—United States, 2016. *MMWR Morb Mortal Wkly Rep* 2016;65:458.

Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(RR-03):1–137.

Centers for Disease Control and Prevention (CDC). Prevention and control of haemophilus influenzae type b disease: Recommendations of the advisory committee on immunization practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2014;63(RR-01):1–14.

Centers for Disease Control and Prevention (CDC). Prevention and control of meningococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2013;62(RR-2):1–28.

Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease: Revised guidelines from CDC, 2010. *MMWR Morb Mortal Wkly Rep*. 2010;55(RR-10):1–36.

Centers for Disease Control and Prevention (CDC). Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. *MMWR*. 2005;54(RR14):1–16.

Hendricks KA, Wright ME, Shadomy SV, et al. Centers for disease control and prevention expert panel meetings on prevention and treatment of anthrax in adults. *Emerg Infect Dis*. 2014;20(2).

Mourad MM, Evans R, Kalidindi V, et al. Prophylactic antibiotics in acute pancreatitis: Endless debate. *Ann R Coll Surg Engl*. 2017;99(2):107–112.

Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10–52.

Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med*. 2013;368(18):1695–703.

Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):895–902.

Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev*. 2010;(5): CD002941.

Watters W 3rd, Rethman MP, Hanson NB, et al. Prevention of orthopaedic implant infection in patients undergoing dental procedures. *J Am Acad Orthop Surg*. 2013;21(3):180–189.

Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43(9):1089–1134.

Zacharioudakis IM, Zervou FN, Arvanitis M, et al. Antimicrobial lock solutions as a method to prevent central line-associated bloodstream infections: A meta-analysis of randomized controlled trials. *Clin Infect Dis*. 2014;59(12):1741–1749.

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Surgical prophylaxis

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Introduction

Surgical site infections (SSIs) are infections related to operative procedures involving the incision site or surrounding tissues and organs. In the United States, an estimated 95 million operative procedures are performed annually in ambulatory settings and hospitals.[1] The annual incidence of SSIs in acute care hospitals has ranged from 2% to 5%; however, these rates are likely underestimates since 50% of SSIs are diagnosed after discharge.[2,3] According to national surveillance data from 2011 to 2014, SSIs were one of the most common hospital-acquired infections (HAI), accounting for 36.4% of HAIs.[4]

SSIs increase direct and indirect healthcare costs related to prolonged hospital stays, emergency room visits, readmissions for treatment, and repeat surgical procedures.[5] SSIs prolong the length of hospital stay by an average of 9.7 days and are the most common reason (19.5%) for unplanned readmission after surgical procedures.[6] Societal costs related to SSIs include loss of productivity and temporary or permanent disability. The annual cost of SSIs is an estimated $3.2 billion ($20,000 per case) and accounts for the largest proportion of costs related to HAIs (44.7%).[7] The healthcare and societal costs of SSIs are expected to increase since the number of operative procedures continues to rise each year and more procedures are performed on patients with complex comorbidities.[8]

The application of evidence-based strategies can prevent up to 55% of SSIs.[9] Starting in the early 2000s, the Centers for Disease Control and Prevention (CDC), the Centers for Medicare and Medicaid Services (CMS), healthcare facilities, and state health departments developed several measures to improve the safety and quality of surgical procedures. In 2005, the CDC established the National Healthcare Safety Network (NHSN) to track HAIs, including SSIs, to help healthcare facilities identify problem areas and measure the progress of prevention efforts. Since its inception, the NHSN has become the largest national surveillance system, with the participation of more than 17,000 healthcare facilities.[10] In 2006, the CDC and CMS created the Surgical Care Improvement Project to identify best practices for perioperative management including antimicrobial prophylaxis, glucose and temperature control, and venous thromboembolism prophylaxis.[11] CMS developed the Physicians Quality Reporting System to provide financial incentives to physicians meeting performance standards for quality measures, including measures related to surgical procedures. Based on physician performance, CMS and insurers can reduce or deny payments for surgical complications including SSIs.[12]

Definitions

Surgical site infections

SSIs are infections of the incision, surrounding tissues, or organs that occur within 90 days of an operative procedure.[13] For the purposes of research, quality improvement, and national surveillance, the NHSN has established a classification system for SSIs based on the degree of involvement: superficial incisional, deep incisional, and organ or space SSI (Box 112.1). *Superficial incisional* SSIs involve the skin and subcutaneous tissue surrounding the incision. *Deep incisional* SSIs extend to the fascia and muscle layers around the incision.

BOX 112.1

The National Healthcare Safety Network criteria for surgical site infections (SSI)[13]

Superficial incisional SSI

Date of event for infection occurs within 30 days after any operative procedure (where day 1 = the procedure date),

AND

Involves only skin and subcutaneous tissue of the incision,

AND

Patient has at least one of the following:

A. Purulent drainage from the superficial incision,

B. Organisms identified from an aseptically obtained specimen from the superficial incision or subcutaneous tissue by a culture- or nonculture-based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment,

C. Superficial incision that is deliberately opened by a surgeon, attending physician, or other designee and culture- or nonculture-based testing is not performed,

AND

Patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat,

D. Diagnosis of a superficial incisional SSI by the surgeon or attending physician or other designee.

Deep incisional SSI

Date of event for infection occurs within 30 or 90 days depending on the operative procedure (where day 1 = the procedure date),

AND

Involves deep soft tissues of the incision (for example, fascial and muscle layers),

AND

Patient has at least one of the following:

A. Purulent drainage from the deep incision,

B. A deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, attending physician or other designee,

AND

Organism is identified by a culture- or nonculture-based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment culture or non-culture based microbiologic testing method is not performed,

AND

Patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness. A culture- or nonculture-based test that has a negative finding does not meet this criterion,

C. An abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or on imaging test.

Organ/Space SSI

Date of event for infection occurs within 30 or 90 days depending on the operative procedure (where day 1 = the procedure date),

AND

Infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure,

AND

Patient has at least one of the following:

A. Purulent drainage from a drain that is placed into the organ/space (for example, closed suction drainage system, open drain, T-tube drain, CT-guided drainage),

B. Organisms are identified from fluid or tissue in the organ/space by a culture- or nonculture-based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment,

C. An abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test evidence is suggestive of infection.

Organ or *space* SSIs involve any area deeper than the fascia and muscle layer opened or manipulated during the operative procedure.[13]

Patients with SSIs may present with one or more of the following signs or symptoms: fevers (>38°C/100°F); pain or tenderness of the surgical site; localized swelling, erythema, or heat of the incision; purulent drainage from the superficial or deep incision; and spontaneous dehiscence of the deep incision. A microbiological diagnosis of SSIs is confirmed by obtaining an aseptic specimen from the superficial incision, subcutaneous tissue, or organ space and identifying organisms by culture or molecular testing. Imaging, gross anatomy, and histopathology are additional tools used to diagnose deep incisional and organ space infections.[13]

Surgical wound classification system

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) developed a surgical wound classification (SWC) system to assist with operative planning, develop perioperative protocols, and estimate infectious risk.[14] Surgeries are categorized at the time of the procedure into four SWCs based on the expected degree of contamination: class I clean, class II clean-contaminated, class III contaminated, and class IV dirty or infected (Box 112.2). In clean operations, the respiratory, alimentary, genital, or urinary tracts are not entered, and no inflammation is encountered during the procedure. During clean-contaminated procedures, the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions without contamination. Contaminated procedures include those with major breaks in sterile technique such as open cardiac massage or gross spillage from the gastrointestinal tract. Contaminated procedures also include surgeries traversing open, fresh, accidental wounds or acute, nonpurulent, and possibly necrotic incisions. Dirty or infected operations address existing clinical infections or perforated viscera. Dirty operations also include those performed on old traumatic wounds with retained devitalized tissue.[14]

BOX 112.2

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) surgical wound classification system[14]

Class I: Clean
An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or urinary tracts are not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet criteria.

Class II: Clean-Contaminated
Operative wounds in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

Class III: Contaminated
Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract and incisions in which acute, non-purulent inflammation is encountered are included in this category.

Class IV: Dirty or Infected
Includes old traumatic wounds with devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation

A cross-sectional study evaluated rates of SSI by wound class among 634,426 surgical cases reported to the ACS-NSQIP between 2005 and 2008.[14] The proportion of surgeries classified as clean was 49.7%, clean-contaminated was 35%, contaminated was 8.56%, and dirty was 6.7%. The rates of superficial, deep incisional, and organ/space SSIs were 1.8%, 0.5%, 0.3%, respectively, for clean; 3.9%, 0.9%, 1.9% for clean-contaminated; 4.8%, 1.3%, 2.6% for contaminated; and 5.2%, 2.1%, 4.5% for dirty procedures.[14]

Microbiology

According to the National Nosocomial Infections Surveillance System, the pathogens responsible for SSIs in US hospitals have shifted from primarily gram-negative to gram-positive organisms over the past three decades; the prevalence of SSIs caused by gram-negative bacilli decreased from 56.5% in 1986 to 33.8% in 2003.[15] Possible reasons behind the shift toward gram-positive organisms include the implementation of antimicrobial prophylaxis and the increased use of laparoscopy for intra-abdominal procedures.[15]

In clean procedures, the predominant organisms responsible for SSIs are skin flora including *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS). In clean-contaminated procedures involving the respiratory, gastrointestinal, genital, or urinary tract, the main causative pathogens include skin flora, gram-negative bacilli, and *Enterococcus* species. Contaminated and dirty procedures are usually polymicrobial with organisms reflective of the endogenous flora of the manipulated organ system.[16]

Between 2011 and 2014, 149,009 pathogens from 133,080 SSIs across 4,515 hospitals were reported to the NHSN (Table 112.1). The most common pathogens across all surgeries were

TABLE 112.1 **SURGICAL SITE INFECTIONS (SSIS) REPORTED TO THE NATIONAL HEALTHCARE SAFETY NETWORK (NHSN) FROM 2011 TO 2014[4]**

Type of surgery	Number (%) of SSIs (*n* = 133,080)	Number (%) of pathogens (*n* = 149,009)
Abdominal	63,508 (47.7)	76,307 (51.2)
Breast	886 (0.7)	946 (0.6)
Cardiac	10,439 (7.8)	11,281 (7.6)
Kidney	251 (0.2)	285 (0.2)
Neck	146 (0.1)	212 (0.1)
Neurological	1,945 (1.5)	2,168 (1.5)
Obstetrical and gynecological	22.231 (16.7)	20,725 (13.9)
Orthopedic	31,539 (23.7)	34,341 (23.0)
Prostate	53 (<0.1)	61 (<0.1)
Transplant	644 (0.5)	815 (0.5)
Vascular	1,438 (1.1)	1,868 (1.3)

S. aureus (20.7%), *Escherichia coli* (13.7%), CoNS (7.9%), *Enterococcus faecalis* (7.5%), and *Pseudomonas aeruginosa* (5.7%) (Table 112.2). The operations accounting for the majority of SSIs were abdominal (47.7%), orthopedic (23.7%), obstetrics and gynecology (16.7%), and cardiac (7.8%) procedures. The most common pathogens isolated from SSIs after abdominal procedures were *E. coli* (19.6%), *E. faecalis* (9.4%), and *S. aureus* (9.1%). For orthopedic surgery SSIs, the most prevalent organisms were *S. aureus* (44.2%), CoNS (13.0%), and *P. aeruginosa* (4.9%).[4]

The number of SSIs caused by antibiotic-resistant organisms has increased since the 2000s. In a study of patients with culture-confirmed SSIs, the proportion of infections caused by methicillin-resistant *S. aureus* (MRSA) increased from 16.1% in 2003 to 20.6% in 2007 ($p < 0.0001$). MRSA infections were associated with higher mortality rates, longer hospital stays, and higher hospital costs compared with infections caused by other pathogens.[17] Among the SSI pathogens reported to the NHSN from 2011 to 2014, MRSA accounted for 43% of *S. aureus* isolates, and 60% of *E. faecium* isolates were vancomycin-resistant enterococci (VRE).[4]

Risk factors for surgical site infections

Several factors influence the risk of SSIs, including the patient's underlying medical condition, perioperative management, operative techniques, and the operating room environment (Box 112.3). Patient-related risk factors include extremes of age, diabetes mellitus, obesity, tobacco use, nutritional status, and altered immune response. Perioperative risk factors include improper skin preparation, hair removal, antimicrobial prophylaxis, and glycemic and temperature control. Procedural risk factors include surgeon inexperience and poor technique, timing of the operation (emergency vs. elective), and the length of the procedure. Risk factors related to the operating room environment include improper surgical scrub, skin antisepsis, and equipment sterilization.[18]

Guidelines for prevention of surgical site infections

Three national guidelines were developed for the prevention of SSIs: the 2013 American Society of Health-System Pharmacists (ASHP) Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery, the 2016 American College of Surgeons (ACS) and Surgical Infection Society (SIS) Surgical Site Infection Guidelines, and the 2017 CDC Guidelines for Prevention of Surgical Site Infection.[18–20] This section summarizes the guideline recommendations and highlights any meta-analyses or large, well-conducted, randomized controlled trials (RCTs) supporting the recommendation.

TABLE 112.2 **DISTRIBUTION OF PATHOGENS ASSOCIATED WITH SURGICAL SITE INFECTIONS REPORTED TO THE NATIONAL HEALTHCARE SAFETY NETWORK (NHSN) FROM 2011 TO 2014**[4]

Pathogen	Total number (%) of pathogens (*n* = 149,009)	Number of pathogens by surgery type (%)				
		Abdominal (*n* = 76,307)	Orthopedic (*n* = 34,341)	Ob/Gyn (*n* = 20,725)	Cardiac (*n* = 11,281)	Other (*n* = 6,355)
Staphylococcus aureus	30,902 (20.7)	6,922 (9.1)	15,163 (44.2)	3,680 (17.7)	3,430 (30.4)	1,707 (26.9)
Escherichia coli	20,429 (13.7)	14,955 (19.6)	1.625 (4.7)	2,787 (13.4)	647 (5.7)	2,038 (32.1)
Coagulase-negative staphylococci	11,799 (7.9)	3,273 (4.3)	4,461 (13.0)	1,520 (7.3)	1,641 (14.5)	904 (14.2)
Enterococcus faecalis	11,156 (7.5)	7,197 (9.4)	1,620 (4.7)	1,710 (8.3)	325 (2.9)	304 (4.8)
Pseudomonas aeruginosa	8,458 (5.7)	4,469 (5.9)	1,672 (4.9)	990 (4.8)	918 (8.1)	409 (6.4)
Klebsiella (*pneumoniae/oxytoca*)	7,067 (4.7)	4,318 (5.7)	943 (2.7)	856 (4.1)	650 (5.8)	300 (4.7)
Bacteroides spp.	7,041 (4.7)	5,690 (7.5)	128 (04)	1,108 (5.3)	40 (0.4)	75 (1.2)
Enterobacter spp.	6,615 (4.4)	3,475 (4.6)	1,401 (4.1)	741 (3.6)	650 (5.8)	348 (5.5)
Other *Enterococcus* spp.	6,410 (4.3)	4,692 (6.1)	592 (1.7)	806 (3.9)	160 (1.4)	160 (2.5)
Proteus spp.	4,196 (2.8)	1,473 (1.9)	1,108 (3.2)	919 (4.4)	516 (4.6)	180 (2.8)
Enterococcus faecium	4,140 (2.8)	3,451 (4.5)	271 (0.8)	152 (0.7)	105 (0.9)	161 (2.5)
Candida albicans	3,351 (2.2)	2,736 (3.6)	132 (0.4)	215 (1.0)	160 (1.4)	108 (1.7)
Virdans streptococci	2,639 (1.8)	1,849 (2.4)	254 (0.7)	368 (1.8)	81 (0.7)	87 (1.4)
Group B streptococci	1,879 (1.3)	291 (0.4)	765 (2.2)	680 (3.3)	80 (0.7)	63 (1.0)
Serratia spp.	1,857 (1.2)	333 (0.4)	527 (1.5)	235 (1.1)	579 (5.1)	183 (2.9)
Other pathogen	21,070 (14.1)	11,183 (14.7)	3,679 (10.7)	3,968 (19.1)	1,299 (11.5)	941 (14.8)

BOX 112.3

American College of Surgeons and Surgical Infection Society surgical site infection risk factors

Intrinsic (patient-related)
Nonmodifiable
Increased age
Recent radiotherapy
History of skin or soft tissue infection
Modifiable
Diabetes
Obesity
Alcoholism
Current smoker
Preoperative albumin <3.5 mg/dL
Immunosuppression
Extrinsic (procedure-related)
Procedure
Emergency
Increasing complexity
Higher wound classification
Facility
Inadequate ventilation
Increased operating room traffic
Contaminated environmental services
Nonsterile equipment
Preoperative
Preexisting infection
Inadequate skin preparation
Inappropriate antibiotic choice, timing, and weight-based dosing
Hair removal method
Poor glycemic control
Intraoperative
Longer procedure duration
Blood transfusion
Breach in asepsis
Inappropriate antibiotic redosing
Inadequate gloving
Inappropriate surgical scrub
Poor glycemic control

The first part of the section summarizes the 2014 ASHP Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery developed jointly by ASHP, SIS, the Infectious Diseases Society of America, and the Society for Healthcare Epidemiology of America.[19] These guidelines provide recommendations on the safe and effective use of antimicrobial agents for the prevention of SSIs based on a systematic review of the primary literature from 1999 through June 2010.

The second part of the section is a combined review of the 2016 ACS/SIS and 2017 CDC guidelines on perioperative interventions to address patient- and procedure-related risk factors.[18] The CDC guidelines were developed by clinical experts in collaboration with the Healthcare Infection Control Practices Advisory Committee, a federal advisory committee of the CDC.[20] These guidelines update the 1999 CDC recommendations,[21] with a systematic review of the primary literature from January 1998 through April 2014.[20] The section highlights recommendations relevant to the clinical practice of the infectious diseases specialist.

Prophylactic antimicrobial agents

The goals of preoperative antimicrobial prophylaxis are to prevent SSIs, prevent morbidity and mortality related to SSIs, and reduce healthcare costs. The benefits of surgical prophylaxis need to be weighed against the risks of antibiotic exposure, such as adverse drugs reactions and alterations to the patient's microbial flora. For the majority of procedures, cefazolin is the recommended antimicrobial agent for surgical prophylaxis because it is a safe and inexpensive antibiotic with an appropriate duration of action and activity against the pathogens most likely to contaminate the surgical site. For patients with a documented β-lactam allergy, acceptable alternatives include vancomycin or clindamycin. Antimicrobial agents should be administered at the appropriate time and dosage so that an adequate concentration reaches the serum and tissue during the procedure.

Timing of initial dose

A single dose of cefazolin should be administered within 60 minutes prior to incision to ensure a bactericidal concentration is established in the serum and tissues during the procedure.[20] For vancomycin and fluoroquinolones, the initial dose should be administered within 60 to 120 minutes prior to incision.[19,22] The optimal timing for surgical antimicrobial prophylaxis was established in the Trial to Reduce Antimicrobial Prophylaxis Errors (TRAPE), a large prospective multicenter study of patients undergoing cardiac surgery, hysterectomy, or hip or knee arthroplasty (n = 4,472). Patients were categorized into four groups based on the timing of surgical prophylaxis: group 1 (n = 1,844) received either a cephalosporin within 30 minutes before incision or vancomycin or a fluoroquinolone within one hour before incision; group 2 (n = 1,796) received either a cephalosporin 31 to 60 minutes before incision or vancomycin or a fluoroquinolone 61 to 120 minutes before incision; group 3 (n = 644) received antimicrobials earlier than recommended; and group 4 (n = 188) received the initial antimicrobial dose after incision. The study found rates of SSI increased as the interval of time between the antibiotic infusion and incision increased (2.1% in group 1, 2.4% group 2, and 2.8% group 3).[23]

Dosing

The ASHP recommendations for prophylactic antimicrobial agent dosing are summarized in Table 112.3. The dose of preoperative antimicrobial prophylaxis should be increased in obese and morbidly obese patients. A cefazolin dose of 2 g is recommended for

TABLE 112.3 **AMERICAN SOCIETY OF HEALTH SYSTEM PHARMACISTS RECOMMENDED DOSES AND REDOSING INTERVALS FOR ANTIMICROBIALS USED IN SURGICAL PROPHYLAXIS[19]**

Antimicrobial	Dose in adults	Half-life with normal renal function, hr	Redosing interval, hr
Ampicillin-sulbactam	3 g	0.8–1.3	2
Ampicillin	2 g	1–1.9	2
Aztreonam	2 g	1.3–2.4	4
Cefazolin	2 g, 3 g if ≥120 kg	1.2–2.2	4
Cefuroxime	1.5 g	1–2	4
Cefotaxime	1 g	0.9–1.7	3
Cefoxitin	2 g	0.7–1.1	2
Cefotetan	2 g	2.8–4.6	6
Ceftriaxone	2 g	5.4–10.9	NA
Ciprofloxacin	400 mg	3–7	NA
Clindamycin	900 mg	2–4	6
Ertapenem	1 g	3–5	NA
Gentamicin	5 mg/kg	2–3	NA
Levofloxacin	500 mg	6–8	NA
Metronidazole	500 mg	6–8	NA
Moxifloxacin	400 mg	8–15	NA
Piperacillin-tazobactam	3.375 g	0.7–1.2	2
Vancomycin	15 mg/kg	4–8	NA

patients weighing >60 kg and 3 g if >120 kg. The use of ideal body weight versus actual body weight depends on the lipophilicity of the drug; ideal body weight for lipophilic drugs (vancomycin) results in subtherapeutic concentrations in serum and tissue, while actual body weight for hydrophilic drugs (aminoglycoside) results in excessive concentrations in serum and tissue. For aminoglycosides, dosing is calculated using the patient's ideal body weight plus 40% of the difference between the actual and ideal body weight. Vancomycin should be dosed at 15 mg/kg.[19,22]

A pharmacokinetic study investigated cefazolin concentrations in the serum and tissues of 38 morbidly obese patients undergoing Roux-en-Y gastric bypass surgery. The patients were classified into three groups based on their body mass index (BMI): (A) BMI = 40 to 49, (B) BMI = 50 to 59, (C) BMI ≥60. Two grams of cefazolin was administered to all patients 30 to 60 minutes before the incision and a second 2 g dose 3 hours later. Tissue antimicrobial concentrations exceeded the therapeutic levels in only 48.1%, 28.6%, and 10.2% of BMI groups A, B, and C, respectively. This study highlighted the need to increase the cefazolin dose in obese patients to achieve therapeutic levels in the serum and tissue at the time of incision.[24]

Redosing

The ASHP recommendations for prophylactic antimicrobial agent redosing are summarized in Table 112.3. Redosing of prophylactic antimicrobial agents is recommended when the procedure time exceeds the half-life of the antibiotic. Redosing is also appropriate in patients with major blood loss (>1,500 mL) or extensive burns. Redosing should be performed at intervals of one to two times the antibiotic half-life.[19,22] Among patients in the TRAPE study undergoing operations lasting more than 4 hours, patients given a second dose of prophylactic antibiotics had a threefold reduction in the risk of SSI compared to those who were not redosed.[23]

Duration

In clean and clean-contaminated procedures, additional doses of prophylactic antimicrobial agents are not recommended after the surgical incision is closed.[20] The duration of antimicrobial prophylaxis should be <24 hours for most procedures. A meta-analysis was performed of 21 RCTs comparing no postoperative antimicrobial prophylaxis to postoperative antimicrobial prophylaxis for <24 hours among patients undergoing cardiac; thoracic; vascular; ear, nose, and throat; gynecologic; orthopedic; or general surgery procedures (n = 14,285). The study found no benefit in continuing antimicrobial prophylaxis after intraoperative closure of the surgical incision (odds ratio [OR] 1.84, p = 0.14).[20]

Penicillin allergy

Patients with a type I immunoglobulin E-mediated allergy to β-lactams develop anaphylaxis, urticaria, and/or bronchospasm within 30 to 60 minutes of β-lactam administration. Patients with a documented β-lactam allergy should receive an alternative to cefazolin for the prevention of SSIs. Patients with a history of exfoliative dermatitis to β-lactams (Stevens-Johnson syndrome, toxic epidermal necrolysis) should also receive an alternative antimicrobial agent. Acceptable alternatives include vancomycin, clindamycin, fluoroquinolones, and aminoglycosides.

A careful history should be obtained preoperatively to determine if a true β-lactam allergy exists because alternative antimicrobial agents are associated with decreased efficacy, increased costs, and adverse events. A single-center retrospective cohort study found patients with reported penicillin allergy had increased odds of developing an SSI. Among patients undergoing hip arthroplasty, knee arthroplasty, hysterectomy, colon surgery, or coronary artery bypass grafting (CABG) from 2010 to 2014 (n = 8,385), 922 (11%) reported a penicillin allergy and 241 (2.7%) developed an SSI.[25] Patients with reported penicillin allergies were administered cefazolin less often and received clindamycin, vancomycin, or gentamicin more frequently compared to those without a reported allergy. Patients reporting a penicillin allergy had 50% increased odds of SSIs attributed to the receipt of second-line antimicrobial prophylaxis. Accordingly, the study concluded that clarifying the type of reaction to penicillin should be included in routine perioperative care to prevent SSIs.

Type of surgery

The ASHP recommendations for prophylactic antimicrobial agents based on the type of surgery are summarized in Table 112.4.

TABLE 112.4 AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS RECOMMENDATIONS FOR SURGICAL ANTIMICROBIAL PROPHYLAXIS[19]

Type of procedure	Recommended agents	Alternative agents in patients with β-lactam allergy
Cardiac (coronary artery bypass, cardiac device insertion, ventricular assist devices)	Cefazolin, cefuroxime	Clindamycin, vancomycin
Thoracic (lobectomy, pneumonectomy, lung resection, thoracotomy, video-assisted thoracoscopic surgery)	Cefazolin, ampicillin-sulbactam	Clindamycin, vancomycin
Gastroduodenal	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Biliary tract	Cefazolin, cefoxitin, cefotetan, ceftriaxone, ampicillin-sulbactam	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone Metronidazole + aminoglycoside or fluoroquinolone
Laparoscopic procedure		
• Elective, low-risk	None	None
• Elective, high-risk	Cefazolin, cefoxitin, cefotetan, ceftriaxone, ampicillin-sulbactam	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone Metronidazole + aminoglycoside or fluoroquinolone
Appendectomy for uncomplicated appendicitis	Cefoxitin, cefotetan, cefazolin + metronidazole	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone Metronidazole + aminoglycoside or fluoroquinolone
Small intestine		
• Nonobstructed	Cefazolin	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone
• Obstructed	Cefazolin + metronidazole, cefoxitin, cefotetan	Metronidazole + aminoglycoside or fluoroquinolone
• Hernia repair	Cefazolin	Clindamycin, vancomycin
Colorectal	Cefazolin + metronidazole, cefoxitin, cefotetan, ampicillin-sulbactam, ceftriaxone + metronidazole, ertapenem	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone Metronidazole + aminoglycoside or fluoroquinolone
Head and neck		
• Clean	None	None
• Clean with placement of prosthesis	Cefazolin, cefuroxime	Clindamycin
• Clean-contaminated	Cefazolin + metronidazole, cefuroxime + metronidazole, ampicillin-sulbactam	Clindamycin
Neurosurgery	Cefazolin	Clindamycin, vancomycin
Cesarean delivery	Cefazolin	Clindamycin, vancomycin
Hysterectomy	Cefazolin, cefotetan, cefoxitin, ampicillin-sulbactam	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone Metronidazole + aminoglycoside or fluoroquinolone
Ophthalmic	Topical neomycin-polymyxin B-gramicidin, gatifloxacin, moxifloxacin (given as 1 drop every 5-15 minutes for 5 doses)	

TABLE 112.4 **CONTINUED**

Type of procedure	Recommended agents	Alternative agents in patients with β-lactam allergy
Orthopedic		
• Clean (involving hand, knee, foot not involving implantation of foreign material)	None	None
• Spinal procedures, implantation of internal fixation devices, total joint replacement	Cefazolin	Clindamycin, vancomycin
Urologic		
• Lower tract instrumentation with risk factors for infection	Fluoroquinolone, trimethoprim-sulfamethoxazole, cefazolin	Aminoglycoside
• Clean without entry into urinary tract	Cefazolin	Clindamycin, vancomycin
• Clean with entry into urinary tract	Cefazolin	Fluoroquinolone, aminoglycoside
• Clean-contaminated	Cefazolin + metronidazole, cefoxitin	Fluoroquinolone, aminoglycoside
Vascular	Cefazolin	Clindamycin, vancomycin
Transplantation		
• Heart, lung, heart-lung	Cefazolin	Clindamycin, vancomycin
• Liver	Piperacillin-tazobactam, cefotaxime + metronidazole	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
• Pancreas, pancreas-kidney	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Plastic surgery	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone

Cardiac procedures

Surgical prophylaxis is recommended for the following cardiac procedures: CABG, valve repair, ventricular assist device, and cardiac device insertion procedures (pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization device). Infections complicating cardiac procedures have severe consequences including sternal wound infections, mediastinitis, and device pocket infections. *Staphylococcus* spp. (*S. aureus* and CoNS) are isolated in almost half of SSIs after cardiac procedures. A preoperative dose of cefazolin or cefuroxime with appropriate redosing is recommended as surgical prophylaxis in cardiac procedures. Vancomycin should be administered in patients with a history of MRSA colonization. Patients with a documented β-lactam allergy should receive vancomycin or clindamycin as an alternative agent. Patients with *S. aureus* colonization should be treated preoperatively with intranasal mupirocin.

In cardiac procedures, administration of antimicrobial prophylaxis for up to 48 hours postoperatively is accepted practice. However, the primary literature suggests the risk of prolonged antibiotics exposure outweighs any potential benefit of SSI prevention. A 4-year cohort study of 2,461 patients undergoing CABG found antimicrobial prophylaxis for an extended duration (>48 hours) compared to a shorter duration (<48 hours) failed to reduce the risk of SSI (OR 1.2, 95% confidence interval [CI] [0.8, 1.6]). Prolonged prophylaxis was associated with an increased risk of acquiring antimicrobial-resistant organisms, including cephalosporin-resistant Enterobacteriaceae and VRE (OR 1.6, 95% CI [1.1, 2.6]).[26]

Thoracic procedures

Surgical prophylaxis is recommended for noncardiac thoracic procedures including lobectomy, pneumonectomy, thoracoscopy, lung resection, and thoracotomy. Thoracic procedures can be complicated by SSIs, pneumonia, and empyema. Similar to cardiac procedures, half of SSIs after thoracic procedures are caused by gram-positive organisms (*S. aureus* and CoNS). Causes of pneumonia after thoracic procedures include gram-positive organisms (*Streptococcus* species, *Staphylococcus* species) and common respiratory pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis*).[27] For surgical prophylaxis, cefazolin or ampicillin-sulbactam is recommended for patients undergoing thoracic procedures. Acceptable alternatives include vancomycin or clindamycin for patients with a documented β-lactam allergy.

Ampicillin-sulbactam is a recommended antimicrobial agent for prophylaxis in thoracic procedures because it targets the normal lung flora responsible for postoperative pneumonia. In a prospective study of 445 patients undergoing lung resections for noninfectious diseases, patients receiving amoxicillin-clavulanate had significantly decreased rates of postoperative pneumonia compared to those receiving cefamandole ($p = 0.0027$).[27]

Gastrointestinal procedures

The ASHP antimicrobial prophylaxis guidelines divide gastrointestinal (GI) procedures into the following sections: gastroduodenal (with or without entry into GI lumen), biliary (open, low-risk

laparoscopic, high-risk laparoscopic), appendectomy, small intestine (nonobstructive, obstructive, hernia repair), and colorectal procedures. The most common organisms isolated from SSIs after gastrointestinal procedures are gram-negative bacilli (*E. coli*, *Proteus* spp., *Klebsiella* spp.) followed by gram-positive cocci (*Enterococcus* spp., *Streptococcus* spp., *Staphylococcus* spp.) and anaerobic organisms (*Bacteroides* spp., *Clostridium* spp.).

Antimicrobial prophylaxis is not necessary in low-risk patients undergoing elective laparoscopic cholecystectomy. For the majority of gastrointestinal procedures, a single dose of cefazolin is recommended for antimicrobial prophylaxis. For patients with a documented β-lactam allergy, acceptable alternative regimens include (1) clindamycin or (2) vancomycin for coverage of gram-positive organisms plus (1) an aminoglycoside, (2) aztreonam, or (3) a fluoroquinolone for coverage of gram-negative bacilli. Antimicrobial prophylaxis with both aerobic and anaerobic coverage is recommended for colorectal procedures, appendectomy for uncomplicated appendicitis, open biliary tract procedures, and obstructed small intestine procedures. Recommended regimens including anaerobic coverage include (1) a second-generation cephalosporin (cefoxitin or cefotetan), (2) cefazolin plus metronidazole, or (3) ampicillin-sulbactam. Alternative regimens for patients with documented β-lactam allergy are (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone, or (2) metronidazole plus an aminoglycoside or a fluoroquinolone.

Meta-analyses performed for the following gastrointestinal procedures have found antimicrobial prophylaxis decreases the risk of SSIs: percutaneous endoscopic gastrostomy (OR 0.35, 95% CI [0.23, 0.48]),[28] appendectomy,[29] hernioplasty (prosthetic mesh repair of hernia) or herniorrhaphy (suture repair of hernia) (OR 0.64, 95% CI [0.50, 0.82]),[30] and colorectal surgery (risk ratio [RR] 0.30, 95% CI [0.22, 0.41]).[31]

For colorectal surgeries, multiple studies have found the addition of mechanical bowel preparation (MBP) and oral antimicrobial prophylaxis to routine perioperative intravenous prophylaxis further reduces postoperative infection rates. A Cochrane review found combined oral and intravenous antibiotic prophylaxis significantly decreased SSI rates compared to intravenous (RR 0.55, 95% CI [0.41, 0.74]) or oral prophylaxis alone (RR 0.34, 95% CI [0.13, 0.87]).[31] The combination of MBP, oral antibiotics, and intravenous antibiotics also significantly reduces the risk of anastomotic leaks, ileus, prolonged hospitalization, and readmission after colorectal surgery.[32,33] Oral antimicrobial prophylaxis should be administered 10 hours prior to the operation and after MBP. Appropriate oral regimens for prophylaxis include (1) neomycin plus erythromycin or (2) oral neomycin plus metronidazole.

Head and neck procedures

Head and neck procedures requiring an incision through the oropharyngeal mucosa are classified as clean-contaminated. The majority of SSIs after head and neck procedures are polymicrobial and involve the normal oropharyngeal flora including *Streptococcus* spp. and anaerobes (*Bacteroides* spp., *Peptostreptococcus* spp., *Prevotella* spp., *Fusobacterium* spp., *Veillonella* spp.). For clean-contaminated head and neck procedures, (1) cefazolin or cefuroxime plus metronidazole or (2) ampicillin-sulbactam are recommended for surgical prophylaxis. Clindamycin is an alternative agent for patients with a documented β-lactam allergy.

Based on the findings of several studies, antimicrobial prophylaxis is not required for clean (thyroidectomy, lymph node excision) and certain clean-contaminated head and neck procedures (adenoidectomy, tonsillectomy, endoscopic sinus procedure). In a multicenter RCT of 500 patients undergoing thyroidectomy for goiter or thyroid cancer, there was no significant difference in the rate of SSIs between patients who received antibiotic prophylaxis with ampicillin-sulbactam and those without antibiotic prophylaxis.[34] A Cochrane review of 10 trials comprising 1,035 patients found no clinically significant impact of antibiotics in reducing the main adverse outcomes related to tonsillectomy, including reduction of pain, need for analgesics, and secondary hemorrhage rates.[35]

Neurologic procedures

Infections related to neurologic procedures have severe consequences including repeat neurologic surgery, prolonged course of parenteral antimicrobials, and death. Gram-positive organisms (*S. aureus,* CoNS) are responsible for almost half of SSIs after neurologic procedures. A single dose of cefazolin is recommended for patients undergoing craniotomy, spinal procedures, cerebrospinal fluid shunt procedures, or intrathecal pump placement. Vancomycin and clindamycin are alternative agents for patients with a documented β-lactam allergy.

There are no guidelines on the use of antimicrobial agent prophylaxis for patients with external ventricular drains (EVDs) or intracranial pressure monitors. Many centers initiate antibiotics to prevent drain-related infections although no prospective trials support the practice. In an international survey of current practices, the majority of neurosurgeons reported continuing prophylactic antibiotics for the duration of EVDs.[36] A minority of infectious disease specialists and about half of intensivists routinely used prophylactic antibiotics for EVDs.[36] A retrospective single-center study of 308 patients with EVDs found no significant difference in the rate of bacterial ventriculitis between patients who received periprocedural antibiotics and those who received antibiotics for the duration of the EVD.[37] Prospective studies are needed to investigate the use of prophylactic antibiotics for the prevention of EVD-related infections.

Obstetric and gynecologic surgery

A serious infectious complication of cesarean delivery is endometritis, an infection of the uterine lining that presents with fever, abdominal pain, uterine tenderness, or foul-smelling lochia. Prolonged labor in the presence of ruptured membranes is the main risk factor for endometritis as the vaginal bacterial flora enter the uterus during periods of relaxation between contractions. Most postpartum infections are polymicrobial and involve the normal vaginal flora including aerobic (*E. coli*, *Enterococci* spp., *Streptococci* spp.) and anaerobic (*Bacteroides bivius*, *Peptococcus* spp., *Peptostreptococcus* spp.) organisms. A single dose of cefazolin timed before incision is recommended for women undergoing cesarean delivery.

Clindamycin plus gentamicin is an acceptable alternative agent for patients with a documented β-lactam allergy.

A Cochrane review of 81 RCTs including 11,937 women assessed the use of prophylactic antibiotics on infectious complications in women undergoing cesarean delivery.[38] Women who received prophylactic antibiotics had a significantly decreased risk of endometritis (RR 0.39, 95% CI [0.31, 0.43]) and wound infections (RR 0.41, 95% CI [0.29, 0.43]).[38] Prophylactic antibiotics have typically been administered after cord clamping to avoid altering the neonate's microbial flora and masking early signs of neonatal sepsis, but studies suggest antibiotic prophylaxis is most effective prior to skin incision. A meta-analysis reviewed three RCTs and two nonrandomized trials comparing prophylactic antibiotics for cesarean delivery before skin incision and after cord clamping. The risk of postpartum endometritis was significantly decreased with the administration of antibiotics before skin incision (RR 0.47, 95% CI [0.26, 0.85]).[39]

After cesarean delivery, hysterectomies are the second most common gynecologic procedure performed in the United States and involve removal of the uterus and occasionally removal of one or both ovaries and fallopian tubes. Hysterectomies are performed through the vagina or the abdominal wall using laparoscopic or robotic methods. Infectious complications of hysterectomies include vaginal cuff infection, pelvic cellulitis, and pelvic abscess. Infections are usually polymicrobial, involving the normal vaginal flora including aerobic (*Streptococci* spp., *Enterococci* spp., gram-negative bacilli) and anaerobic (*Bacteroides* spp.) pathogens. For coverage of the typical surgical pathogens, a single dose of cefazolin, cefoxitin, cefotetan, or ampicillin-sulbactam is recommended for women undergoing vaginal or abdominal hysterectomy. For patients with a documented β-lactam allergy, the alternative agents recommended include (1) clindamycin or vancomycin plus an aminoglycoside, aztreonam or a fluoroquinolone, or (2) metronidazole plus an aminoglycoside or a fluoroquinolone.

Orthopedic procedures

The ASHP antimicrobial prophylaxis guidelines classify orthopedic procedures into four groups: (1) clean orthopedic procedures, (2) spinal procedures with or without instrumentation, (3) repair of hip fractures or implantation of internal fixation devices, and (4) total joint replacement procedures. Infections related to orthopedic procedures are costly given the need for hospital readmission, repeat orthopedic procedures, and prolonged courses of intravenous antibiotics. Orthopedic infections also contribute to significant morbidity given the loss of functionality, possible limb loss, or paralysis. Given these risks related to infection, antimicrobial prophylaxis with orthopedic implantation is widely accepted and practiced. Skin pathogens (*S. aureus, S. epidermidis*) are responsible for more than half of infections from orthopedic procedures. Gram-negative organisms (*E. coli*, *P. aeruginosa,* and *Enterobacter* spp.) are also frequently isolated from orthopedic infections.

Antimicrobial prophylaxis is not recommended in clean orthopedic procedures without instrumentation or implementation of foreign materials given the low risk of infection. Cefazolin is recommended for antimicrobial prophylaxis in the other three groups of orthopedic procedures: spinal procedures with or without instrumentation, repair of hip fractures or implantation of internal fixation devices, and total joint replacement procedures. Acceptable alternative agents for patients with a documented β-lactam allergy include vancomycin and clindamycin. Patients with *S. aureus* colonization should be treated preoperatively with intranasal mupirocin.

Multiple studies have found antimicrobial prophylaxis effectively prevents organ space infections in spinal procedures, hip fracture repair, and total joint replacement. In an RCT of 1,237 patients undergoing surgery for herniated disk, patients receiving cefuroxime prophylaxis had a significantly decreased rate of spondylodiscitis or epidural abscess (0%) compared to patients with no antimicrobial prophylaxis (1.4%) ($p < 0.01$).[40] In a meta-analysis of 15 RCTs performed to assess the most effective antimicrobial prophylaxis in hip fracture surgery, the following comparisons were examined: antibiotics at any dose versus placebo, multiple doses (>24 hours) versus one dose of antibiotics, and multiple doses versus 24-hour antibiotic coverage.[41] The meta-analysis found patients with antibiotic prophylaxis had a significantly decreased risk of superficial and deep wound infections compared to placebo. Furthermore, there was no significant difference in receiving a single dose versus multiple doses of antimicrobial prophylaxis. For total joint arthroplasty, a meta-analysis of seven studies including 3,064 patients found antimicrobial prophylaxis decreased the relative risk of wound infections by 81% compared with no prophylaxis ($p < 0.00001$).[42] The US Food and Drug Administration has approved premixed aminoglycoside (gentamicin, tobramycin) in bone cement products in second-stage revision of total joint arthroplasty, but no evidence suggests this is an effective strategy for the prevention of infection in primary joint arthroplasty.

Solid organ transplantation

Solid organ transplant (SOT) recipients are at increased risk of infection related to drug-induced immunosuppression, reactivation of latent infections, donor-derived infections, and preoperative colonization of antibiotic-resistant organisms. Patients are at the highest risk of infection during the first year posttransplant when receiving the highest level of immunosuppression. Antimicrobial prophylaxis is routinely administered posttransplant for the prevention of opportunistic infections including cytomegalovirus, herpes simplex virus, *Pneumocystis jiroveci*, and *Aspergillus*. Most infections in the first month after transplantation are hospital-acquired including SSIs, pneumonia, urinary tract infections, and bloodstream infections. Antimicrobial prophylaxis for the prevention of SSIs after SOT is recommended given the high risk of infection and the severe consequences related to infection, including transplant rejection and death. However, there are a limited number of well-conducted prospective studies on the optimal regimen and duration for antimicrobial prophylaxis after SOT.

SSIs related to heart and lung transplantation include mediastinitis and sternal osteomyelitis. Gram-positive organisms (*S. aureus,* CoNS, *Enterococcus* spp.) are the most common pathogens isolated from SSIs after heart and lung transplant. Other frequently isolated pathogens include Enterobacteriaceae, *P. aeruginosa*,

Stenotrophomonas maltophilia, and *Candida* spp. Infectious complications unique to lung transplantation include bronchial anastomotic infections and pneumonia related to bacterial or fungal colonization of the donor or recipient upper and lower airways. Patients with a history of cystic fibrosis receive frequent courses of antibiotics to treat exacerbations, and, as a result, their sinuses and upper airways are colonized with multidrug-resistant gram-negative organisms (*P. aeruginosa*, *S. maltophilia*, *Burkholderia* spp.) and *Aspergillus* spp. These pathogens can be transmitted to the lower airways after lung transplantation and cause pneumonia.

Infectious complications after liver transplantation include SSIs, intra-abdominal infections, and biliary tract infections. After kidney transplant, the most common infections include SSIs and urinary tract infections. Normal bowel and skin flora are responsible for most infections after abdominal transplant including aerobic gram-negative bacilli (*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp.), *Enterococcus* spp., skin flora (*S. aureus*, CoNS), and *Candida* spp.

Cefazolin is recommended for antimicrobial prophylaxis in heart, lung, heart-lung, pancreas, kidney, and pancreas-kidney transplantation. Vancomycin or clindamycin are alternative agents for patients with a documented β-lactam allergy. In liver transplantation, (1) piperacillin-tazobactam or (2) cefotaxime plus ampicillin are recommended for antimicrobial prophylaxis. Alternative agents for patients with documented β-lactam allergy include (1) vancomycin or (2) clindamycin *plus* (1) an aminoglycoside, (2) aztreonam, or (3) a fluoroquinolone. Antimicrobial prophylaxis should be modified to cover any organisms isolated from the donor or recipient pretransplant.

Urologic procedures

Prophylactic antibiotics are administered in urologic procedures to prevent SSIs as well as postoperative bacteremia. *E. coli* is the most common pathogen associated with bacteriuria after urologic procedures. Gram-positive organisms (*S. aureus*, CoNS, *Streptococcus* spp.) are frequently associated with urologic procedures requiring skin incisions without entry into the urinary tract. Biofilm-producing pathogens (*Staphylococcus epidermidis*, *P. aeruginosa*) are a concern for urologic procedures involving placement of prosthetic material (penile prosthesis). Risk factors for postoperative infections include anatomic abnormalities of the urinary tract, urinary obstruction, urinary stones, and indwelling or externalized catheters.

Patients with preoperative bacteriuria are treated prior to urologic procedures to prevent postoperative infections. A single dose of cefazolin is recommended for clean urologic procedures with or without entry into the urinary tract. A single dose of an aminoglycoside is recommended in procedures involving placement of prosthetic material. Vancomycin and clindamycin are alternative agents for patients with a documented β-lactam allergy undergoing clean urologic procedures without entry into the urinary tract. Alternative agents for urologic procedures with entry into the urinary tract include (1) a fluoroquinolone, (2) an aminoglycoside plus metronidazole, or (3) an aminoglycoside plus clindamycin.

Vascular procedures

Infections after vascular surgery using prosthetic material can result in severe consequences including limb loss. The predominant pathogens include *S. aureus*, CoNS, and enteric gram-negative bacilli. Antimicrobial prophylaxis is used in vascular procedures with a high risk of infection, including procedures involving implantation of prosthetic material, aneurysm repair, thromboendarterectomy, and vein bypass. Cefazolin is the recommended regimen for those undergoing vascular procedures with a high risk of infection. Alternative agents for patients with a documented β-lactam allergy include clindamycin and vancomycin.

Perioperative management

The 2016 ACS/SIS and 2017 CDC guidelines recommend perioperative interventions to address patient and procedure-related risk factors (Box 112.4). This section highlights interventions relevant to the practice of an infectious diseases specialist. Modifiable

BOX 112.4

Summary of the 1999 and 2017 Centers for Disease Control and Prevention guidelines for the prevention of surgical site infections[20,21]

Preparation of the patient

a. Identify and treat all infections remote to the surgical site before elective operations. Postpone elective operations with remote site infections until the infection has resolved.
b. Do not remove hair preoperatively unless the hair at or around the incision site will interfere with the operation. If hair removal is necessary, remove immediately before the operation with clippers.
c. Encourage tobacco cessation for a minimum of at least 30 days before elective operations.
d. Ensure skin around the incision site is free of gross contamination before performing antiseptic skin preparation.[21]

Antiseptic prophylaxis

a. Advise patients to shower or bathe (full body) with soap (antimicrobial or nonantimicrobial) or an antiseptic agent on at least the night before the operative day.
b. Perform intraoperative skin preparation with an alcohol-based antiseptic agent unless contraindicated.[21]

Hand and forearm antisepsis for surgical team

a. Perform preoperative surgical hand and forearm antisepsis according to manufacturer's recommendations for the product being used.
b. 2005 Guidelines for Hand Hygiene in Healthcare Settings provide additional surgical hand antisepsis recommendations.[56]

Operating room ventilation

a. Maintain positive pressure ventilation in the operating room and adjoining spaces.
b. Maintain the number of air exchanges, airflow patterns, temperature, humidity, location of vents, and use of filters in accordance with recommendations from the most recent version of the Facilities Guideline Institute—Guidelines for Design and Construction of Hospitals and Outpatient Facilities 2014.[57]

Cleaning and disinfection of environmental surfaces

a. Do not perform special cleaning or closing of operating rooms after contaminated or dirty operations.[21]

Reprocessing of surgical instruments

a. Sterilize all surgical instruments according to published guidelines and manufacturer's recommendations.
b. Immediate-use steam sterilization should never be used for reasons of convenience, as an alternative to purchasing additional instrument sets, or to save time. This practice should be reserved only for patient care items that will be used immediately in emergency situations when no other options are available.
c. Additional recommendations available at CDC and HIPAC Guideline for Disinfection and Sterilization in Healthcare Facilities 2008.[58]

Surgical attire and drapes

a. Wear a surgical mask that fully covers the mouth and nose when entering the operating room if an operation is about to begin or already under way, or if sterile instruments are exposed. Wear the mask throughout the operation.
b. Wear a new, disposable, or hospital-laundered head covering for each case, when entering the operating room. Ensure it fully covers all hair on the head and all facial hair not covered by the surgical mask.
c. Wear sterile gloves if serving as a member of the scrubbed surgical team. Put on sterile gloves after donning a sterile gown.
d. Use surgical gowns and drapes that are effective barriers when wet (i.e., materials that resist liquid penetration).
e. Change scrub suits that are visibly soiled, contaminated, and/or penetrated by blood or other potentially infectious materials.[21]

Sterile and surgical technique

a. Adhere to principles of sterile technique when performing all invasive surgical procedures
b. If drainage is necessary, use a closed suction drain. Place a drain through a separate incision distant from the operative incision. Remove the drain as soon as possible.[21]

Parenteral antimicrobial prophylaxis

a. Administer preoperative antimicrobial agents only when indicated based on published clinical practice guidelines and timed such that an inhibitory concentration of the agents is established in the serum and tissues when the incision is made.
b. In clear and clean-contaminated procedures, do not administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room.[20]

Glycemic control

a. mplement perioperative glycemic control and use blood glucose target levels <200 mg/dL in patients with and without diabetes.[20]

Normothermia

a. Maintain perioperative normothermia.[20]

Oxygenation

a. For patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation, administer increased FiO2 during surgery and after extubation in the immediate postoperative period. To optimize tissue oxygen delivery, maintain perioperative normothermia and adequate volume replacement.[20]

Postoperative incision care

a. Protect primarily closed incisions with a sterile dressing for 24–48 hours postoperatively.
b. Do not apply antimicrobial agents (i.e. ointments, solutions, or powders) to the surgical incision for the prevention of SSI.[21]

patient-related risk factors include tobacco use and colonization with microorganisms. Perioperative interventions that decrease the risk of SSIs include antiseptic prophylaxis, skin preparation, and glycemic and temperature control.

Tobacco cessation

Multiple studies have described the increased risk of SSIs among smokers after general and orthopedic surgery. Smoking induces vasoconstriction of the vessels in the surgical bed, leading to a reduction

in the oxygenation and nutrients needed for an immune response and wound healing. Tobacco cessation is recommended for a minimum of 30 days before elective operations.[21] A multicenter RCT of 120 smokers undergoing hip and knee replacement found patients randomized to the smoking cessation group 6 to 8 weeks before elective surgery had a significantly decreased incidence of SSIs (5%) compared to the control group (31%) (p = 0.001).[43]

Preoperative *Staphylococcus aureus* screening and decolonization

Nasal colonization with *S. aureus* occurs in approximately 30% of the US population and increases the risk of SSIs 2- to 14-fold.[44,45] Perioperative mupirocin ointment is a safe and inexpensive treatment that reduces the rates of *S. aureus* nasal carriage and postoperative infection. In an RCT of 891 patients with nasal carriage of *S. aureus* undergoing general, gynecologic, neurologic, or cardiothoracic surgery, patients randomized to mupirocin had a significantly decreased rate of *S. aureus* SSIs (4.0%) compared with those receiving placebo (7.7%) (p <0.02).[46] These results were confirmed in a meta-analysis of three randomized trials and four before-after trials assessing the risk of SSIs following perioperative intranasal mupirocin versus usual care in non-general surgery (cardiothoracic, orthopedic, and neurosurgery) patients.[47] The ASHP recommends preoperative *S. aureus* screening and nasal decolonization for all patients undergoing total joint replacement and cardiac procedures. A typical preoperative *S. aureus* decolonization protocol includes the application of 2% nasal mupirocin twice a day for 5 days. Because *S. aureus* can develop resistance to mupirocin, universal *S. aureus* screening and decolonization are not recommended in the general population.

Antiseptic prophylaxis

Patients are advised to shower or bathe their full body with antimicrobial or non-antimicrobial soap or an antiseptic agent on at least the night before the operative day.[20] Perioperative bathing or showering with chlorhexidine is a well-accepted practice for reducing skin bacteria; however, no evidence suggests a benefit of chlorhexidine compared to other wash products for the reduction of SSIs. A 2015 Cochrane Database Systematic Review examined six high-quality RTCs comparing the efficacy of perioperative 4% chlorhexidine gluconate washes to nonantiseptic shower or bathing products for preventing SSIs.[48] Chlorhexidine did not significantly reduce the risk of SSI compared to placebo in a meta-analysis of three RTCs comprising 7,791 patients. Similarly, a meta-analysis of three RTCs including 1,443 patients found no significant difference in SSI rates between chlorhexidine and bar soap.[48]

Hair removal and skin preparation

Removal of hair preoperatively is not recommended unless the hair at or around the incision site will interfere with the operation.[21] If hair removal is necessary, it should be performed immediately before the operation with clippers. Shaving with a razor is not advised as microscopic abrasions and cuts are created, allowing pathogens to cross the natural skin barrier. Intraoperative skin preparation with an alcohol-based antiseptic agent is recommended unless contraindicated.[21] Alcohol-based solutions have a rapid bactericidal effect but the antimicrobial effect is not as persistent as that of iodine- or chlorhexidine-based solutions.

Glycemic control

Perioperative glycemic control is recommended with a target blood glucose level of <200 mg/dL in diabetic and non-diabetic patients.[20] Hyperglycemia is associated with multiple adverse consequences including increased risk of mortality during surgical intensive care unit admissions. Multiple studies have found intensive perioperative glycemic control is associated with increased episodes of hypoglycemia without decreasing the risk of SSIs. In an RCT comparing intensive glycemic control (80–100 mg/dL) to conventional glycemic control (<200 mg/dL) among patients undergoing cardiac surgery ($n = 371$), intensive glycemic control increased the risk of mortality and stroke without reducing the length of intensive care unit and hospital stay.[49] A single-center RCT comparing intensive glycemic control (80–130 mg/dL) with conventional glycemic control (160–200 mg/dL) in cardiac surgery patients ($n = 109$) found no significant difference in the composite infection outcome, including pneumonia, urinary tract infection, sepsis, septic shock, wound infection, bloodstream infection, and catheter infection.[50] Both studies concluded that intensive glycemic control provides no additional morbidity or mortality benefit compared to conventional glycemic control.

Normothermia

Maintenance of perioperative normothermia is recommended for the prevention of SSI. Hypothermia triggers thermoregulatory vasoconstriction leading to a decrease in oxygen levels in the surgical bed. A reduced level of oxygen in the tissues impairs neutrophil production of superoxide radicals used in the oxidative killing of surgical pathogens. In addition, other immune functions are directly impaired by hypothermia, including chemotaxis and phagocytosis of granulocytes, motility of macrophages, and productions of antibodies.[51] Multiple studies have found normothermia decreases the incidence of SSI. In an RCT of 200 patients undergoing colorectal surgery, the normothermia group had a significantly lower rate of SSI (6%) compared to the hypothermia group (19%) (p = 0.009). The duration of hospitalization was also significantly reduced in the normothermia group by 2.6 days (p = 0.01).[51] In a study of 421 patients undergoing clean (breast, varicose vein, or hernia) surgery, the warmed group had significantly decreased rate of SSI (5%) compared to the nonwarmed group (14%) (p = 0.001).[52]

Oxygenation

Administration of increased fraction of inspired oxygen (FIO_2) during surgery and after extubation in the immediate postoperative period is recommended for patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation. Maintenance of perioperative normothermia and adequate volume replacement optimize tissue oxygen delivery.[48] Neutrophil production of bactericidal superoxide radicals depends on the partial pressure of oxygen in tissues. Optimizing the partial pressure of oxygen in tissues

allows for neutrophilic oxidative killing for prevention of SSIs. Three double-blind RCTs found administering supplemental inspired oxygen was an effective intervention for reducing SSIs. In an RCT of 500 patients undergoing colorectal resection, the risk of SSI among patients receiving 80% FIO_2 was 50% lower compared to patients receiving 30% FIO_2 (11.2%).[53] An RCT of 300 patients undergoing elective colorectal surgery found administration of 80% FIO_2 was protective against SSIs (RR 0.61, 95% CI [0.38, 0.98]).[54] In an RCT study of 210 patients undergoing open appendectomy, oxygenation with 80% FIO_2 reduced the risk of SSI (5.6% versus 13.6%, p = 0.04) and the mean hospital stay (2.51 days versus 2.92 days, p = 0.01).[55]

Postoperative wound management

Protection of primarily closed incisions with a sterile dressing for 24 to 48 hours postoperatively is recommended. Triclosan antibiotic-coated sutures should be considered for the prevention of SSI. Topical antimicrobial agents (ointments, solutions, or powders) applied to the surgical incision for the prevention of SSI are not recommended. The literature is mixed regarding the use of intraoperative antimicrobial irrigation and antimicrobial dressing applied to surgical incisions after primary closure in the operating room for the prevention of SSI.

Suggested reading

Ban KA, Minei JP, Laronga C, et al. American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update. *J Am Coll Surg*. 2017;224(1):59–74.

Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg*. 2017;152(8):784–791.

Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Sys Pharm*. 2013;70(3):195–283.

References

1. Forum NQ. National Quality Forum Endorsed Measure for Surgical Procedures, 2015–2017. https://www.qualityforum.org/Publications/2017/04/Surgery_2015-2017_Final_Report.aspx
2. Mu Y, Edwards JR, Horan TC, Berrios-Torres SI, Fridkin SK. Improving risk-adjusted measures of surgical site infection for the national healthcare safety network. *Infect Contr Hosp Epidemiol*. 2011;32(10):970–986.
3. McKibben L, Horan T, Tokars JI, et al. Guidance on public reporting of healthcare-associated infections: Recommendations of the Healthcare Infection Control Practices Advisory Committee. *Am J Infect Contr*. 2005;33(4):217–226.
4. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. *Infect Contr Hosp Epidemiol*. 2016;37(11):1288–301.
5. Urban JA. Cost analysis of surgical site infections. *Surg Infect*. 2006;7 Suppl 1: S19–22.
6. Merkow RP, Ju MH, Chung JW, et al. Underlying reasons associated with hospital readmission following surgery in the United States. *JAMA*. 2015;313(5):483–495.
7. Zimlichman E, Henderson D, Tamir O, et al. Health care-associated infections: A meta-analysis of costs and financial impact on the US health care system. *JAMA Inter Med*. 2013;173(22):2039–2046.
8. Fry DE. Fifty ways to cause surgical site infections. *Surg Infect*. 2011;12(6):497–500.
9. Umscheid CA, Mitchell MD, Doshi JA, Agarwal R, Williams K, Brennan PJ. Estimating the proportion of healthcare-associated infections that are reasonably preventable and the related mortality and costs. *Infect Contr Hosp Epidemiol*. 2011;32(2):101–114.
10. Centers for Disease Control and Prevention. National Healthcare Surveillance Network. https://www.cdc.gov/nhsn/index.html.
11. Rosenberger LH, Politano AD, Sawyer RG. The surgical care improvement project and prevention of post-operative infection, including surgical site infection. *Surg Infect*. 2011;12(3):163–168.
12. Centers for Medicare and Medicaid Services. Physician Quality Reporting System. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/index.html?redirect=/PQRS/.
13. National Healthcare Safety Network. Surgical site infection (SSI) event. http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf
14. Ortega G, Rhee DS, Papandria DJ, et al. An evaluation of surgical site infections by wound classification system using the ACS-NSQIP. *J Surg Res*. 2012;174(1):33–38.
15. Gaynes R, Edwards JR. Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis*. 2005;41(6):848–854.
16. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: Antimicrobial-resistant pathogens associated with healthcare-associated infections: Annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infect Contr Hosp Epidemiol*. 2008;29(11):996–1011.
17. Weigelt JA, Lipsky BA, Tabak YP, Derby KG, Kim M, Gupta V. Surgical site infections: Causative pathogens and associated outcomes. *Am J Infect Contr*. 2010;38(2):112–120.
18. Ban KA, Minei JP, Laronga C, et al. American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update. *J Am Coll Surg*. 2017;224(1):59–74.
19. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70(3):195–283.
20. Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surg*. 2017;152(8):784–791.
21. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Contr*. 1999;27(2):97–132; quiz 3–4; discussion 96.
22. Anderson DJ, Podgorny K, Berrios-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Contr Hosp Epidemiol*. 2014;35(Suppl 2): S66–88.
23. Steinberg JP, Braun BI, Hellinger WC, et al. Timing of antimicrobial prophylaxis and the risk of surgical site infections: Results from the Trial to Reduce Antimicrobial Prophylaxis Errors. *Ann Surg*.2009;250(1):10–16.

24. Edmiston CE, Krepel C, Kelly H, et al. Perioperative antibiotic prophylaxis in the gastric bypass patient: Do we achieve therapeutic levels? *Surgery*. 2004;136(4):738–747.
25. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis*. 2018;66(3):329–336.
26. Harbarth S, Samore MH, Lichtenberg D, Carmeli Y. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. *Circulation*. 2000;101(25):2916–2921.
27. Schussler O, Dermine H, Alifano M, et al. Should we change antibiotic prophylaxis for lung surgery? Postoperative pneumonia is the critical issue. *Ann Thorac Surg*. 2008;86(6):1727–1733.
28. Gossner L, Keymling J, Hahn EG, Ell C. Antibiotic prophylaxis in percutaneous endoscopic gastrostomy (PEG): A prospective randomized clinical trial. *Endoscopy*.1999;31(2):119–124.
29. Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. *Cochrane Database Syst Rev*.2003;(2):CD001439.
30. Sanchez-Manuel FJ, Lozano-Garcia J, Seco-Gil JL. Antibiotic prophylaxis for hernia repair. *Cochrane Database Syst Rev*.2012;(2):CD003769.
31. Nelson RL, Glenny AM, Song F. Antimicrobial prophylaxis for colorectal surgery. *Cochrane Database Syst Rev*.2009;(1):CD001181.
32. Kiran RP, Murray AC, Chiuzan C, Estrada D, Forde K. Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. *Ann Surg*. 2015;262(3):416–425; discussion 23–25.
33. Morris MS, Graham LA, Chu DI, Cannon JA, Hawn MT. Oral antibiotic bowel preparation significantly reduces surgical site infection rates and readmission rates in elective colorectal surgery. *Ann Surg*. 2015;261(6):1034–1040.
34. Avenia N, Sanguinetti A, Cirocchi R, et al. Antibiotic prophylaxis in thyroid surgery: A preliminary multicentric Italian experience. *Ann Surg Innovat Res*. 2009;3:10.
35. Dhiwakar M, Clement WA, Supriya M, McKerrow W. Antibiotics to reduce post-tonsillectomy morbidity. *Cochrane Database Syst Rev*. 2010;(7):CD005607.
36. McCarthy PJ, Patil S, Conrad SA, Scott LK. International and specialty trends in the use of prophylactic antibiotics to prevent infectious complications after insertion of external ventricular drainage devices. *Neurocrit Care*. 2010;12(2):220–224.
37. Alleyne CH, Jr., Hassan M, Zabramski JM. The efficacy and cost of prophylactic and perioprocedural antibiotics in patients with external ventricular drains. *Neurosurgery*. 2000;47(5):1124–1127; discussion 7–9.
38. Smaill F, Hofmeyr GJ. Antibiotic prophylaxis for cesarean section. *Cochrane Database Syst Rev*. 2002;(3):CD000933.
39. Costantine MM, Rahman M, Ghulmiyah L, et al. Timing of perioperative antibiotics for cesarean delivery: A metaanalysis. *Am J Obstet Gynecol*. 2008;199(3):301.e1–6.
40. Petignat C, Francioli P, Harbarth S, et al. Cefuroxime prophylaxis is effective in noninstrumented spine surgery: A double-blind, placebo-controlled study. *Spine*. 2008;33(18):1919–1924.
41. Southwell-Keely JP, Russo RR, March L, Cumming R, Cameron I, Brnabic AJ. Antibiotic prophylaxis in hip fracture surgery: A metaanalysis. *Clin Orthopaed Related Res*. 2004;(419):179–184.
42. AlBuhairan B, Hind D, Hutchinson A. Antibiotic prophylaxis for wound infections in total joint arthroplasty: A systematic review. *J Bone Joint Surg. Br Vol*. 2008;90(7):915–919.
43. Sorensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: A randomized controlled trial. *Ann Surg*. 2003;238(1):1–5.
44. Kluytmans JA, Mouton JW, Ijzerman EP, et al. Nasal carriage of Staphylococcus aureus as a major risk factor for wound infections after cardiac surgery. *J Infect Dis*. 1995;171(1):216–219.
45. Gorwitz RJ, Kruszon-Moran D, McAllister SK, et al. Changes in the prevalence of nasal colonization with Staphylococcus aureus in the United States, 2001–2004. *J Infect Dis*. 2008;197(9):1226–1234.
46. Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. *N Engl J Med*. 2002;346(24):1871–1877.
47. Kallen AJ, Wilson CT, Larson RJ. Perioperative intranasal mupirocin for the prevention of surgical-site infections: Systematic review of the literature and meta-analysis. *Infect Contr Hosp Epidemiol*. 2005;26(12):916–22.
48. Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. *Cochrane Database Syst Rev*.2015;(2):CD004985.
49. Gandhi GY, Nuttall GA, Abel MD, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: A randomized trial. *Ann Intern Med*.2007;146(4):233–243.
50. Chan RP, Galas FR, Hajjar LA, Bello CN, Piccioni MA, Auler JO, Jr. Intensive perioperative glucose control does not improve outcomes of patients submitted to open-heart surgery: A randomized controlled trial. *Clinics* (*Sao Paulo, Brazil*). 2009;64(1):51–60.
51. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med*. 1996;334(19):1209–1215.
52. Melling AC, Ali B, Scott EM, Leaper DJ. Effects of preoperative warming on the incidence of wound infection after clean surgery: A randomised controlled trial. *Lancet*. 2001;358(9285):876–880.
53. Greif R, Akca O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med*. 2000;342(3):161–167.
54. Belda FJ, Aguilera L, Garcia de la Asuncion J, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: A randomized controlled trial. *JAMA*. 2005;294(16):2035–2042.
55. Bickel A, Gurevits M, Vamos R, Ivry S, Eitan A. Perioperative hyperoxygenation and wound site infection following surgery for acute appendicitis: A randomized, prospective, controlled trial. *Arch Surg.* (*Chicago, Ill. 1960)*. 2011;146(4):464–470.
56. Centers for Disease Control and Prevention HICPAC. Guideline for hand hygiene in healthcare settings: Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *MMWR*. 2005;51(RR-16):1–56.
57. Facilities Guideline Institute, American Society for Healthcare Engineering, American Hospital Association. Guidelines for design and construction of hospitals and outpatient facilities 2014. https://www.ashe.org/advocacy/orgs/fgi
58. Centers for Disease Control and Prevention HICPAC, Rutala WA, Weber DJ. Guideline for disinfection and sterilization in healthcare facilities, 2008. https://www.cdc.gov/infectioncontrol/guidelines/disinfection/index.html

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Immunizations

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Long-lasting immunity against many serious infectious diseases can be elicited through *active immunization*, the administration of specific antigens (killed or attenuated microorganisms; purified polysaccharides, proteins, or other components; or recombinant antigens produced by genetic engineering) that stimulate the recipient host's production of protective antibodies. New vaccine technologies include using mRNA (messenger RNA) or DNA in vaccines that enable cells in recipients' bodies to produce the specific targeted antigens that will subsequently elicit a protective immune response. Vaccine doses may be given orally, administered as mucosal vaccines, or given by injection using intradermal, subcutaneous, or intramuscular routes. *Passive immunization* is the process by which protective immunity is obtained through transfer of preformed antibodies from an immune host to a nonimmune recipient, either as immunoglobulin or antibody-specific immunoglobulin.

Protective efficacy resulting from active immunization with a vaccine depends on several factors: the age of the host, with decreased efficacy of certain vaccines observed in the very young and very old; the immune status of the host, with decreased efficacy observed in persons with compromised immune status because of disease or therapy; and the characteristics of the vaccine product itself.

In active immunization, protective levels of specific antibodies usually develop within 2 to 4 weeks upon completion of the primary immunization regimen. The antibody response may be recalled and boosted when the immune system is challenged by additional "booster" doses of the vaccine antigen(s) or by exposure to the naturally occurring pathogen. Passive immunization can confer rapid protection, but serum levels of protective antibodies in recipients are highest immediately after receipt, decreasing with the passage of time, and there is no immune recall on challenge.

Several different vaccines may be administered concomitantly at separate sites without decreased efficacy, although the timing and sequence of vaccines have to be taken into account. For example, when immunoglobulin is given for passive immunization against hepatitis A, antibodies against several common infections in addition to antibodies against hepatitis A may be present in sufficient amounts to interfere with the response to the corresponding vaccines. Immunoglobulin should not be given for 3 months before or 3 weeks after measles, mumps, and rubella vaccine and not for 2 months after varicella vaccine. However, vaccines against tetanus, diphtheria, yellow fever, typhoid fever, hepatitis B, rabies, and meningococcal meningitis can be given on the same day as immunoglobulin. If immunoglobulin is given on the same day as hepatitis A vaccine, the vaccine is still efficacious, although the resulting peak antibody titer is lower than when the vaccine is given alone.

The US Food and Drug Administration (FDA) is responsible for licensure of all pharmaceuticals including vaccine products for use in the United States. The Advisory Committee on Immunization Practices (ACIP) at the Centers for Disease Control and Prevention (CDC) issues recommendations for routine use of vaccines in children and adolescents, harmonizing its recommendations to the greatest extent possible with those issued by the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetrics and Gynecology (ACOG). The ACIP recommendations for routine use of vaccines in adults are harmonized with those of the AAFP, ACOG, and the American College of Physicians (ACP).

Federal law requires that potential vaccine recipients be informed of the potential benefits and possible adverse side effects of each vaccine. Vaccine Information Statements (VISs) prepared by the CDC are used for this purpose: these forms can be downloaded and copies printed for use in patient education from the CDC website (http://www.cdc.gov/vaccines/hcp/vis/index.html). The VISs are available in English and 40 additional languages.

Tolerance to minor adverse effects associated with each vaccine and the potential for more serious vaccine-associated symptoms must be taken into account in the person who is a candidate for multiple vaccine doses on the same day. If clinically significant adverse events are associated with any vaccination, such occurrences should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).

Childhood and adolescent immunizations

The routine immunizations recommended during childhood and adolescence cover communicable diseases of public health importance that cause significant morbidity and mortality in susceptible populations. The ACIP immunization schedules are updated and published on an annual basis, and interim updated recommendations are published in the *Morbidity and Mortality Weekly Report* (*MMWR*) as needed. Figure 113.1 shows the immunization schedule for persons aged 0 through 18 years according to recommendations from the CDC ACIP (http://www.cdc.gov/vaccines/acip/index.html).

In the following summary, minimal ages for administration of the first dose of the various vaccines are given, and the detailed schedule for subsequent doses may be found in Figure 113.1. Figure 113.2 provides the CDC ACIP schedule for catch-up immunizations. The minimal interval between doses shown in this figure can be used to reset the schedule for a given vaccine series in persons aged 4 months through 18 years who start late or who are more than 1 month behind the recommended schedule. If more time elapses than the recommended interval between scheduled doses in a vaccine series, the series does not need to be restarted, but the next dose(s) should be administered according to the recommended intervals until the series is complete.

At birth, the first dose of the hepatitis B vaccine three-dose series (HepB: Recombivax HB, Merck; Engerix-B, GlaxoSmithKline) is initiated. At 2 months of age, the first doses of the following vaccine series are given: rotavirus (RV-1: Rotarix, GlaxoSmithKline; RV-5: RotaTeq, Merck), diphtheria, tetanus and acellular pertussis (DTaP: Daptacel, Sanofi Pasteur; Infanrix, GlaxoSmithKline), *Haemophilus influenzae* type b conjugate (Hib PRP-T: ActHIB, Sanofi Pasteur; Hiberix, GlaxoSmithKline; or Hib PRP-OMP: PedvaxHIB, Merck), pneumococcal conjugate (PCV13: Prevnar 13, Sanofi Pasteur) and inactivated poliovirus (IPV: Ipol, Sanofi Pasteur).

At 6 months of age, annual flu vaccination commences with inactivated influenza vaccine (IIV: Fluarix, Glaxo-SmithKline; Fluvirin, Chiron; Fluzone, Sanofi Pasteur) or live attenuated influenza vaccine administered intranasally (LAIV4: FluMist Quadrivalent, AstraZeneca). At 12 months of age, the first doses of measles, mumps, and rubella (MMR: M-M-R II, Merck), varicella (VAR: Varivax, Merck) and hepatitis A (HepA: Havrix, GlaxoSmithKline; Vaqta, Merck) vaccines are recommended. Varicella vaccine may be administered at the same time as the MMR vaccine. Both VAR and MMR are live-virus vaccines administered by injection. If the two vaccines are not given simultaneously at different sites, the vaccine doses should be separated by 28 days if possible to reduce or eliminate possible interference of the vaccine given first with the vaccine given second. A second dose of MMR and VAR vaccines is recommended for children, between 4 and 6 years old on entry into school to boost waning immunity from the first dose received in infancy.

The ACIP recommends *routine* vaccination of adolescents at 11 to 12 years of age with quadrivalent meningococcal conjugate vaccine (MenACWY) against meningococcal serogroups A, C, Y, W-135 disease, with a booster dose at 16 years old. MenACWY vaccines available in the US are: meningococcal groups ACWY polysaccharide diphtheria toxoid conjugate vaccine (MenACWY-D: Menactra, Sanofi Pasteur) meningococcal groups ACWY polysaccharide CRM197 conjugate vaccine (MenACWY-CRM: Menveo, Novartis), and meningococcal groups ACWY polysaccharide tetanus toxoid conjugate vaccine (MenACWY-TT: MenQuadfi, Sanofi Pasteur) If the first dose of MenACWY vaccine is received between 13 and 15 years old, a booster should be given at 18 years of age. MenACWY vaccine is also recommended for some infants and children with certain medical conditions. Meningococcal group B (MenB) vaccination is recommended only for *selected* groups of children, adolescents and adults (10 through 25 years of age) and certain adults ≥26 years of age at increased risk for meningococcal serogroup B disease due to certain underlying chronic medical conditions (complement component deficiencies; anatomic or functional asplenia, including sickle cell disease; treatment with eculizumab) or persons who are at increased risk of exposure (laboratory personnel; community or institutional outbreak of meningococcal serogroup B disease). At the time of writing, two MenB vaccines are commercially available (MenB-4C: Bexsero, Novartis; MenB-FHbp: Trumenba, Wyeth).

The immunization status of tetanus, diphtheria, and acellular pertussis vaccine should be reviewed among 11- to 12-year-olds as well. The ACIP recommends a single dose of the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine for persons aged 11 through 18 years who completed the recommended childhood DTP/DTaP vaccinations series. There are two Tdap vaccines: one is licensed for use in persons aged 10 through 64 years (Boostrix, GlaxoSmithKline) and the other is licensed for use in persons aged 11 through 64 years (Adacel, Sanofi Pasteur), and both are licensed for use at an interval of at least 5 years between the Td and Tdap dose. However, due to the poor control of pertussis observed in the United States in recent years, ACIP now recommends expanded use of Tdap. Tdap vaccine may be given *regardless of interval* since the last tetanus-toxoid- or diphtheria-toxoid-containing vaccine, it may be used in undervaccinated children aged 7 through 10 years, and it may be used in certain adults aged ≥65 years according to current ACIP recommendations.

Table 1 Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2021

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Table 2). School entry and adolescent vaccine age groups are shaded in gray.

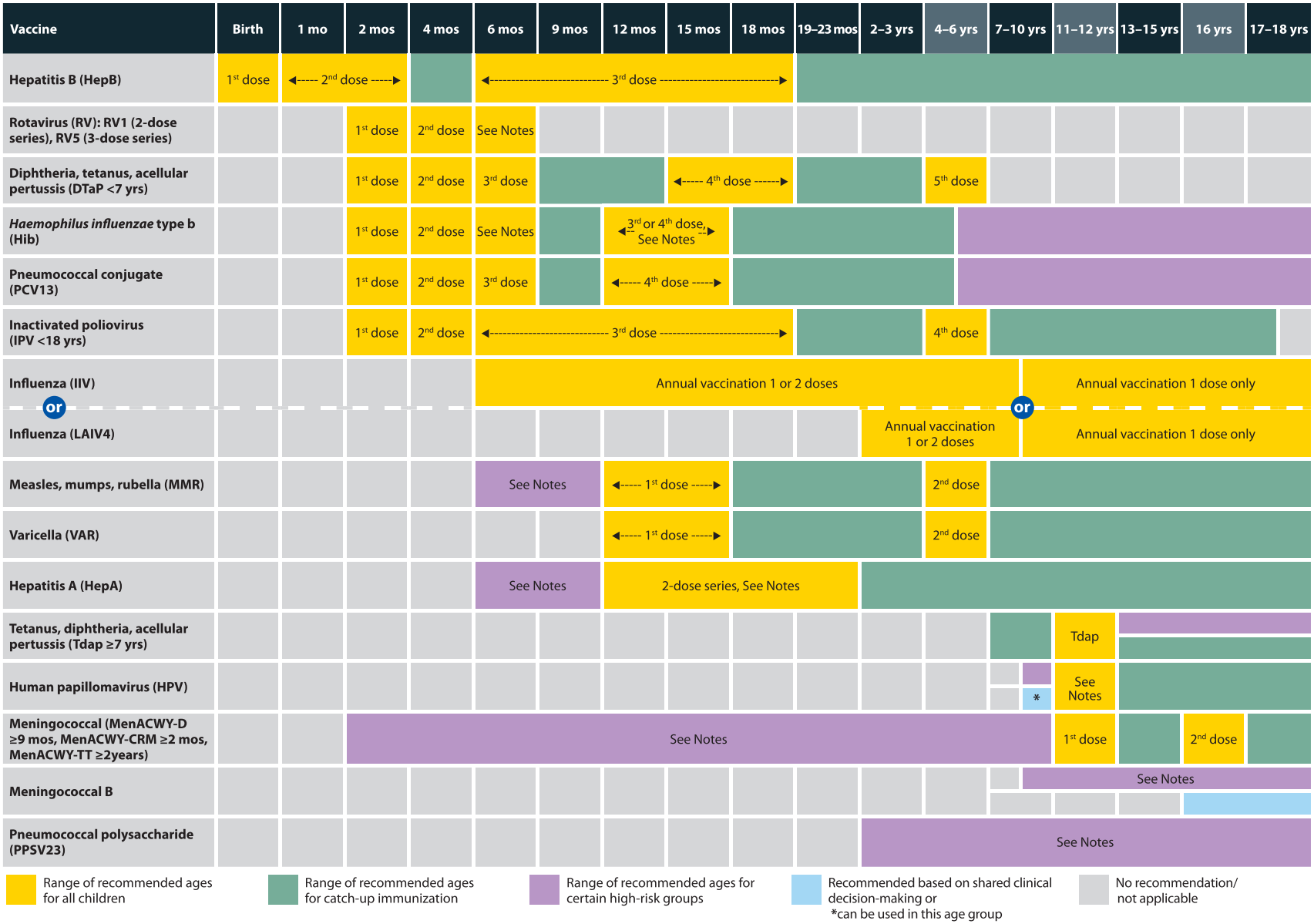

FIGURE 113.1

Table 2 Recommended Catch-up Immunization Schedule for Children and Adolescents Who Start Late or Who Are More than 1 month Behind, United States, 2021

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. **Always use this table in conjunction with Table 1 and the notes that follow.**

Children age 4 months through 6 years					
Vaccine	**Minimum Age for Dose 1**	**Minimum Interval Between Doses**			
		Dose 1 to Dose 2	**Dose 2 to Dose 3**	**Dose 3 to Dose 4**	**Dose 4 to Dose 5**
Hepatitis B	Birth	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose.** Minimum age for the final dose is 24 weeks.		
Rotavirus	6 weeks Maximum age for first dose is 14 weeks, 6 days.	**4 weeks**	**4 weeks** Maximum age for final dose is 8 months, 0 days.		
Diphtheria, tetanus, and acellular pertussis	6 weeks	**4 weeks**	**4 weeks**	**6 months**	**6 months**
Haemophilus influenzae type b	6 weeks	**No further doses needed** if first dose was administered at age 15 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose)** if first dose was administered at age 12 through 14 months.	**No further doses needed** if previous dose was administered at age 15 months or older. **4 weeks** if current age is younger than 12 months ***and*** first dose was administered at younger than age 7 months ***and*** at least 1 previous dose was PRP-T (ActHib, Pentacel, Hiberix) or unknown. **8 weeks *and* age 12 through 59 months (as final dose)** if current age is younger than 12 months ***and*** first dose was administered at age 7 through 11 months; OR if current age is 12 through 59 months ***and*** first dose was administered before the 1st birthday ***and*** second dose was administered at younger than 15 months; OR if both doses were PRP-OMP (PedvaxHIB, Comvax) ***and*** were administered before the 1st birthday.	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal conjugate	6 weeks	**No further doses needed** for healthy children if first dose was administered at age 24 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose for healthy children)** if first dose was administered at the 1st birthday or after.	**No further doses needed** for healthy children if previous dose was administered at age 24 months or older. **4 weeks** if current age is younger than 12 months and previous dose was administered at <7 months old. **8 weeks (as final dose for healthy children)** if previous dose was administered between 7–11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was administered before age 12 months.	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus	6 weeks	**4 weeks**	**4 weeks** if current age is <4 years. **6 months (as final dose)** if current age is 4 years or older.	**6 months** (minimum age 4 years for final dose).	
Measles, mumps, rubella	12 months	**4 weeks**			
Varicella	12 months	**3 months**			
Hepatitis A	12 months	**6 months**			
Meningococcal ACWY	2 months MenACWY-CRM 9 months MenACWY-D 2 years MenACWY-TT	**8 weeks**	See Notes	See Notes	
Children and adolescents age 7 through 18 years					
Meningococcal ACWY	Not applicable (N/A)	**8 weeks**			
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis	7 years	**4 weeks**	**4 weeks** if first dose of DTaP/DT was administered before the 1st birthday. **6 months (as final dose)** if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday.	**6 months** if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus	9 years	**Routine dosing intervals are recommended.**			
Hepatitis A	N/A	**6 months**			
Hepatitis B	N/A	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose.**		
Inactivated poliovirus	N/A	**4 weeks**	**6 months** A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.	A fourth dose of IPV is indicated if all previous doses were administered at <4 years or if the third dose was administered <6 months after the second dose.	
Measles, mumps, rubella	N/A	**4 weeks**			
Varicella	N/A	**3 months** if younger than age 13 years. **4 weeks** if age 13 years or older.			

FIGURE 113.2

ACIP recommends routine human papilloma virus (HPV) vaccination of females aged 11 or 12 years old, catch-up vaccination for females aged 13 to 26 years old, and administration as early as 9 years old if the girl is at risk of exposure. HPV vaccine is contraindicated in pregnancy, but may be used in lactating women. ACIP also recommends routine HPV vaccination of males aged 11 to 12 years, and males 13 to 21 years not vaccinated previously. Additionally, the ACIP recommends routine HPV vaccination through the age of 26 years for men who have sex with men (MSM) because of increased risk for disease associated with HPV, and for immunocompromised males (including those with HIV infection).

The HPV vaccine (HPV: Gardisil 9, Merck) is an inactivated recombinant nine-valent vaccine directed against nine HPV types associated with human disease. The vaccine is given as a series of two or three doses depending on age at initial vaccination, and it is given by intramuscular injection. All nine HPV types covered by the vaccine (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) may cause precancerous or dysplastic genital lesions in both males and females; Types 16, 18, 31, 33, 45, 52, and 58 may cause cervical, vulvar, vaginal, and anal cancers in females and anal cancer in males; Types 6 and 11 are associated with genital warts.

Although clinical trials of concomitant administration of HPV vaccine with the other vaccines recommended for adolescents have not been performed, there are no theoretical reasons not to administer the first dose of HPV during the same clinic visit as MenACWY and Tdap vaccines, with the vaccines being administered at different anatomic sites.

Combination vaccines

The number of recommended early childhood immunizations creates issues of compliance and scheduling for parents, patients, and healthcare providers. Several commercially prepared combination vaccines are available for pediatric use (Table 113.1), and their use, when appropriate, instead of individual vaccines administered by separate injections is encouraged to promote patient and parent compliance. However, special care must be taken in terms of scheduling missed doses, completing a vaccine series with a different vaccine product than originally used, and recognizing differences in antigen content and dose scheduling between monovalent vaccines and corresponding combination vaccines. For more details pertaining to adaptation of the recommended vaccine schedule for special situations, see Figure 113.2, Figure 113.3, and 113.4.

Adult immunizations

Recommendations for adult immunizations are based on the history of immunizations received in the past and on the need to give booster doses for certain vaccines. A detailed review of the personal immunization history is indicated for international travelers, healthcare workers, and other persons who have risks of exposure related to occupational activities, advanced age, or compromised immune status due to disease (HIV), medications, cancer, or other chronic medical conditions.

The immunization history should be updated and documented at the time of initial intake into a primary care practice, during interim health maintenance visits, on employment in one of the healthcare or social services professions, and/or prior to international travel. Travel immunizations will be covered in Chapter 114, "Advice for travelers." If the immunization history of the person is uncertain or unknown, a conceptual framework of the prevalent practices pertaining to childhood, school, military service, and occupational immunization programs and standards will be helpful for assessing the current immunization status. The recommended adult immunization schedule is given in Figure 113.5. The recommended adult immunization schedule by medical condition and other indications and detailed notes are given in Figures 113.6 and 113.7.

Routine immunizations for adults

Tetanus and diphtheria and acellular pertussis vaccine

The combined diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) series is a routine immunization of childhood. A formulation of the tetanus and diphtheria vaccine (Td) (Tenivac, Sanofi

TABLE 113.1 **SELECTED FDA-LICENSED COMBINATION VACCINES**[a]

Vaccine product	Age range
DTaP-IPV-HepB (Pediarix, GlaxoSmithKline)	6 weeks through 7 years
DTaP-IPV-Hib-HepB (Vaxelis, MSP Vaccine)	6 weeks through 4 years
DTap-IPV/Hib (Pentacel, Sanofi Pasteur)	2 months through 5 years
DTaP-IPV (Kinrix, GlaxoSmithKline; Quadracel, Sanofi Pasteur)	4 through 6 years
HepA-HepB (Twinrix, GlaxoSmithKline)	18 years or older
Hib-HepB (Comvax, Merck)	6 weeks through 5 years
MMRV (ProQuad, Merck)	12 months through 12 years

[a] Consult the package insert for details of licensed use for each combination vaccine.

Table 3 Recommended Child and Adolescent Immunization Schedule by Medical Indication, United States, 2021

Always use this table in conjunction with Table 1 and the notes that follow.

VACCINE	INDICATION									
	Pregnancy	Immunocompromised status (excluding HIV infection)	HIV infection CD4+ count[1]: <15% and total CD4 cell count of <200/mm³	HIV infection CD4+ count[1]: ≥15% and total CD4 cell count of ≥200/mm³	Kidney failure, end-stage renal disease, or on hemodialysis	Heart disease or chronic lung disease	CSF leak or cochlear implant	Asplenia or persistent complement component deficiencies	Chronic liver disease	Diabetes
Hepatitis B										
Rotavirus		SCID[2]								
Diphtheria, tetanus, and acellular pertussis (DTaP)										
Haemophilus influenzae type b										
Pneumococcal conjugate										
Inactivated poliovirus										
Influenza (IIV)										
or										
Influenza (LAIV4)						Asthma, wheezing: 2–4yrs[3]				
Measles, mumps, rubella	*									
Varicella	*									
Hepatitis A										
Tetanus, diphtheria, and acellular pertussis (Tdap)										
Human papillomavirus	*									
Meningococcal ACWY										
Meningococcal B										
Pneumococcal polysaccharide										

- Vaccination according to the routine schedule recommended
- Recommended for persons with an additional risk factor for which the vaccine would be indicated
- Vaccination is recommended, and additional doses may be necessary based on medical condition. See Notes.
- Not recommended/ contraindicated—vaccine should not be administered.
- *Vaccinate after pregnancy.
- Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction
- No recommendation/not applicable

1 For additional information regarding HIV laboratory parameters and use of live vaccines, see the *General Best Practice Guidelines for Immunization*, "Altered Immunocompetence," at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html and Table 4-1 (footnote D) at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.
2 Severe Combined Immunodeficiency
3 LAIV4 contraindicated for children 2–4 years of age with asthma or wheezing during the preceding 12 months

FIGURE 113.3

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2021

For vaccination recommendations for persons ages 19 years or older, see the Recommended Adult Immunization Schedule, 2021.

Additional information

COVID-19 Vaccination

ACIP recommends use of COVID-19 vaccines within the scope of the Emergency Use Authorization or Biologics License Application for the particular vaccine. Interim ACIP recommendations for the use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/hcp/acip-recs/.

- Consult relevant ACIP statements for detailed recommendations at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For information on contraindications and precautions for the use of a vaccine, consult the *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html and relevant ACIP statements at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For calculating intervals between doses, 4 weeks = 28 days. Intervals of ≥4 months are determined by calendar months.
- Within a number range (e.g., 12–18), a dash (–) should be read as "through."
- Vaccine doses administered ≤4 days before the minimum age or interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum age or minimum interval should not be counted as valid and should be repeated as age appropriate. **The repeat dose should be spaced after the invalid dose by the recommended minimum interval.** For further details, see Table 3-1, Recommended and minimum ages and intervals between vaccine doses, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
- Information on travel vaccination requirements and recommendations is available at www.cdc.gov/travel/.
- For vaccination of persons with immunodeficiencies, see Table 8-1, Vaccination of persons with primary and secondary immunodeficiencies, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Immunization in Special Clinical Circumstances (In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:67–111).
- For information about vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. All routine child and adolescent vaccines are covered by VICP except for pneumococcal polysaccharide vaccine (PPSV23). For more information, see www.hrsa.gov/vaccinecompensation/index.html.

Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix or Quadracel])

Routine vaccination

- 5-dose series at 2, 4, 6, 15–18 months, 4–6 years
  - **Prospectively:** Dose 4 may be administered as early as age 12 months if at least 6 months have elapsed since dose 3.
  - **Retrospectively:** A 4th dose that was inadvertently administered as early as age 12 months may be counted if at least 4 months have elapsed since dose 3.

Catch-up vaccination

- Dose 5 is not necessary if dose 4 was administered at age 4 years or older and at least 6 months after dose 3.
- For other catch-up guidance, see Table 2.

Special situations

- Wound management in children less than age 7 years with history of 3 or more doses of tetanus-toxoid-containing vaccine: For all wounds except clean and minor wounds, administer DTaP if more than 5 years since last dose of tetanus-toxoid-containing vaccine. For detailed information, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

Haemophilus influenzae type b vaccination (minimum age: 6 weeks)

Routine vaccination

- **ActHIB, Hiberix, or Pentacel:** 4-dose series at 2, 4, 6, 12–15 months
- **PedvaxHIB:** 3-dose series at 2, 4, 12–15 months

Catch-up vaccination

- **Dose 1 at age 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at age 12–15 months or 8 weeks after dose 2 (whichever is later).
- **Dose 1 at age 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.
- **Dose 1 before age 12 months and dose 2 before age 15 months:** Administer dose 3 (final dose) 8 weeks after dose 2.
- **2 doses of PedvaxHIB before age 12 months:** Administer dose 3 (final dose) at 12–59 months and at least 8 weeks after dose 2.
- **1 dose administered at age 15 months or older:** No further doses needed
- **Unvaccinated at age 15–59 months:** Administer 1 dose.
- **Previously unvaccinated children age 60 months or older who are not considered high risk:** Do not require catch-up vaccination
- For other catch-up guidance, see Table 2.

Special situations

- **Chemotherapy or radiation treatment:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Doses administered within 14 days of starting therapy or during therapy should be repeated at least 3 months after therapy completion.
- **Hematopoietic stem cell transplant (HSCT):**
  - 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant, regardless of Hib vaccination history
- **Anatomic or functional asplenia (including sickle cell disease):**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5 years or older*
  - 1 dose
- **Elective splenectomy:**
  Unvaccinated persons age 15 months or older*
  - 1 dose (preferably at least 14 days before procedure)
- **HIV infection:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5–18 years*
  - 1 dose
- **Immunoglobulin deficiency, early component complement deficiency:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

**Unvaccinated* = Less than routine series (through age 14 months) OR no doses (age 15 months or older)

FIGURE 113.4

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2021

Hepatitis A vaccination
(minimum age: 12 months for routine vaccination)

Routine vaccination
- 2-dose series (minimum interval: 6 months) beginning at age 12 months

Catch-up vaccination
- Unvaccinated persons through age 18 years should complete a 2-dose series (minimum interval: 6 months).
- Persons who previously received 1 dose at age 12 months or older should receive dose 2 at least 6 months after dose 1.
- Adolescents age 18 years or older may receive the combined HepA and HepB vaccine, **Twinrix®**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).

International travel
- Persons traveling to or working in countries with high or intermediate endemic hepatitis A (www.cdc.gov/travel/):
  - **Infants age 6–11 months**: 1 dose before departure; revaccinate with 2 doses, separated by at least 6 months, between age 12–23 months.
  - **Unvaccinated age 12 months or older**: Administer dose 1 as soon as travel is considered.

Hepatitis B vaccination
(minimum age: birth)

Birth dose (monovalent HepB vaccine only)
- **Mother is HBsAg-negative:** 1 dose within 24 hours of birth for **all** medically stable infants ≥2,000 grams. Infants <2,000 grams: Administer 1 dose at chronological age 1 month or hospital discharge (whichever is earlier and even if weight is still <2,000 grams).
- **Mother is HBsAg-positive:**
  - Administer **HepB vaccine** and **hepatitis B immune globulin (HBIG)** (in separate limbs) within 12 hours of birth, regardless of birth weight. For infants <2,000 grams, administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.
- **Mother's HBsAg status is unknown:**
  - Administer **HepB vaccine** within 12 hours of birth, regardless of birth weight.
  - For infants <2,000 grams, administer **HBIG** in addition to HepB vaccine (in separate limbs) within 12 hours of birth. Administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, administer **HBIG** to infants ≥2,000 grams as soon as possible, but no later than 7 days of age.

Routine series
- 3-dose series at 0, 1–2, 6–18 months (use monovalent HepB vaccine for doses administered before age 6 weeks)
- Infants who did not receive a birth dose should begin the series as soon as feasible (see Table 2).
- Administration of **4 doses** is permitted when a combination vaccine containing HepB is used after the birth dose.
- **Minimum age** for the final (3rd or 4th) dose: 24 weeks
- **Minimum intervals:** dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks (when 4 doses are administered, substitute "dose 4" for "dose 3" in these calculations)

Catch-up vaccination
- Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months.
- Adolescents age 11–15 years may use an alternative 2-dose schedule with at least 4 months between doses (adult formulation **Recombivax HB** only).
- Adolescents age 18 years or older may receive a 2-dose series of HepB **(Heplisav-B®)** at least 4 weeks apart.
- Adolescents age 18 years or older may receive the combined HepA and HepB vaccine, **Twinrix**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).
- For other catch-up guidance, see Table 2.

Special situations
- Revaccination is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, adolescents, or adults.
- **Revaccination** may be recommended for certain populations, including:
  - **Infants born to HBsAg-positive mothers**
  - **Hemodialysis patients**
  - **Other immunocompromised persons**
- For detailed revaccination recommendations, see www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html.

Human papillomavirus vaccination
(minimum age: 9 years)

Routine and catch-up vaccination
- HPV vaccination routinely recommended at **age 11–12 years (can start at age 9 years)** and catch-up HPV vaccination recommended for all persons through age 18 years if not adequately vaccinated
- 2- or 3-dose series depending on age at initial vaccination:
  - **Age 9–14 years at initial vaccination**: 2-dose series at 0, 6–12 months (minimum interval: 5 months; repeat dose if administered too soon)
  - **Age 15 years or older at initial vaccination**: 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
- **Interrupted schedules:** If vaccination schedule is interrupted, the series does not need to be restarted.
- No additional dose recommended after completing series with recommended dosing intervals using any HPV vaccine.

Special situations
- **Immunocompromising conditions, including HIV infection:** 3-dose series as above
- **History of sexual abuse or assault:** Start at age 9 years.
- **Pregnancy:** HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination

Influenza vaccination
(minimum age: 6 months [IIV], 2 years [LAIV4], 18 years [recombinant influenza vaccine, RIV4])

Routine vaccination
- Use any influenza vaccine appropriate for age and health status annually:
  - 2 doses, separated by at least 4 weeks, for **children age 6 months–8 years** who have received fewer than 2 influenza vaccine doses before July 1, 2020, or whose influenza vaccination history is unknown (administer dose 2 even if the child turns 9 between receipt of dose 1 and dose 2)
  - 1 dose for **children age 6 months–8 years** who have received at least 2 influenza vaccine doses before July 1, 2020
  - 1 dose for **all persons age 9 years or older**
- For the 2021–22 season, see the 2021–22 ACIP influenza vaccine recommendations.

Special situations
- **Egg allergy, hives only**: Any influenza vaccine appropriate for age and health status annually
- **Egg allergy with symptoms other than hives** (e.g., angioedema, respiratory distress, need for emergency medical services or epinephrine): Any influenza vaccine appropriate for age and health status annually. If using an influenza vaccine other than Flublok or Flucelvax, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions.
- Severe allergic reactions to vaccines can occur even in the absence of a history of previous allergic reaction. All vaccination providers should be familiar with the office emergency plan and certified in cardiopulmonary resuscitation.
- A previous severe allergic reaction to influenza vaccine is a contraindication to future receipt of any influenza vaccine.
- **LAIV4 should not be used** in persons with the following conditions or situations:
  - History of severe allergic reaction to a previous dose of any influenza vaccine or to any vaccine component (excluding egg, see details above)
  - Receiving aspirin or salicylate-containing medications
  - Age 2–4 years with history of asthma or wheezing
  - Immunocompromised due to any cause (including medications and HIV infection)
  - Anatomic or functional asplenia
  - Close contacts or caregivers of severely immunosuppressed persons who require a protected environment
  - Pregnancy
  - Cochlear implant
  - Cerebrospinal fluid-oropharyngeal communication
  - Children less than age 2 years
  - Received influenza antiviral medications oseltamivir or zanamivir within the previous 48 hours,. peramivir within the previous 5 days, or baloxavir within the previous 17 days

FIGURE 113.4 Continued

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2021

Measles, mumps, and rubella vaccination (minimum age: 12 months for routine vaccination)

Routine vaccination
- 2-dose series at 12–15 months, 4–6 years
- Dose 2 may be administered as early as 4 weeks after dose 1.

Catch-up vaccination
- Unvaccinated children and adolescents: 2-dose series at least 4 weeks apart
- The maximum age for use of MMRV is 12 years.

Special situations
International travel
- **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2-dose series at age 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later.
- **Unvaccinated children age 12 months or older:** 2-dose series at least 4 weeks apart before departure

Meningococcal serogroup A,C,W,Y vaccination (minimum age: 2 months [MenACWY-CRM, Menveo], 9 months [MenACWY-D, Menactra], 2 years [MenACWY-TT, MenQuadfi])

Routine vaccination
- 2-dose series at 11–12 years, 16 years

Catch-up vaccination
- Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval: 8 weeks)
- Age 16–18 years: 1 dose

Special situations
Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:
- **Menveo**
  - Dose 1 at age 8 weeks: 4-dose series at 2, 4, 6, 12 months
  - Dose 1 at age 3–6 months: 3- or 4- dose series (dose 2 [and dose 3 if applicable] at least 8 weeks after previous dose until a dose is received at age 7 months or older, followed by an additional dose at least 12 weeks later and after age 12 months)
  - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart
- **Menactra**
  - **Persistent complement component deficiency or complement inhibitor use:**
    - Age 9–23 months: 2-dose series at least 12 weeks apart
    - Age 24 months or older: 2-dose series at least 8 weeks apart
  - **Anatomic or functional asplenia, sickle cell disease, or HIV infection:**
    - Age 9–23 months: Not recommended
    - Age 24 months or older: 2-dose series at least 8 weeks apart
    - **Menactra** must be administered at least 4 weeks after completion of PCV13 series.
- **MenQuadfi**
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart

Travel in countries with hyperendemic or epidemic meningococcal disease, including countries in the African meningitis belt or during the Hajj (www.cdc.gov/travel/)**:**
- Children less than age 24 months:
  - **Menveo (age 2–23 months)**
    - Dose 1 at age 8 weeks: 4-dose series at 2, 4, 6, 12 months
    - Dose 1 at age 3–6 months: 3- or 4- dose series (dose 2 [and dose 3 if applicable] at least 8 weeks after previous dose until a dose is received at age 7 months or older, followed by an additional dose at least 12 weeks later and after age 12 months)
    - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
  - **Menactra (age 9–23 months)**
    - 2-dose series (dose 2 at least 12 weeks after dose 1; dose 2 may be administered as early as 8 weeks after dose 1 in travelers)
- Children age 2 years or older: 1 dose Menveo, Menactra, or MenQuadfi

First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:
- 1 dose **Menveo, Menactra,** or **MenQuadfi**

Adolescent vaccination of children who received MenACWY prior to age 10 years:
- **Children for whom boosters are recommended** because of an ongoing increased risk of meningococcal disease (e.g., those with complement deficiency, HIV, or asplenia): Follow the booster schedule for persons at increased risk.
- **Children for whom boosters are not recommended** (e.g., a healthy child who received a single dose for travel to a country where meningococcal disease is endemic): Administer MenACWY according to the recommended adolescent schedule with dose 1 at age 11–12 years and dose 2 at age 16 years.

Note: Menactra should be administered either before or at the same time as DTaP. For MenACWY **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

Meningococcal serogroup B vaccination (minimum age: 10 years [MenB-4C, Bexsero; MenB-FHbp, Trumenba])

Shared clinical decision-making
- **Adolescents not at increased risk** age 16–23 years (preferred age 16–18 years) based on shared clinical decision-making:
  - **Bexsero:** 2-dose series at least 1 month apart
  - **Trumenba:** 2-dose series at least 6 months apart; if dose 2 is administered earlier than 6 months, administer a 3rd dose at least 4 months after dose 2.

Special situations
Anatomic or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:
- **Bexsero:** 2-dose series at least 1 month apart
- **Trumenba:** 3-dose series at 0, 1–2, 6 months

Bexsero and **Trumenba** are not interchangeable; the same product should be used for all doses in a series.
For MenB **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

Pneumococcal vaccination (minimum age: 6 weeks [PCV13], 2 years [PPSV23])

Routine vaccination with PCV13
- 4-dose series at 2, 4, 6, 12–15 months

Catch-up vaccination with PCV13
- 1 dose for healthy children age 24–59 months with any incomplete* PCV13 series
- For other catch-up guidance, see Table 2.

Special situations
Underlying conditions below: When both PCV13 and PPSV23 are indicated, administer PCV13 first. PCV13 and PPSV23 should not be administered during same visit.

Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma treated with high-dose, oral corticosteroids); diabetes mellitus:

Age 2–5 years
- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after completing all recommended PCV13 doses)

Age 6–18 years
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after completing all recommended PCV13 doses)

Cerebrospinal fluid leak, cochlear implant:

Age 2–5 years
- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years
- No history of either PCV13 or PPSV23: 1 dose PCV13, 1 dose PPSV23 at least 8 weeks later
- Any PCV13 but no PPSV23: 1 dose PPSV23 at least 8 weeks after the most recent dose of PCV13
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent dose of PPSV23

FIGURE 113.4 Continued

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2021

Sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiency; HIV infection; chronic renal failure; nephrotic syndrome; malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and other diseases associated with treatment with immunosuppressive drugs or radiation therapy; solid organ transplantation; multiple myeloma:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose) and a 2nd dose of PPSV23 5 years later

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- Any PCV13 but no PPSV23: 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after the most recent dose of PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent PPSV23 dose and a 2nd dose of PPSV23 administered 5 years after dose 1 of PPSV23 and at least 8 weeks after a dose of PCV13

Chronic liver disease, alcoholism:

Age 6–18 years

- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

**Incomplete series* = Not having received all doses in either the recommended series or an age-appropriate catch-up series See Tables 8, 9, and 11 in the ACIP pneumococcal vaccine recommendations (www.cdc.gov/mmwr/pdf/rr/rr5911.pdf) for complete schedule details.

Poliovirus vaccination (minimum age: 6 weeks)

Routine vaccination

- 4-dose series at ages 2, 4, 6–18 months, 4–6 years; administer the final dose on or after age 4 years and at least 6 months after the previous dose.
- 4 or more doses of IPV can be administered before age 4 years when a combination vaccine containing IPV is used. However, a dose is still recommended on or after age 4 years and at least 6 months after the previous dose.

Catch-up vaccination

- In the first 6 months of life, use minimum ages and intervals only for travel to a polio-endemic region or during an outbreak.
- IPV is not routinely recommended for U.S. residents age 18 years or older.

Series containing oral polio vaccine (OPV), either mixed OPV-IPV or OPV-only series:

- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm?s_%20cid=mm6601a6_w.
- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements.
  - Doses of OPV administered before April 1, 2016, should be counted (unless specifically noted as administered during a campaign).
  - Doses of OPV administered on or after April 1, 2016, should not be counted.
  - For guidance to assess doses documented as "OPV," see www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?s_cid=mm6606a7_w.
- For other catch-up guidance, see Table 2.

Rotavirus vaccination (minimum age: 6 weeks)

Routine vaccination

- **Rotarix:** 2-dose series at 2 and 4 months
- **RotaTeq:** 3-dose series at 2, 4, and 6 months
- If any dose in the series is either **RotaTeq** or unknown, default to 3-dose series.

Catch-up vaccination

- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.
- For other catch-up guidance, see Table 2.

Tetanus, diphtheria, and pertussis (Tdap) vaccination (minimum age: 11 years for routine vaccination, 7 years for catch-up vaccination)

Routine vaccination

- **Adolescents age 11–12 years:** 1 dose Tdap
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Catch-up vaccination

- **Adolescents age 13–18 years who have not received Tdap:** 1 dose Tdap, then Td or Tdap booster every 10 years
- **Persons age 7–18 years not fully vaccinated* with DTaP:** 1 dose Tdap as part of the catch-up series (preferably the first dose); if additional doses are needed, use Td or Tdap.
- **Tdap administered at age 7–10 years:**
  - **Children age 7–9 years** who receive Tdap should receive the routine Tdap dose at age 11–12 years.
  - **Children age 10 years** who receive Tdap do not need the routine Tdap dose at age 11–12 years.
- **DTaP inadvertently administered on or after age 7 years**:
  - **Children age 7–9 years**: DTaP may count as part of catch-up series. Administer routine Tdap dose at age 11–12 years.
  - **Children age 10–18 years**: Count dose of DTaP as the adolescent Tdap booster.
- For other catch-up guidance, see Table 2.

Special situations

- **Wound management** in persons age 7 years or older with history of 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons age 11 years or older who have not previously received Tdap or whose Tdap history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant adolescent, use Tdap.
- For detailed information, see www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm.

**Fully vaccinated* = 5 valid doses of DTaP OR 4 valid doses of DTaP if dose 4 was administered at age 4 years or older

Varicella vaccination (minimum age: 12 months)

Routine vaccination

- 2-dose series at 12–15 months, 4–6 years
- Dose 2 may be administered as early as 3 months after dose 1 (a dose administered after a 4-week interval may be counted).

Catch-up vaccination

- Ensure persons age 7–18 years without evidence of immunity (see *MMWR* at www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have a 2-dose series:
  - **Age 7–12 years**: routine interval: 3 months (a dose administered after a 4-week interval may be counted)
  - **Age 13 years and older**: routine interval: 4–8 weeks (minimum interval: 4 weeks)
  - The maximum age for use of MMRV is 12 years.

FIGURE 113.4 Continued

Table 1 Recommended Adult Immunization Schedule by Age Group, United States, 2021

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV) or **Influenza recombinant** (RIV4)	1 dose annually			
or		or		
Influenza live, attenuated (LAIV4)	1 dose annually			
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)			2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal conjugate (PCV13)	1 dose			1 dose
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses depending on indication			1 dose
Hepatitis A (HepA)	2 or 3 doses depending on vaccine			
Hepatitis B (HepB)	2 or 3 doses depending on vaccine			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19 through 23 years			
***Haemophilus influenzae* type b** (Hib)	1 or 3 doses depending on indication			

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

Recommended vaccination based on shared clinical decision-making

No recommendation/ Not applicable

FIGURE 113.5

Table 2 Recommended Adult Immunization Schedule by Medical Condition and Other Indications, United States, 2021

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 count		Asplenia, complement deficiencies	End-stage renal disease; or on hemodialysis	Heart or lung disease, alcoholism[1]	Chronic liver disease	Diabetes	Health care personnel[2]	Men who have sex with men
			<200 mm³	≥200 mm³							
IIV or RIV4	1 dose annually										
or										or	
LAIV4	Not Recommended									1 dose annually	
						Precaution					
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td or Tdap booster every 10 years									
MMR	Not Recommended*	Not Recommended	1 or 2 doses depending on indication								
VAR	Not Recommended*	Not Recommended			2 doses						
RZV					2 doses at age ≥50 years						
HPV	Not Recommended*	3 doses through age 26 years			2 or 3 doses through age 26 years depending on age at initial vaccination or condition						
PCV13		1 dose									
PPSV23		1, 2, or 3 doses depending on age and indication									
HepA					2 or 3 doses depending on vaccine						
HepB					2, 3, or 4 doses depending on vaccine or condition				<60 years		
									≥60 years		
MenACWY	1 or 2 doses depending on indication, see notes for booster recommendations										
MenB	Precaution	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations									
Hib		3 doses HSCT[3] recipients only			1 dose						

- Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
- Recommended vaccination for adults with an additional risk factor or another indication
- Precaution—vaccination might be indicated if benefit of protection outweighs risk of adverse reaction
- Recommended vaccination based on shared clinical decision-making
- Not recommended/ contraindicated—vaccine should not be administered.
- No recommendation/ Not applicable

*Vaccinate after pregnancy.

1. Precaution for LAIV4 does not apply to alcoholism. **2.** See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. **3.** Hematopoietic stem cell transplant.

FIGURE 113.6

Notes

Recommended Adult Immunization Schedule for ages 19 years or older, United States, 2021

For vaccine recommendations for persons 18 years of age or younger, see the Recommended Child/Adolescent Immunization Schedule.

Additional Information

COVID-19 Vaccination

ACIP recommends use of COVID-19 vaccines within the scope of the Emergency Use Authorization or Biologics License Application for the particular vaccine. Interim ACIP recommendations for the use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html

Haemophilus influenzae type b vaccination

Special situations

- **Anatomical or functional asplenia (including sickle cell disease):** 1 dose if previously did not receive Hib; if elective splenectomy, 1 dose, preferably at least 14 days before splenectomy
- **Hematopoietic stem cell transplant (HSCT):** 3-dose series 4 weeks apart starting 6–12 months after successful transplant, regardless of Hib vaccination history

Hepatitis A vaccination

Routine vaccination

- **Not at risk but want protection from hepatitis A** (identification of risk factor not required): 2-dose series HepA (Havrix 6–12 months apart or Vaqta 6–18 months apart [minimum interval: 6 months]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 5 months])

Special situations

- **At risk for hepatitis A virus infection:** 2-dose series HepA or 3-dose series HepA-HepB as above
  - **Chronic liver disease** (e.g., persons with hepatitis B, hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)
  - **HIV infection**
  - **Men who have sex with men**
  - **Injection or noninjection drug use**
  - **Persons experiencing homelessness**
  - **Work with hepatitis A virus** in research laboratory or with nonhuman primates with hepatitis A virus infection
  - **Travel in countries with high or intermediate endemic hepatitis A** (HepA-HepB [Twinrix] may be administered on an accelerated schedule of 3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months)
  - **Close, personal contact with international adoptee** (e.g., household or regular babysitting) in first 60 days after arrival from country with high or intermediate endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks before adoptee's arrival)
  - **Pregnancy** if at risk for infection or severe outcome from infection during pregnancy
  - **Settings for exposure, including** health care settings targeting services to injection or noninjection drug users or group homes and nonresidential day care facilities for developmentally disabled persons (individual risk factor screening not required)

Hepatitis B vaccination

Routine vaccination

- **Not at risk but want protection from hepatitis B** (identification of risk factor not required): 2- or 3-dose series (2-dose series Heplisav-B at least 4 weeks apart [2-dose series HepB only applies when 2 doses of Heplisav-B are used at least 4 weeks apart] or 3-dose series Engerix-B or Recombivax HB at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 5 months])

Special situations

- **At risk for hepatitis B virus infection:** 2-dose (Heplisav-B) or 3-dose (Engerix-B, Recombivax HB) series or 3-dose series HepA-HepB (Twinrix) as above
  - **Chronic liver disease** (e.g., persons with hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice upper limit of normal)
  - **HIV infection**
  - **Sexual exposure risk** (e.g., sex partners of hepatitis B surface antigen [HBsAg]-positive persons; sexually active persons not in mutually monogamous relationships; persons seeking evaluation or treatment for a sexually transmitted infection; men who have sex with men)
  - **Current or recent injection drug use**
  - **Percutaneous or mucosal risk for exposure to blood** (e.g., household contacts of HBsAg-positive persons; residents and staff of facilities for developmentally disabled persons; health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids; hemodialysis, peritoneal dialysis, home dialysis, and predialysis patients; persons with diabetes mellitus age younger than 60 years, shared clinical decision-making for persons age 60 years or older)
  - **Incarcerated persons**
  - **Travel in countries with high or intermediate endemic hepatitis B**
  - **Pregnancy** if at risk for infection or severe outcome from infection during pregnancy (Heplisav-B not currently recommended due to lack of safety data in pregnant women)

Human papillomavirus vaccination

Routine vaccination

- **HPV vaccination recommended for all persons through age 26 years:** 2- or 3-dose series depending on age at initial vaccination or condition:
  - **Age 15 years or older at initial vaccination:** 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
  - **Age 9–14 years at initial vaccination and received 1 dose or 2 doses less than 5 months apart:** 1 additional dose
  - **Age 9–14 years at initial vaccination and received 2 doses at least 5 months apart:** HPV vaccination series complete, no additional dose needed
- **Interrupted schedules:** If vaccination schedule is interrupted, the series does not need to be restarted
- **No additional dose recommended after completing series with recommended dosing intervals using any HPV vaccine**

Shared clinical decision-making

- **Some adults age 27–45 years: Based on shared clinical decision-making,** 2- or 3-dose series as above

Special situations

- **Age ranges recommended above for routine and catch-up vaccination or shared clinical decision-making also apply in special situations**

FIGURE 113.7

Notes Recommended Adult Immunization Schedule, United States, 2021

- **Immunocompromising conditions, including HIV infection**: 3-dose series as above, regardless of age at initial vaccination
- **Pregnancy**: HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination

Influenza vaccination

Routine vaccination

- **Persons age 6 months or older:** 1 dose any influenza vaccine appropriate for age and health status annually
- For additional guidance, see www.cdc.gov/flu/professionals/index.htm

Special situations

- **Egg allergy, hives only:** 1 dose any influenza vaccine appropriate for age and health status annually
- **Egg allergy–any symptom other than hives** (e.g., angioedema, respiratory distress): 1 dose any influenza vaccine appropriate for age and health status annually. If using an influenza vaccine other than RIV4 or ccIIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions.
- Severe allergic reactions to any vaccine can occur even in the absence of a history of previous allergic reaction. Therefore, all vaccine providers should be familiar with the office emergency plan and certified in cardiopulmonary resuscitation.
- A previous severe allergic reaction to any influenza vaccine is a contraindication to future receipt of the vaccine.
- **LAIV4 should not be used** in persons with the following conditions or situations:
  - History of severe allergic reaction to any vaccine component (excluding egg) or to a previous dose of any influenza vaccine
  - Immunocompromised due to any cause (including medications and HIV infection)
  - Anatomic or functional asplenia
  - Close contacts or caregivers of severely immunosuppressed persons who require a protected environment
  - Pregnancy
  - Cranial CSF/oropharyngeal communications
  - Cochlear implant
  - Received influenza antiviral medications oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days
  - Adults 50 years or older
- **History of Guillain-Barré syndrome within 6 weeks after previous dose of influenza vaccine:** Generally, should not be vaccinated unless vaccination benefits outweigh risks for those at higher risk for severe complications from influenza

Measles, mumps, and rubella vaccination

Routine vaccination

- **No evidence of immunity to measles, mumps, or rubella:** 1 dose
  - **Evidence of immunity:** Born before 1957 (health care personnel, see below), documentation of receipt of MMR vaccine, laboratory evidence of immunity or disease (diagnosis of disease without laboratory confirmation is not evidence of immunity)

Special situations

- **Pregnancy with no evidence of immunity to rubella:** MMR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose
- **Nonpregnant women of childbearing age with no evidence of immunity to rubella:** 1 dose
- **HIV infection with CD4 count ≥200 cells/mm^3 for at least 6 months and no evidence of immunity to measles, mumps, or rubella:** 2-dose series at least 4 weeks apart; MMR contraindicated for HIV infection with CD4 count <200 cells/mm^3
- **Severe immunocompromising conditions:** MMR contraindicated
- **Students in postsecondary educational institutions, international travelers, and household or close, personal contacts of immunocompromised persons with no evidence of immunity to measles, mumps, or rubella:** 2-dose series at least 4 weeks apart if previously did not receive any doses of MMR or 1 dose if previously received 1 dose MMR
- **Health care personnel:**
  - **Born in 1957 or later with no evidence of immunity to measles, mumps, or rubella:** 2-dose series at least 4 weeks apart for measles or mumps or at least 1 dose for rubella
  - **Born before 1957 with no evidence of immunity to measles, mumps, or rubella:** Consider 2-dose series at least 4 weeks apart for measles or mumps or 1 dose for rubella

Meningococcal vaccination

Special situations for MenACWY

- **Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:** 2-dose series MenACWY-D (Menactra, Menveo or MenQuadfi) at least 8 weeks apart and revaccinate every 5 years if risk remains
- **Travel in countries with hyperendemic or epidemic meningococcal disease, microbiologists routinely exposed to *Neisseria meningitidis*:** 1 dose MenACWY (Menactra, Menveo or MenQuadfi) and revaccinate every 5 years if risk remains
- **First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) and military recruits:** 1 dose MenACWY (Menactra, Menveo or MenQuadfi)
- For MenACWY **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting (e.g., in community or organizational settings and among men who have sex with men) and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm

Shared clinical decision-making for MenB

- **Adolescents and young adults age 16–23 years (age 16–18 years preferred) not at increased risk for meningococcal disease:** Based on shared clinical decision-making, 2-dose series MenB-4C (Bexsero) at least 1 month apart or 2-dose series MenB-FHbp (Trumenba) at 0, 6 months (if dose 2 was administered less than 6 months after dose 1, administer dose 3 at least 4 months after dose 2); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series)

Special situations for MenB

- **Anatomical or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use, microbiologists routinely exposed to *Neisseria meningitidis*:** 2-dose primary series MenB-4C (Bexsero) at least one month apart or

FIGURE 113.7 Continued

Notes Recommended Adult Immunization Schedule, United States, 2021

- MenB-4C (Bexsero) at least 1 month apart or 3-dose primary series MenB-FHbp (Trumenba) at 0, 1–2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not needed); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series); 1 dose MenB booster 1 year after primary series and revaccinate every 2–3 years if risk remains
- **Pregnancy:** Delay MenB until after pregnancy unless at increased risk and vaccination benefits outweigh potential risks
- For MenB **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting (e.g., in community or organizational settings and among men who have sex with men) and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm

Pneumococcal vaccination

Routine vaccination

- **Age 65 years or older** (immunocompetent—see www.cdc.gov/mmwr/volumes/68/wr/mm6846a5.htm?s_cid=mm6846a5_w): 1 dose PPSV23
  - If PPSV23 was administered prior to age 65 years, administer 1 dose PPSV23 at least 5 years after previous dose

Shared clinical decision-making

- **Age 65 years or older** (immunocompetent): 1 dose PCV13 based on **shared clinical decision-making** if previously not administered.
  - PCV13 and PPSV23 should not be administered during the same visit
  - If both PCV13 and PPSV23 are to be administered, PCV13 should be administered first
  - PCV13 and PPSV23 should be administered at least 1 year apart

Special situations

(www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm)

- **Age 19–64 years with chronic medical conditions (chronic heart [excluding hypertension], lung, or liver disease, diabetes), alcoholism, or cigarette smoking:** 1 dose PPSV23
- **Age 19 years or older with immunocompromising conditions (congenital or acquired immunodeficiency [including B- and T-lymphocyte deficiency, complement deficiencies, phagocytic disorders, HIV infection], chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression [e.g., drug or radiation therapy], solid organ transplant, multiple myeloma) or anatomical or functional asplenia (including sickle cell disease and other hemoglobinopathies):** 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later, then another dose PPSV23 at least 5 years after previous PPSV23; at age 65 years or older, administer 1 dose PPSV23 at least 5 years after most recent PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)
- **Age 19 years or older with cerebrospinal fluid leak or cochlear implant:** 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later; at age 65 years or older, administer another dose PPSV23 at least 5 years after PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)

Tetanus, diphtheria, and pertussis vaccination

Routine vaccination

- **Previously did not receive Tdap at or after age 11 years:** 1 dose Tdap, then Td or Tdap every 10 years

Special situations

- **Previously did not receive primary vaccination series for tetanus, diphtheria, or pertussis:** At least 1 dose Tdap followed by 1 dose Td or Tdap at least 4 weeks after Tdap and another dose Td or Tdap 6–12 months after last Td or Tdap (Tdap can be substituted for any Td dose, but preferred as first dose), Td or Tdap every 10 years thereafter
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- **Wound management:** Persons with 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons who have not previously received Tdap or whose Tdap history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant woman, use Tdap. For detailed information, see www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm

Varicella vaccination

Routine vaccination

- **No evidence of immunity to varicella:** 2-dose series 4–8 weeks apart if previously did not receive varicella-containing vaccine (VAR or MMRV [measles-mumps-rubella-varicella vaccine] for children); if previously received 1 dose varicella-containing vaccine, 1 dose at least 4 weeks after first dose
  - Evidence of immunity: U.S.-born before 1980 (except for pregnant women and health care personnel [see below]), documentation of 2 doses varicella-containing vaccine at least 4 weeks apart, diagnosis or verification of history of varicella or herpes zoster by a health care provider, laboratory evidence of immunity or disease

Special situations

- **Pregnancy with no evidence of immunity to varicella:** VAR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose if previously received 1 dose varicella-containing vaccine or dose 1 of 2-dose series (dose 2: 4–8 weeks later) if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- **Health care personnel with no evidence of immunity to varicella:** 1 dose if previously received 1 dose varicella-containing vaccine; 2-dose series 4–8 weeks apart if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- **HIV infection with CD4 count ≥200 cells/mm^3 with no evidence of immunity:** Vaccination may be considered (2 doses 3 months apart); VAR contraindicated for HIV infection with CD4 count <200 cells/mm^3
- **Severe immunocompromising conditions:** VAR contraindicated

Zoster vaccination

Routine vaccination

- **Age 50 years or older:** 2-dose series RZV (Shingrix) 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon), regardless of previous herpes zoster or history of zoster vaccine live (ZVL, Zostavax) vaccination (administer RZV at least 2 months after ZVL)

Special situations

- **Pregnancy:** Consider delaying RZV until after pregnancy if RZV is otherwise indicated.
- **Severe immunocompromising conditions (including HIV infection with CD4 count <200 cells/mm^3):** Recommended use of RZV under review

FIGURE 113.7 Continued

Pasteur; Td vaccine, Merck) with reduced content of diphtheria toxoid is used to boost immunity in persons 7 years of age or older, and booster doses of Td are recommended every 10 years throughout adult life.

Poor control of pertussis in the United States has been noted since the late 1990s, and epidemiologic studies suggest that waning immunity to pertussis over time following childhood DTaP immunization contributes to this. In partially immune adolescents and adults, pertussis often causes a prolonged respiratory illness without the characteristic "whooping cough" and thus may not be recognized as such. Adolescents and adults with undiagnosed pertussis may transmit the infection to infants at highest risk of serious complications from the infection. For this reason, ACIP currently recommends that a single dose of Tdap vaccine (tetanus toxoid with reduced diphtheria toxoid and acellular pertussis content) (Adacel, Sanofi Pasteur; Boostrix, GlaxoSmithKline) be used to replace the next booster dose of Td vaccine among persons 19 years or older to boost levels of pertussis immunity in the adult population. Depending on community outbreaks of pertussis, occupational exposures, and/or personal health risks, Tdap vaccine may be administered with no minimal interval from the last Td vaccine dose based on current vaccine safety data. In wound management, Tdap or Td may be administered if more than 5 years have elapsed since the last dose of tetanus toxoid-containing vaccine was received; Tdap is preferred for persons whose Tdap history is unknown.

Healthcare workers

Healthcare workers exposed to patients with confirmed pertussis infections may warrant antibiotic prophylaxis and should consult the facility's infection control or occupational health consultant. ACIP recommends the use of Tdap vaccine as a one-time substitute for a Td vaccine booster among healthcare workers, especially for those providing care to pediatric patients.

Measles, mumps, and rubella

The measles, mumps, and rubella vaccines are given as a combination vaccine (MMR) in early childhood, at 12 to 15 months of age. However, up to 5% of vaccine recipients may fail to respond to primary immunization and have inadequate or waning immunity to measles by young adulthood. For this reason, the ACIP and AAP recommend that a second dose of measles vaccine (as a component of MMR vaccine) be given in childhood at 4 to 6 years of age upon primary school entry. Outbreaks of measles among college-aged individuals in campus communities have occurred over the past two decades and have resulted in significant disruption of campus activities. At present, most American colleges and universities require documentation of receipt of a second dose of measles vaccine or evidence of immunity (obtained by a serum test for measles antibodies) for registration as a preventive measure against future outbreaks of measles on campus. There is no contraindication to using the MMR vaccine to boost measles immunity even if the recipient is already immune to mumps and rubella.

In recent years, an increase in mumps cases has been reported in the United States among young adults and their cohorts. Outbreaks of mumps have occurred at universities among students with high vaccine coverage rates from childhood immunization programs, suggestive that MMR vaccine-induced immunity to mumps also wanes in the years following vaccination, resulting in increased susceptibility to infection among adolescent and young adult populations. During outbreak situations, a third dose of MMR vaccine to boost immunity may be administered to persons at risk of exposure, as directed by local or state public health officers. Monovalent measles, mumps, and rubella vaccines are commercially available but are not commonly recommended, stocked, and/or used in vaccine immunization programs.

Potential vaccine adverse reactions include the rare occurrence of usually transient, but occasionally prolonged, arthralgias and arthritis attributed to the rubella component of the MMR vaccine in nonimmune women of reproductive age—the very group most likely to benefit from immunization against rubella. As with any vaccine, the potential risks versus benefits of immunization with MMR vaccine should be discussed with potential vaccine recipients, along with the VIS statements.

Contraindications

MMR vaccine is a live-virus combination vaccine. Women of childbearing age should not be pregnant at the time of receiving MMR vaccine and should defer pregnancy for 3 months after MMR immunization.

HIV-infected persons

MMR immunization is recommended for use in susceptible persons with asymptomatic HIV infection because the potential benefits of immunization appear to outweigh the serious course of natural measles infections in this population.

Healthcare workers

People born before 1957 are generally considered immune to measles, mumps, and rubella by virtue of having had the natural infectious diseases in the pre-MMR vaccine era. However, because a small percentage in this group did not acquire lasting immunity from historical accounts of diagnosed/presumed infections, and because healthcare workers may be at increased risk of acquiring measles and mumps infections and transmitting them to other patients/clients, healthcare workers should provide proof of prior receipt of two doses of MMR vaccine or serologic immunity to measles and mumps.

Varicella vaccine and zoster (shingles) vaccine

Varicella (chickenpox) infections are more likely to result in severe disease among adults compared to children, often accompanied by complications such as varicella pneumonia. A live attenuated viral

vaccine against varicella (VAR: Varivax, Merck) was released in the mid-1990s. The primary series for adults born in 1980 or later consists of two doses given by injection 1 month apart.

Varicella-zoster virus (VZV) causes varicella (chickenpox) and becomes dormant within the nerves following exposure but can reactivate later in life, usually around 50 years old. The risk of virus reactivation increases with age, causing herpes zoster or "shingles," a condition characterized by a vesicular rash that follows a dermatomal distribution that is often associated with debilitating chronic pain. For protection against shingles, the ACIP recommends that a two-dose series of zoster recombinant vaccine be given to persons aged ≥50 (RZV, Shingrix, GlaxoSmithKline).

Contraindications

Varicella vaccine is contraindicated in pregnant women. Women of childbearing age should not be pregnant at the time of receiving varicella vaccine and should defer pregnancy for 3 months after varicella immunization. Varicella vaccine is contraindicated in persons with compromised immunity, including individuals with HIV infection.

Healthcare workers

Current occupational health recommendations for healthcare workers include documentation of varicella immunity or varicella immunization as a condition for working in certain clinics and hospitals.

Polio vaccine

Immunization against polio is a part of the routine childhood immunization program, and booster doses are not given routinely in adulthood in the Western Hemisphere (North and South America) and Western Europe, where polio is considered eradicated. Current pediatric regimens use the enhanced inactivated polio vaccine (IPV: Ipol, Sanofi Pasteur) administered by injection for primary immunization. A single dose of IPV is recommended as a booster in adults when there is imminent risk of exposure, such as travel to certain regions of Africa and Asia where polio is still transmitted, or for occupational exposure (e.g., work in certain research laboratories).

Hepatitis B vaccine

Hepatitis B immunization has been included as one of the regular immunizations in the United States since 1991. Hepatitis B vaccine should be considered a "catch-up" immunization among young adults born before the hepatitis B vaccine was incorporated into the routine childhood immunization programs. Hepatitis B immunization should also be recommended to individuals at risk of exposure to hepatitis B virus through occupational risk; treatment with blood products; contact with infected family, friends, or others; or international travel.

The primary series for hepatitis B immunization consists of three doses given by intramuscular injection into the deltoid muscle at 0, 1, and 6 months (HepB: Recombivax HB, Merck; Engerix-B, GlaxoSmithKline). An accelerated schedule consisting of three doses of hepatitis B vaccine given at 0, 1, and 2 months, with a booster dose at 12 months, has FDA approval (Engerix-B).

The recombinant CpG-adjuvanted hepatitis B vaccine (HepB-CpG: Heplisav, Dynavax Technologies Corp.) was FDA-approved in 2018 for use in adults aged ≥18. HepB-CpG is given as two doses by intramuscular injection one month apart, and is highly efficacious. In limited clinical studies, the HepB-CpG vaccine elicits a high rate of seroprotection in vaccine recipients aged ≥40 years, an age group in which suboptimal seroprotection rates from HepB vaccine previously had been observed.

A combination vaccine against hepatitis A plus hepatitis B (HepA-HepB: Twinrix, GlaxoSmithKline) is licensed for those ≥18 years of age and is given on a standard schedule of 0, 1, and 6 months. An accelerated schedule for HepA-HepB is FDA-approved for administration on an accelerated dosing schedule of three doses given on 0, 7, and 21 to 28 days, followed by a fourth dose at 12 months. Protective immunity against hepatitis A and hepatitis B is elicited following receipt of the first three doses; the fourth dose is a booster dose given to assure long-lasting immunity. The accelerated schedule could be useful for international travelers with <1 month's time before departure and for healthcare workers who need rapid protection before duty assignments. The antibody response to hepatitis B is enhanced when A and B antigens are given simultaneously in the same syringe or concomitantly when monovalent hepatitis A and hepatitis B vaccines are given at the same time but at separate sites. The adjuvant effect of hepatitis A in the combination HepA-HepB vaccine is of potential benefit to hepatitis B-susceptible adults aged ≥30 years who tend to respond with lower antibody levels to monovalent hepatitis B vaccine compared with younger hepatitis B vaccine recipients.

Healthcare workers

Hepatitis B immunization or immunity is required for work in certain occupations, including healthcare workers, policemen, firemen, morticians, and others who are likely to have work-related contact with human blood and other bodily substances.

Pneumococcal vaccine

As of 2014, the ACIP recommends that all adults ≥65 years of age receive both PCV13 (pneumococcal conjugate vaccine 13-valent: Prevnar 13, Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.) and PPSV23 (pneumococcal polysaccharide vaccine 23-valent: Pneumovax 23, Sanofi Pasteur). If not previously vaccinated with a pneumococcal vaccine, PCV13 should be administered first, followed by a dose of PPSV23 6–12 months later. If PPSV23 was previously received, then PCV13 should be administered 12 months or more after PPSV23.

The FDA licensed the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010, and the ACIP recommended PCV13 for children ages 6 weeks through 71 months to prevent invasive

pneumococcal disease. In 2011, the FDA expanded the licensure of PCV13 to include adults aged ≥50 years, and, in 2012, the ACIP recommended routine use of PCV13 in adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid (CSF) leaks, or cochlear implants. In pneumococcal vaccine-naïve persons in the 19- to 64-year age group, it is preferable to administer PCV13 first, followed by PPSV23 at least 8 weeks later if additional immunization is desirable. If one or more PPSV23 doses have been previously received, the PCV13 should be given ≥1 year after the last PPSV23 dose was received. Any additional dose of PPSV23 should be separated by at least 5 years from the most recent dose of PPSV23.

Viral influenza vaccine

Viral influenza vaccine is reformulated annually based on recent worldwide epidemiology of influenza viruses according to World Health Organization data. Annual immunization with the "flu" vaccine is recommended for all persons ≥6 months of age, with rare exception, with priority given to infants aged 6–59 months and adults aged ≥50 years in case of vaccine shortage.

The flu vaccine distributed for a given season may not be totally protective against all strains of influenza viruses in circulation following the annual flu vaccine formulation, thus antiviral drugs may be considered a second line of defense. Prompt treatment within 48 hours after the onset of flu symptoms with oral oseltamivir (Tamiflu, Genentech) or inhaled zanamivir (Relenza, GlaxoSmithKline) during outbreaks of influenza A or B may ameliorate illness in breakthrough attacks. Other antiviral drugs used to treat the flu include peramivir (Rapivab, BioCryst Pharmaceuticals) administered intravenously by a health care provider, and baloxovir (XoFluza, Genentech) taken orally. Due to potential interference with vaccine efficacy, peramivir treatment should be avoided for two weeks after receipt of a live attenuated influenza vaccine (LAIV4) and should not be given for 48 hours before LAIV4.

Vaccines include inactivated influenza vaccine quadrivalent (IIV4); inactivated influenza vaccine trivalent (IIV3) standard dose, high dose, and intradermal dose; cell-cultured inactivated influenza vaccine trivalent (ccIIV3); recombinant influenza vaccine trivalent (RIV), and live attenuated influenza vaccine quadrivalent (LAIV4). LAIV4 (FluMist Quadrivalent, AstraZeneca) administered by a nasal spray, is licensed for recipients aged 2–49 years. Intradermal IIV3 (Fluzone Intradermal, Sanofi Pasteur) is licensed for use in persons aged 18–64 years, and high-dose IIV3 (Fluzone High Dose, Sanofi Pasteur) is licensed for persons ≥65 years. Current information on brands, manufacturers, dosage, and age range are posted on the CDC website http://www.cdc.gov/flu.

Hepatitis A vaccine

The conditions allowing transmission of hepatitis A are ubiquitous, although the relative risk appears to be highest in countries where sanitation and hygiene are suboptimal and there is widespread fecal contamination of food and water supplies. In countries of low endemicity for hepatitis A virus (HAV), outbreaks of the disease are related to contamination of food during preparation by infected food handlers and to ingestion of fresh or frozen fruits and vegetables imported from areas highly endemic for hepatitis A and contaminated during cultivation or processing. Shellfish from sewage-contaminated beds are another source of foodborne transmission.

In the United States, adults identified by the CDC as being at increased risk for hepatitis A or severe outcomes include international travelers, MSM, users of injecting and non-injecting drugs, persons who have clotting factor disorders, persons working with nonhuman primates, and persons with chronic liver disease. Hepatitis A outbreaks are increasingly reported in cities with large homeless populations living under poor conditions of sanitation and hygiene, so homelessness is another indication for HepA vaccine.

Children can serve as a significant reservoir of HAV in outbreaks and in endemic communities. Hepatitis A infections are mild and often anicteric in young children, so infected children are not detected. Fecal–oral transmission to other children and family members, as well as to adult teachers or caretakers, can easily occur in household, daycare, and institutional settings, especially if children in diapers are present. It is important to note that HAV case fatality rates in healthy individuals rise with age, so although the rate is 0.1% from younger than 1 to 14 years of age, it is 0.4% in those from 15 to 39 years of age, 1.1% in those older than 40 years, and 2.7% in persons older than 49 years.

A safe and highly efficacious inactivated hepatitis A vaccine became available with the 1994 release of Havrix (Smithkline Beecham; now, GlaxoSmithKline), an inactivated HAV vaccine derived from the HM-175 viral strain. VAQTA (Merck), an inactivated HAV vaccine derived from the CR-326 F strain, was licensed a few years later. Havrix and VAQTA are available in the United States and Canada as well as worldwide. Other hepatitis A vaccine products are also in use in Europe and Asia.

The immunization schedules for both hepatitis A vaccines licensed in the United States consist of a single primary dose given by intramuscular injection into the deltoid muscle, resulting in protective antibody titers within 4 weeks that confer protection for 6 months up to 1 year. The first vaccine dose is followed by a booster dose 6 to 12 months later, producing levels of antibody predicted by mathematical modeling to give protection up to 10 years or more. Vaccine protection against hepatitis A may also be obtained by receipt of the combined hepatitis A and B vaccine (HepA-HepB: Twinrix, GlaxoSmithKline) (see earlier discussion).

Immunoglobulin

Immunoglobulin (IG) is purified human immunoglobulin used to provide protection against HAV infection through the passive transfer of preformed antibodies against HAV present in the IG (at least 100 IU/μL). IG is recommended for prevention of hepatitis A following known exposure to a confirmed case of HAV (0.02 mL/kg) and in nonimmune travelers going to HAV-endemic areas when there is <2 weeks remaining before departure (0.02 mL/kg to 0.06 mL/kg).

Special considerations

Attenuated live viral or bacterial vaccines are generally contraindicated for pregnant women and patients with compromised immunity. Exceptions are the recommendations for giving the MMR vaccine to children with HIV infection and giving the yellow fever vaccine to a pregnant female traveler with imminent departure to a high-risk destination in a foreign country. In these cases, the theoretical risk of serious adverse vaccine complications may be outweighed by the anticipated benefits of vaccine-elicited protection.

Vaccine efficacy can be affected by various conditions (including age) and therapies that lead to compromise of the immune system. In persons >65 years, the high-dose IIV flu vaccine is used to elicit improved immunoprotection against influenza compared to the standard dose. In patients receiving hemodialysis, the suboptimal immune response to hepatitis A and B vaccines may necessitate higher than standard antigen doses, given as a special vaccine formulation or as additional doses after the standard series has been administered.

Limited data suggest that administration of toxoid, killed virus, and purified derivative vaccines to HIV patients as appropriate may elicit protective immunity in the vaccine recipient if the CD4 count is ≥200/mm^3. An observed rise in viral loads in some HIV patients following vaccination has been of some concern, but the phenomenon is thought to be frequently transient. The current consensus is that a severe infection with a given vaccine-preventable pathogen is more likely to be associated with a more detrimental rise in viral load than that seen secondary to the corresponding immunization. High-dose vaccine formulations or additional doses in certain vaccine series may be used in off-license protocols to improve vaccine efficacy in this group of patients and other groups with altered immune response (e.g., end-stage renal disease on hemodialysis, heart or lung disease, alcoholism, chronic liver disease, diabetes).

The conjugate vaccines against encapsulated bacteria (*H. influenzae* type b, pneumococcal, and meningococcal vaccines) are recommended for adults who have a history of functional or anatomic asplenia because of the risk of overwhelming sepsis associated with infections from these agents, although data on protective efficacy of these vaccines in this patient group are incomplete.

Travel immunizations

The patient seeking vaccine advice for international travel presents an opportunity to review and update routine immunizations as well as assess the risk of exposure to exotic diseases during the trip (see Chapter 114, "Advice for travelers").

Disclaimer

The use of trade names and commercial sources in this chapter is for identification only and does not imply endorsement and is not meant to constitute a comprehensive listing.

Suggested reading

Centers for Disease Control and Prevention (CDC). Updated recommendations for use of meningococcal conjugate vaccines: Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Morb Mortal Wkly Rep*. 2011;60:72–76.

Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: Recommendation of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61:816–819.

Dooling KI, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. *MMWR Morb Mortal Wkly Rep*. 2018;67:103–108. https://www.doi.org/10.155585/mmwr6703a5

Doshani M, Weng M, Moore KL, et al. Recommendations of the Advisory Committee on Immunization Practices for use of hepatitis A vaccine for persons experiencing homelessness. *MMWR Morb Mortal Wkly Rep*. 2019;68:153–156. http://dx.doi.org/10.15585/mmwr.mm6806a6

Freedman MS, Ault K, Bernstein H. Advisory Committee on Immunization Practices Recommended Immunization Schedules for Adults Aged 19 years or Older—United States, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:193–196. http://dx.doi.org/10.15585/mmwr.mm7006a2

Liang JL Tiwari T, Moro P, et al. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2018:67 (No.RR-2). https://doi.org/10.15585/mmwr.m6702a1

Hickey PW. Introduction to vaccine-preventable diseases in children and adolescents. In Jong EC, Stevens DL, eds. *Netter's infectious diseases, 2nd edition*. Philadelphia: Elsevier; 2021: 2–4.

Petrosky E, Bocchini JA Jr, Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: Updated HPV vaccination recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mort Wkly Rep*. 2015;64:300–304.

Wodi AP, Ault K, Hunter P, et al. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger—United States, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:189–196. http://dx.doi.org/10.15585/mmwr.mm7006a1

Schillie S, Harris A, Link-Gelles R, et al. Recommendations of the Advisory Committee on Immunization Practices for use of a hepatitis B vaccine with a novel adjuvant. *MMWR Morb Mortal Wkly Rep*. 2018;67:455–458. https://doi.org/10.15585/mmwr.mm6715a5

Section 16

Travel and recreation

114

Advice for travelers

Henry M. Wu and Jessica K. Fairley

Whether for business, tourism, study, or aid work, more individuals are traveling to more parts of the world. The World Tourism Organization estimates that, in 2015, there were 1.2 billion international tourist arrivals worldwide. Health problems associated with travel are common, especially in low-income countries where travelers frequently self-report a travel-associated health problem and often seek healthcare while traveling or after return. Healthcare providers can play a critical role in minimizing the risk of illness and injury during travel.

General approach

While administration of travel-related vaccinations and malaria prophylaxis remain cornerstones of the pre-travel consultation, providing advice on managing chronic medical conditions, food and water hygiene, physical safety, and disease vector avoidance is also important. Noninfectious causes of morbidity and mortality such as injury and exacerbation of chronic illness are typically the most common health issues travelers encounter. Important considerations include:

- Preexisting medical conditions, current medications, and allergies
- Itinerary, including details of travel within countries, duration of stay, and sequence of countries visited
- Purpose of travel, accommodations, and activities
- Previous vaccination history and recommended vaccines for the itinerary
- Need for prophylactic and self-treatment medications, including those for malaria prevention, treatment of travelers' diarrhea, and altitude sickness

Referral to a travel health specialist should be considered, particularly for medically complex travelers, for those traveling to low-income countries, and when travel-specific vaccines are indicated. Since vaccines typically take 10 to 14 days to elicit full immune responses, and some require multiple doses to complete a primary series, travelers should ideally be evaluated in a travel clinic at least 4 to 6 weeks prior to departure. However, when this is not possible, travelers should still be seen, even when travel is imminent.

Preexisting medical conditions

International travel is increasingly common among individuals of all ages and health statuses, including those with medical conditions that predispose to infection or injury. Exacerbations of underlying conditions are a common cause of morbidity; furthermore, individuals in these groups can be at increased risk for complications from infections including travelers' diarrhea, influenza, and malaria. Current medications

should be reviewed for drug interactions or contraindications with travel-related medications or vaccinations. Immunocompromising conditions are generally contraindications to live vaccine administration. Pregnancy presents a particular challenge for travel to malarious areas, as pregnancy is a risk factor for severe infection and a contraindication to some of the commonly used prophylaxis medications. Pregnancy is also a risk factor for severe complications of other infections potentially acquired during travel, including hepatitis E, toxoplasmosis, and Zika virus infection. The physical ability of the traveler to withstand environmental conditions at their destinations should also be considered. For example, travel involving high altitude, difficult terrain, and even commercial flying may be inappropriate for some. When risks of travel are significant, advising against nonessential travel can be important.

Itinerary and purpose of travel

Review of the traveler's itinerary is important to determine the specific infectious, environmental (e.g., altitude, climate, etc.), and public safety risks that will be encountered. Country-specific health advisories, vaccine recommendations, and malaria prophylaxis recommendations are available from the Centers for Disease Control and Prevention (CDC) Travelers' Health website and other online resources (Box 114.1). Although most recommended vaccinations are not required for entry, countries can have individual yellow fever or polio vaccination requirements. Timing and duration of travel is also important to consider when prescribing malaria prophylaxis (see Chapter 199, "Malaria").

The purpose of the trip, accommodations, and likely activities are essential considerations when providing individualized advice. Tourist and business travelers typically take short-term trips to visit major cities and often stay in high-end accommodations, while long-term travelers (e.g., missionaries, aid workers, business expatriates, students, etc.) stay for durations that make health problems more likely and often adopt accommodations and eating habits closer to that of locals. Similarly, immigrants visiting friends and relatives (VFRs) in their countries of origin often travel to non-tourist destinations and adopt local living conditions; however, many VFR travelers have barriers to accessing travel medicine providers or do not recognize the importance of malaria prophylaxis and vaccinations when visiting their countries of origin.

The usual activities of the business, tourist, and adventure travelers are very different, and each traveler should be counseled about the infections, injuries, and exposures that are most likely. For example, popular freshwater activities in Africa, such as white-water rafting in the Nile River in Uganda or diving in East African Rift Valley Lakes can result in schistosomiasis infection. Rural itineraries and direct animal contact can be risk factors for various vaccine-preventable (e.g., rabies, Japanese encephalitis [JE]) and nonvaccine preventable (e.g., avian influenza, African tick-bite fever) infections.

Travelers should be aware that blood- and bodily fluid-borne infections such as HIV, hepatitis B, and hepatitis C may be more prevalent in travel destinations than at home, and routine advice of avoiding unprotected sexual contact and percutaneous exposures (e.g., tattooing, piercings) is prudent. All travelers might encounter risk of bloodborne infections when seeking medical care, especially in areas where unsafe injection practices exist or when administration of inadequately screened blood products occurs. Those working in healthcare settings (i.e., medical missionaries, healthcare trainees, etc.) should be advised to investigate the availability of reliable HIV postexposure prophylaxis medications should an occupational percutaneous bodily fluid exposure occur.

BOX 114.1

Sources of information for travel health advisers

1. Centers for Disease Control and Prevention (CDC) Travelers' Health website. Provides country-specific immunization and malaria prophylaxis recommendations, as well as helpful links to locate travel medicine and insurance providers. The *Health Information for International Travel 2018* is also available online here. Website: www.cdc.gov/travel
2. US Department of State. Provides updated travel advisories and alerts, as well as country-specific advice for US travelers. Website: www.travel.state.gov
3. International Association for Medical Assistance to Travelers (IAMAT). Nonprofit organization providing travel health advice, country-specific recommendations, and listing of international clinics. Website: www.iamat.org
4. International Society of Travel Medicine (ISTM). Association of travel health advisors and publisher of the *Journal of Travel Medicine*. Provides a listing of travel clinics. Website: www.istm.org

Immunizations

When providing pre-travel advice, it is important to review both routine immunizations as well as those recommended or required for the particular itinerary. Travelers should be up to date on routine vaccinations (see Chapter 113, "Immunizations"). Some vaccinations, such as polio or meningococcal vaccination, are routinely administered to children and adolescents in the United States, although adult boosters are recommended for travel to specific areas. Measles and hepatitis A vaccination are also routine childhood vaccines in the United States; however, many adults are inadequately vaccinated. On the other hand, yellow fever, typhoid, cholera, and JE vaccinations are used in the United States and Europe almost exclusively for international traveler. Vaccination for tuberculosis with Bacille Calmette–Guérin (BCG) vaccination is rarely indicated for travelers. Table 114.1 lists the immunizations of special importance for travel and their schedules.

Unless required, immunizations should generally be recommended according to risk of disease. The risk of infections can vary significantly among different countries in a region, Furthermore,

TABLE 114.1 **IMMUNIZATIONS FOR FOREIGN TRAVEL**

Vaccine	Adult dosage	Duration of efficacy
Live attenuated		
Yellow fever	1 (0.5 mL) SC 10 days before travel	Lifelong immunity for most individuals (see exceptions in text)
Typhoid	1 enteric-coated capsule taken on alternate days for 4 doses with cool liquid 1 h before a meal[a]	Booster series q5yr
Cholera	Single oral dose prepared and administered in a healthcare setting	3 months (long-term data unavailable to guide booster recommendation)
Inactivated		
Typhoid	1 dose (0.5 mL) IM	Booster q2yr
Rabies pre-exposure	3 doses (1.0 mL) IM on days 0, 7, and 21 or 28	No boosters recommended for most travelers at routine exposure risk
Meningococcal (quadrivalent A/C/Y/W-135)	1 dose (0.5 mL) IM	Reimmunization recommended q5yr[b]
Japanese encephalitis, inactivated Vero cell culture-derived	2 doses (0.5 mL) IM on days 0 and 7 to 28	Booster recommended at 1 yr; data unavailable regarding efficacy of booster given ≥2 yrs after primary vaccination and need for subsequent booster doses
Hepatitis A	2 doses, at 0 and 6–12 mo (HAVRIX) or 0 and 6–18 mo (VAQTA)	Probable lifelong immunity
Passive prophylaxis		
Immunoglobulin for protection against hepatitis A[c]	0.1 mL/kg for travel ≤1 mo, 0.2 mL/kg for travel ≤2 mo (0.2 mL/kg q2 mo for travel ≥2 mo)	

Abbreviations: SC = subcutaneous; IM = intramuscular.
[a] Must not be taken while taking antibiotics, including doxycycline malaria prophylaxis.
[b] For participation in Hajj pilgrimage vaccination within previous 3 years and ≥10 days prior to arrival required.
[c] Must be administered at least 3 months prior to administration of measles or vaccination.

infection risk can vary with different activities, accommodations, and eating habits. Trip duration is also important to consider due to the increased risk of infection exposure over time, and some vaccinations such as JE, hepatitis B, or rabies vaccination, are of higher priority in long-term travelers.

Most vaccines can be administered simultaneously at separate sites, and this is often necessary when multiple are indicated. However, immunologic response to live-virus vaccines (i.e., MMR, varicella, yellow fever, or intranasal live attenuated influenza vaccines) might be attenuated when administered within 30 days of another live-virus vaccine. Therefore, live-virus vaccines should be administered on the same day or spaced apart at least 30 days.

Influenza

Though many travelers and physicians underrecognize the importance of influenza vaccination prior to travel, influenza is the most common vaccine-preventable illness seen in travelers, and vaccination is recommended for all travelers aged ≥6 months. Influenza occurs year-round in the tropics and from May through November in the southern hemisphere. For these reasons vaccine should be administered in the United States to all travelers until the vaccine expiration date (usually in May–June of the year following its availability). The southern hemisphere vaccine is not available in the United States.

Hepatitis A and immunoglobulin

Hepatitis A is one of the most common vaccine-preventable infections in travelers. While risk is higher in rural areas or for those with adventurous eating habits, many travel-related cases have occurred with typical tourist itineraries, and hepatitis A vaccination is strongly recommended for all travelers. Although vaccination is now routine for US children with a two-dose series, many adults have not been vaccinated. For routine vaccination, the minimum age for the first dose of hepatitis A vaccine is 12 months; however, infants aged 6 to 11 months traveling to higher risk areas may receive one dose of vaccine, followed by revaccination with the usual two-dose series after the infant reaches 12 months of age. Prior to the availability of the hepatitis A vaccine, immunoglobulin (IG), was used for protection. Though IG protects travelers immediately, its duration of protection is short and its availability is limited. IG is still recommended for travelers <6 months old or those with vaccine contraindications. IG can also be given in addition to vaccine to travelers aged >40, with chronic liver disease, or those who are immunocompromised when travel is imminent (in <2 weeks).

Hepatitis B

Although hepatitis B vaccination is now recommended in the United States for all infants, children, and adolescents, many adults have not been vaccinated. Among travelers, hepatitis B vaccination has typically been reserved for persons at higher risk of exposure, such as healthcare workers, those who may have casual sex, and for long-term travelers to high-prevalence countries. However, all travelers to low-resourced countries are at risk when seeking healthcare due to potentially unsafe injection practices and inadequately screened blood products. In addition to the recombinant hepatitis B vaccine, which is usually given in a three-dose series (over 6 months), a newer hepatitis B vaccination (HepB-CpG) is now available in the United States. HepB-CpG is given as a two-dose series given 1 month apart. This two-dose series might be favorable for travelers leaving too soon to consider the primary and accelerated vaccination schedules recommended for the recombinant hepatitis B vaccines. A combined hepatitis A and B vaccine is available in the United States, and an accelerated regimen is also approved for the combined vaccine (0, 7, 21–30 days). When using the accelerated schedule with combined vaccine, a booster dose should be given at 1 year to provide long-term immunity.

Measles, mumps, rubella, and varicella

Measles continues to be a major cause of morbidity and mortality in many regions of the world, including Europe, which has had recent increases in cases due to suboptimal vaccination coverage. Since measles is extremely transmissible, ensuring that travelers have immunity to measles is particularly important to prevent outbreaks resulting from its introduction into areas with susceptible persons. Although mumps and rubella are less of a health threat to travelers, both infections can have serious complications. For international travelers, two doses of the MMR vaccine are recommended for those without contraindications unless there is serologic evidence of immunity, prior history of disease, or birth prior to 1957. Of note, children between 1 and 4 years old may have only had one MMR dose. It is recommended that they get their second dose prior to travel (as long as it is administered at least 4 weeks after the first dose), and additional doses are unnecessary. For those under 1 year of age, immunization may be given between 6 and 12 months of age and is recommended for international travel. Two doses after age 12 months are still indicated in this circumstance. The combination MMRV vaccine (measles, mumps, rubella, and varicella), can be used when needed, although it is not licensed in the United States for infants <1 year.

Varicella does present a health risk to nonimmune individuals. International travelers should have evidence of immunity, which can include age-appropriate vaccination (one dose of varicella vaccine for children aged 1 to 4 years and two doses for individuals aged ≥4 years), history of chickenpox or zoster, serologic evidence of immunity, or birth before 1980 (not a criterion for healthcare workers, pregnant women, or immunocompromised individuals).

Typhoid

Although *Salmonella enterica* serotype Typhi is prevalent in many countries in Africa, Asia, and Central and South America, typhoid fever is not common in travelers. However, given the serious nature of the infection and availability of well-tolerated vaccines, live Ty21a oral capsular vaccine or the injectable inactivated vaccine should be considered in travelers to endemic areas. Immunocompromised travelers should receive the inactivated vaccine. While those traveling off usual tourist routes or adventurous eaters are at highest risk, long-term and frequent short-term travelers to developing countries are also at increased risk. Vaccine recipients should be aware that the vaccines are only 50% to 80% effective and do not prevent typhoid fever caused by *S. enterica* serotype Paratyphi; therefore, vaccination alone can not be relied on to prevent typhoid fever.

Cholera

Cholera, the severe diarrheal illness caused by *Vibrio cholerae* O-group 1 or O-group 139 is endemic in numerous countries in Africa, South Asia, and Southeast Asia. A large cholera epidemic also began in Haiti in 2010, and the disease is now endemic in Hispaniola. Transmission primarily occurs via drinking water with naturally occurring *V. cholerae* or water contaminated with feces from an infected person. Transmission can also occur from person to person during epidemics. Risk to travelers is primarily in those who travel to epidemic or endemic areas and do not practice to safe food and water hygiene or have close contact with cholera patients. Persons with low gastric acidity or type O blood are at higher risk for severe cholera illness.

A live attenuated single-dose oral cholera vaccine (CVD 103-HgR) was approved in the United States in 2016 for use in adults aged 18 to 64 years. Studies have demonstrated vaccine efficacy of 80% at 3 months after vaccination. Concurrent or recent use of antibiotics or chloroquine may diminish the immune response to CVD 103-HgR. Although travelers who follow safe food, water, and handwashing recommendations are at extremely low risk for cholera infection, vaccination can be can be considered in travelers who are traveling to areas of active cholera transmission, especially those without access to safe food and water, persons with risk factors for severe disease, or those will not have access to treatment if illness occurs. Healthcare workers in cholera endemic and epidemic areas might also consider vaccination. Safety and efficacy of CVD 103-HgR in immunocompromised or pregnant persons is not established. Data are also unavailable to guide any recommendation regarding the need and safety of revaccination. Studies in children are ongoing.

Polio

Infants and children should be current on routine polio immunizations prior to travel. Intervals between doses may be reduced to optimize immunization status before departure. Adults aged ≥18 years who are traveling to an endemic or epidemic area should complete a primary series prior to travel if they have never received one. Details on accelerated schedules are available from the CDC Health Information for International Travel (Table 114.1). Furthermore, as a precaution, all adults who have received the routine childhood series should also receive a single booster dose of the inactivated polio vaccine before travel to polio endemic or epidemic countries. A single booster dose might also be recommended for adults working in healthcare settings, refugee camps, or other

humanitarian aid settings in certain countries that share a border with endemic and epidemic countries. Long-term travelers staying >4 weeks in certain polio-affected countries may also be subject to recent requirements for proof of polio vaccination 1–12 months prior to departure from the affected country. Readers are encouraged to refer to the CDC Travelers' Health website for updated country-specific recommendations (Table 114.1). Oral polio vaccine is no longer available in the United States.

Tetanus, diphtheria, and pertussis

All travelers should be up to date with tetanus, diphtheria, and pertussis vaccination as per routine. Diphtheria continues to be endemic in many countries outside the United States and Western Europe. Pertussis is increasingly recognized worldwide, including in the United States. Adult travelers who have not previously received the combined tetanus/diphtheria/acellular pertussis vaccine (Tdap) should receive one dose of Tdap instead of tetanus and diphtheria toxoid (Td) for booster immunization.

Yellow fever

Yellow fever is a viral illness transmitted by mosquitoes in tropical Africa and South America. It is rare in travelers, but, because of its high mortality, vaccination is recommended for individuals visiting endemic areas. Some countries have specific yellow fever vaccination entry requirements, including some that require documentation of vaccination for all visitors, and others that require vaccination only when arriving from an endemic country. Country-specific entry requirements (available from the CDC Travelers' Health website and country embassies) should be reviewed for each international traveler. In the United States vaccination is available only at approved yellow fever vaccination clinics (see the CDC Travelers' Health website, Table 114.1, for a listing).

Vaccination is documented on an International Certificate of Vaccination or Prophylaxis (ICVP, "yellow card") and considered valid 10 days after the date of vaccination. Previous recommendations for routine boosting at 10 years have been revised, and now booster doses at 10 years are now only recommended for women who were pregnant when they received their first dose, those who received a hematopoietic stem cell transplant after yellow fever vaccination (if sufficiently immunocompetent to receive vaccine), those who were HIV-infected when receiving their last dose of vaccine, and travelers who may be in higher risk situations for yellow fever. In 2016, the International Health Regulations were amended by the World Health Assembly, and certificates of vaccination for yellow fever are now considered valid for life (for entry purposes). This amendment applies to new and existing certificates.

Yellow fever vaccine is a live-virus vaccine and is contraindicated in infants <6 months of age and individuals with thymus disorders or immunodeficiencies (including AIDS and those receiving immunosuppressive or immunomodulatory therapies for transplanted organs, malignancies, autoimmune disorders, or other conditions). Precautions to vaccination include ages between 6 and 9 months or >60 years, pregnant or breastfeeding women, and HIV-infected individuals without AIDS. Following yellow fever vaccination, rare cases of encephalitis or autoimmune neurologic disease have been reported, as well as multiorgan system illness similar to yellow fever illness. Although severe adverse events occur with an overall frequency of only 3.8 per 100,000 doses, risk is increased among those age ≥60 years. Individuals with vaccine contraindications who travel to countries with entry requirements should carry a waiver documented on the ICVP and physician's letterhead to avoid being denied entry or subject to penalty (or vaccination) upon arrival.

Meningococcal meningitis

Quadrivalent meningococcal vaccines protect against *Neisseria meningitidis* serogroups A, C, Y, and W-135. Routine vaccination in the United States is recommended for adolescents and other groups with increased risk of infection. Travelers to countries that are hyperendemic or epidemic are considered at increased risk, including travelers to the African "meningitis belt" during the dry season (December through June). Vaccination is also required by the Saudi Arabia government for those attending the Hajj pilgrimage in Mecca.

Japanese encephalitis

From 1973 to 2015, there were 79 reports of JE infection among travelers from nonendemic countries. JE transmission occurs in Asia during the summer to autumn in temperate regions, and during the rainy season or potentially year-round in the subtropics and tropics. JE is transmitted by night-biting *Culex* mosquitoes, typically in rural areas with rice cultivation and pig-farming. Up to 30% of symptomatic infections are fatal, and 30% to 50% of survivors have neurologic sequelae. Short-term urban travelers are at very low risk; however, travelers on prolonged itineraries to rural areas can have similar risks as that of the local population. Therefore, vaccination should be particularly considered in long-term travelers and those with extensive overnight rural exposures. The inactivated Vero cell culture-derived vaccine (Ixiaro) is licensed in the United States for individuals aged ≥2 months. Vaccine is given in a two-dose series 28 days apart (or 7 to 28 days apart for adults 18 to 65 years old).

Rabies

The decision to administer rabies pre-exposure vaccination should be based on various considerations including endemicity of rabies in the countries visited, exposure risk, duration of stay, and availability of postexposure biologics. Rabies is transmitted through inoculation of saliva from an infected mammal, typically resulting from a bite, though non-bite exposures can occur via mucous membranes or open wounds. All travelers should avoid contact with wild and feral mammals, as well as unvaccinated domesticated dogs and cats. Children have increased risk for animal bites and may potentially not report exposures. Any possible exposure should be washed immediately with soap and water, and medical care should be sought immediately to determine if postexposure prophylaxis is indicated. Although individuals who have received pre-exposure vaccinations do not need rabies immunoglobulin (RIG) following an exposure, booster doses of vaccine are still needed, so all travelers should be advised to seek urgent care following potential exposures.

Other advice

Malaria prophylaxis

Because malaria infection represents a significant risk to nonimmune travelers, prescription of malaria prophylaxis can be a critical part of the pre-travel consultation. For details, see Chapter 199, "Malaria."

Food and water hygiene

Prevention of travelers' diarrhea and other food- and waterborne gastrointestinal infections requires careful selection of food and beverages while traveling in the developing world. Foods that are well-cooked and still hot are safest. Fruits washed and peeled by the traveler are safe. Raw salads, salsas, and fruits eaten whole are risky. Commercially bottled carbonated beverages, alcohol, hot tea, and coffee are generally safe. Tap water consumption is generally unsafe (see www.cdc.gov/travel for country-specific recommendations), and only boiled, bottled (from reliable sources), or properly disinfected water should be consumed. Ice cubes are typically made from untreated tap water. Milk and dairy products should be pasteurized or cooked. For more details on the treatment and prevention of travelers' diarrhea, see Chapter 119, "Travelers' diarrhea."

Altitude illness

Acute mountain sickness (AMS) can occur with rapid ascent to altitudes >8,000 ft (2,500 m), and symptoms can include headache, fatigue, nausea, and loss of appetite. Symptoms usually resolve with acclimatization in 1 to 3 days or descent; however, progressive ascent (e.g., in mountain climbing) can cause persistent symptoms or increase the risk of high-altitude cerebral edema or high-altitude pulmonary edema. Since many popular high-altitude destinations such as Cusco, Peru, are reached by direct flight, travelers visiting these areas might be at particular risk for AMS. Susceptibility to AMS is unpredictable; therefore, prophylaxis medication such as acetazolamide should be considered for travelers going to these areas.

Injuries

Accidents can be the cause of nearly half of fatalities among international travelers. These can include traffic accidents, drownings, and other injuries resulting from outdoor activities. Travelers should be aware that traffic laws, road quality, fire codes, and other safety regulations in the developing world are typically at much lower standards or nonexistent. Alcohol consumption is a significant risk factor for travel-related injury, and individuals often consume more during travel. Crimes such as robberies, sexual assault, and homicide are worldwide problems. Politically unstable countries or those in the midst of social unrest can be particularly dangerous for travelers. The US State Department provides updated travel alerts and country-specific safety advice (www.travel.state.gov).

Jet lag

Travel across several time zones typically results in disrupted sleep as the traveler's internal body clock adjusts to the local time, a process that takes about 1 day for each time zone crossed. Adequate hydration, resting after arrival, and judicious use of sedatives can help with adjustment or symptom management. Bright light exposure can help reset the internal clock. For travel eastward, it is recommended that travelers seek bright light in the early morning, and, for westward travel, exposure should be in the late afternoon. Melatonin can be helpful for jet lag; however, it is considered a supplement in the United States and is not regulated by the US Food and Drug Administration (FDA).

Insect avoidance

Mosquito and other arthropod avoidance measures such as insect repellents, bednets, and permethrin-treated clothing can be important, particularly when visiting areas endemic for dengue, malaria, and other arthropod-borne infections including Zika virus infections. See Chapter 199, "Malaria," for insect avoidance recommendations.

Travelers' health kit

A travel health kit can be important and might include prescription medications, over-the-counter medications (analgesics and fever medications, antidiarrheals, antinausea medications, antihistamines, topical medications for insect bites and rashes, etc.), a digital thermometer, oral rehydration solution packets, and first-aid supplies. Travelers should anticipate airline security regulations that restrict carry-on items. Some over-the-counter or prescription medications may be subject to stricter regulations overseas (e.g., diphenhydramine is considered a controlled substance in Zambia). Prescription medications are best carried in the original containers with the patient's name and prescribing physician information. Carrying a physician's letter that lists medical conditions and medications (with generic names and dosages) is advised.

Health and evacuation insurance

If urgent healthcare is needed during travel, travelers should be advised to seek the best quality medical care available. Online resources for finding reliable providers of care overseas can be very helpful (Table 114.1). Travelers should be aware that healthcare obtained overseas might not be covered by their usual health insurance, and supplemental insurance might be prudent. Furthermore, medical evacuation by air ambulance is typically not covered, and travelers should consider purchasing evacuation insurance when traveling to countries where standards of care are significantly lower.

Suggested reading

Centers for Disease Control and Prevention (CDC). *Health information for international travel 2018*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service; 2017.

Keystone JS, Kozarsky PE, Connor BA, Nothdurft HD, Freedman DO, Mendelson M, Leder K, eds. *Travel medicine*. Edinburgh: Elsevier Ltd.; 2019.

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Fever in the returning traveler

Alimuddin Zumla

General considerations

Fever is a frequent problem in travelers returning from holidays, business trips, or employment outside their country of residence. In 2018, >1 billion people traveling for business or pleasure arrived at international destinations. Up to half of tourists to tropical countries become ill during or after travel. A wide range of infectious and parasitic diseases can cause fever, some of which can be rapidly fatal if not detected and treated early. For example *Plasmodium falciparum* malaria is a medical emergency, and prompt diagnosis and treatment is essential. All patients should be assessed for risk of malaria, viral hemorrhagic fever, dengue, and antibiotic-resistant urinary, gastrointestinal, or respiratory infections.

Fever in a traveler may not be specifically related to travel and may be related to more universal causes such as common cold, viral pharyngitis, sinusitis, influenza (Flu A and Flu B), Covid-19, bacterial pneumonia, otitis media, or urinary tract infections. The subject of this chapter is fever related to more "imported" diseases acquired during travel to which the physician practicing in the West may be unfamiliar (see Box 115.1). With the great increase in volume and speed of travel between developed and developing countries, physicians in the United States, Europe, and other developed countries are increasingly seeing more patients with imported infections.

Careful assessment of travelers with fever must involve a detailed history, a thorough examination, and targeted laboratory investigations. The following are essential in the clinical management of fever in the returning traveler:

1. A comprehensive history:
   a. Symptoms, time of onset, duration, and progression and evolution of symptoms over time. Try to localize symptoms to organ systems.
   b. Travel history: Destinations, type of accommodation, prophylaxis measures taken, activities (e.g., game viewing, camping, farms, caves, swimming in lakes/rivers, sex, drug abuse, consumption of uncooked or semi-cooked food, and water source), bites (insects, mosquito, tsetse flies, ticks, fleas, lice, mites, animal, other).
2. A complete physical examination of all systems: Clinical features to look for are: skin rash (maculopapular, petechiae, ecchymosis), skin lesions (eschars, insect bites, erythema nodosum, boils, erysipelas), lymphadenopathy, hepatomegaly, splenomegaly, jaundice, wheeze, crackles, crepitations, joint or muscle involvement, stiff neck, photophobia, conjunctivitis, neurologic signs, or evidence of bleeding.
3. Urgent investigations:
   a. CBC
   b. Malaria thin and thick blood films including rapid malaria diagnostic test
   c. Blood culture
   d. Urine culture and dipsticks analysis (blood, protein, sugar)
   e. Stool: Bacteriology, virology, and parasitology (ova, cysts, and parasites)
   f. Blood biochemistry (C-reactive protein, urea, electrolytes, creatinine, and liver function tests)

g. Chest x-ray
h. Specific polymerase chain reaction (PCR) tests on clinical specimens for those suspected of having rapidly fatal diseases (e.g., arboviruses, viral hemorrhagic fevers [VHF], Middle East respiratory syndrome [MERS]-coronavirus.

4. Other investigations in persisting fever:
   a. Serology: Bacterial, viral, fungal, spirochetal (save serum for paired serology)
   b. Bone marrow and/or lymph node aspirates: Microscopy and culture may be required if fever persists without localizing signs.
   c. Further imaging: CT scan, positron emission tomography (PET), PET/CT scans.

The most common tropical fevers in travelers are malaria, enteric fever, hepatitis, amebic liver abscess, and rickettsial and arboviral infections.

BOX 115.1

Causes of tropical fevers in travelers

Most common
- Cosmopolitan infections (common cold, sinusitis, upper respiratory tract infections, urinary tract infections, etc.)
- Malaria
- Enteric fever (typhoid and paratyphoid)
- Atypical pneumonia, acute respiratory tract infections (bacterial and viral pneumonia)
- Hepatitis (hepatitis A, hepatitis E)
- Rickettsial infections
- Arboviral infections (dengue, chikungunya, yellow fever, Western equine encephalitis [WEE], Eastern equine encephalitis [EEE], and others)
- Bacterial diarrhea or dysentery
- Viral gastroenteritis
- Protozoal diarrhea (giardiasis or amebiases)
- Amebic liver abscess
- Sexually transmitted diseases

Less common
- African trypanosomiasis
- Tuberculosis
- Human immunodeficiency virus (HIV)
- Brucellosis
- Leptospirosis
- Histoplasmosis
- Atypical pneumonia (Legionnaires' disease, pulmonary histoplasmosis, psittacosis)
- Acute schistosomiasis (Katayama fever)
- Leptospirosis
- Filariasis
- Drug fever

Uncommon
- Visceral leishmaniasis (kala-azar)
- Cutaneous leishmaniasis
- Lyme disease
- Relapsing fever (borreliosis)
- Melioidosis
- Middle East respiratory Syndrome coronavirus (MERS-CoV)
- Viral hemorrhagic fevers (e.g., Ebola, yellow fever, Crimean Congo hemorrhagic fever)
- Tropical pulmonary eosinophilia
- Cutaneous larva migrans
- Endocarditis
- Fungal infections (Histoplasmosis, Cryptococcosis)
- Noninfectious causes (malignancy, autoimmune)

Malaria

Malaria is the most important potentially fatal cause of fever in travelers returning from the tropics. Thus, all febrile travelers returning from malaria endemic areas must be evaluated for malaria, even those who have taken appropriate malaria chemoprophylaxis. Antimalarial prophylaxis regimens cannot be considered fully protective.

Nearly all malaria cases due to *Plasmodium falciparum* present with fever within 4 weeks of returning but could present several months after leaving a malarious area. *P. vivax* and *P. ovale* malaria may occur up to 3 years after exposure due to persistence of hypnozoites (latent parasites) in the liver. *P. malariae*, which does not have a latent liver phase, is the least common species causing fever in travelers but may present up to a year or longer (up to 20 years) after first infection. Typical symptoms are high fever, shaking, chills, sweats, headache, and myalgias. Symptoms may be modified or masked according to the immune status, as in an immune native of an endemic area or by the use of prophylactic antimalarial drugs. Severe *P. falciparum* infections can rapidly lead to such lethal complications as cerebral malaria, renal failure, severe hemolysis, and adult respiratory distress syndrome.

Diagnosis is by appropriately prepared and carefully examined Giemsa-stained thin and thick malaria smears. A single negative set of smears cannot rule out malaria; smears should be repeated at 6-hour intervals for at least 24 hours. Rapid malaria antigen detection tests are now available. Specific prophylaxis and therapy for malaria is discussed in Chapter 199, "Malaria."

Enteric fever (typhoid and paratyphoid)

Typhoid and paratyphoid fevers can be contracted from contaminated food or water where the prevalence of these bacteria is high. Typhoid vaccines offer protection to no more than 70% of recipients. Enteric fever should be suspected in travelers returning from an endemic area with fever, headaches, abdominal pain, diarrhea, or cough. Symptoms may not develop until several weeks after return. Diagnosis is confirmed by positive blood, stool, or

urine culture. The agglutinin test (Widal) lacks sensitivity and specificity and is not recommended. Newer rapid serologic tests that detect IgM antibodies to *Salmonella typhi* antigens are available. Blood and bone marrow cultures have the highest yield within 1 week of symptoms, and urine and stool cultures become positive after the first week. *S. typhi* worldwide has developed multiple antibiotic resistance, including to fluoroquinolones. See Chapter 148, "Salmonella," for specific therapy details.

Hepatitis

Travelers to the developing world who have not received hepatitis A vaccine or immune serum globulin (ISG) run a significant risk of contracting hepatitis A from ubiquitously contaminated water or food. Rare cases of hepatitis E have been contracted in South Asia and elsewhere, and this type of hepatitis may not be prevented by ISG. Hepatitis B is usually contracted from sexual contact and is uncommon in travelers. In the pre-icteric phase of acute hepatitis, fever, chills, myalgias, and fatigue may occur, and this syndrome can mimic malaria and other acute tropical fevers. Hepatitis serologic testing can confirm the type of infection, but when these tests are negative in a patient with apparent hepatitis, cytomegalovirus or infectious mononucleosis (Epstein–Barr virus [EBV]) should be considered.

Amebic liver abscess

A period of acute diarrhea often precedes development of an amebic liver abscess. A returned traveler with fever and right upper quadrant pain should be suspected of this infection. Stools are positive for *Entamoeba histolytica* in only 10% to 15%. Sonography or CT of the liver will show a filling defect, and an amebic serology test will confirm infection. Needle aspiration is seldom required for diagnosis or treatment. There is very rapid clinical response to metronidazole, 750 mg three times daily for 10 days, followed by a luminal drug such as paromomycin (Humatin), 500 mg three times daily for 7 days.

Rickettsial infections

Tick typhus can be contracted in West, East, and South Africa and in the Mediterranean littoral. Infection typically begins with a skin eschar at the tick bite site; fever, chills, and headache; and, in a few days, a diffuse papular rash can develop. Epidemic, scrub, and murine typhus and Q fever are much less commonly contracted by travelers. Diagnosis is made by indirect fluorescent antibody tests or PCR of eschar and skin lesion for specific rickettsial organisms. Tetracycline is highly effective, and response is generally rapid. A single 200 mg dose of doxycycline may be adequate, but 100 mg twice a day for 5 to 7 days may be required for some *Rickettsia* species.

Viral fevers

Dengue fever, endemic in most parts of the tropical world, especially Asia, Africa, and the Indian subcontinent, is the most commonly imported arbovirus infection. Symptoms include fever, fatigue, headache, body and bone aches, and eye pain. Typically, a diffuse rash appears on the third to fifth day as other symptoms abate. Chikungunya virus is a mosquito-borne disease that has similar clinical symptoms to dengue but differs in causing severe joint pains rather than deep bone pain. A recent outbreak of chikungunya in islands of the Indian Ocean has led to numerous imported cases into Europe, North America, and parts of Asia. Japanese B encephalitis is a rare infection of travelers to rural areas of the Far East. A number of other rarer acute viral illnesses have been imported from endemic areas, including lethal Lassa and Marburg fever viruses from West and Central Africa. Diagnosis is usually confirmed serologically; there is no specific treatment, and management is generally supportive. (See Chapter 181, "Dengue" and Chapter 193, "Viral hemorrhagic fevers.")

Less common febrile illnesses in travelers

African *trypanosomiasis* is uncommon in American travelers, although it has been reported from travelers to East Africa. Even short-term travelers to game parks of East and Central Africa should take precautions against tsetse fly bites. Travelers should inform their physician of exposure if symptoms such as trypanosomal chancre at a bite site, fever, evanescent rash, headache, and lethargy develop up to 4 weeks after returning home. (See Chapter 201, "Trypanosomiases and leishmaniases.")

Tuberculosis (both drug-sensitive and drug-resistant) remains a threat worldwide. Any returnee with fever, cough, and chest radiography evidence suggestive of pulmonary disease should be screened for tuberculosis. Screening with the interferon-γ release assay (IGRA) before and after travel is recommended.

Brucellosis is contracted from contaminated raw goat or cow milk or soft cheese. Presentation can be with fever, chills, sweats, body aches, headache, monoarticular arthritis, weight loss, fatigue, or depression. Diagnosis is by blood culture and/or specific agglutination tests. Treatment is with a tetracycline plus streptomycin or rifampin.

Leptospirosis is common in the tropics but is rarely contracted by travelers. Infection is acquired through direct or indirect contact (such as contaminated water) with infected animals. Recreational activities, such as water sports and adventure travel, are emerging as important risk factors for this infection. Most infections are anicteric and mild. Initial symptoms may include high remittent fever, chills, headache, myalgias, nausea, and vomiting. No more than 10% of patients develop jaundice. Diagnosis is usually made with serology. Early therapy with penicillin or tetracycline is usually beneficial.

Histoplasmosis, a cosmopolitan disease, has rarely infected travelers to Latin America. Visitors to caves contaminated with bat droppings are at particular risk. Consideration should be given to

histoplasmosis in a returned traveler with fever and pulmonary or, less likely, disseminated disease. Ketoconazole or itraconazole given for 3 to 6 weeks is effective treatment.

Visceral *leishmaniasis* (kala-azar) is extremely rare in American tourists, although European travelers have been infected around the Mediterranean littoral. Symptoms include fever, hepatosplenomegaly, and wasting. Diagnosis is confirmed by demonstrating leishmanial organisms in a biopsy specimen of liver, spleen, or bone marrow or detection of parasite DNA by PCR test. Pentavalent antimonial compounds (sodium stibogluconate [Pentostam] and meglumine antimonate [Glucantime]) are first-line drugs. Second-line drugs are amphotericin B and pentamidine.

Classically associated with tick bites during visits to forests, *Lyme disease* occurs in Europe and the United States and may also be present in other parts of the world. Hikers in particular should take precautions against tick bites in any recognized endemic area.

Relapsing fever is caused by a spirochetal organism of the *Borrelia* spp. and occurs in a louse-borne, primarily epidemic form and in a more widely scattered tick-borne, endemic form. The latter form is present in the western United States and has been diagnosed in returnees from that area to the eastern United States. Imported relapsing fever is uncommon, but cases have been contracted in West Africa, Spain, and Central America. Diagnosis is by finding the spirochetes in a thick or thin Giemsa-stained blood smear. Treatment is with a tetracycline.

Legionnaires' disease cases in travelers have continued to rise since its first identification in Philadelphia in 1976. Many cases are associated with travel on cruise ships, hotels, and aircraft within and outside Europe. Infection is acquired from contaminated air conditioning systems, whirlpool spas, or swimming pools. While diagnosis in suspected cases can be confirmed from culture, seroconversion, and urinary antigen detection, the mainstay of clinical management for Legionnaires' disease is prompt empiric administration of *Legionella*-specific antibiotic treatment for community-acquired pneumonia and *Legionella* spp. with azithromycin, levofloxacin, or tetracyclines.

Melioidosis is endemic primarily in Southeast Asia and sporadically occurs in other areas. The majority of imported cases are seen in refugees from Southeast Asia, in returned servicemen from that area, and occasionally in tourists. An asymptomatic form of infection is most common, but acute pneumonic and septicemic forms may occur. Chronic suppurative forms may also develop in various organs. These forms can lie dormant for many years and have the capacity to flare into acute fulminant symptoms. Any patient with a pneumonic process who is returning from rural areas of Southeast Asia should be considered to have possible melioidosis. Diagnosis is by special culture techniques or by serology. The most effective treatment is with intravenous ceftazidime, imipenem, or meropenem. Oral therapy is with trimethoprim-sulfamethoxazole or doxycycline.

HIV infection is a particular hazard from sexual contact, blood transfusion, or contaminated needle or syringe contact worldwide. A number of disposable syringes and needles should be carried by the traveler who may need injections while traveling in areas where only nondisposable products are used. HIV serology screening should be done on any traveler with such exposure. Postexposure prophylaxis (PEP) involves taking anti-HIV medications as soon as possible after exposure to HIV.

Most viral and bacterial causes of diarrhea, amebic dysentery, and occasionally parasitic diarrhea due to *Giardia lamblia* may often present as intermittent diarrhea, nausea, headache, and fatigue and also cause fever, which may precede diarrhea by some hours or days. Acute schistosomiasis, acute fascioliasis, and acute bancroftian filariasis are uncommon causes of fever in travelers.

Drugs used for prophylaxis or treatment of travel-related infections may themselves be a cause of fever. These include sulfonamide-containing drugs such as trimethoprim-sulfamethoxazole and pyrimethamine with sulfadoxine (Fansidar) (used for malaria treatment). Quinine and doxycycline may rarely cause fever. Drugs obtained abroad, often in combinations and without prescription, may cause a cryptic fever. It is worthwhile to stop all nonessential medications pending an etiologic diagnosis in febrile travelers.

While some illnesses with fever may begin during travel, others may occur days, weeks, or even years after return from travel. Thus travel history must be part of the routine medical history for every ill patient. Furthermore, clinicians should consider the public health implications of certain infections (such as drug-resistant tuberculosis, influenza, measles, viral hemorrhagic fever, and newer viral threats such as the Middle East respiratory syndrome coronavirus [MERS-CoV] and H7N9 influenza) and notify appropriate public health authorities in their home countries.

Suggested reading

Centers for Disease Control and Prevention (CDC). 2018. Travelers' health. https://wwwnc.cdc.gov/travel/?s_cid=cs_458

Centers for Disease Control and Prevention. Health information for international travel 2018: The yellow book. https://wwwnc.cdc.gov/travel/page/yellowbook-home

Ellis J, Hearn P, Johnston V. Assessment of returning travelers with fever. *Medicine*. 2017;46(1):2–9.

Fink D. Fever in the returning traveler. BMJ. 2018:360:j5773.

Hospital for Tropical Diseases, London, www.thehtd.org; https://www.uclh.nhs.uk/OurServices/OurHospitals/UCH/htd/Pages/Tropicaldiseaseswalkinclinic.aspx

Leder K, Torresi J, Libman MD, et al. GeoSentinel surveillance network. GeoSentinel surveillance of illness in returned travelers, 2007–2011. *Ann Intern Med*. 2013;158(6):456–468.

Promed. Home page. http://www.promedmail.org/

Public Health England. Home page. https://www.gov.uk/government/organisations/public-health-england

Ross AG, Olds GR, Cripps AW, Farrar JJ, McManus DP. Enteropathogens and chronic illness in returning travelers. *N Engl J Med*. 2013;368(19):1817–1825. doi:10.1056/NEJMra1207777.

Ryan ET, Hill DR, Solomon T, Endy TP, Aronson N. *Hunter's tropical medicine and emerging Infectious Disease*, 10th ed. Amsterdam: Elsevier; 2019.

Schmitt BH, Rosenblatt JE, Pritt BS. Laboratory diagnosis of tropical infections. *Infect Dis Clin North Am*. 2012;26(2):513–554.

Spencer H, Ustianowski A, Farooq H. Assessment of fever in the returning traveller. *Br J Hosp Med (Lond)*. 2018 Oct 2;79(10):560–566.

Thwaites GE, Day NP. Approach to fever in the returning traveler. *N Engl J Med*. 2017;376:548.

Travax. Home page. http://www.travax.nhs.uk/

United Kingdom. Office for National Statistics. Travel trends. https://www.ons.gov.uk/peoplepopulationandcommunity/leisureandtourism/articles/traveltrends/2015

Weaver SC, Charlier C, Vasilakis N, Lecuit M. Zika, chikungunya, and other emerging vector-borne viral diseases. *Annu Rev Med*. 2018 Jan 29;69:395–408.

Wilder-Smith A, Boggild AK. Sentinel surveillance in travel medicine: Twenty years of GeoSentinel Publications (1999–2018). *J Travel Med*. 2018 Dec 3. doi:10.1093/jtm/tay139.

World Health Organization. International travel and health. 2018. https://www.who.int/ith/en/

World Tourism Organization (UNWTO). Home page. http://www2.unwto.org/annual-reports

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Systemic infection from animals

David J. Weber, Jonathan J. Juliano, and William A. Rutala

Introduction

Zoonoses are defined as diseases and infections that are transmitted between vertebrate animals and humans. Currently there are more than 200 recognized zoonotic diseases, and 75% of emerging infectious diseases fit into this category. Zoonotic diseases can be transmitted to humans through bites and scratches, direct contact, aerosols, arthropod vectors, or contamination of food or water. There are many reasons for the increased impact of zoonotics in current times. Contact with domestic animals continues to be frequent, even in urban centers. Pets are a major reservoir and source of zoonoses, especially for children. In 2011–2012, 62% of US households, or approximately 72.9 million total households, owned a pet: 39% of households owned a dog, 33% owed a cat, 5% owned a pet bird, and 4% owned a reptile. The total number of animals owned was 78 million dogs, 86 million cats, 16 million birds, and 4.6 million reptiles. Other common pets include fish, rabbits, hamsters, gerbils, mice, and farm animals such as horses.

Recent factors that have had a substantial impact on emergence of zoonotics are human encroachment on wildlife habitat, wildlife trade and translocation, the ownership of exotic pets, petting zoos, and ecotourism. The epidemics of severe acute respiratory syndrome (SARS), West Nile virus, and monkeypox in North America have demonstrated the role of wildlife and exotic pets in the emergence of zoonotic diseases in industrialized nations. Traditional leisure pursuits such as hunting, camping, and hiking are increasingly common and continue to bring people into close contact with wild animals, arthropods, and sometimes contaminated water. Occupational exposures to domestic animals or animal products, especially in backyard operations, remain a leading cause of zoonotic disease exposure.

For all of the reasons described above, it is increasingly important for physicians, veterinarians, and public health professionals to work together in recognizing and controlling zoonotic diseases. The Centers for Disease Control and Prevention (CDC) has become a World Organization for Animal Health (OIE) Collaborating Center for Emerging and Remerging Zoonoses and now dedicates an entire issue of the *Emerging Infectious Disease* journal to zoonotics. The key to controlling zoonoses continues to lie with the astute clinician diagnosing and reporting these diseases, and the goal of this chapter is to assist in these efforts.

Clinical approach

Zoonoses are caused by a diverse group of microorganisms. Infectious syndromes caused by zoonotic pathogens are equally diverse. Hence, classification of zoonoses is difficult for the clinician. Diseases may be classified by the nature of the pathogen, animal host, mode of transmission from animal to human, geographic range of host, or clinical syndrome (i.e., systemic disease or specific organ system of infection). Although most zoonoses are relatively unusual, they must be included in the differential diagnosis of many clinical syndromes. All patients with an infectious syndrome whose cause is not apparent after a standard

history and physical examination should be questioned to assess the possibility of a zoonosis. First, the clinician should question patients about exposure to pets and ask whether they own or have had recent contact with a dog, cat, bird, fish, reptile, or rodent. If contact may have occurred, the clinician should ask about a history of bites or scratches. Second, the patient should be asked about exposure to farm animals (which may also be pets) such as horses, pigs, cattle, and fowl (i.e., chickens and turkeys). The clinician should determine the amount and degree of exposure. Third, patients should be asked about leisure pursuits such as hunting, fishing, hiking, and camping. The clinician should assess specific animal contacts such as dressing or skinning animals, ingestion of water from streams and lakes, and bites by arthropods such as ticks (see also Chapter 119, Tick-borne disease). Fourth, the clinician should obtain a careful travel history to determine the risks of exposure to geographically limited zoonoses. In particular, it is important to ascertain whether a patient has had an animal bite or scratch while visiting an area endemic for rabies. Because the incubation period for rabies may extend for years, persons bitten or scratched by dogs or other possible rabid hosts should be considered for postinjury prophylaxis. In general, evaluation for specific zoonoses should be based on the possibility of exposure (Table 116.1).

A brief description of the approach to possible systemic infections caused by animals is provided in subsequent paragraphs. More detailed information may be found in specific chapters in this book or in the Suggested Reading at the end of this chapter.

Zoonotic diseases acquired by animal bite or scratch

Dog bites account for 70% to 90% of animal bites and cat bites account for 3% to 15%. Bites from wild animals constitute <1% of bite wounds. The infection rate from penetrating dog bites is approximately 3% to 12%. Cat bites are much more likely to become infected. Most dog and cat bites occur on the extremities. Males are more likely to be bitten by a dog than are females, whereas the opposite is true for cat scratches and bites. The highest incidence of dog bites is in children ages 5 to 9 years and the highest incidence of cat bites/scratches is now in adults >75 years of age. Approximately 1% of rodent bites become infected.

Although infections following animal bites may be caused by various flora, some generalizations can be made. The most common pathogen to cause infection following feline bites is *Pasteurella multocida* (see Chapter 23, Animal and human bites), which generally results in rapid progressive cellulitis similar to that caused by *Streptococcus pyogenes*. Occasionally sepsis may result, especially in the immunocomprised host. The agents of rat-bite fever, *Streptobacillus moniliformis* and *Spirillum minus*, may be transmitted by several small rodents, including the rat, mouse, and gerbil. Both agents cause a systemic illness. Infections with *Aeromonas hydrophila* may follow bites inflicted in fresh or brackish water or by aquatic animals such as snakes and alligators. Severe local infection progressing to crepitant cellulitis with systemic toxicity may occur. Although most cases of tularemia follow the handling of rabbits, infection may be transmitted by animal bites or scratches, especially domestic cats (other animals include the coyote, pig, and squirrel). *Capnocytophaga canimorsus* is an unusual systemic infection strongly associated with dog bites. More than 50% of patients have reported dog bites before clinical infection, although infection has also been reported following scratches from dogs, cat bites or scratches, and contact with wild animals. Approximately 80% of patients reported in the literature have a predisposing condition, most commonly splenectomy. Other predisposing conditions have included Hodgkin's disease, trauma, idiopathic thrombocytopenia purpura, alcohol abuse, steroid therapy, and chronic lung disease. Bites from seals, whales, and walruses may transmit a murine mycoplasma. *Erysipelothrix rhusiopathiae* is carried most commonly by swine but is also found in sheep, horses, cattle, chickens, crabs, fish, dogs, and cats. A local infection, erysipeloid, may result from bites or injury with these animals usually during occupational exposure. Thus, abattoir workers, butchers, fishermen, farmers, and veterinarians are at risk for infection with *E. rhusiopathiae*. Sepsis and endocarditis may result from local infection.

Zoonotic diseases acquired by arthropod bites

Due to major changes in the environment the incidence of zoonotic diseases vectored by arthropods has increased dramatically in recent years. The most significant of these diseases are vectored by ticks and include Rocky Mountain spotted fever (RMSF), Lyme disease, ehrlichiosis, and anaplasmosis. RMSF is caused by the rickettsial agent *Rickettsia rickettsii* and is the most severe rickettsial disease occurring in the United States. This disease is characterized with an acute onset of fever, malaise, headaches, chills, and in most cases a maculopapular rash. The rash of RMSF typically appears between the third and fifth days of illness but is absent in 5% to 15% of patients. Initially maculopapular, it begins on extremities, often around the wrist and ankles. As the rash progresses, it spreads centripetally to the trunk and characteristically involves the palms and/or soles. As it evolves, it becomes more clearly defined and more petechial and may rarely progress to skin necrosis and gangrene. RMSF has a case-fatality rate of 13% to 25% when untreated. Lyme disease has been reportable since 1992, and almost 10 000 cases were reported that year. In 2011 there were approximately 24 000 definite and 9000 probable cases of Lyme disease reported in the United States. Lyme disease is characterized by a distinctive circular rash, called erythema migrans (EM). Erythema migrans is characteristically an expanding annular erythematous plaque with central clearing, most commonly seen in the axilla, thigh, and groin. Color varies from pink to violaceous. Erythema migrans may last up to 4 weeks and may recur during the secondary stage of infection. Ehrlichiosis is a tick-borne disease caused by *Ehrlichia chaffeensis*, *E. ewingii,* and *E muris*-like which is characterized by fever, headache, malaise, mylagias, nausea/vomiting/diarrhea, and conjunctival injection and rash (in up to 60% of children, less than 30% of adults).

TABLE 116.1 **INFECTIOUS DISEASES ACQUIRED FROM ANIMALS**

Disease	Persons at risk[a]	Birds, fowl	Cats, dogs	Farm animals	Fish, reptiles,[b] water	Rabbits	Rodents	Arthropod vectors	Wild animals
Viral									
Avian influenza (H5N)	I, V, VI	+++							
Bovine papular stomatitis	I, II			+					
California encephalitis	III, rural, public							+++	
Colorado tick fever	III							+++	
Eastern equine encephalitis	III, public							+++	
Hantavirus pulmonary syndrome	I, III, public						+++		
B virus (*Herpesvirus simiae*)	IV, V								Macaca monkeys
Lymphocytic choriomeningitis	III, IV, V, public						+++		
Milker nodule (pseudocowpox)	I, II			+					
Newcastle disease	I, II, IV, V	++							
Orf (contagious ecthyma)	I, II			+					
Powassan encephalitis	I, III, public							+++	
Rabies	III, VI, public		++	+					+++
Rotavirus	I, III, IV, public			++					
SARS-coV	I, II, IV, V								+
St. Louis encephalitis	I, III, public							+++	
Venezuelan encephalitis	I, III, public							+++	
Western equine encephalitis	I, III, public							+++	
Yellow fever	III, VI							+++	
Bacterial									
Aeromonas	III, IV, VIII, public				+++				
Anthrax (wool sorter disease)	I, II, IV, X		+	+++					
Brucellosis	I, II, III, V		+	+++					
Campylobacteriosis	I, II, III, IV	+	++	+++	++		++		
Capnocytophaga canimorsus sepsis	III, IV, IX, public		+++						
Cat scratch fever	III, IV, IX, public		+++						
Edwardsiella tarda infection	IV, VIII				++				
Ehrlichiosis	I, III, IV, VI, IX, public							+++	

TABLE 116.1 **CONTINUED**

Disease	Persons at risk[a]	Birds, fowl	Cats, dogs	Farm animals	Fish, reptiles,[b] water	Rabbits	Rodents	Arthropod vectors	Wild animals
Erysipeloid	I, II, III, VIII	++	+	+	++		++		
Leptospirosis	I, III, IV, V	++	+	++	+		++		
Listeriosis	IX, public	+	+	+++		+			
Lyme disease	I, III, IV, VI, public							+++	+
Murine typhus	I, III, VI						(Vector)	+++	
Mycobacteriosis (*M. marinum*)	VIII				+++				
Pasteurellosis	III, IV, public	+++	+++			++			++
Plague	III, IV, V, VII, X		+				++		
Plesiomonas infection	VIII				+++				
Psittacosis	I, II, III, IV, V, VI	+++							
Q fever	I, II, V		++	+++					++
Rat-bite fever	I, III, IV						++		
Relapsing fever	I, III, IV							+++	(Vector)
Rhodococcus	I, II, IV			++					
Rocky Mountain spotted fever	I, III, IV, IX, public		(Vector)					+++	
Salmonellosis	I, II, III, IV, VIII, IX	+++	+	+++	+++	+++	+++	+	+++
Staphylococcus aureus infection	I, II, IV, V, IX		+	++					
Group A streptococcal infection	I, II, IV, public		+	+					
Tuberculosis	I, V, IX	+	+			+			
Tularemia	I, III, IV, X		++	++		+++	++	+++	++
Vibriosis	III, VIII					++			
Vibrio vulnificus infection	VIII, IX					+++			
Yersiniosis	I, II, III, IV, VIII	+	+	++	+	++	++		
Fungi									
Ringworm	I, II, III, IV, V, VI		++						
Babesiosis	III, IV, IX							+++	
Cryptosporidiosis	I, II, III, IV, VI, IX	+	++	+++ ++	+	+			
Cystircercosis	Public		++						
Dipylidiasis	IV		++						
Dirofilariasis	III		(Vector)					+++	
Echinococcosis	I		+	++					

(*continued*)

TABLE 116.1 **CONTINUED**

Disease	Persons at risk[a]	Birds, fowl	Cats, dogs	Farm animals	Fish, reptiles,[b] water	Rabbits	Rodents	Arthropod vectors	Wild animals
Giardiasis	I, III, IV	+		++		+			+++
Toxocariasis	IV		++						
Toxoplasmosis	IV, IX		+++	+					
Trichinosis	Public			+					++

Abbreviation: SARS-coV = severe acute respiratory syndrome-coronavirus.
+, Rare source; ++, occasional source; +++, most-common source; (vector), not spread directly by animal but always via vector.
[a] Persons at risk: Group I (agriculture), farmers and other people in close contact with livestock and their products; group II (animal-product processing and manufacture), all personnel of abattoirs and of plants processing animal products or by-products; group III (forestry, outdoors), persons frequenting wild habitats for professional or recreational reasons; group IV (recreation), persons in contact with pets or wild animals in the urban environment; group V (clinics, laboratories), healthcare personnel who attend patients and healthcare workers, including laboratory personnel, who handle specimens, corpses, or organs; group VI (epidemiology), public health professionals who do field research; group VII (emergency), public affected by catastrophes, refugees, or people temporarily living in crowded or highly stressful situations; group VIII (fisherman), people catching or cleaning fish or engaging in recreational activities in the water; group IX (immunocompromised hosts), people who are immunocompromised because of immunodeficiency, cancer chemotherapy, organ transplants, immunosuppressive medications, liver and/or renal disease; group X (disaster responders, public), potential bioterrorist agent.
[b] Reptiles include lizards, snakes, and turtles.
[c] Rodents include hamsters, mice, and rats.

It is a serious disease with a case-fatality rate of 1.8%. Anaplasmosis is a tick-borne disease caused by *Anaplasma phagocytophilum*. Symptoms are similar to ehrlichiosis but rash is rare.

Mosquito-borne zoonotic diseases are common and significant throughout much of the world but play only a minor role domestically. The most common in the United States is West Nile virus. The vast majority of infected have subclinical or mild disease, whereas 1 in 150 infected will develop encephalitis. A unique feature is the ascending paralysis ("West Nile polio"). Other mosquito-borne zoonotics that occur in the United States are western equine encephalitis (WEE), eastern equine encephalitis (EEE), St. Louis encephalitis, and Lacrosse encephalitis. Other than EEE, these agents generally cause mild disease but can occasionally cause severe encephalitis in immunocompromised patients. EEE is rare but has a case-fatality rate of about 33%.

Plague, caused by *Yersinia pestis*, persists in wild rodents in the western half of the United States and is vectored by rodent fleas. Tularemia, caused by *Francisella tularensis*, occurs throughout the entire United States and is vectored by ticks, deer flies, and other insects. Tularemia also has several reservoirs such as rabbits, voles, and badgers. Both plague and tularemia may cause local skin and soft-tissue infection and serious systemic illness.

Zoonotic diseases acquired by inhalation

Although community-acquired pneumonia (CAP) is a common disease, few cases of pneumonia are due to zoonotic agents. Lower respiratory infection due to zoonotic agents generally causes an "atypical" pneumonia and may be mistaken for infection caused by *Legionella* spp., *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*. Zoonotic diseases that may be acquired in the home include *P. multocida* infection (cats and dogs), psittacosis (birds), and Q fever (parturient cats). Hunting or hiking in the United States may bring people into contact with animals capable of transmitting brucellosis (farm animals), plague (rodents, ground squirrels, prairie dogs), Q fever (farm animals, cats), tularemia (rabbits), and RMSF (ticks). The hantavirus cardiopulmonary syndrome (HCPS) due to Sin Nombre virus (SNV) results from inhalation of aerosols of excreta from infected rodents and is characterized by fever, headache, myalgias, and respiratory failure with a mortality rate of ~40%. In 2012 there was an outbreak in people visiting Yosemite National Park. Persons engaged in processing animal products such as hides are at risk for brucellosis and anthrax.

Few zoonotic pneumonias are capable of being transmitted from person to person. However, person-to-person transmission has been reported of avian influenza (H5N1 strain), *Coxiella burnetii* (Q fever), *Mycobacterium bovis*, and *Y. pestis* (plague). Avian influenza (H5N1) and pneumonic plague represent potentially serious nosocomial pathogens, and patients with these diseases should be placed on isolation precautions. Several zoonotic agents acquired via the respiratory route are potential agents of bioterrorism, including anthrax, brucellosis, plague, Q fever, and tularemia. Because of transmissibility and global migration, zoonotic pneumonias have the potential to cause significant epidemics across continents. A worldwide epidemic of SARS occurred in 2003 due to a novel coronavirus (SARS-coV). Molecular epidemiology suggested transmission from the palm civet and that the ultimate reservoir for the virus was bats. In 2009 a variant H1N1 triple assortment strain (human, avian, pig) led to a worldwide pandemic of influenza.

Zoonotic diseases acquired via ingestion

Zoonotic diseases acquired through ingestion are the most commonly acquired zoonotic diseases in the world. The main category is

bacterial diarrhea, with fever and abdominal cramps. *Campylobacter* is the most common agent and is normally found in the intestines of birds. Birds are also the primary reservoir of *Salmonella*, but it can also be found in many reptiles and mammals. The main reservoir of *Escherichia coli* O157:H7 is cattle and similar ungulates. One possible consequence of infection with *E. coli* O157:H7, especially in children and the elderly, is hemolytic-uremic syndrome (HUS), with hemolysis and renal failure. Brucellosis and listeriosis are bacterial foodborne zoonotic diseases of increasing importance in the United States due to the consumption of unpasteurized dairy products, causing a generalized febrile illness. Pregnant women are at higher risk for severe listeriosis.

There are also zoonotic agents that are transmitted via contaminated water. The most common disease is cryptosporidiosis, a protozoal disease spread by drinking and recreational water throughout the entire United States. Cryptosporidiosis generally causes a self-limited mild diarrheal illness. Giardiasis is also a protozoal waterborne zoonotic disease that is common and causes a mild diarrheal illness. Leptospirosis is generally transmitted through contaminated water. Although not common in the United States, there are sporadic outbreaks. Most cases produce a febrile illness that may progress to severe hepatic, renal, or neurologic disease. The reservoirs for leptospirosis are rodents, cattle, pigs, and small mammals (e.g., raccoons, opossums).

Systemic infections result from zoonotic diseases

Many zoonoses cause severe systemic symptoms. The range of possible pathogens can often be narrowed if the patient manifests specific organ involvement. Diseases to consider in patients with fever without focal signs on initial history and physical examination include *Aeromonas* sepsis, babesiosis, brucellosis, *C. canimorsus* sepsis, ehrlichiosis, cat scratch disease, leptospirosis, listeriosis, plague, Q fever, rat-bite fevers, relapsing fever, RMSF and other rickettsial infections, salmonellosis, tularemia, and viral hemorrhagic fevers.

Zoonoses may be associated with skin lesions. A generalized maculopapular rash may accompany cat scratch fever, Colorado tick fever, ehrlichiosis, leptospirosis, lymphocytic choriomeningitis, psittacosis, RMSF and other rickettsial infections (exceptions include Q fever and trench fever), rat-bite fever resulting from *Spirillum minus*, relapsing fever, and salmonellosis. Most rashes associated with zoonoses are too nonspecific to be of significant clinical utility. Crepitant or gangrenous lesions may complicate *Aeromonas*, *C. canimorsus*, or *Vibrio vulnificus* and related species. Petechial and purpuric lesions may occur with viral hemorrhagic fevers (e.g., dengue, yellow fever, Ebola, Lassa), RMSF, *Rickettsia prowazekii* infection, rat-bite fever resulting from *Streptobacillus moniliformis*, relapsing fever, and *C. canimorsus* sepsis. A local eschar often occurs with *Rickettsia conorii*, *Rickettsia australis*, *Rickettsia sibirica*, *Rickettsia akari*, and *Rickettsia tsutsugamushi*. Local skin lesions with or without lymphangitis may occur with cat scratch fever, rat-bite fever resulting from *Spirillum minus*, and tularemia.

Suggested reading

Acha PN, Szyfres B. *Zoonoses and Communicable Diseases Common to Man and Animals, 3rd edn. Scientific Publication No. 580*. Washington, DC: Pan American Health Organization; 2003.

Al-Dabbagh M, Dobson S. Infectious hazards from pets and domestic animals. *Adv Exp Med Biol*. 2011;697:261–272.

Chomel BB, Sun B. Zoonoses in the bedroom. *Emerg Infect Dis*. 2011;17:167–172.

Colville JL, Berryhill DL. *Handbook of Zoonoses: Identification and Prevention*. St. Louis, MO: Mosby Inc; 2007.

Esch KJ, Petersen CA. Transmission and epidemiology of zoonotic protozoal diseases of companion animals. *Clin Microbiol Rev*. 2013;26:58–85.

Kilpatrick AM, Randolf SE. Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. *Lancet*. 2012;380:1946–1955.

Lieberman JM. North American zoonoses. *Pediatr Ann*. 2009;38:193–198.

Rabinowitz PM, Conti LA. *Human-Animal Medicine: Clinical Approaches To Zoonoses, Toxicants and Other Shared Health Risks*. Maryland Heights, MO: Saunders; 2010.

Weinberg AN, Weber DJ. Animal-associated human infections. *Infect Dis Clin North Am*. 1991;5:1–6.

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Tick-borne disease

Steven C. Buckingham

Ticks can transmit numerous bacterial, parasitic, and viral pathogens to humans, and the secretions of some species can induce allergic reactions or cause paralysis. This chapter aims to provide a broad overview of tick-borne infections endemic to North America and to discuss general principles regarding their epidemiology, therapy, and prevention. Details about each of these infections are provided in their respective chapters.

Epidemiology

Tick-borne infections occur most often in the spring and summer, when ticks are most active, but are reported in colder months as well. Some patients with tick-borne infections will recall a recent tick bite, and many, but not all, report having spent time in a rural or wooded area within 2 to 4 weeks before the onset of illness. Frequently, however, patients are unaware of their recent tick exposure, for several reasons: Tick bites are usually painless, ticks may attach in sites covered by hair or clothing, and ticks in their larval and nymphal stages are very small but still capable of transmitting infection. Tick-borne infections have been reported in urban areas and, in endemic areas, among patients whose only outdoor exposures occurred in their own backyards. Thus the historical findings of tick bite or outdoor exposure may provide useful diagnostic clues, but their absence never excludes the possibility of a tick-borne illness.

Clinicians must understand the epidemiology of tick-borne infections to make presumptive diagnoses. The geographic distributions of tick-borne infections (listed in Table 117.1) correspond to the distributions of their associated tick vectors; thus, patients' geographic residence and travel history are keys to deciding which tick-borne illnesses are possible or likely.

Clinical manifestations

Most tick-borne infections present with nonspecific signs and symptoms, similar to those observed in viral syndromes (e.g., fever, malaise, headache, and myalgias). Sometimes, certain constellations of symptoms suggest a specific diagnosis. For example, the combination of erythema migrans, arthritis, and neurologic abnormalities suggests Lyme disease, whereas a cutaneous ulcer with associated regional adenopathy suggests tularemia.

Some of the typical physical and laboratory findings associated with specific tick-borne infections endemic to the United States are listed in Table 117.1. It must be emphasized, however, that not all patients with these illnesses will have all of their typical findings; for example, fewer than two-thirds of patients with Rocky Mountain spotted fever (RMSF) have the "classic triad" of fever, rash, and headache. Moreover, these illnesses have broad differential diagnoses; for example, the symptoms and signs of RMSF overlap considerably with those of ehrlichiosis, brucellosis, salmonellosis, Q fever, numerous viral infections (e.g., Epstein–Barr virus, cytomegalovirus, and enterovirus) and many other illnesses.

TABLE 117.1 **PRINCIPAL TICK-BORNE DISEASES OF THE UNITED STATES**

Disease	Organism	Geographic distribution and vector	Typical clinical findings[a]
Rocky Mountain spotted fever (RMSF)	*Rickettsia rickettsii*	Eastern United States: *Dermacentor variabilis* (dog tick) Mountain West: *Dermacentor andersoni* (wood tick) Southwestern deserts: *Rhipicephalus sanguineus* (brown dog tick)	Fever, headache, petechial rash, hyponatremia, thrombocytopenia
Rickettsia parkeri infection	*Rickettsia parkeri*	Southeastern United States: *Amblyomma maculatum* (Gulf Coast tick)	Similar to RMSF, but with eschar at inoculation site; rash may be vesicular or pustular; gastrointestinal symptoms less prominent
Human monocytotropic ehrlichiosis (HME)	*Ehrlichia chaffeensis*	Southeastern and southcentral states: *Amblyomma americanum* (Lone Star tick)	Similar to RMSF, but rash less common; leukopenia, thrombocytopenia, elevated transaminases
Human granulocytotropic anaplasmosis (HGA)[b]	*Anaplasma phagocytophilum*	Northeast and upper Midwest: *Ixodes scapularis* (blacklegged tick) Pacific coast: *Ixodes pacificus*	Similar to HME, but rash is rarely present
Ehrlichia ewingii infection	*Ehrlichia ewingii*	Southeastern and southcentral states: *A. americanum*	Same as HGA
Lyme disease	*Borrelia burgdorferi*	Northeast and upper Midwest: *I. scapularis* Pacific coast: *I. pacificus*	First stage: fever, erythema migrans Second stage: multiple skin lesions, conjunctivitis, arthralgias, myalgias, headache, cranial nerve palsies Third stage: arthritis; encephalopathy, dementia, peripheral neuropathy
Southern tick-associated rash illness	*Borrelia lonestari*	Southeastern and southcentral states: *A. americanum*	Rash similar to erythema migrans
Endemic relapsing fever	*Borrelia hermsii B. turicatae B. parkeri*	Western mountains and deserts: *Ornithodoros* species	Fever, chills, relapsing course
Tularemia	*Francisella tularensis*	Eastern United States: *D. variabilis* Mountain West: *D. andersoni* Southeastern and southcentral states: *A. americanum*	Fever, cutaneous eschar, lymphadenopathy, pulse–temperature dissociation
Babesiosis	*Babesia microti*	Northeast, Midwest, and West Coast: *I. scapularis*, other *Ixodes* species	Fever, malaise, headache, hepatosplenomegaly, thrombocytopenia, hemolytic anemia
Colorado tick fever	Coltivirus	Mountain West: *D. andersoni*	Fever, headache, leukopenia, thrombocytopenia; biphasic course
Powassan encephalitis	Powassan virus	Northeastern, north-central United States: *Ixodes* species, *D. andersoni*	Headache, seizures, altered sensorium, focal neurologic signs, meningismus
Tick paralysis[c]	Neurotoxin	Widespread: *Dermacentor* species, others	Ascending flaccid paralysis

[a] Not all patients will have all of the "typical" findings for these diseases. Many cases present simply with fever and vague constitutional symptoms.
[b] Formerly termed *human granulocytic ehrlichiosis*.
[c] Tick paralysis is not caused by an infection, but its epidemiology is similar to that of tick-borne infections.

Therapy

Tick-borne infections should, in general, be diagnosed presumptively, based on clinical findings and epidemiologic history. Because most specific tests yield negative results in early disease or must be sent out to a reference laboratory, the clinician often must prescribe antibiotics empirically (i.e., before a diagnosis is confirmed by laboratory testing). This is particularly true with regard to RMSF, in which mortality rates are significantly higher among patients who receive antirickettsial therapy on the fifth day of illness or later.

Details regarding the treatment of specific tick-borne infections are provided in the respective chapters. Generally speaking, doxycycline is appropriate for treatment of most tick-borne infections endemic to North America. At one time, chloramphenicol was

advocated for use in children younger than 8 years, owing to concerns over doxycycline's perceived potential to stain permanent teeth. Now, however, doxycycline is recognized as the drug of choice for the treatment of all suspected rickettsioses or ehrlichioses in North America, regardless of the patient's age. The principal reason for this change is that doxycycline treatment achieves superior outcomes in patients with RMSF or human monocytic ehrlichiosis, compared to chloramphenicol. Moreover, doxycycline does not penetrate teeth as well as tetracycline does; whereas repeated administrations of tetracycline to young children certainly can cause unsightly tooth discoloration, there is no evidence that a single course of doxycycline will do so.

Prevention of tick-borne diseases

Prevention of tick-borne diseases consists of avoidance of tick bites and prompt removal of attached ticks. During spring and summer months, it is prudent to examine persons and pets that have been outdoors at least daily for attached ticks. Wearing light-colored clothing will facilitate the identification of ticks. Nymphs and larvae are very small and may hide in areas such as the head, neck, axillae, belt line, or scrotum; thus, these areas must be scrutinized closely.

Attached ticks should be removed by grasping with tweezers close to the skin and pulling gently with steady pressure; the bite site should then be washed with soap and water. Attempts to detach ticks by applying petroleum jelly, fingernail polish, isopropyl alcohol, or a hot, extinguished kitchen match are discouraged, as these methods are both ineffective and potentially dangerous.

The repellant *N*,*N*-diethyl-*meta*-toluamide (DEET) is very effective for preventing tick, mosquito, chigger, and fly bites. Because protection increases with increasing concentrations, repellants containing 20% to 30% DEET are currently recommended for adults and children. When used appropriately, DEET is quite safe; concerns over its toxicity have been vastly overstated. Nevertheless, a few cautionary statements are in order. DEET must not be ingested and should be applied only to exposed, intact skin, or to clothing. It should not be introduced to the mouth, eyes, or other mucous membranes (and thus should not be applied to the hands of children). Children should not apply DEET-containing products to themselves, and DEET is not recommended for use on children younger than 2 months. DEET should not be overused; in most cases, one application per day is adequate. Treated skin should be washed with soap and water after coming indoors.

Permethrin is an insecticide that may be sprayed on clothing, providing an additional layer of protection against tick bites (and those of other arthropods). Clothes should be sprayed on each side of the fabric for 30 to 45 seconds and allowed to dry for 2 to 4 hours before wearing. Permethrin maintains potency for at least 2 weeks after application, even if clothes are washed. Although permethrin is occasionally associated with skin erythema or edema, systemic adverse effects have not been noted.

Suggested reading

Buckingham SC. Tick-borne diseases in children: epidemiology, clinical manifestations and optimal treatment strategies. *Paediatr Drugs*. 2005;*7*:163–176.

Centers for Disease Control and Prevention (CDC). Diagnosis and management of tick-borne rickettsial diseases in the United States—Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis: a practical guide for physicians and other health care and public health professionals. *MMWR Recomm Rep*. 2006;55(RR-4):1–27.

Graham J, Stockley K, Goldman RD. Tick-borne illnesses: a CME update. *Pediatr Emerg Care*. 2011;27:141–150.

Needham GR. Evaluation of five popular methods for tick removal. Pediatrics. 1985;75:997–1002.

Pickering LK. Prevention of tickborne infections. In: *Red Book: 2012 Report of the Committee on Infectious Diseases*, 29th edn. Elk Grove Village, IL: American Academy of Pediatrics; 2012: 207–209.

Romero JR, Simonsen KA. Powassan encephalitis and Colorado tick fever. *Infect Dis Clin North Am*. 2008;22:545–559.

Salinas LJ, Greenfield RA, Little SE, Voskuhl GW. Tickborne infections in the southern United States. *Am J Med Sci*. 2010;340:194–201.

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Recreational water exposure

Mary E. Wilson and Andrea K. Boggild

Many common forms of recreation involve water exposure. Pathogens in water infect susceptible humans by multiple routes: through skin and mucous membranes, via inhalation of aerosols, aspiration, and ingestion. Clinical manifestations of these infections range from superficial skin lesions to fatal, systemic infections. The survival of many water-associated pathogens is influenced by climate, season, other environmental conditions, and the level of sanitation. The types and abundance of organisms vary depending on the salinity, pH, temperature, and other characteristics of the water. Hence, many are found only or primarily in certain geographic regions or during some seasons of the year. The risk of infection by waterborne pathogens is a function of the duration and type of exposure, concentration density of organisms in water, and host immunity. This chapter describes the types of pathogens, geographic distribution, sources and routes of transmission, clinical presentations, and management of water-associated infections. Water can also be a source of toxins, including heavy metals. Oceans and beaches are the sites of marine envenomations. These topics are beyond the scope of this chapter.

Visits to recreational water venues are common, as are outbreaks of infections related to them. In the United States in 2011–2012, for example, 90 waterborne disease outbreaks in 32 states were reported to the Centers for Disease Control and Prevention (CDC). Almost 2,000 persons were affected by these outbreaks, with at least 95 associated hospitalizations and 1 death. Over the past 20 years, the number of reported diarrheal illnesses following recreational water exposure has steadily increased. Of the 90 outbreaks associated with recreational water exposure reported in 2011–2012, more than half (52%) were outbreaks of gastroenteritis specifically due to cryptosporidiosis. Cryptosporidiosis, giardiasis, *Escherichia coli* O157:H7 gastroenteritis, norovirus, shigellosis, leptospirosis, and *Pseudomonas* dermatitis have been the most commonly reported infections related to recreational water exposures in the United States in recent years. During the more prolonged reporting period of 2000–2014, almost 500 outbreaks associated with treated recreational waters were reported to the US CDC. The most common causes were *Cryptosporidium* (58%), *Legionella* (16%), and *Pseudomonas* (13%) (see Hlavsa 2018, in "Suggested Reading" section), pathogens characterized by chlorine-resistance and capacity to form biofilms. Outbreaks of adenoviruses (causing pharyngitis, conjunctivitis), cercarial dermatitis, and hepatitis A (public swimming pool) have also been reported. Chlorinated swimming pools, water parks, lakes, ponds, and whirlpools have been common sources. Although outbreaks related to recreational water use can occur throughout the calendar year, most occur in the summer months, with 61% of outbreaks associated with treated recreational water in 2011–2012 beginning in June, July, or August.

Patients typically do not volunteer specific descriptions of water exposures because they may not recognize their relevance. Box 118.1 lists several sources of water exposures that have been associated with infections and can be used as a checklist to help the clinician obtain relevant history. Most water-associated infections will become apparent within hours to days (usually ≤14 days) of exposure. An important exception is schistosomiasis, which may first manifest months or longer after exposure. Relevant history includes types of exposures; dates, duration, and location of exposures; and type of water (e.g., mountain stream, lake, hot tub, chlorinated pool, salt water). During participation in water sports, people commonly ingest water and inhale aerosols.

BOX 118.1

Types of activities associated with water exposure

Swimming, wading, diving
Near-drowning events
Fishing, hunting
Rafting, boating, kite sailing, sailing, surfing, windsurfing, water-skiing
Water parks (wave pools and water slides)
Sitting in hot tubs, whirlpools
Showering and bathing, ritual washing
Drinking water and water-containing beverages (untreated surface water consumed during hiking, camping)
Care of fish tanks, aquaria

Ingestion of contaminated water, whether during swimming, showering, or drinking, often causes infections manifested by diarrhea. Some pathogens have the capacity to cause systemic infection after ingestion. Fecally contaminated water may contain a potpourri of microbes—bacteria, viruses, protozoa, and helminths—causing a variety of illnesses with differing manifestations and incubation periods. Swimming at beaches near a sewage outlet, for example, leads to increased rates of conjunctivitis, otitis externa, skin, and soft tissue infections, as well as gastrointestinal infections. Interactive fountains are known to be particularly vulnerable to contamination as they are open to young children, the homeless, and animals and recirculate potentially contaminated water back onto users.

Recreational water activities are often group activities, so contaminated water may be associated with outbreaks, sometimes involving dozens or even hundreds of people. In addition to caring for the acutely ill patient, the clinician must consider the public health implications and alert the appropriate authorities. Early interventions may slow or halt an outbreak and allow early recognition of other cases. In many instances, outbreaks are the result of inadequate operation or maintenance procedures. For example, in a recent US-wide inspection of >5,000 spas, nearly 3,000 were found to be in violation of water quality and other maintenance parameters, resulting in the immediate closure of 11% of those inspected. As further illustration of this point, in August 2003, inadequate disinfection of an athletic facility spa resulted in an outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) skin infections among college football players, thus establishing this emerging pathogen as one with potential for waterborne transmission. A review of 18 outbreaks of *Pseudomonas* from spas implicated substandard levels of chlorination in each case. And, among almost 14,000 routine inspections of public hot tubs and spas conducted in 2013 across 16 jurisdictions, suboptimal disinfectant concentrations were noted in 20%.

The route of entry may influence the clinical findings for several of the water-associated pathogens, with skin penetration causing local wound infections and ingestion causing diarrheal infections. Box 118.2 lists the range of clinical manifestations of infections that follow water exposure. With some of the more virulent organisms or in the setting of immune compromise, infection may enter the bloodstream after any one of several entry points. Minor trauma, cuts, bites, and breaks in the skin can provide the portal of entry for many water-dwelling microbes. Table 118.1 summarizes infections and infestations that enter through the skin. Table 118.2 lists specific infections acquired via aspiration, inhalation, and ingestion.

BOX 118.2

Clinical manifestations of infections related to recreational water exposure

Skin and mucosal surface exposure
Conjunctivitis
Keratitis
Otitis externa
Dermatitis (including folliculitis)
Mastitis
Cellulitis
Fasciitis
Endometritis (reported after intercourse in water)
Systemic infection

Aspiration, inhalation, ingestion
Pharyngitis
Sinusitis
Meningoencephalitis
Pneumonitis
Gastroenteritis, colitis
Systemic infection

Several water-associated infections and intoxications can be rapidly progressive or can lead to serious complications. Because some of these are infrequent or rare, they may be unfamiliar to most physicians. The following section provides a brief summary of each. More common infections, such as shigellosis, campylobacteriosis, salmonellosis, and *E. coli* O157:H7 that can be acquired through water exposure are covered in more detail in other chapters of this book. Table 118.3 lists the recommended treatment for the less familiar water-associated infections and ones that are not covered in other chapters of the text.

Acquired by penetration through skin

Pseudomonas dermatitis or folliculitis

Use of hot tubs and whirlpools (spas), and, occasionally, swimming pools and water slides has been associated with development of a characteristic diffuse rash caused by the aerobic, gram-negative organism *Pseudomonas aeruginosa*. The rash, which is maculopapular or vesiculopustular and usually pruritic, develops within 48 hours of exposure and typically resolves within a week. Lesions are more prominent in areas covered by a bathing suit or clothing. Associated findings may include otitis externa, mastitis (in men and women), conjunctivitis, and lymphadenopathy. Infection is typically self-limited in healthy hosts; immunocompromised persons may

TABLE 118.1 **INFECTIONS AND INFESTATIONS ACQUIRED VIA PERCUTANEOUS AND PERMUCOSAL RECREATIONAL WATER EXPOSURE**

Pathogen or disease	Source
Bacteria	
Aeromonas hydrophila[a,b]	Freshwater streams, lakes, soil
Burkholderia pseudomallei (melioidosis)[a,b]	Fresh water, soil (tropics, subtropics)
Chromobacterium violaceum[a,b]	Freshwater rivers, soil (tropics, subtropics)
Leptospirosis[b]	Fresh water contaminated with animal urine (especially tropics, subtropics)
Mycobacterium marinum[a]	Fish tanks, swimming pools
Pseudomonas aeruginosa[a]	Hot tubs, whirlpools, swimming pools
Vibrio vulnificus, other vibrios[a,b]	Seawater
Tularemia[a,b,c] (*Francisella tularensis*)	Fresh water contaminated by infected animal; inoculation of skin, conjunctiva, oropharyngeal mucosa
Helminths	
Schistosomiasis[a,b]	Freshwater streams, lakes (focal in Asia, Africa, South America, parts of Caribbean)
Cercarial dermatitis (avian schistosomes)[a]	Fresh and salt water (worldwide)
Protozoa	
Acanthamoeba species[a,b] (keratitis); *Naegleria fowleri*[b]; *Balamuthia mandrillaris*[a,b]	Fresh water, especially stagnant ponds during hot summers; hot tubs, swimming pools, thermal springs
Viruses	
Adenovirus[a,b] (swimming pool conjunctivitis; pharyngitis)	Swimming pools; likely other freshwater sites
Coxsackieviruses[a,b]	Fresh water
Other	
Seabather's eruption[a]	Seawater

Pseudomonas dermatitis and *M. marinum* are rarely associated with systemic infection, primarily in compromised hosts.
[a] Skin and soft tissue.
[b] Systemic infection.
[c] Conjunctivitis.

develop hemorrhagic bullae, pneumonia, and bacteremia. From 2000–2014, 40 outbreaks caused by *Pseudomonas* were linked to hotel/motel pools or spas, leading to cases of skin- or ear-related disease. Infections can be prevented if water is maintained at a pH of 7.2 to 7.8 with adequate chlorination (free, residual chlorine levels should be in the range of 2.0 to 6.0 mg/L), with levels <0.5 mg/L consistently detected in outbreak situations.

Otitis externa (swimmer's ear)

Infection of the external ear canal, otitis externa, is common in swimmers. Usual symptoms are mild pain and pruritus around the ear. Pain may become more severe if infection progresses to involve deep tissues and bone, as more commonly occurs in patients with underlying medical conditions, such as diabetes mellitus. Common organisms are *S. aureus* and *P. aeruginosa*; multiple bacterial species are often recovered from cultures. Purulent drainage and local lymphadenopathy may develop. Occasionally infections progress to cellulitis that requires systemic antibiotic therapy. Topical therapy can be effective in early infections. See Chapter 6, "Otitis," for treatment.

Cercarial (schistosome) dermatitis

Cercarial dermatitis, also known as *swimmer's* or *clam digger's itch*, is caused by an allergic response to penetration of skin by cercariae of nonhuman larval trematodes of the genus *Schistosoma* (often avian schistosomes). A pruritic, maculopapular rash develops in water-exposed areas of the body (Figure 118.1). Both total duration of exposure and duration of exposure to shallow water correlate with increased likelihood of developing cercarial dermatitis. Shallow water exposure is a particular risk factor as this is where snail beds are most dense and cercarial accumulation is greatest. In 2011–2012, four outbreaks leading to 65 cases of cercarial dermatitis in the United States were linked to recreational water exposure.

Lesions appear hours to a day or more after water exposure and are often less prominent in areas covered by a bathing suit or other protective clothing. Papules may become vesicular. Secondary bacterial infection may result from scratching-related skin abrasions. Lesions peak in 2 to 3 days and typically resolve over 1 to 2 weeks without specific therapy. In persons with previous exposures lesions may develop sooner and may be more severe. Treatment is symptomatic and may include antihistamines and topical steroids. Systemic steroids have been used in severe cases. Nonhuman schistosomes are widely distributed, including in temperate areas, and may contaminate fresh, brackish, and seawater.

Schistosomiasis

Penetration of the skin by human schistosomes (e.g., *Schistosoma mansoni*, *S. haematobium*, *S. japonicum, S. mekongi*) may cause redness, urticaria, and pruritic papules, typically less severe than the cercarial dermatitis just described. Systemic manifestations of schistosomiasis may develop months or years later. Among 28 travelers who developed schistosomiasis after water exposure in Mali, 36% gave a history of schistosomal dermatitis. Infection can follow even brief water exposure, including river rafting. Attack rates have often been high in travelers who swim, wade, or bathe in infested water. An acute illness characterized by fever, malaise, and eosinophilia (Katayama syndrome) may develop 2 to 6 weeks after exposure and corresponds to larval migration following initial skin penetration. Dry cough, dyspnea, and pulmonary infiltrates may be present.

TABLE 118.2 **SPECIFIC INFECTIONS OR TOXINS ACQUIRED VIA INHALATION, ASPIRATION, OR INGESTION DURING RECREATIONAL WATER EXPOSURE**

Disease or pathogen	Main clinical finding
Adenovirus 3	Pharyngitis, fever, conjunctivitis
Amebiasis (*Entamoeba histolytica*)	Colitis, liver abscess
Aerosolized red tide respiratory irritation (ARTRI)	Rhinorrhea, cough, bronchospasm
Balantidiasis (*Balantidium coli*)	Diarrhea or dysentery
Campylobacteriosis	Diarrhea
Cholera (*Vibrio cholerae*)	Diarrhea, dehydration
Coxsackieviruses	Diarrhea
Cryptosporidiosis	Diarrhea, fever, nausea, vomiting
Cyclospora	Diarrhea, fever, nausea, vomiting
E. *coli* O157:H7	Bloody diarrhea
Free-living amoebae *(*especially *Naegleria fowleri)*	Meningoencephalitis
Giardiasis	Subacute diarrhea, fever, nausea, vomiting
Hepatitis A virus	Acute hepatitis
Hepatitis E virus	Acute hepatitis (potentially fatal in pregnancy)
Legionnaires' disease (*Legionella*)	Pneumonia
Leptospirosis	Fever, severe myalgia, conjunctival suffusion; may cause severe icterohemorrhagic fever
Melioidosis	Pneumonia, sepsis, skin lesions; protean manifestations
Norovirus ("Norwalk-like viruses")	Diarrhea, vomiting
Pfiesteria (possible estuary-associated syndrome)	Eye irritation, cough, rash, vomiting, abdominal cramps, neurocognitive changes
Poliovirus	Nonspecific febrile illness; flaccid paralysis 1%
Pontiac fever (*Legionella*)	Fever (self-limited)
Primary amebic meningoencephalitis (PAM)	See Free-living amoebae
Rotavirus	Watery diarrhea
Salmonellosis	Diarrhea; extraintestinal manifestations if bacteremic diarrhea; dysentery
Shigellosis	Diarrhea, dysentery
Toxoplasmosis	Fever, lymphadenopathy, lymphocytosis
Tularemia	Fever, lymphadenopathy, pneumonia; manifestations depend on route of transmission
Typhoid/paratyphoid fever (enteric fever due to *Salmonella enterica* serotype Typhi or Paratyphi)	Fever, systemic infection, gastrointestinal sequelae
Vibrio parahaemolyticus	Watery diarrhea; occasionally dysentery
Vibrio vulnificus	Sepsis, bullous skin lesions; high rate of hospitalization and mortality
Yersinia enterocolitica	Fever, diarrhea, acute mesenteric lymphadenitis

Neurologic complications (including transverse myelitis) can occur early or late. Clinical findings vary with the species of schistosome and are related to granulomatous reactions to eggs in tissue (Figure 118.2). Maps showing the geographic distribution of schistosomiasis are found on World Health Organization (WHO) and CDC websites and in the CDC reference.

Seabather's eruption (also marine dermatitis or sea lice)

Seabather's eruption is caused by penetration of the skin by *Linuche unguiculata*, *Edwardsiella lineata*, and other larvae of the phylum Cnidaria. Characteristic findings include an intensely pruritic, papular rash that begins 4 to 24 hours after swimming in the ocean. The

TABLE 118.3 **DIAGNOSIS AND TREATMENT OF SELECTED INFECTIONS**

Pathogen or disease	Diagnosis[a]	Treatment
Aeromonas hydrophila	C	TMP-SMX or FQ[b,c] (third-generation cephalosporins; AG; imipenem)
Burkholderia pseudomallei	C	Ceftazidime[b,c] (imipenem[b,c] or meropenem; TMP-SMX + doxycycline[c])
Chromobacterium violaceum	C	Limited clinical data; may be sensitive to FQ, TMP-SMX, tetracyclines, AG, extended-spectrum penicillins
Francisella tularensis (tularemia)	S, C	Gentamicin,[b] streptomycin,[b] or tobramycin[b] (doxycycline or ciprofloxacin; chloramphenicol)
Leptospirosis	S, C	Penicillin G[b,c] or doxycycline[b]
Mycobacterium marinum	C (at 30°C/86°F), M	Minocycline or clarithromycin (TMP-SMX; rifampin + ethambutol; doxycycline)
Primary amebic meningoencephalitis (due to free-living amoebae)	Visualization of trophozoites in CSF; C, M	*Naegleria*[d]: miltefosine; amphotericin B IV and IT *Acanthamoeba*: miltefosine; itraconazole, TMP-SMX, rifampin; pentamidine *Balamuthia*: miltefosine; pentamidine + fluconazole + sulfadiazine + flucytosine + clarithromycin
Schistosomiasis	Demonstration of eggs in tissue, urine, or stool; S	Praziquantel[b,c]
Vibrio vulnificus	C	Doxycycline + ceftazidime[b] (cefotaxime; ciprofloxacin; doxycycline + AG [FQ])

Abbreviations: AG = aminoglycoside; CSF = cerebrospinal fluid; FQ = fluoroquinolone; IT = intrathecal; IV = intravenously; TMP–SMX = trimethoprim–sulfamethoxazole.
[a] Method of diagnosis: C = culture, M = molecular testing (such as PCR), S = serology.
[b] Considered first-line therapy at time of printing.
[c] Randomized controlled trial level of evidence for therapy.
[d] Reports of treatment success are scant.

lesions are found in areas covered by a bathing suit and at points of contact (e.g., flexural areas, wristbands of diving suits). The tiny larvae are entrapped by the bathing suit, which acts as a mechanical stimulus for the release of nematocysts and injection of toxin by the larvae. Outbreaks are sporadic. Persons with extensive involvement may have systemic symptoms, including fever. Lesions usually clear within 10 days. Antihistamines and topical steroids may provide symptomatic relief. Systemic steroids have been used in severe cases.

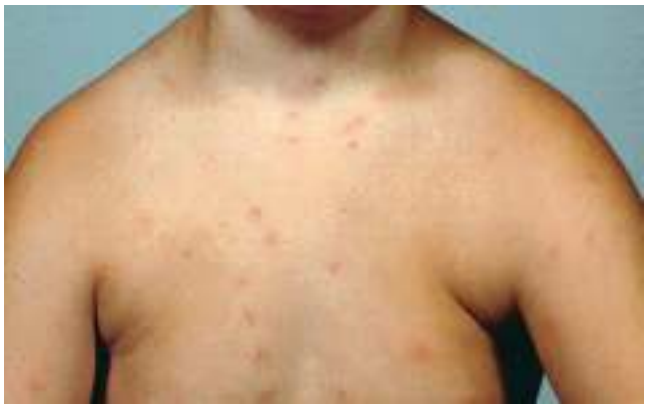

FIGURE 118.1 Skin lesions of cercarial dermatitis. (Courtesy of Jay Keystone, MD.)

Vibrio soft tissue infections

As resident marine flora, *Vibrio vulnificus*, *V. parahaemolyticus*, *V. alginolyticus*, and other *Vibrio* spp. can cause soft tissue infections through recreational water exposure. In 2007–2008, 236 cases of vibrioses linked to recreational water exposure were reported from 25 states, which represents one-fifth of the total cases of vibrioses in the country over that period of time. Almost one-third required hospitalization, and nine patients died. Organisms can be introduced by injuries (often on the lower extremity) that break the skin during swimming in the ocean or walking on beaches or can enter via preexisting open skin lesions. After trauma, *V. vulnificus* can cause pustular lesions, lymphangitis, and cellulitis, which may be mild or rapidly progressive, causing pain, myositis, skin necrosis, and gangrene. Surgical debridement (or amputation) in addition to antibiotic therapy and general support may be necessary. Of all *Vibrio*-associated illnesses secondary to recreational water exposure reported to the CDC in 2007–2008, *V. vulnificus* carried the highest rate of hospitalization and mortality.

Vibrio soft tissue infections, including necrotizing fasciitis, can also follow ingestion of contaminated food (commonly raw shellfish). Many vibrios, in addition to *V. cholerae*, can cause diarrheal illness, and gastroenteritis may be associated with high-grade bacteremia and high mortality. Large bullous skin lesions may occur with primary *Vibrio* bacteremia (especially *V. vulnificus*). Severe infections are more common in persons with chronic liver disease or other underlying diseases that compromise immune function.

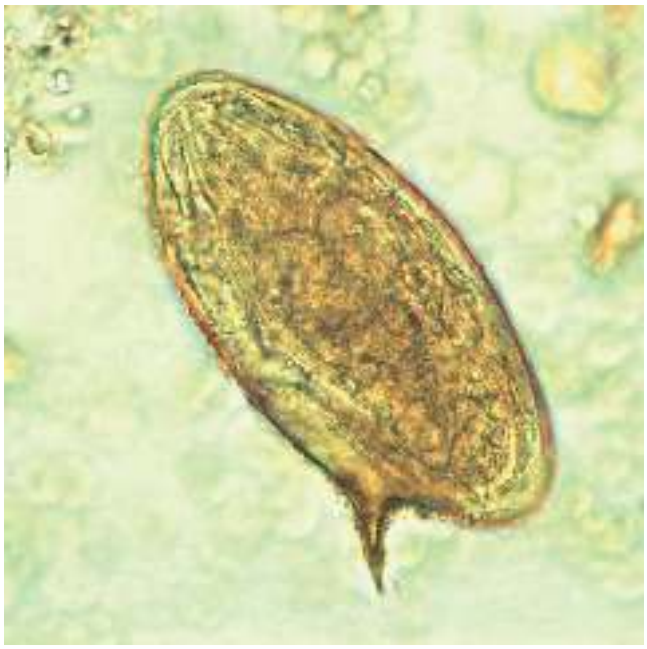

FIGURE 118.2 Egg of *Schistosoma mansoni* from stool.

Vibrios are found in seawater or brackish water and are part of the usual bacterial flora of coastal waters in the United States and elsewhere. They are more abundant in warmer months, and most reported infections occur in the summer. Rising water temperatures in the Baltic Sea over the past three decades have led to an increase in the number of outbreaks due to *Vibrio* spp. in countries that have been historically protected from these organisms due to their cooler climate.

Treatment of soft tissue and systemic infections following seawater exposure should include coverage for *Vibrio* species.

Aeromonas hydrophila

Aeromonas hydrophila is a non–spore-forming, motile, facultatively anaerobic gram-negative organism found in freshwater lakes, streams, and soil. Puncture wounds or soft-tissue injury in contaminated water may lead to cellulitis that can resemble acute streptococcal infection with lymphangitis and fever. If not treated with effective drugs, it can progress to bullae formation and necrotizing myositis with gas in soft tissues. Findings can mimic gas gangrene. Soft tissue infections may require local debridement along with systemic antibiotic therapy.

Ingestion of *Aeromonas* may cause diarrhea. Although *Aeromonas* is frequently isolated from environmental waters, evidence of clearly defined outbreaks of diarrhea attributable to aeromonads is lacking. Aspiration of *Aeromonas*-contaminated water may lead to *Aeromonas* pneumonia and bacteremia.

Melioidosis (*Burkholderia pseudomallei*)

This water- and soil-associated gram-negative organism, found especially in tropical and subtropical areas, is a common cause of pneumonia, skin lesions, and sepsis predominantly in Southeast and South Asia and Australia, though also in Oceania, the Caribbean, and South America. The organism can be acquired through minor skin wounds or via aspiration or ingestion. Infection can be acute, subacute, or chronic and has protean manifestations, including cavitary lung disease, splenic abscesses, and osteomyelitis. The organism can persist silently in the human host and reactivate decades after acquisition, mimicking tuberculosis.

Acanthamoeba infections, including primary amebic meningoencephalitis

Free-living amebae of the genus *Acanthamoeba*, found in soil and fresh water, can enter human tissues and cause local or disseminated infection. Several species of *Acanthamoeba* have been reported to cause keratitis and granulomatous inflammation, which may be acute or subacute. Soft tissue infections have also been reported, although are more likely to result from infection with the related free-living ameba *Balamuthia mandrillaris*. Minor trauma to the cornea, as may occur in persons who wear contact lenses, predisposes to infection. The diagnosis is confirmed by finding *Acanthamoeba* on biopsy, corneal scrapings, or culture (Figure 118.3). Treatment typically requires both debridement and topical therapy (several agents have been tried: combination of miconazole nitrate, propamidine isethionate, and Neosporin; propamidine isethionate and dibromopropamidine; oral voriconazole and miltefosine; among others, although level of evidence is case series only).

The free-living ameba, *Naegleria fowleri*, may cause primary amebic meningoencephalitis (PAM) following recreational water exposure, typically in young healthy persons. Trophozoites enter the nasal passages during swimming or diving, penetrate the cribriform plate, and invade the central nervous system via olfactory neuroepithelium, causing rapid destruction of gray and white matter. Symptoms usually begin 3 to 7 days after exposure to water. Infection causes high fever, headache, and stiff neck, resembling bacterial meningitis, which rapidly progresses to coma and, usually, death. Diagnosis is confirmed by detection of trophozoites in the cerebrospinal fluid (CSF) (wet mount, Giemsa staining after fixation, or by culture) or by polymerase chain reaction (PCR) of CSF, although in most cases of PAM, diagnosis is postmortem. Infections have followed exposures in lakes, rivers, stagnant ponds, thermal springs, canals, and hot tubs and are more common during very warm periods, due to the thermophilic nature of these free-living protozoa. Disruption of lake or riverbed sediment by deep swimming or digging is a particular risk factor for PAM and may therefore serve as an important historical clue for clinicians. Ritualistic washing before prayers, which involves sniffing water to cleanse the nose, has also emerged as a risk factor for PAM in rural Nigeria. In 2007–2008, eight fatal cases of PAM due to *N. fowleri* were reported from Florida, Texas, Arizona, California, and Oklahoma.

Chromobacterium violaceum

This gram-negative organism is found in abundance in tropical and subtropical freshwater rivers and soils. The rarely reported infections have usually followed penetrating skin injury and are typically bacteremic. Persons with chronic granulomatous disease are at risk for

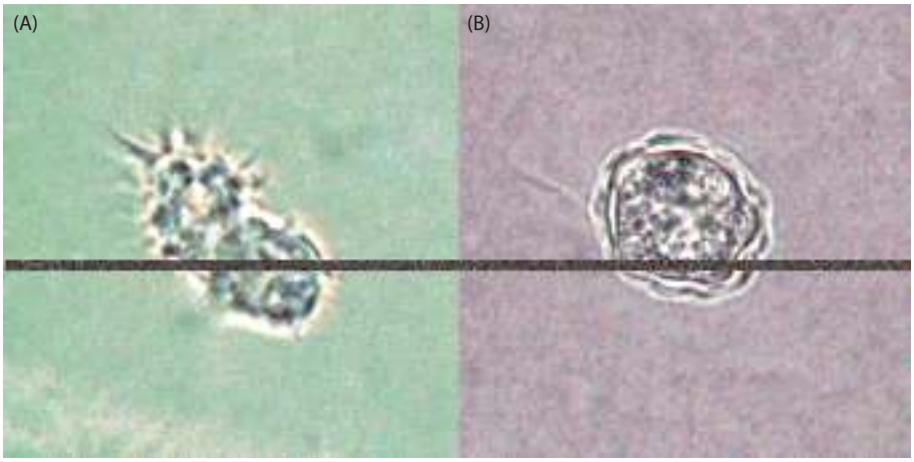

FIGURE 118.3 (A) Trophozoite and (B) cyst of *Acanthamoeba* spp. from corneal specimen, wet mount.

severe infection. Clinical data are limited, and evidence to guide management decisions is lacking.

Leptospirosis

Spirochetes of the genus *Leptospira* cause leptospirosis, a zoonosis of global significance. Leptospirosis has caused outbreaks in swimmers (lake, stream, other fresh water), kayakers, whitewater rafters (e.g., in Costa Rica), and, more recently, in 2011, among members of the French Armed Forces training in canyon rescue along the Absalon River of Martinique. Fresh water becomes contaminated with the urine of infected domestic and wild animals. Humans become infected when organisms enter through skin (especially if abraded) or mucous membranes, or after ingestion of contaminated water or food. Infections are more common in tropical and subtropical areas and during warm seasons in temperate regions. In the United States, infections have been especially common in Hawaii, although sporadic infections and occasional clusters occur in other areas, primarily in warmer months. In July 1998, an outbreak of leptospirosis occurred in Springfield, Illinois, primarily affecting triathletes who swam in Lake Springfield. Imported cases in travelers, however, can be seen throughout the year in North America. The single outbreak of leptospirosis (n = 2 cases) reported to the CDC in 2014 was related to lakewater exposures in a state park.

Infected persons can develop a systemic infection with protean manifestations, commonly including fever, headache, severe myalgia, and conjunctival suffusion. The spectrum of clinical disease can range from asymptomatic or mild infection to the most serious form, Weil's disease, characterized by an icterohemorrhagic fever. A biphasic course is classic, and complications such as aseptic meningitis, pneumonia, and acute renal failure are seen in one-quarter to one-third of all cases of leptospirosis. A large flood in Metro Manila, Philippines, in 2009 led to 471 hospitalizations and 51 deaths, with a case-fatality rate of 8%. A recent systematic review and meta-analysis estimated the overall mortality rate of untreated leptospirosis to be 2.2%, with a range of 0% to almost 40%, and mortality was almost exclusively associated with icterohemorrhagic fever and advanced age, rather than non-icteric manifestations such as meningitis (see Taylor 2015).

Mycobacterium marinum

Mycobacterium marinum usually invades only superficial tissue after local inoculation. Infection manifests as red plaques, papules, or nodules (sometimes with sporotrichoid or lymphocuticular spread) (Figure 118.4). The infection is referred to as "swimming pool granuloma" and "fish tank granuloma" because of the associations with fish and water. This subacute infection, most often on the hand or arm, can occur after exposure to fresh or salt water in aquariums and in swimming pools. Because the organism is relatively chlorine-resistant, infection can follow exposures in chlorinated pools.

Tularemia

Tularemia, caused by *Francisella tularensis*, an organism that sometimes contaminates water (from infected animals), can infect via multiple routes, including through conjunctivae, skin, oropharynx, and gastrointestinal tract. Ticks and other arthropods can transmit infection. It is mentioned in this chapter because infection can be severe, even fatal, but does respond to appropriate antibiotic therapy.

Acquired by inhalation, aspiration, or ingestion

Legionnaires' disease

Legionella can infect susceptible hosts through inhalation of aerosols generated by showers, whirlpools/spas, and sinks. Temperature is the most important abiotic factor influencing survival and growth of *Legionella*, which proliferates in hot water tanks and heat-exchanging systems. Several outbreaks of Legionnaires' disease, an acute pneumonic process, have been traced to exposures in resort hotels and whirlpools on cruise ships. Hence, this is an infection to consider in persons with febrile illness and pneumonia after travel. Pontiac fever results from the aerosolized antigens of *Legionella pneumophila* and is characterized by a self-limited febrile illness. In 2011–2012, 11 outbreaks caused by *Legionella* were linked to pools

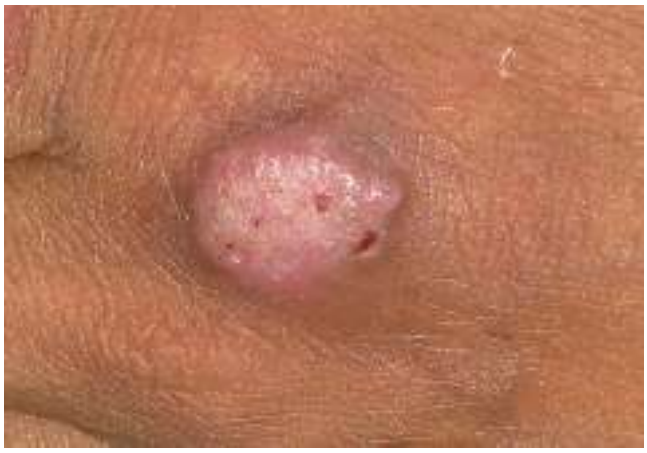

FIGURE 118.4 Cutaneous nodule of *Mycobacterium marinum* several months after repeated fish tank exposure.

or spas, leading to 85 cases of Pontiac fever or Legionnaires' disease. Randomized controlled trials support the use of either macrolides (clarithromycin, azithromycin) or fluoroquinolones (levofloxacin) for the management of Legionnaires' disease or for empiric coverage of *L. pneumophila* in cases of community-acquired pneumonia.

Cryptosporidiosis

Cryptosporidium, an apicomplexan protozoan, has eclipsed *Giardia* as the most common parasitic cause of gastroenteritis outbreaks following recreational water exposure in the United States. Of 69 outbreaks related to treated recreational water reported in the United States in 2011–2012, 36 (52%) were caused by *Cryptosporidium*. Over the past 30 years, the number of annual outbreaks of cryptosporidiosis attributable to treated recreational water exposure (range 0–40 outbreaks) has steadily increased. Among 363 outbreaks with a confirmed pathogen reported to the CDC from 2000 to 2014, 212 (58%) were due to cryptosporidiosis, and, of these, 24 (11%) affected >100 people in each case, with four outbreaks affecting >2,000 people. In 2007, for instance, a single community-wide outbreak in Utah related to recreational water exposure led to almost 5,700 cases of cryptosporidiosis. Most cases of *Cryptosporidium* occur following exposure at treated water venues, such as swimming pools. A number of factors contribute to the spread and transmission of *Cryptosporidium*, notably the wide range of animal reservoirs; the large number of fully infectious oocysts excreted by human and animal hosts (Figure 118.5); the relative resistance of oocysts to standard disinfection practices, including chlorination; and a low minimum infective dose. Oocysts of *Cryptosporidium* may be difficult to distinguish from those of *Cyclospora cayetanensis* (Figure 118.6), which causes a similar clinical syndrome to cryptosporidiosis, although cyclosporiasis tends not to have the same association with recreational water exposures because the oocysts are not immediately infectious upon shedding; rather, they must undergo environmental sporulation over a 1- to 2-week period prior to being transmissible.

Although the clinical course is usually self-limited, severe and prolonged diarrhea may occur in young children and in those who are immunocompromised. Nitazoxanide has emerged through randomized controlled trials as an effective agent for the treatment of cryptosporidiosis in both healthy adults and children and in those who are immunocompromised.

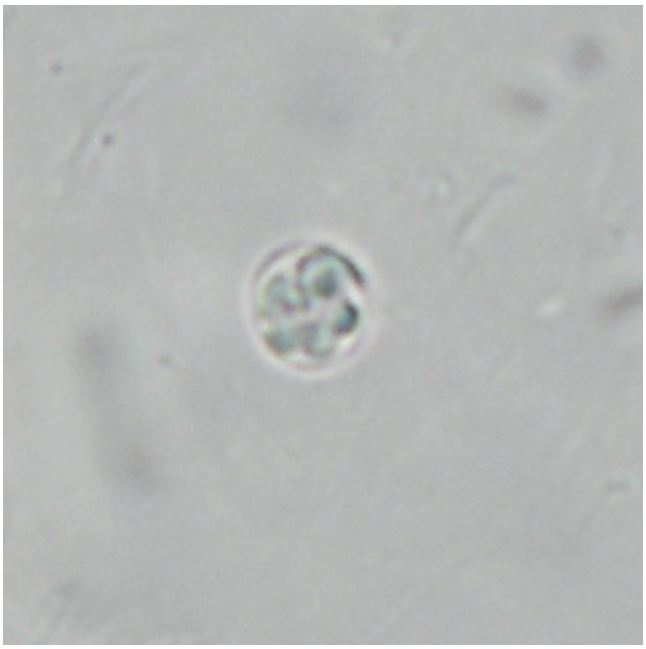

FIGURE 118.5 Oocyst of *Cryptosporidium* spp. from stool, wet preparation.

Giardiasis

Since the first documented outbreak in 1965, >100 waterborne outbreaks have been attributable to the flagellated protozoan

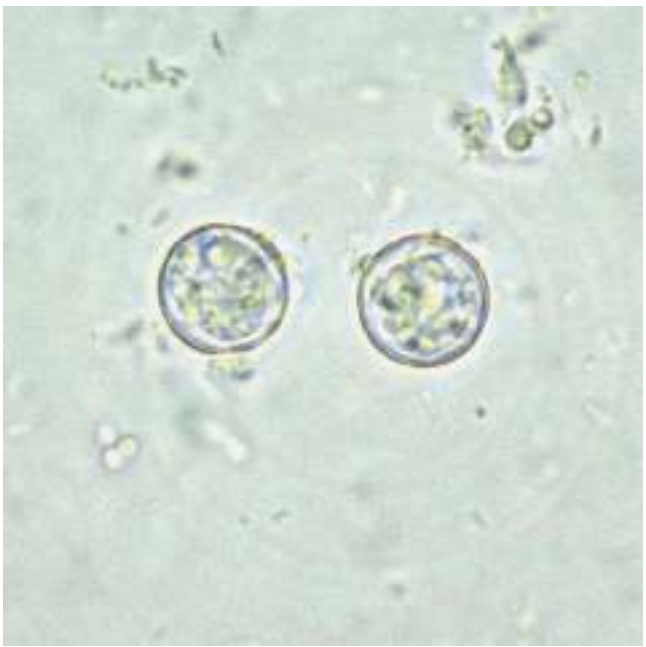

FIGURE 118.6 Oocyst of *Cyclospora cayetanensis* from stool, wet preparation.

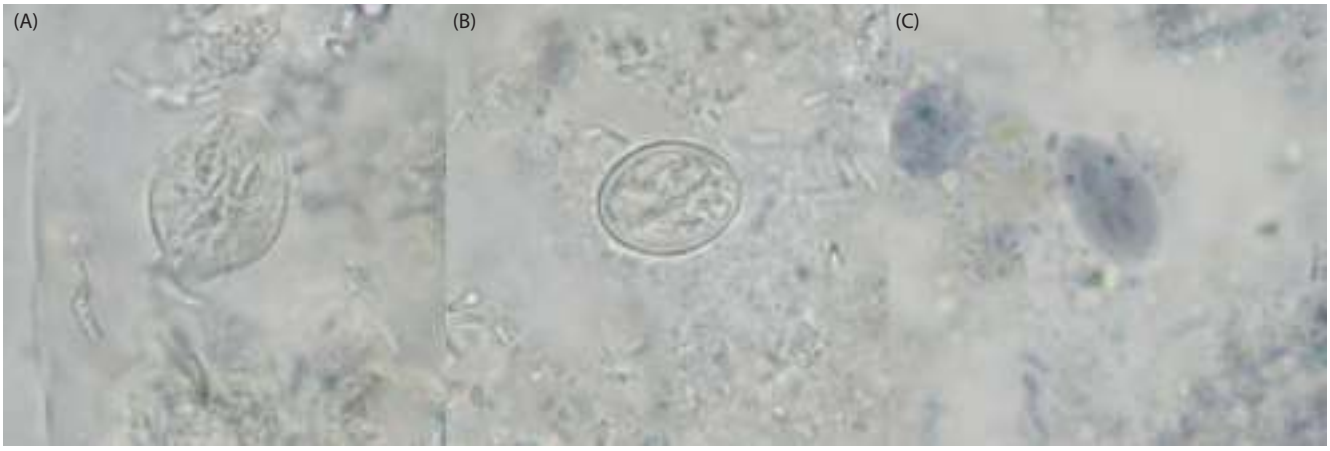

FIGURE 118.7 Trophozoite and cysts of *Giardia lamblia*, (A) wet preparation trophozoite; (B) wet preparation cyst; (C) iron–hematoxylin stain cyst.

Giardia. In 2011–2012, four outbreaks leading to 159 cases reported to the CDC were due to giardiasis acquired from recreational water exposure. Some outbreaks have been caused by both *Giardia* and *Cryptosporidium* (see Hlavsa 2018). Outbreaks of giardiasis have frequently been traced to ingesting unfiltered, unchlorinated, or inadequately chlorinated surface waters. Many infections in campers and hikers have followed drinking from mountain streams, even in remote wilderness areas. Like *Cryptosporidium*, *Giardia* has a broad mammalian host range, and cysts are excreted in fully infectious form (Figure 118.7). There are a number of effective therapeutic options for giardiasis that have been evaluated in randomized controlled trials, including metronidazole, nitazoxanide, tinidazole, mebendazole, albendazole, and furazolidone.

Norovirus ("Norwalk-like viruses")

In the 2011–2012 reporting period, norovirus was responsible for seven waterborne disease outbreaks, which caused 231 cases of gastroenteritis, rendering it second only to *Cryptosporidium* in the number of individuals who were sickened by a specific etiologic agent causing gastroenteritis. The majority of individuals were sickened by norovirus following exposure at treated water venues, notably swimming pools. Although community outbreaks of norovirus are often linked to transmission via doorknobs, toilets, and shared utensils, recreational water exposure significantly contributes to the overall case burden. The increasing number of cases reported over the past few years has been attributed to improved awareness and availability of viral detection methods, although diagnostic test underutilization is still likely to result in underreporting of viral agents of gastroenteritis. Visualization of norovirus in stool via electron microscopy is definitive (Figure 118.8). Management is supportive.

Chemical exposures and intoxications

Recreational use of marine water systems can lead to intoxications including, but not limited to, possible estuary-associated syndrome (PEAS) and aerosolized red tide respiratory irritation (ARTRI), caused by toxins liberated by the species of dinoflagellates, *Pfiesteria* and *Gymnodinium breve*, respectively. PEAS due to *Pfiesteria* leads to respiratory and eye irritation along with rash, vomiting, abdominal cramps, and cognitive changes, all of which appear to be self-limited. ARTRI occurs due to inhalation of brevetoxins present in sea spray during algal blooms and is characterized by a syndrome of rhinorrhea, cough, and bronchospasm. In both cases, treatment is supportive.

In 2011–2012, eight outbreaks following recreational water exposure to chemicals or toxins sickened 87 individuals. The largest such outbreak was associated with a wading pool, led to skin and eye symptoms in employees and patrons, and was caused by high free and combined chlorine levels. Other outbreaks related to recreational water exposure reported in the same time period were due to chlorine gas, trichloroamines, and microcystin toxin of cyanobacteria.

The recent phenomenon of *Sargassum* (seaweed) invasion throughout the Caribbean (Figures 118.9 and 118.10) has led to increasing reports of beachgoers and local hotel workers with acute and often severe inhalational poisoning due to hydrogen sulfide (H_2S) and ammonia, byproducts of *Sargassum* decomposition (see Resiere 2019). In addition to respiratory symptoms, chronic

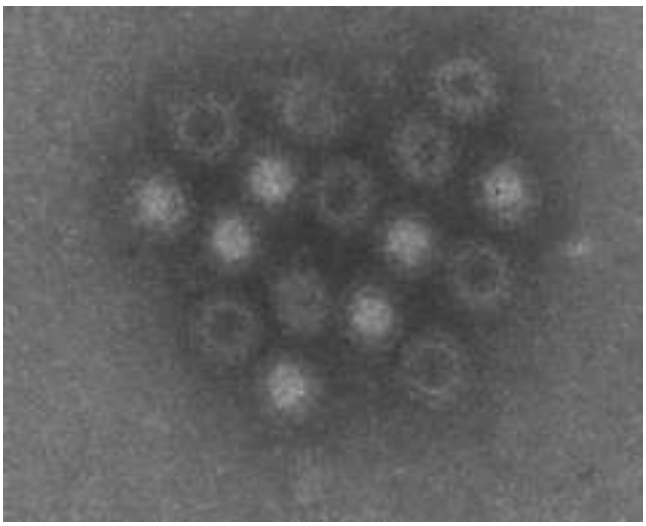

FIGURE 118.8 Electron micrograph of norovirus isolated from stool of a patient with acute gastroenteritis.

FIGURE 118.9 & 118.10 *Sargassum* weed befouling a beach in the Caribbean.

exposure to H_2S may lead to cardiac, neurologic, and neurocognitive manifestations. In the Caribbean, *Sargassum* weed incursion tends to peak during the months of January to April, precisely when tourist volumes are greatest. Consequently, in preparation for high tourist volumes, resorts and hotels grappling with *Sargassum* invasion retain more local workers to remove the weed, thereby also increasing the risk of occupational exposure among locals. While the mechanisms underpinning the huge global increases in "Yellow Tide" due to *Sargassum* weed are unclear, the scale of the economic, ecological, and health impacts of this phenomenon are enormous. Thus, efforts to remediate this situation are urgent and ongoing.

Suggested reading

Baker-Austin C, Trinanes JA, Taylor NGH, et al. Emerging Vibrio risk at high latitudes in response to ocean warming. *Nat Clim Change*. 2013;3:73–77.

Centers for Disease Control and Prevention. *CDC health information for international travel 2018*. New York: Oxford University Press; 2018.

Dorevitch S, Pratap P, Wroblewski M, et al. Health risks of limited-contact water recreation. *Env Health Perspect*. 2012;120(2): 192–197.

Hlavsa MC, Cikesh BL, Roberts VA, et al. Outbreaks associated with treated recreational water—United States, 2000-2014. *MMWR Morbid Mortal Wkly Rep*. 2018;67:547–551.

Leclerc H, Schwartzbrod L, Dei-Cas E. Microbial agents associated with waterborne diseases. *Crit Rev Microbiol*. 2002;*28*(4): 371–409.

Li J, Lu X, Sun Y, et al. A swimming pool-associated outbreak of pharyngoconjunctival fever caused by human adenovirus type 4 in Beijing, China. *Int J Infect Dis*. 2018;*75*:89–91.

Resiere D, Mehdaoui H, Névière R, Mégarbane B. Sargassum invasion in the Caribbean: The role of medical and scientific cooperation. *Rev Panam Salud Publica*. 2019 Jun 7;43:e52. doi:10.26633/RPSP.2019.52.

Taylor AJ, Paris DH, Newton PN. A systematic review of the mortality from untreated leptospirosis. *PLoS Negl Trop Dis*. 2015;9(6):e0003866. doi:10.1371/journal.pntd.0003866

World Health Organization. *Guidelines for safe recreational water environments, vol. 2, Swimming pools and similar environments*. Geneva: WHO; 2006: 1–146. http://www.who.int/iris/handle/10665/43336

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Travelers' diarrhea

Karen J. Vigil and Herbert L. DuPont

Diarrhea is the most frequent health problem encountered by persons going from industrialized to developing countries. Of the 100 million people traveling annually from industrialized to developing countries, approximately 40% will suffer from so-called travelers' diarrhea (TD), many more than once.

Classically, TD is defined as the passage of three or more unformed stools within 24 hours in association with at least one of the following symptoms of enteric infection: nausea, vomiting, abdominal pain or cramps, fever, fecal urgency, tenesmus, or the passage of bloody/mucoid (dysenteric) stools. This definition includes illness occurring up to 10 days after travelers return to their home countries.

Cases of TD can be categorized by severity as being mild (no disturbance in normal activities), moderate (modified travel activities required), or severe (illness requires confinement to bed). Fewer than 1% of patients are admitted to a hospital, but almost 40% are required to change their travel schedule.

Acute TD lasts for less than 2 weeks. Illness lasting more than 2 weeks is considered "persistent" and is seen in 2% to 10% of travelers. Possible etiologies of persistent diarrhea include intestinal infection by protozoal parasites, for example, giardiasis or cryptosporidiosis, and occasionally bacterial enteropathogens can cause a more protracted diarrhea. Unmasked gastrointestinal disease is seen in this setting occasionally, including irritable bowel syndrome, inflammatory bowel disease, and malabsorptive syndromes. Postinfectious irritable bowel syndrome, a recognized complication of bacterial enteric infection, has been shown to occur in as many as 10% of people after an episode of TD.

Food is the most important source of bacterial enteropathogens, which explains a majority of cases of TD. Water, which becomes more contaminated during rainy seasons, is often the source of viral gastroenteritis. Genetic factors contribute significantly to susceptibility to enteric infections. Fecal levels of inflammatory cytokines, including interleukin (IL)-8 and IL-1β, are often elevated in people who developed bacterial diarrhea. Host polymorphisms in the IL-8, IL-10, CD14, osteoprotegerin and lactoferrin genes were found to be associated with an increased susceptibility to TD.

Etiology

Bacterial enteropathogens cause up to 80% of TD cases. There is a relationship between geographic areas and the enteropathogens responsible for illness. For example, the diarrheagenic *Escherichia coli*, particularly enterotoxigenic *E. coli* (ETEC) and enteroaggregative *E. coli* (EAEC), are the major etiologic organisms in most areas of the developing world, responsible for ~50% to 60% of cases. Invasive pathogens, such as *Shigella, Salmonella*, and *Campylobacter*, represent 10% to 15% of cases but may account for up to 30% of cases in Asia, of which ciprofloxacin-resistant *Campylobacter* is of the greatest concern as it may not respond to customary self-treatment. Noncholera vibrios are found to cause TD in coastal areas of the world in a small number of cases. *Vibrio cholerae*, the causative agent of cholera, is a rare but serious cause of TD. *Klebsiella oxytoca, Laribacter hongkongensis*, enterotoxigenic *Bacteroides fragilis*, and *Arcobacter* have also been described as less frequent causes of TD.

Other than bacterial pathogens, parasites and viruses also cause TD. *Giardia* is an important pathogen in mountainous areas of North America and Russia. *Cryptosporidium* spp. are an important cause of diarrhea in travelers to Russia. *Cyclospora cayetanensis* has been found to be a causative organism of TD in Nepal, Haiti, and Peru. Rotavirus and norovirus are among the most common viruses described. Noroviruses have been identified in 10% to 20% of TD cases and remain a special problem on cruise ships.

The causes of TD in some areas of the world are also affected by the regional climate. ETEC was shown to be the major pathogen in the rainy, summer season in Mexico, with emergence of *Campylobacter jejuni* in the dry wintertime. In semitropical Morocco, *C. jejuni* was also found to be the most important pathogen in the dry winter season.

Prevention and chemoprophylaxis

Disease prevention is important to facilitate the purpose of the leisure or business trip and to prevent chronic enteric complications. Prevention measures consist of education for the future traveler on usually safe and occasionally unsafe foods and chemoprophylaxis.

Travelers should be instructed to avoid consuming moist foods served at room temperature and tap water (including ice). Food served steaming hot (>59°C), dry foods (e.g., bread), fruits that can be peeled, and foods with high sugar content (e.g., syrup, honey, or jelly) generally are safe.

Chemoprophylaxis may be used for short-term travel (≤3 weeks) in persons on a tight schedule (musicians, athletes, business persons, tourists, and politicians), in those who have experienced TD before (possibly related to genetic susceptibility), and for those who request it. Additional persons who might routinely employ chemoprophylaxis include those with underlying illness that might predispose them to increased risk of diarrhea or complications of illness, including persons with achlorhydria (from prior gastric surgery or regular use of proton pump inhibitors), inflammatory bowel diseases, human immunodeficiency virus (HIV) infection, transplant recipients or other immunosuppressions.

Bismuth subsalicylate (BSS) is modestly effective in the prevention of TD, with protection rates of approximately 65%. The dosage recommended for prophylaxis is two tablets (262 mg/tablet) orally with meals and at bedtime (eight tablets/day). Quinolones can prevent TD in up to 80% to 100% of cases. The emergence of quinolone-resistant *Campylobacter* spp. in South East Asia precludes their use in some areas of the world. Also, this class of drugs is too important for serious bacterial infection, and use for diarrhea prevention, which could encourage resistance development, cannot be justified. Rifaximin was shown to have a protection rate of 72% to 77% in a study in Mexico where diarrheagenic *E. coli* were the major pathogens. The drug was free of side effects when given for 2 weeks and was associated with minimal changes in fecal flora. We recommend rifaximin as the routine approach when chemoprophylaxis is desired because of its convenience and safety. It should not be given for trips longer than 2 to 3 weeks. The recommended dose is 200 mg (one tablet) with each of the major daily meals (usually two tablets a day) for as long as the person remains in the high-risk region.

Immunologic protection against ETEC diarrhea is feasible. An oral vaccine consisting of cholera toxin B subunit and inactivated whole-cell cholera strains has become available in some parts of the world. This vaccine confers protection against ETEC in up to 67%. However, it only has a 28% prevention rate for TD. A novel transcutaneous patch ETEC vaccine is also in development. Vaccination for TD with an anti-ETEC preparation can offer important protection from the major cause of the illness but cannot be completely protective because TD is a syndrome caused by multiple organisms.

Treatment

Hydration and dietary recommendations

Travelers' diarrhea can cause dehydration in infants, the elderly, or persons who have underlying medical illness. Fluids combined with electrolytes are the most important form of therapy. In the nondehydrated person without important underlying medical illness, commercially available sports drinks, diluted fruit juices, and other flavored soft drinks taken with saltine crackers and/or soups are usually enough to meet the fluid and salt needs during TD. Oral rehydration powders or solutions are also commercially available (e.g., CeraLyte).

During the early hours of diarrheal illness, it may be helpful to temporarily withhold solid foods that are complicated to absorb and that act as a stimulant of intestinal motility. In most cases of diarrhea, carbohydrates (noodles, rice, potatoes, oat, wheat, bananas) and steamed or baked white meats (fish and chicken) can be ingested. As illness improves and stools become formed, the diet can return to normal. In general, dairy products should be avoided in adults for the first day or two. It is important to feed patients with diarrhea to facilitate enterocyte renewal.

Nonantimicrobial therapy

Symptomatic therapy can be used in cases of mild TD. BSS is a commonly used antidiarrheal drug. This agent has antimicrobial, antisecretory, and anti-inflammatory properties. BSS can decrease the number of unformed stools passed in cases of TD by approximately 40%. BSS rarely causes mild tinnitus, and it commonly produces blackening of the tongue and stools from bismuth sulfide, a harmless salt of the nonabsorbed bismuth moiety. If a person is taking antimalarials for malaria prophylaxis, BSS should not be used concomitantly, because it can prevent absorption of the antimalarial drug.

Antimotility agents such as loperamide (Imodium) and diphenoxylate with atropine (Lomotil) are synthetic opioids that have selective effects on the intestine. These agents can improve diarrhea by slowing intestinal transit, leading to greater absorption of fluids and electrolytes. Loperamide is a drug of choice for symptomatic treatment of subjects without fever and not passing bloody

TABLE 119.1 **RECOMMENDED EMPIRIC TREATMENT OF TRAVELERS' DIARRHEA IN ADULTS**

Agent	Dosages	Comments
Loperamide	4 mg initially, then 2 mg after each stool, not to exceed 8 mg/d[a]	Should not be used in patients with fever and dysentery
Bismuth subsalicylate	30 mL or 2 tablets (262 mg/tablet) PO q 30 min up to 8 doses/d[a]	Should not be used with doxycycline when used for malaria prophylaxis Caution in people taking aspirin
Ciprofloxacin	500 mg PO BID or 750 mg PO qd for 1–3 d	Treatment failures most common because of resistant strains of *Campylobacter*
Rifaximin	200 mg PO TID for 3 d	Not recommended for febrile dysenteric diarrhea
Azithromycin	1000 mg single dose or 500 mg PO 1× and then 250 mg qd for 1 or 2 more d	Treatment of choice for febrile dysentery when *Campylobacter* is known to be the causative agent

[a] To be used for no more than 48 h.

stools. This agent will reduce the number of stools passed during a diarrhea episode by approximately 60%.

Antisecretory agents are being developed that work through a variety of pathways including calmodulin inhibition, chloride channel inhibition, and enkephalinase inhibition. In the United States a chloride channel inhibitor, crofelemer, is being developed for acute secretory diarrhea.

Antimicrobial therapy

Antimicrobial therapy in patients with TD shortens the duration of diarrhea and cures the disease. Clinical trials use time from initiation of therapy to passage of the last unformed stool (TLUS) as a primary parameter of efficacy. Antibiotic therapy is indicated in patients with moderate to severe disease because it has been shown to reduce TLUS by 1 to 3 days compared with placebo.

A variety of effective treatments for TD are available (Table 119.1). Rifaximin, 200 mg three times a day (TID) for 3 days, has a TLUS of 25.7 hours and a treatment failure of 10%, similar to ciprofloxacin, 500 mg twice a day (BID) for 3 days (25 hours and 6%, respectively), for treatment of noninvasive forms of the disease. Poorly absorbed (≤0.4%) rifaximin has an advantage for uncomplicated watery diarrhea in its safety profile. Rifaximin is not effective in the treatment of invasive forms of TD, particularly those associated with fever or dysentery.

For febrile dysenteric diarrhea, a systemic antibiotic, including the fluoroquinolones (ciprofloxacin, levofloxacin) or azithromycin, is preferred. Fluoroquinolones should not be used in children and pregnant women because they have been shown to damage articular cartilage in growing animals. These agents may interfere with xanthine metabolism, so patients taking theophylline may need to adjust their dosage of the drug. Fluoroquinolone resistance has become a problem with *Campylobacter* strains seen worldwide, which is a limitation of ciprofloxacin or levofloxacin.

Azithromycin is an azalide antibiotic related to macrolides and is more active than erythromycin against ETEC, *Salmonella* species, *Shigella* species, *V. cholerae*, and *C. jejuni*. In a clinical trial in Thailand, where *Campylobacter* has become resistant to ciprofloxacin, azithromycin was more effective than ciprofloxacin against *Campylobacter*. Azithromycin is effective against most forms of bacterial diarrhea and can be given as a single 1000-mg dose or daily in a lower dose for 3 days (see Table 119.1). Azithromycin may be the drug of choice for some regions of Asia where invasive pathogens are most common and is also the drug of choice for rescue therapy when rifaximin chemoprophylaxis is employed.

Travelers to high-risk areas should be encouraged to take with them an antibiotic for self-treatment of diarrhea that develops. It takes approximately 24 hours for a drug to cure the diarrhea. The antibiotic can be started after passage of the third unformed stool, to avoid unnecessary exposure to antibiotics for milder self-limiting syndromes. Some travel medicine experts prefer to begin the treatment with passage of the first unformed stool in a diarrheal episode to help reduce the duration of illness.

Combination therapy

Perhaps the optimal approach for empiric treatment of nondysenteric TD is to give the combination of loperamide with an antibiotic to combine a near-immediate effect of the loperamide with a curative effect of the antibiotic. This approach is not appropriate for patients with febrile, dysenteric diarrhea where a systemically absorbed antimicrobial agent alone should be used.

Suggested reading

DuPont HL, Ericsson CD, Farthing MJ, et al. Expert review of the evidence base for prevention of travelers' diarrhea. *J Travel Med*. 2009;16(3):149–160.

DuPont HL, Ericsson CD, Farthing MJ, et al. Expert review of the evidence base for self-therapy of travelers' diarrhea. *J Travel Med*. 2009;*16*(3):161–171.

Jiang ZD, Dupont HL, Brown EL, et al. Microbial etiology of travelers' diarrhea in Mexico, Guatemala, and India: importance of enterotoxigenic *Bacteroides fragilis* and *Arcobacter* species. *J Clin Microbiol*. 2010;48 (4):1417–1419.

Lopez-Gigosos R, Campins M, Calvo MJ, et al. Effectiveness of the WC/rBS oral cholera vaccine in the prevention of traveler's diarrhea: a prospective cohort study. *Hum Vaccin Immunother*. 2013;9(3):692–698.

Martinez-Sandoval F, Ericsson CD, Jiang ZD, et al. Prevention of travelers' diarrhea with rifaximin in US travelers to Mexico. *J Travel Med*. 2010;*17*(2):111–117.

Rivera FP, Medina AM, Aldasoro E, et al. Genotypic characterization of enterotoxigenic *Escherichia coli* strains causing traveler's diarrhea. *J Clin Microbiol*. 2013;51(2):633–635.

Shah N, DuPont HL, Ramsey DJ. Global etiology of travelers' diarrhea: systematic review from 1973 to the present. *Am J Trop Med Hyg*. 2009;80(4):609–614.

Section 17

Bioterrorism

120

Bioterrorism

Megan C. Gallagher and Andrew W. Artenstein

Introduction

Bioterrorism (BT), the deliberate use of microbial agents or their toxins as weapons for political gain, continues to represent a persistent global threat due to the widespread availability of these substances and the opportunities for terrorists to deploy them against civilian targets. Despite the relative paucity of known BT events in the recent past, the potential for catastrophic consequences associated with exposure to biologic threat agents remains high. A precise calculation of "risk" as it relates to BT is not possible as the probability of exposure to these hazards is unknown—it remains in the unpredictable and malicious minds of terrorists. Nonetheless, due to the potential for devastating sequelae, it is important for clinicians to understand the diagnostic and therapeutic approach to illnesses caused by agents of BT in order to mitigate the effects of an attack.

BT agents are considered weapons of mass terror because of their potential for large-scale morbidity and mortality. For example, one early model predicted nearly 200,000 casualties from a release of 50 kg of aerosolized anthrax spores upwind of a population center of 500,000. Based on more recent experience—the US anthrax attacks of 2001 that resulted in 11 cases of systemic disease associated with 5 deaths—it is evident that even relatively small-scale events may cause mass terror.

Unlike conventional, chemical, and nuclear weapons, BT agents are associated with a clinical latency period during which transmission may occur and detection is difficult. The US Centers for Disease Control and Prevention (CDC) has classified BT threats into priority groupings based on their feasibility for deployment and their potential for mortality, morbidity, and public health impact; this categorization (Table 120.1) has continued to inform current biodefense strategies.

Clinical presentation

The clinical pictures of diseases caused by agents of BT are varied but, with few exceptions among the CDC category A and B threats, can be categorized into a limited number of syndromic presentations (Table 120.2). Unfortunately, there are scant pathognomonic features of BT-related illness, only suggestive ones, mandating a high index of suspicion among clinicians to capitalize on subtle clues, many of which may be epidemiologic in nature. However, the suggestive clinical and laboratory findings (Table 120.2) associated with the agents, when interpreted in the appropriate clinical and epidemiologic contexts, should prompt further, targeted evaluations and warrant empiric management. More detailed clinical information on each agent is covered in organism-specific chapters of this book.

TABLE 120.1 **AGENTS OF CONCERN FOR USE IN BIOTERRORISM**

Microbe/Toxin	Disease
Highest priority—Category A	
Based upon high potential mortality, morbidity, virulence, transmissibility, aerosolization feasibility, psychosocial implications of an attack, and major public health impact	
Bacillus anthracis	Anthrax: Inhalational, gastrointestinal, cutaneous, injection
Variola virus	Smallpox and its variants
Yersinia pestis	Plague: Pneumonic, bubonic, septicemic
Clostridium botulinum	Botulism
Francisella tularensis	Tularemia: Pneumonic, typhoidal
Viral hemorrhagic fevers	
Filoviruses	Ebola, Marburg
Arenaviruses	Lassa fever, South American hemorrhagic fevers
Bunyaviruses	Rift Valley fever, Congo–Crimean hemorrhagic fever
Moderately high priority—Category B	
Based upon moderate potential morbidity, aerosolization feasibility, dissemination characteristics, and diagnostic difficulty	
Coxiella burnetii	Q fever
Brucella species	Brucellosis
Burkholderia mallei	Glanders
Burkholderia pseudomallei	Melioidosis
Chlamydia psittaci	Psittacosis
Rickettsia prowazekii	Epidemic typhus
Alphaviruses	Viral encephalitides
Ricin	Ricin intoxication
Staphylococcus enterotoxin B	Staphylococcal toxin illness
Epsilon toxin of Clostridium perfringens	Intoxication
Salmonella species, Shigella dysenteriae, Escherichia coli 0157;H7, Vibrio cholerae, Cryptosporidium parvum	Food- and waterborne gastroenteritis
Emerging threat agents—Category C	
Based upon potential to be engineered due to ease of production and dissemination, availability, potential for high morbidity/mortality	
Hantaviruses	Viral hemorrhagic fevers
Flaviviruses	Yellow fever
Mycobacterium tuberculosis	Multidrug-resistant tuberculosis
Nipah virus	Systemic, flu-like illness
Miscellaneous	
Other examples of candidate threat agents that possess some elements of future BT concern	
Genetically engineered vaccine, and/or antimicrobial-resistant Category A or B agents	
Human immunodeficiency virus 1	
Adenoviruses	
Influenza	
Rotaviruses	
Hybrid pathogens: e.g., smallpox/plague, smallpox/Ebola	

Diagnosis

Rapid detection and accurate identification of BT agents is important not only for confirming that a BT event has occurred but also for treating individual patients and implementing appropriate public health measures. By definition, BT is insidious; in the absence of credible advance notification, it is likely that clustered, syndromic, clinical illness will be the initial manifestation of a BT attack. Although critical, early recognition is challenging for a variety of reasons: (1) targets of BT, especially in an open society, are myriad, diverse, and unpredictable; (2) the clinical latency of BT agents makes it likely that clusters of symptomatic individuals will present for medical care days to weeks after an "event" and at geographically diverse locations; (3) initial clinical manifestations of many BT-related illnesses are nondiagnostic and may be mistaken for other, more common but less impactful diagnoses; (4) clinicians are inexperienced with the clinical manifestations of these infections; and (5) even if the classic clinical findings are known, because BT agents are manipulated in the laboratory, their associated clinical syndromes may present differently from those arising from naturally occurring infection. Conversely, in the setting of a high level of suspicion, early recognition may be aided by a number of epidemiologic and clinical clues: (1) *case clustering*, which, because of the clinical latency of BT, requires attention to geographic surveillance and robust communications systems; (2) *unusual clinical presentations* of common syndromes, such as fulminant pneumonia in otherwise healthy young adults; or (3) *unusual disease patterns*, such as rare diseases occurring in traditionally nonendemic areas or concurrent disease in humans and animal populations.

The CDC has developed a national laboratory response network (LRN) for BT that integrates selected microbiologic laboratories across the United States into a network and mandates uniform practices for specimen collection, processing, shipping, security, and testing. Laboratories within the LRN consortium are designated as having screening, confirmatory, or reference functions. The network of laboratories is connected by a secure communications system, thus ensuring the timely flow of information among the CDC, other governmental agencies, state health authorities, and other laboratories. The mission of the LRN is to enable a rapid and organized response to BT; the CDC routinely audits the performance of network members using panels of unknown pathogens.

Although diagnostic tests are available for most BT agents, many are not readily available in clinical laboratories, are time-consuming, have less than optimal sensitivity and specificity, or cannot test for multiple agents simultaneously. Diagnostic platforms that can assess for the presence of multiple pathogens concurrently, so-called *multiplex strategies*, offer attractive advantages, especially in the arenas of environmental surveillance and in screening either patients presenting with nonspecific symptoms or asymptomatic individuals who have possible exposure to an unknown agent.

The preferred methods for the laboratory diagnosis of BT agents differ depending on the agent in question. For most bacterial agents the gold-standard diagnostic assay remains standard culture; other supporting assays include modified staining with light microscopy, motility testing, lysis by γ-phage, capsule production staining, hemolysis, wet mounts, staining for spores, slide agglutination, direct fluorescent antibody, enzyme-linked immunosorbent assay (ELISA), and rapid immunochromatography. Routine assays for viral agents include virus isolation through tissue culture or growth in eggs, direct and indirect immunofluorescence, immunodiffusion in agar, electron microscopy, modified staining and light microscopy, plaque reduction neutralization, hemagglutination inhibition, neuraminidase activity, complement fixation, and ELISA. Pathologic examination of tissues and immunohistochemistry also play an important role in diagnosing BT agents.

Molecular assays are becoming the new gold standard for BT detection, with sensitivities and specificities close to 100% when compared with culture or serologic assays. These assays detect infectious agents in humans through target nucleic acid isolation and amplification followed by specific pathogen identification. Several technologies and methods have been used for multiplex detection of different BT agents. Although still in the developmental stages, it is likely that DNA microfluidic devices will be commonly used diagnostic platforms in the future. These methods are sensitive and specific and theoretically can be used on unprocessed specimens in field settings, thus obviating laborious microbial isolation steps. However, several challenges, including sampling issues, data analysis, development of specific probes, quality control, cost containment, automation, performance, and integration, must be addressed before such methods replace the standard ones.

Laboratory diagnosis of specific Category A agents

Bacillus anthracis

Presumptive laboratory identification of *Bacillus anthracis* (Figures 120.1 and 120.2) is based on the presence of large gram-positive bacilli in either gram- or immunohistochemical-stained material from skin lesions, cerebrospinal fluid, pleural fluid, or blood in an appropriate clinical setting or on the growth of aerobic, nonhemolytic, large, catalase-positive, gray-white colonies on sheep-blood-agar cultures containing nonmotile, nonencapsulated, gram-positive, spore-forming rods. Although the diagnosis may be suspected at the screening laboratory level, confirmatory diagnostic tests must be performed in containment facilities of the LRN. Such tests include susceptibility to lysis by γ-phage and polymerase chain reaction (PCR); the US Food and Drug Administration (FDA) has approved a real-time PCR assay for the diagnosis of anthrax. There is ongoing investigation into rapid and point-of-care tests, including GeneXpert, a PCR-based test, and matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF), which uses mass spectrometry on peptides. Although there are no assays that have been rigorously and prospectively validated for the rapid diagnosis of inhalational anthrax during its early, nonspecific clinical stages, the development of assays that detect cell wall and capsular antibodies and anti-protective antigen responses should improve the outlook for early diagnosis of anthrax.

Serologic testing is of little value in the diagnosis of acute disease but may have some use in exposed survivors who demonstrate

TABLE 120.2 **SYNDROMIC DIFFERENTIAL DIAGNOSES AND CLINICAL CLUES FOR CATEGORY A AGENTS OF BIOTERRORISM (BT)**

Syndrome	Clinical presentation	Differential diagnosis	BT-associated disease	BT disease-specific clues
Influenza-like illness	Nonspecific constitutional and upper respiratory symptoms: malaise, myalgias, nausea, emesis, dyspnea, cough ± chest discomfort, without coryza or rhinorrhea → abrupt onset of respiratory distress ± shock ± mental status changes, with CXR abnormalities (wide mediastinum or infiltrates or pleural effusions)	Influenza, community-acquired bacterial pneumonia, viral pneumonia, *Legionella*, Q fever, psittacosis, mycoplasma, *Pneumocystis* pneumonia, tularemia, dissecting aortic aneurysm, bacterial mediastinitis, SVC syndrome, histoplasmosis, coccidioidomycosis, sarcoidosis, ricin, and *Staphylococcus* enterotoxin B (pulmonary edema/ARDS)	Inhalational anthrax	3-day average symptom duration before presentation Abdominal pain, headache, mental status abnormalities, hypoxemia common Mediastinal adenopathy: ~90% (Figure 120.1) Hemorrhagic pleural effusions: ~70% CT more sensitive than CXR in early hemorrhagic mediastinal adenopathy Meningoencephalitis: possibly ~50% Blood cultures positive in untreated; pleural fluid cultures or antigen-specific immunohistochemical stain usually positive
Skin lesions	Pruritic, painless papule on exposed areas→vesicle(s)→ulcer→edematous black eschar ± massive local edema and regional adenopathy, ± fever, evolving over 3–7 days	Recluse spider bite, staphylococcal lesion, atypical Lyme disease, Orf, glanders, tularemia, plague, rat-bite fever, ecthyma gangrenosum, rickettsialpox, atypical mycobacteria, cutaneous diphtheria, cutaneous leishmaniasis	Cutaneous anthrax	Painless; spider bite is painful lesion Nonpitting local edema may be massive (Figure 120.2) If untreated, may progress to systemic involvement Blood cultures, skin biopsy (from vesicular edge or erythema at edge of eschar)
Fulminant pneumonia	Abrupt-onset constitutional symptoms and rapidly progressive respiratory illness with cough, fever, rigors, headache, sore throat, myalgias, dyspnea, pleuritic chest pain, GI symptoms, lung consolidation, ± hemoptysis, ± shock; variable progression to respiratory failure	Severe community-acquired bacterial or viral pneumonia, inhalational anthrax, pulmonary infarct, pulmonary hemorrhage, influenza, mycoplasma pneumonia, *Legionella*, Q fever, SARS, tuberculosis	Pneumonic plague Pulmonary tularemia	Lobar or multilobar involvement ± buboes Hemoptysis common Characteristic sputum Gram stain Cough generally nonproductive Pulse–temperature dissociation in 40% Hilar adenopathy, pleural effusions Ulceroglandular form most common after natural or cutaneous exposures Erythema multiforme or nodosum in significant minority of systemic disease

TABLE 120.2 **CONTINUED**

Syndrome	Clinical presentation	Differential diagnosis	BT-associated disease	BT disease-specific clues
Sepsis with bleeding diathesis and capillary leak	Sepsis syndrome, GI symptoms, mucosal hemorrhage, altered vascular permeability, DIC, purpura, acral gangrene, hepatitis, hypotension, ± CNS findings, multiorgan system failure	Meningococcemia; gram-negative sepsis, streptococcal, pneumococcal, or staphylococcal bacteremia with shock; malaria, leptospirosis, typhoid fever, borrelioses, typhoidal tularemia; overwhelming postsplenectomy sepsis; acute leukemia; Rocky Mountain spotted fever; fulminant hepatitis, TTP, hemolytic-uremic syndrome, SLE, hemorrhagic smallpox; hemorrhagic varicella (in immunocompromised)	Septicemic plague Viral hemorrhagic fever	Occurs in minority of aerosol exposures Cutaneous findings as late sequelae ± buboes High-density bacteremia Maculopapular rash in Ebola, Marburg Certain organ systems preferentially involved with specific VHF etiologies
Febrile prodrome with generalized exanthem	Fever, malaise, prostration, headache, myalgias, and enanthema followed by development of synchronous, progressive, centrifugal papular→vesicular→pustular rash on face, mucous membranes, extremities→trunk→generalization ± hemorrhagic component, with systemic toxicity	Varicella, drug eruption, Stevens–Johnson syndrome, measles, secondary syphilis, erythema multiforme, severe acne, disseminated herpes zoster or simplex, meningococcemia, monkeypox, generalized vaccinia related to smallpox vaccination, insect bites, Coxsackievirus, vaccine reaction	Smallpox	Palms and soles involved Rash is denser peripherally even after fully evolved (Figures 120.3, 120.4) Lesions are well circumscribed, uniform, and almost nodular (Figure 120.5) Secondary bacterial infection common Hemorrhagic variant in pregnant and immunocompromised patients associated with severe systemic toxicity, bleeding diathesis, and early mortality
Progressive weakness	Acute onset of afebrile, symmetric, descending flaccid paralysis that begins in bulbar muscles, dilated pupils, diplopia or blurred vision, dysphagia, dysarthria, ptosis, dry mucous membranes→airway obstruction + respiratory muscle paralysis, clear sensorium and absence of sensory changes	Myasthenia gravis, brainstem CVA, polio, Guillain–Barré syndrome variant, tick paralysis, chemical intoxication	Botulism	Expect dearth of GI symptoms in aerosol attack as opposed to foodborne botulism Low-dose inhalation exposure may delay symptom onset Prominent anticholinergic effects

Abbreviations: CXR = chest x-ray; SVC = superior vena cava; ARDS = acute respiratory disease syndrome; CT = computed tomography; GI = gastrointestinal; SARS = severe acute respiratory syndrome; DIC = disseminated intravascular coagulation; CNS = central nervous system; TTP = thrombotic thrombocytopenic purpura; SLE = systemic lupus erythematosus; VHF = viral hemorrhagic fever; CVA = cerebrovascular accident.

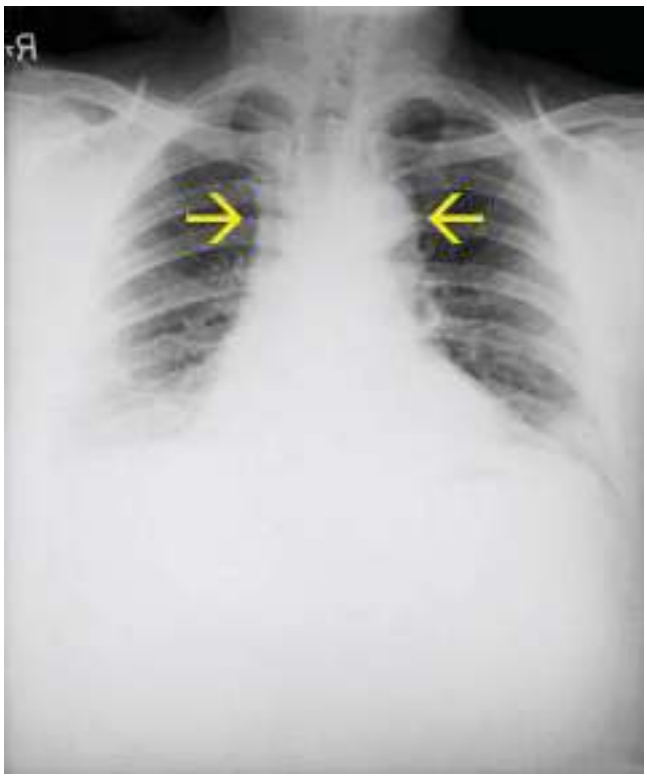

FIGURE 120.1 Inhalational anthrax. Note widened mediastinum (arrows). (Courtesy of Centers for Disease Control and Prevention).

seroconversion. The use of nasal cultures for detecting *B. anthracis* early after potential exposure may be of some use in defining the epidemiologic parameters of exposure but is not useful in making individual decisions about the use of treatment or prophylaxis.

Yersinia pestis

The gold standard for *Y. pestis* diagnosis remains standard microbiologic techniques such as microscopy of stained specimens and culture applied to expectorated sputum, bronchial washings, blood, or lymph node aspirates. The organism is suggested by its characteristic appearance as small gram-negative coccobacillary forms with bipolar, "safety-pin," uptake of Wright–Giemsa stain. *Y. pestis* grows slowly at routine incubation temperatures and may be misidentified by automated identification systems. Confirmation of the diagnosis requires the deployment of specialized testing: direct fluorescent antibody tests to detect the presence of F1 envelope antigen or PCR. Rapid tests to detect the F1 antigen are under investigation for potential field applicability on direct clinical specimens.

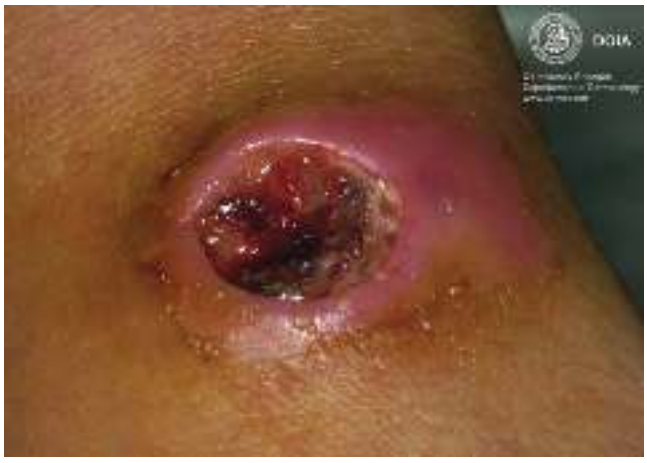

FIGURE 120.2 Cutaneous anthrax. (Courtesy of University of Heidelberg).

Francisella tularensis

Francisella tularensis appear as small, intra- and extracellular gram-negative coccobacilli in stains of clinical specimens. Because the organism does not grow readily in standard laboratory media and because it is highly infectious to laboratory personnel, specialized microbiologic and safety procedures must be instituted for this pathogen. For this reason, the diagnosis is usually based on clinical features, and cultures should be pursued in higher level laboratories of the LRN. Blood cultures are often negative, but samples that can be tested include swabs of skin lesions, lymph node aspirates, pharyngeal swabs, and sputum samples. Presumptive diagnosis can be made using direct fluorescent antibody, immunohistochemical staining, or PCR. Serology is generally useful only in retrospect as it takes >2 weeks to develop a serologic response in most individuals.

Clostridium botulinum

The diagnosis of botulism is largely based on epidemiologic and clinical features and the exclusion of other possible differential diagnoses. If laboratory diagnosis is necessary, the gold standard currently remains a mouse bioassay at a reference laboratory; PCR may have some utility in detecting *C. botulinum* nucleic acids in environmental samples.

Smallpox

The majority of smallpox cases present with a vesicular, centrifugal rash (Figures 120.3, 120.4, and 120.5) that, in the appropriate clinical and epidemiologic context, should prompt immediate notification of state or local public health authorities; specimens from suspected smallpox patients must be collected and transported under the direction of health authorities and in collaboration with the facilities of the LRN. Laboratory confirmation of the clinical diagnosis, especially in early or atypical cases in a suspected outbreak, is important; clinical diagnosis is probably sufficient in a confirmed outbreak. Infection control measures should be implemented prior to the acquisition of specimens in suspected cases.

Diagnostic assays in smallpox are typically performed on lesion scrapings, vesicular fluid, crusts, blood, or tonsillar swabs. A presumptive poxvirus diagnosis may be obtained by observing brick-shaped virions on electron microscopy of vesicular scrapings or by noting aggregations of virus particles, *Guarnieri bodies*, on histopathologic examination of tissue specimens. Isolation of variola virus in live cell cultures, followed by nucleic acid identification of specific orthopoxvirus species, is confirmatory but only performed in national reference laboratories with the highest level of biocontainment. The

FIGURE 120.3 Smallpox. Note heavy concentration of lesions on face and extremities compared to trunk. Compare also to the truncal concentration seen in varicella. (Courtesy of World Health Organization).

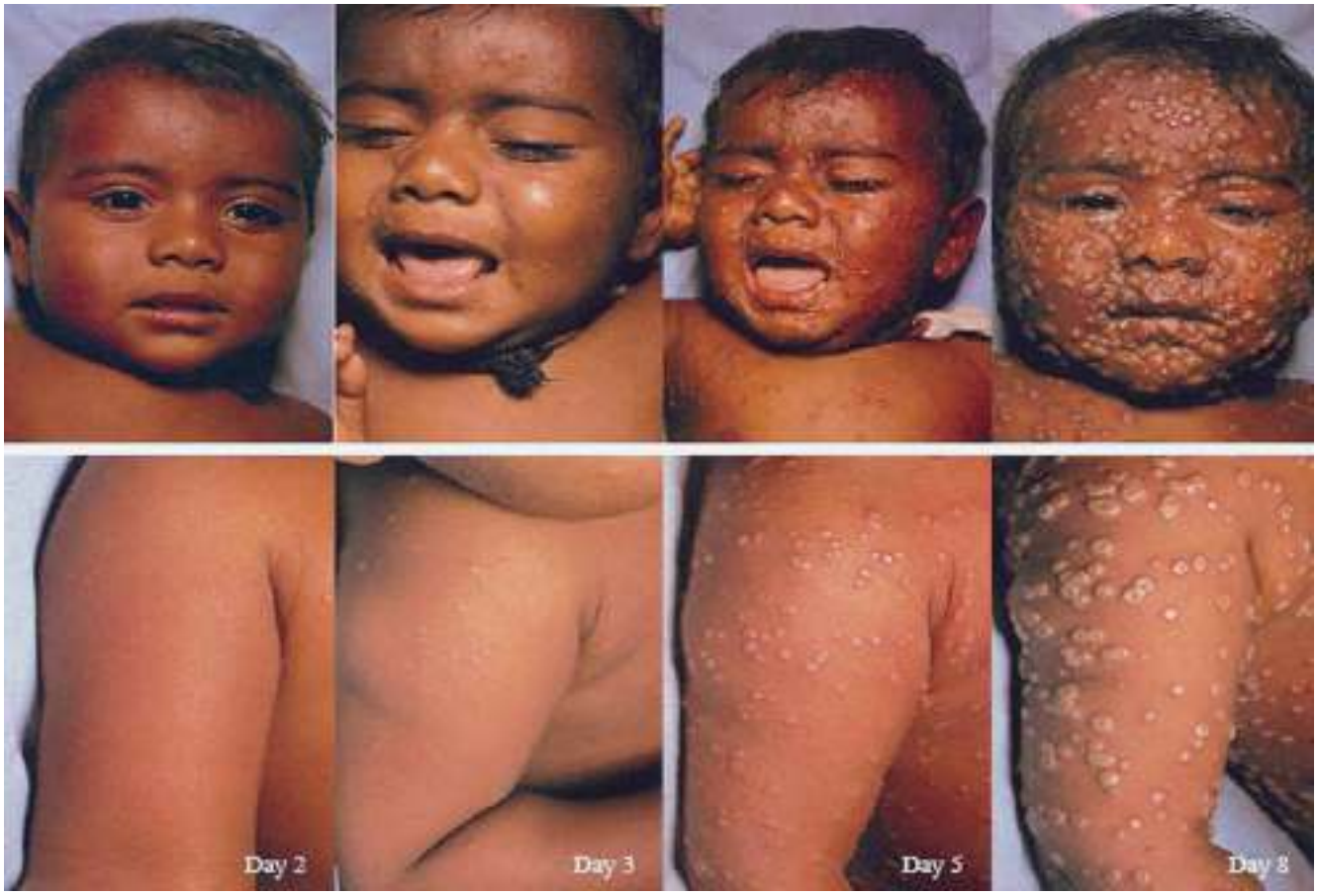

FIGURE 120.4 Progression of smallpox exanthem over the first eight days of illness. (Courtesy of World Health Organization).

FIGURE 120.5 Smallpox. Lesions are characteristically round, uniform in size, and at same stage of development. (Courtesy of Centers for Disease Control and Prevention).

development of standard and multiplexed PCR platforms promises a reliable and less cumbersome way to discriminate between variola and other orthopoxviruses in clinical specimens.

Viral hemorrhagic fevers

For Ebola virus, presumptive testing using real-time RT-PCR, preferably on whole blood, is available at more than 60 LRN laboratories. Confirmatory testing is then performed at the CDC. For other agents of viral hemorrhagic fevers (VHFs), clinical microbiology and public health laboratories are not currently equipped to make a rapid diagnosis; therefore, clinical specimens must be sent to the CDC or the US Army Medical Research Institute of Infectious Diseases (USAMRIID), the highest level laboratories in the LRN. Definitive diagnosis depends on identification of a specific viral etiology. Methods of early diagnosis at specialized laboratories include rapid enzyme immunoassays for antigen detection or viral immunoglobulin M (IgM), reverse transcriptase-PCR, and viral isolation in a biosafety level-4 facility. In general, serology is of limited value in early diagnosis because antibodies to these viruses usually do not appear until after the second week of illness.

Management

Once the diagnosis of BT-associated illness is considered, the initial step in the evaluation and management of an individual or group of patients is the immediate implementation of appropriate infection control measures according to the suspected agents (Table 120.3). This will ensure the maximal protection of first responders and healthcare workers as well as other patients in the healthcare environment. Empiric antimicrobial therapy of BT-associated illness should be initiated once the diagnosis is seriously considered as the early institution of appropriate therapy will not only potentially confer outcome advantages but may also potentially limit the spread of transmissible pathogens. The use of prophylactic antimicrobials is warranted for some agents. Recommendations for specific antimicrobial strategies for diseases caused by category A agents of BT are provided in Table 120.4.

Anthrax

Given the rapid clinical progression and attendant high mortality of inhalational anthrax, the early administration of appropriate, combination antimicrobials is essential and is likely to confer a survival advantage because patients appear to quickly reach a clinical threshold beyond which survival is unlikely. There have been no controlled clinical studies for the treatment of inhalational anthrax in humans because of its rare and sporadic occurrence in nature.

Many patients with cutaneous anthrax can be successfully treated as outpatients; however, those with cutaneous infection involving the head, neck, or upper torso areas or with signs of systemic inflammatory response syndrome or those with inhalational or injection anthrax generally require hospitalization. Although there are different pathophysiologic mechanisms underlying systemic anthrax and traditional severe sepsis, standard guidelines used for hemodynamic support in the latter condition should be followed. Additionally, aggressive and repeated drainage of pleural effusions may improve both ventilation and survival. Limited surgical debridement is indicated in cases of injection anthrax for diagnostic purposes and to debulk potential toxin reservoirs.

During the anthrax attacks in the United States in 2001, the CDC promulgated treatment protocols recommending combination antimicrobials for the initial management of suspected inhalational anthrax; these have recently undergone further refinement (Table 120.4). Reasons to empirically treat with multiple drugs include heightened concerns regarding the deployment of antimicrobial-resistant pathogens by terrorists; the high potential for meningeal involvement in victims of systemic anthrax, necessitating the achievement of adequate drug levels in the central nervous system; and the potential for additive or synergistic effects using multiple therapies with different targets.

Once the antimicrobial susceptibility profile of the organism has been determined and clinical improvement is evident, therapy may be tailored. Isolated cutaneous disease may be managed with single, oral antimicrobials but, as in other forms of anthrax, monotherapy using β-lactam agents is contraindicated due to resistance concerns. The recommended duration of therapy is 60 days for all BT-associated forms of anthrax due to presumed concomitant inhalational exposure to the primary aerosol and experimental animal data supporting a persistent risk of latent infection from delayed germination of spores.

Because anthrax is a toxin-mediated illness, some advocate the use of clindamycin as part of combination therapy despite the dearth of clinical data, citing the drug's theoretical benefit of diminishing bacterial toxin production, a strategy employed in some toxin-mediated streptococcal infections. Central nervous system penetration is another consideration in therapy selection and drives the preferential use of ciprofloxacin over doxycycline, plus augmentation with chloramphenicol, rifampin, or penicillin when meningitis is suspected. Corticosteroids have been used as adjunctive therapy in the setting of meningitis or severe mediastinal or head/neck edema, but there are scant data of their definitive efficacy.

Two new monoclonal antibodies, raxibacumab and obiloxaximab, directed against the protective antigen moiety of

TABLE 120.3 **EPIDEMIOLOGIC CHARACTERISTICS FOR SELECTED BIOTERRORISM-ASSOCIATED DISEASES**

Disease	Incubation period range (days)	Person-to-person transmission	Infection control precautions for patients	Case-fatality rate
Systemic anthrax with probable or confirmed meningitis	2–58[a]	No	Standard	81%[b]
Inhalational anthrax	2–58[a]	No	Standard	65%[b]
Gastrointestinal anthrax		No	Standard	57%[b]
Cutaneous anthrax	1–12	No	Standard	4%[b]
Botulism	12–72 hours	No	Standard	6%
Primary pneumonic plague	1–6	Yes	Droplet	Untreated: ~100% Treated: 57%
Bubonic plague	2–8	No	Standard	Untreated: 60% Treated: <5%
Smallpox	7–19	Yes	Contact + airborne	Unvaccinated: 30% Vaccinated: 3%
Tularemia pneumonia	1–21	No	Standard	Untreated: 60% Treated: <4%
Viral hemorrhagic fevers	2–21	Yes	Contact + airborne	Marburg: 23–70% Ebola: 20–40% with optimal supportive care Ebola: 75-90% without supportive care Other forms: 2%–30%
Viral encephalitides	1–14	No	Standard	10%–35%
Q fever	2–41	No	Standard	3%
Brucellosis	5–60	No	Standard	Untreated: 5%
Glanders	1–21	Yes	Contact + droplet	Untreated: approaches 100% Treated: low

[a] Based on limited data from human outbreaks and animal aerosol challenges.
[b] Based on a cumulative case series from 1941 to 2014, including those receiving a variety of antibiotic treatments

anthrax toxin, are now FDA-approved for the treatment of inhalation anthrax, in conjunction with antibiotics. These antibodies do not cross the blood–brain barrier, so they cannot be used for the treatment or prevention of meningitis.

Anthrax vaccine has been proved effective in preventing cutaneous anthrax in human clinical trials and in preventing inhalational disease after aerosol challenge in nonhuman primates. The vaccine, which acts by generating an immune response to protective antigen, a key component of anthrax toxin, has been generally found to be safe and has been recommended, in combination with antimicrobials, in a three-dose regimen as postexposure prophylaxis following exposure to aerosolized spores. The monoclonal antibodies can also be used as postexposure prophylaxis if elements of the first-line prophylaxis regimen are not available. Passive immunotherapy with anthrax immunoglobulin may serve an adjunct role to antimicrobials and may provide additional benefit in illness caused by multidrug-resistant pathogens.

Plague

Yersinia pestis is typically susceptible in vitro to penicillins, many cephalosporins, carbapenems, aminoglycosides, quinolones, and tetracyclines. It is variably susceptible to trimethoprim, chloramphenicol, and rifampin and is commonly resistant to macrolides and clindamycin. Recommended therapeutic approaches to plague in the BT setting are detailed in Table 120.4.

Naturally occurring antibiotic-resistant strains of *Y. pestis* have been reported in endemic areas of the world and are extremely concerning with respect to the development of biologic weapons.

Production of the currently licensed formalin-inactivated vaccine was discontinued by its manufacturers in 1999; this product had demonstrated efficacy in preventing or ameliorating bubonic disease but not primary pneumonic plague. A subunit vaccine using a bacterial capsular protein has demonstrated protective efficacy in an animal model of pneumonic plague.

TABLE 120.4 TREATMENT RECOMMENDATIONS FOR BIOTERRORISM CATEGORY A AGENTS IN ADULTS

	Anthrax-systemic
Treatment	Initial IV therapy when meningitis possible: ciprofloxacin 400 mg q8h *and* meropenem 2 g q8h *and* linezolid 600 mg q12h (levofloxacin or moxifloxacin as alternates to ciprofloxacin; imipenem, penicillin G, or ampicillin as alternates to meropenem; clindamycin or rifampin as alternates to linezolid) If meningitis is excluded, optimal first-line therapy is ciprofloxacin 400 mg q8h *and* clindamycin 900 mg q8h (PCN G, levofloxacin, moxifloxacin, ampicillin, or meropenem as alternates to ciprofloxacin; linezolid, doxycycline, or rifampin as alternates to clindamycin). Oral follow-up therapy using ciprofloxacin 500 mg q12h or doxycycline 100 mg q12h (levofloxacin, moxifloxacin, or clindamycin as alternatives) Raxibacumab and obiltoxaximab are anti-protective antigen monoclonal antibodies newly approved for the treatment of inhalation anthrax Administer with antibiotics They do not cross the blood-brain barrier, so cannot be used to prevent or treat meningitis Pre-medicate with diphenhydramine as hypersensitivity reactions can occur
Postexposure prophylaxis	Ciprofloxacin 500 mg orally q12h *or* doxycycline 100 mg orally q12h *plus* anthrax vaccine (unlicensed indication) Use levofloxacin or moxifloxacin as alternates • Amoxicillin 500 mg orally q8h for pregnant women Raxibacumab and obiltoxaximab can be used for prophylaxis of inhalation anthrax when alternatives are not available or cannot be used
Comments	IV treatment initially before switching to oral antimicrobial therapy when clinically appropriate; IV treatment should be used for 2 weeks or until patient is stable, whichever is longer Use of β-lactams should be informed by susceptibility profile Continue oral treatment to complete total of 60 days Treatment for immunocompromised individuals and pregnant women as above; recommendation based on life-threatening nature of illness
	Anthrax–cutaneous
Treatment	Oral therapy: ciprofloxacin 500 mg q12h or doxycycline 100 mg q12h (levofloxacin, moxifloxacin, or clindamycin as alternatives) for 60 days
	Botulism
Treatment	Early administration of antitoxin Supportive treatment (hydration, nasogastric suctioning for ileus, mechanical ventilation for respiratory failure)
Postexposure prophylaxis	Antitoxin administration
	Plague
Treatment	Preferred: streptomycin 1 g intramuscular BID *or* gentamicin 5 mg/kg intramuscular or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg intramuscular or IV 3 times daily Alternative: doxycycline 100 mg IV BID or ciprofloxacin 400 mg IV BID or chloramphenicol 25 mg/kg IV 4 times daily
Postexposure prophylaxis	Preferred: doxycycline 100 mg orally BID *or* ciprofloxacin 500 mg orally BID Alternative: chloramphenicol 25 mg/kg orally 4 times daily

TABLE 120.4 CONTINUED

	Anthrax-systemic
Comments	10 days for treatment regimens 7 days for postexposure prophylaxis
	Smallpox
Treatment	Tecovirimat is a new, FDA-approved treatment for smallpox and other orthopoxviruses—600 mg BID for 14 days Antimicrobial agents effective against *Staphylococcus aureus* and streptococci should be used if smallpox lesions are secondarily infected, if bacterial infection endangers the eyes, or if the eruption is very dense and widespread Adequate hydration and nutrition for substantial fluid and protein losses Topical idoxuridine should be considered for the treatment of corneal lesions, although its efficacy is unproved for smallpox
Postexposure prophylaxis	Vaccination within 7 days of exposure unless contraindicated
	Tularemia
Treatment	Preferred: streptomycin 1 g intramuscular BID *or* gentamicin 5 mg/kg intramuscular or IV once daily Alternative: doxycycline 100 mg IV BID or ciprofloxacin 400 mg IV BID *or* chloramphenicol 15 mg/kg IV 4 times daily (not to be used in pregnancy)
Postexposure prophylaxis	Doxycycline 100 mg orally BID or ciprofloxacin 500 mg orally BID
	Viral hemorrhagic fevers
Treatment	Mainstay of treatment is supportive care—maintaining volume and electrolyte balance, correcting acid-base disturbances ZMapp is a cocktail of three neutralizing antibodies used to treat Ebola and is available in the US under an expanded access protocol Ribavirin for confirmed or suspected Bunyaviridae (Old World Hantavirus, Crimean–Congo hemorrhagic fever, Rift Valley fever) and Arenaviridae (Lassa virus) infections under an Investigational New Drug (IND) protocol Ribavirin not useful for Ebola or Marburg viral hemorrhagic fevers

Ribavirin	**Loading dose**	**Maintenance dose**
Intravenous	30 mg/kg IV (maximum 2 g) once	16 mg/kg IV (maximum 1 g per dose) q6h for 4 days followed by 8 mg/kg IV (maximum 500 mg per dose) q8h for 6 days
Oral	2000 mg orally once	Weight >75 kg: 600 mg orally bid for 10 days Weight ≤75 kg: 400 mg orally in a.m., 600 mg orally in p.m. for 10 days

	Convalescent plasma in Argentinian and Bolivian hemorrhagic fevers
Postexposure prophylaxis	Prophylactic ribavirin for Bunyaviridae and Arenaviridae infections, under IND status, may be useful

Tularemia

Francisella tularensis is generally susceptible in vitro to aminoglycosides, tetracyclines, rifampin, and chloramphenicol; however, many strains are resistant to β-lactams. Similar to the treatment of plague and lacking contraindications, therapy with streptomycin or gentamicin is preferred, although alternatives, such as ciprofloxacin, are effective. Because the use of drug-resistant organisms is possible in a bioterrorist event, empiric therapy should account for this, and antimicrobial susceptibility testing of isolates should be expeditiously accomplished. A live attenuated vaccine derived from the avirulent live vaccine strain has been used to protect laboratory personnel working with *F. tularensis* but is not approved for commercial use.

Botulism

Supportive medical care, airway protection, and mechanical ventilation represent the primary modes of therapy for botulism. Advancements in these modalities account for the improvements in clinical outcomes observed since the mid-1950s; the mortality rate from foodborne botulism in the United States has decreased from 60% to 6%. Passive immunization with equine antitoxin, early in the course of clinical illness, remains the specific treatment of choice to neutralize circulating toxin. Timely administration of this product may be neuroprotective and mitigate severity of disease but will not reverse extant paralysis. Antitoxin should be given to patients with neurologic symptoms as soon as possible after the diagnosis of botulism is suspected; treatment should not be delayed for definitive diagnosis. In the United States, antitoxin is available only from the CDC via state and local health departments. As with any equine-based antisera, anaphylaxis is a potential risk in allergic individuals. To screen for hypersensitivity, skin testing with escalating challenge doses may be necessary before proceeding to a full dose. Patients responding to intradermal challenge with systemic symptoms or signs of hypersensitivity may be desensitized with expert guidance and ready access to epinephrine and airway protection in the event of an adverse reaction.

Smallpox

A suspected case of smallpox warrants immediate implementation of stringent contact and airborne precautions in a negative-pressure, respiratory isolation setting and immediate engagement of public health authorities for diagnostic, forensic, and epidemiologic purposes. Vaccination of potential exposures, so-called *ring vaccination and containment*, must be expeditiously performed; vaccination of symptomatic individuals is indicated if in the early stages of illness, as this is known to be effective in controlling the spread of disease, may mitigate the individual course of disease, and/or may prevent death. The smallpox vaccine contains replication-competent vaccinia virus, which can be transmitted to non-vaccinated individuals and cause illness.

Tecorivirmat is a new antiviral, active against orthopoxviruses, that is now FDA-approved for the treatment of smallpox. Additionally, brincidofovir, a lipid conjugate of cidofovir, is currently under investigation for the treatment of smallpox based on promising in vitro studies. Topical idoxuridine may be useful in the setting of ocular involvement. Bacterial superinfection is a common complication of smallpox and a frequent cause of death in infected individuals. Aggressive deployment of penicillinase-resistant antimicrobial agents should be used to manage secondary infections with additional consideration given to the institutional and community prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in specific areas. Vaccinia immune globulin (VIG) is indicated for the management of specific, severe complications of smallpox vaccine; there is no evidence to support the use of VIG in either the treatment or prophylaxis of smallpox infections.

Viral hemorrhagic fevers

The mainstay of treatment for all etiologies of VHFs is supportive medical care, with special attention paid to hemodynamics, volume status, respiratory parameters, and acid–base balance. As many of these agents cause systemic hypotension while at the same time causing capillary leak syndromes, careful monitoring of fluid and electrolyte balance is an important component of patient management. Invasive hemodynamic monitoring, mechanical ventilation, blood product support, dialysis, and neurologic support are often needed.

Although there are no approved antiviral therapies for VHF, the nucleoside analog ribavirin has in vitro and in vivo activity against some arenaviral and bunyaviral etiologies of VHF, such as Rift Valley fever, Lassa fever, and Congo–Crimean hemorrhagic fever. The drug has been shown to reduce morbidity from hemorrhagic fever with renal syndrome caused by Old World hantaviruses and to probably reduce morbidity and mortality from Lassa fever. Intravenous ribavirin given within the first 6 days of fever to patients with Lassa fever who had high levels of viremia decreased mortality from 76% to 9%. The drug is available under investigational new drug (IND) status from the CDC and USAMRIID and is associated with significant hemolysis, cytopenias from marrow suppression, and is teratogenic in animals. Ribavirin has no clinical utility in infections caused by filoviruses, such as Marburg or Ebola, or flaviviruses.

ZMapp is a cocktail of three neutralizing monoclonal antibodies used for the treatment of Ebola. It remains under investigation, but is available in the United States under an expanded access protocol. There are two vaccines currently under investigation for Ebola. A ring vaccination trial using one of the vaccines, rVSV, in Guinea found no secondary cases of Ebola virus disease among those vaccinated. Active investigation into other therapeutics and vaccines is ongoing in naturally occurring outbreaks in Africa.

Suggested reading

Arnon SS, Schechter R, Inglesby TV, et al. Botulinum toxin as a biological weapon: Medical and public health management. *JAMA*. 2001;285:1059–1070.

Artenstein AW. Initial management of a suspected outbreak of smallpox. In Cohen J, Powderly WG, eds. *Infectious diseases*, 2nd ed. London: Mosby; 2003 :1022–1025.

Artenstein AW. Bioterrorism and biodefense. In Cohen J, Powderly WG, Opal SM eds. *Infectious diseases*, 3rd ed. London: Mosby; 2010: 747–758.

Artenstein AW, Opal SM. Novel approaches to the treatment of systemic anthrax. *Clin Infect Dis*. 2012;54:1148–1161.

Banada PP, Deshpande S, Russo R, et al. Rapid detection of Bacillus anthracis bloodstream infections by use of a novel assay in the GeneXpert system. *J Clin Microbiol* 2017 Oct;55(10):2964–2971.

Borio L, Inglesby TV, Peters CJ, et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA*. 2002;287:2391–2405.

Dennis DT, Inglesby TV, Henderson DA, et al. Tularemia as a biological weapon: medical and public health management. *JAMA*. 2001;285:2763–2773.

Duraffour S, Malvy D, Sissoko D. How to treat Ebola virus infections? A lesson from the field. *Curr Opin Virol*. 2017 Jun;24:9–15.

Fan J, Kraft AJ, Henrickson KJ. Current methods for the rapid diagnosis of bioterrorism-related infectious agents. *Pediatr Clin North Am*. 2006;53:817–842.

Grosenbach DW, Honeychurch K, Rose EA, et al. Oral tecovirimat for the treatment of smallpox. *N Engl J Med*. 2018 Jul 5;379(1):44–53.

Gsell PS, Camacho A, Kucharski AJ, et al. Ring vaccination with rVSV-ZEBOV under expanded access in response to an outbreak of ebola virus disease in guinea, 2016: An operational and vaccine safety report. *Lancet Infect Dis*. 2017 Dec;17(12):1276–1284.

Head BM, Rubinstein E, Meyers AF. Alternative pre-approved and novel therapies for the treatment of anthrax. *BMC Infect Dis*. 2016 Nov 3. doi:10.1186/s12879-016-1951-y

Henderson DA, Dennis DT, Inglesby TV, et al. Smallpox as a biological weapon: Medical and public health management. *JAMA*. 1999;281:2127–2137.

Hendriks KA, Wright ME, Shadomy SV, et al. Workgroup on Anthrax Clinical Guidelines. Centers for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults. *Emerg Infect Dis* 2014;20:e130687. doi.org/10–3201/eid2002.130687.

Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: Medical and public health management. *JAMA*. 2000;83:2281–2290.

Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: Updated recommendations for management. *JAMA*. 2002;287:2236–2252.

Kennedy SB, Bolay F, Kieh M, et al. Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia. *N Engl J Med*. 2017 Oct 12;377(15):1438–1447.

Pillai SK, Huang E, Guarnizo JT, et al. Antimicrobial treatment for systemic anthrax: Analysis of cases from 1945 to 2014 identified through a systematic literature review. *Health Secur*. 2015 Nov-Dec;13(6):355–364.

Pien BC, Royden Saah J, Miller SE, et al. Use of sentinel laboratories by clinicians to evaluate potential bioterrorism and emerging infections. *Clin Infect Dis*. 2006;42:1311–1324.

Woods B. *USAMRIID's medical management of biological casualties handbook*, 6th ed. Frederick, MD: US Army Medical Research Institute of Infectious Diseases; 2005.

Section 18

Specific organisms: Bacteria

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Actinomycosis

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Etiologic agents

Actinomycosis is an indolent, slowly progressive infectious syndrome caused by anaerobic or microaerophilic bacteria, primarily from the genus *Actinomyces*. It is most commonly caused by *Actinomyces israelii*. However, *A. naeslundii*, *A. odontolyticus, A. viscosus, A. meyeri*, and *A. gerencseriae* are less common causes of infection. Infections due to *A. neuii* have been increasingly recognized. Advances in microbiologic taxonomy, using genotypic methods such as comparative 16S ribosomal RNA (rRNA) or sequencing of alternative genes, have led to the identification of many new *Actinomyces* species from both human and animal specimens. Presently 50 species and 2 subspecies have been recognized (http://www.bacterio.cict.fr/a/actinomyces.html). Although the syndrome of actinomycosis can be caused by these more recently described agents, most of the infections are not "classical" actinomycosis. Nearly all of actinomycotic infections are polymicrobial in nature where "companion organisms," such as *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Eikenella corrodens, Fusobacterium, Bacteroides, Capnocytophaga, Staphylococcus, Streptococcus*, and Enterobacteriaceae are commonly co-isolated with the agents of actinomycosis in various combinations depending on the site of the infection.

Epidemiology and pathogenesis

The etiologic agents of actinomycosis are members of the normal oral flora and are often isolated from the bronchi, gastrointestinal, and female genital tracts. Although males have a higher incidence of infection (unproved but probably due to more frequent trauma and poorer dental hygiene), actinomycosis occurs in all age groups and geographic locations. Disruption of the mucosal barrier is the critical step for the development of actinomycosis. Subsequently, a local infection may ensue, and, once established, if untreated spreads contiguously, ignoring tissue planes in a slow, progressive manner. Although acute inflammation may initially occur at the site of infection, the hallmark of classical actinomycosis is the characteristic chronic, indolent phase. This stage is manifested by lesions that usually appear as single or multiple indurations. Central necrosis develops that consists of neutrophils and sulfur granules (a finding virtually diagnostic of this disease). The walls of the mass are fibrotic and characteristically described as "wooden." Over time sinus tracts to the skin, adjacent organs, or bone may develop. Rarely, distant hematogenous seeding occurs. Foreign bodies appear to facilitate infection. This occurs most frequently with intrauterine contraceptive devices (IUCDs). Although actinomycosis has been described in the setting of various immunosuppressive therapies or states of host compromise, it remains unclear which arm(s) of host defense prevents/control infection. The contribution of the non-*Actinomyces* co-isolates or companion organisms to the pathogenesis of actinomycosis is also uncertain.

Infectious syndromes

Clinical presentations are myriad. Once common in the pre-antibiotic era, today the incidence of actinomycosis is diminished and, as a result, so is its timely recognition. It has been called "the most misdiagnosed disease" and some have stated that "no disease is so often missed by experienced clinicians." Actinomycosis remains a diagnostic challenge. Knowledge of the full spectrum of disease will expedite diagnosis and treatment and minimize the unnecessary surgical interventions, morbidity, and mortality that all too often occur with this disease. Three clinical presentations of this unique infection, in particular, warrant consideration. First, the combination of chronicity, progression across tissue boundaries, and masslike features mimic malignancy, with which it is often confused. Second, the cure of established actinomycosis requires prolonged treatment. Short courses of therapy with active agents usually result in only transient improvement. Therefore, actinomycosis should be thought of with refractory or relapsing infections. Last, development of a sinus tract, which may spontaneously resolve and recur, should prompt consideration of this disease.

Oral–cervicofacial disease

This is the most frequent site for actinomycosis, which usually presents as a soft tissue swelling, abscess, mass, or ulcer that is often mistaken for a neoplasm. The angle of the jaw is the most commonly involved site (Figure 121.1), but actinomycosis should be considered with any mass lesion or relapsing infection in the head and neck. Dental disease or procedures are a common precipitating factor. Rarely, otitis, sinusitis, and canniculitis can also occur. Isolated masses or ulcerative lesions of the tongue, vallecula, nasal cavity, nasopharynx, soft tissues of the head and neck, salivary glands, patent thyroglossal duct, thyroid, branchial cleft cyst, hypopharynx, or larynx also have been reported. Radiation therapy and particularly bisphosphonate treatment have been increasingly recognized for contributing to an increased incidence of actinomycotic infection of the mandible and maxilla. Pain, fever, and leukocytosis are variably present. Contiguous spread to the cranium, cervical spine, or thorax are potential sequelae.

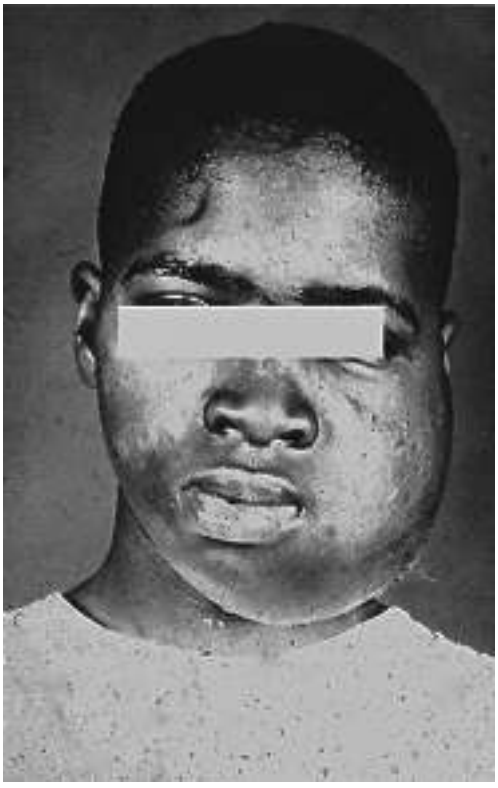

FIGURE 121.1

Thoracic disease

The usual presentation is an indolent, progressive course that involves the pulmonary parenchyma and/or the pleural space. Thoracic actinomycosis may be facilitated by aspirated foreign material. Chest pain, fever, weight loss, and, less frequently, hemoptysis are prominent. A cough, when present, is variably productive. The most common radiographic appearance is either a mass lesion or pneumonia. Cavitary disease may develop, which can be demonstrated on CT scan. Hilar adenopathy may occur. Many cases have pleural thickening, effusion, or empyema. Lesions suggestive of pulmonary actinomycosis include those crossing fissures or pleura, mediastinal extension, spread to contiguous bone or chest wall (empyema necessitates), or the formation a sinus tract. In the absence of these scenarios, thoracic actinomycosis is often mistaken for malignancy, or empyema or pneumonia due to more usual causes. Although uncommon, the structures within the mediastinum and the heart, including heart valves, can be involved in various combinations, resulting in a variety of presentations. Isolated disease of the breast occurs rarely.

Abdominal disease

Abdominal actinomycosis is often unrecognized. Months to years usually pass from the inciting event (e.g., appendicitis, diverticulitis, peptic ulcer disease, spillage of gall stones or bile during cholecystectomy, foreign-body perforation, bowel surgery, or ascension from IUCD-associated pelvic disease) to diagnosis. Because of the flow of peritoneal fluid and/or direct extension of primary disease, virtually any abdominal organ, region, or space can be involved. It usually presents as an abscess or a mass lesion that is often fixed to underlying tissue and mistaken for a tumor. On CT, often heterogenous enhancement and thickening of bowel wall is seen. Sinus tracts to the abdominal wall, to the perianal region, or between bowel and other organs may develop mimicking inflammatory bowel disease. Hepatic infection usually presents as single or multiple abscesses or masses. Isolated disease is presumably via hematogenous seeding from cryptic foci. Imaging and percutaneous techniques have improved diagnosis and treatment. All levels of the urogenital tract can be infected. Bladder involvement, usually due to extension of pelvic disease, may result in obstruction or fistulas to bowel, skin, or uterus. Renal disease usually presents as pyelonephritis and/or renal and perinephric abscess.

Pelvic disease

Actinomycotic involvement of the pelvis is strongly associated with IUCDs but can also occur with other foreign bodies such as a surgical mesh. Although the magnitude of risk is unclear, it would appear to be small. The disease rarely occurs when an IUCD has been in place for <1 year; however, the risk of infection increases with time and is often seen in the setting of the "forgotten" IUCD. Symptoms are typically indolent with fever, weight loss, abdominal pain, and abnormal vaginal bleeding or discharge being most common. An endometritis, if untreated, may progress to a pelvic mass or a tubo-ovarian abscess. Unfortunately, diagnosis is often delayed, and a "frozen pelvis" mimicking malignancy or endometriosis will develop by the time of recognition, leading to unnecessary surgery. Ascites and pelvic lymphadenopathy are uncommon in this setting, in contrast to malignancy and tuberculosis.

Central nervous system

Central nervous system (CNS) infection is rare. Single or multiple brain abscesses are most common, usually appearing on CT as a ring-enhancing lesion with a thick wall that may be irregular or nodular. Rarely, primary meningitis, epidural or subdural space, or cavernous sinus infection occurs.

Musculoskeletal infection

Osteomyelitis is usually due to adjacent soft tissue infection but may be associated with trauma (e.g., fracture of the mandible), injections, surgery, osteoradionecrosis and bisphosphonate osteonecrosis, or hematogenous spread. The uncommon infection of the extremities is usually a result of trauma. Skin, subcutaneous tissue, muscle, and bone are involved alone or in various combinations. Cutaneous sinus tracts frequently develop. Actinomycotic infections of hip and knee prostheses have also been described.

Disseminated disease

Hematogenous spread of infection from any location may rarely result in multiorgan involvement, with the lungs and liver most commonly affected. The presentation of multiple nodules may mimic disseminated malignancy. *A. meyeri* appears to have the greatest capability of causing this syndrome.

Diagnosis

The diagnosis of actinomycosis is rarely considered. Often the first mention of actinomycosis is from the pathologist after extensive surgery (Figure 121.2). As medical therapy alone is often sufficient for cure, the challenge for the clinician is to consider actinomycosis so that this uncommon and unusual infection can be diagnosed in the least invasive fashion and to avoid unnecessary surgery. CT- or ultrasound-guided aspirations or biopsies are successfully being used to obtain clinical material for diagnosis, although surgery may be required. Of note, hypermetabolism has been demonstrated by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in actinomycotic disease. The diagnosis is most commonly made by microscopic identification of sulfur granules (an in vivo matrix of bacteria, calcium phosphate, and host material) in pus or tissues, although occasionally sulfur granules can be grossly identified from draining sinus tracts. Microbiologic identification is less frequent, due to either prior antimicrobial therapy or omission. To optimize yield, the avoidance of even a single dose of antibiotics is mandatory. Although some species can grow aerobically, isolation is maximized under anaerobic conditions, which require 5 to 7 days usually but can take up to 2 to 4 weeks. 16S rRNA gene amplification and sequencing has been successfully used by clinical microbiology laboratory to increase diagnostic sensitivity and specificity. MALDI-TOF MS is promising but databases are still in the process of being optimized.

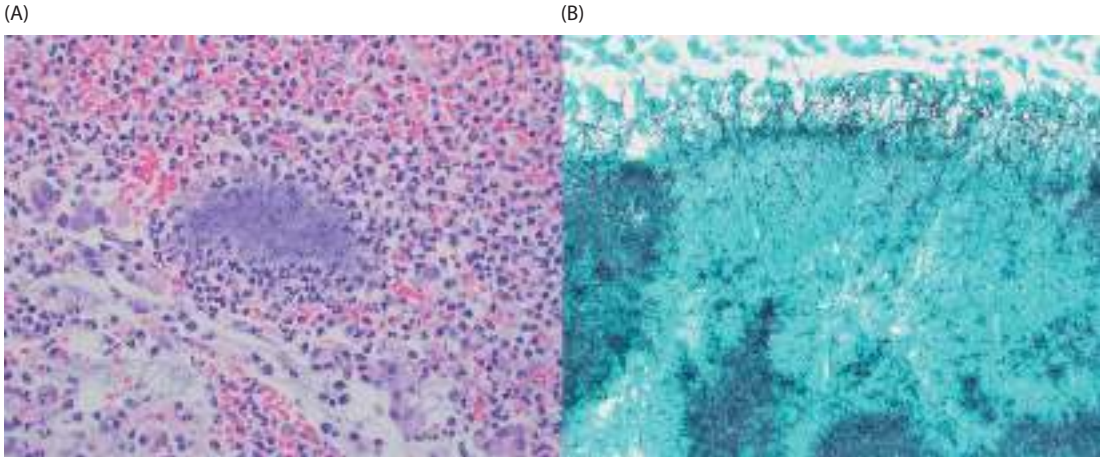

FIGURE 121.2

Because these organisms are normal oral and genital tract flora, their identification in the absence of sulfur granules from sputum, bronchial washings, and cervicovaginal secretions is of little significance.

Treatment

Antimicrobial therapy

Controlled trials either evaluating antimicrobials or designed to define duration of therapy in the treatment of actinomycosis have not been performed and unlikely will be done in future. Therefore, treatment decisions are based primarily on the collective clinical experience. Two principles of therapy have evolved. It is necessary to treat classical disease both with high doses and for a prolonged period. Presumably, this is because of the difficulties of antimicrobials penetrating the thick-walled masses that commonly occur with this infection and/or the sulfur granules themselves, which may represent a biofilm. Although therapy should always be individualized, 18 to 24 million units of intravenous (IV) penicillin for 2 to 6 weeks, followed by oral therapy with penicillin or amoxicillin for 6 to 12 months is justified for serious infections and bulky disease. For penicillin-allergic patients tetracyclines, ceftriaxone, or carbapenems are reasonable alternatives. Less extensive disease, particularly involving the oro-cervicofacial region, may require a shorter course of therapy. If the duration of therapy is extended beyond the resolution of measurable disease, then relapses, one of the clinical hallmarks of this infection, will be minimized. CT and MRI studies are generally the most sensitive and objective modalities to accomplish this goal. In the pregnant, penicillin-sensitive patient erythromycin is a safe alternative. Remarkably, little clinical information is available on the newer antimicrobial agents. Anecdotal successes have been reported with imipenem, ceftriaxone, ceftizoxime, and piperacillin–tazobactam (Box 121.1). Available data suggest that oxacillin, dicloxacillin, cephalexin, metronidazole, fluoroquinolones, and aminoglycosides should be avoided.

Home therapy

For home IV therapy, the ease of once-a-day dosing makes ceftriaxone appealing in certain circumstances; however, a greater body of literature supporting its efficacy would be desirable. The availability of portable infusion pumps for home therapy allows for both the appropriate dosing and practical administration of IV penicillin. For infections in critical sites (e.g., CNS) this approach remains the safest until more information is available on other agents. The pharmacokinetic properties, availability of oral and parenteral formulations, and potential efficacy of azithromycin also make this agent appealing. Unfortunately, few in vitro and no clinical data exist on its use to treat actinomycosis.

Treatment of co-isolates

It is unclear whether other bacteria frequently co-isolated with the etiologic agents of actinomycosis require treatment; however, many of them are pathogens in their own right. Designing a therapeutic regimen that includes coverage for these organisms during the initial treatment course is reasonable. If microbiology is not available, it is important to consider the site of infection when designing empiric coverage. For example, *Aggregatibacter actinomycetemcomitans, Eikenella corrodens, Fusobacterium*, and *Capnocytophaga* are more likely to be co-isolates in head and neck infection, whereas the Enterobacteriaceae are more commonly co-isolated in abdominal infection.

BOX 121.1

Appropriate and inappropriate antibiotic therapy for actinomycosis[a]

Group 1: Extensive successful clinical experience[b]
- Penicillin (3–4 million units IV q4h)[c]
- Amoxicillin (500 mg PO q6h)
- Erythromycin (500–1,000 mg IV q6h or 500 mg PO q6h)
- Tetracycline (500 mg PO q6h)
- Doxycycline (100 mg IV or PO q12h)
- Minocycline (100 mg IV or PO q12h)
- Clindamycin (900 mg IV q8h or 300–450 PO q6h)[d]

Group 2: Anecdotal successful clinical experience
- Ceftriaxone[c]
- Ceftizoxime
- Imipenam-cilastin
- Piperacillin-tazobactam

Group 3: Agents predicted to be efficacious based on in vitro activity
- Vancomycin
  - Linezolid
  - Quinupristin-dalfopristine
- Rifampin
- Ertapenem[c]
- Tigecycline
- Azithromycin[c]

Group 4: Agents that should be avoided
- Metronidazole
- Aminoglycosides
- Oxacillin
- Dicloxacillin
- Cephalexin
- Fluoroquinolones

[a] Additional coverage for concomitant "companion" bacteria may be required.

[b] Controlled evaluations have not been performed. Dose and duration require individualization depending on the host, site, and extent of infection. As a general rule, a maximum antimicrobial dose for 2–6 weeks of parenteral therapy followed by oral therapy for a total duration (6–12 months) is required for serious infections and bulky disease; whereas a shorter duration may suffice for less extensive disease, particularly in the oral–cervicofacial region.

[c] These agents can be considered for at-home parenteral therapy; penicillin requires a continuous infusion pump.

[d] Recent in vitro data have demonstrated resistance in up to 33% of isolates.

Surgery or percutaneous drainage

In the pre-antibiotic era, surgical removal of infected tissue was the only beneficial treatment. Despite the availability of effective antimicrobial therapy, combined surgical therapy is still advocated by some authorities. However, an increasing body of literature now supports the approach of initially attempting a cure with medical therapy alone. Successes have been reported in cases of extensive disease that initially appeared to be incurable using antibiotics alone. CT and MRI should be used to monitor the response to therapy. In most cases either surgery can be avoided or a less extensive procedure will be necessary. This approach is particularly important when the possibility of sparing critical organs is involved, such as the bladder or reproductive organs in women of childbearing age. In a patient with disease in a critical location (e.g., epidural space, selected CNS disease), with significant hemoptysis, or if suitable medical therapy fails, surgical intervention may be appropriate. In the setting of actinomycosis presenting as a well-defined abscess, percutaneous drainage in combination with medical therapy is a reasonable approach.

Treatment of the immunocompromised host

Actinomycosis has been described in association with HIV infection, steroid use, anti–TNF-α therapy, and lymphoproliferative tumors. Whether these infections were because of disease-associated disruptions of mucosa (e.g., cytomegalovirus infection with HIV infection), host defense abnormalities, immunosuppressive therapy, or some combination of these is unclear. From a treatment perspective it is reasonable to initially use the same approach as that for noncompromised hosts. Aggressive treatment directly against HIV (e.g., highly active antiretroviral therapy) and minimizing immunosuppressive therapy is also desirable if possible. Although prospective controlled data are not available, when actinomyces are identified in the setting of bisphosphonate-related osteonecrosis of the jaw (BRONJ) a prolonged course of antimicrobial therapy is reasonable and appears to be efficacious. The role of surgical debridement for BRONJ is less clear but resection of at least necrotic bone seems prudent.

Refractory disease

Usually actinomycosis responds well to medical therapy. However, refractory or perceived refractory disease has been described in HIV-infected individuals as well as in apparently normal hosts. In this setting basic principles of infectious disease apply. Exclude infection elsewhere (e.g., line-related, *Clostridium difficile* colitis) and/or non-infectious causes (e.g., drug fever, unrelated disease) as being responsible. Confirm that high-dose parenteral therapy is being utilized for initial treatment. Identify and drain significant purulent collections associated with the actinomycotic infection. Consider the possibility that untreated co-isolates (companion organisms) may be responsible. Although penicillin-resistant strains or evolution of resistance during therapy have not yet been clearly documented in vivo, this possibility should be considered when other more likely scenarios are excluded. Finally, surgery should be considered when infection is refractory to medical therapy, although, as stated, this usually can be avoided, at least initially.

Actinomyces-like organisms

An unresolved issue is whether screening cervical or endometrial specimens for *Actinomyces*-like organisms (ALOs) or their detection by immunofluorescence (IF) can predict/prevent IUCD-associated disease. Furthermore, a Papanicolaou smear may fail to detect ALOs even in the presence of active actinomycosis. Although the risk appears to be small, the consequences of infection are significant. Therefore, until more quantitative data become available, in the presence of symptoms that cannot be accounted for, regardless of whether ALOs or IF-positive organisms are detected, it would appear prudent to remove the IUCD and, if advanced disease is excluded, empirically treat for 14 days for possible early pelvic actinomycosis. The detection of ALOs or IF-positive organisms in the absence of symptoms warrants patient education and close follow-up but not removal of the IUCD unless an equally suitable means of contraception can be agreed upon.

Suggested reading

Acevedo F, Baudrand R, Letelier LM, et al. Actinomycosis: A great pretender. Case reports of unusual presentations and a review of the literature. *Int J Infect Dis*. 2008;*12*(4):358–362.

Choi MM, Baek JH, Lee JN, et al. Clinical features of abdominopelvic actinomycosis: Report of twenty cases and literature review. *Yonsei Med J*. 2009;50(4):555–559.

Clarridge JE III, Zhang Q. Genotypic diversity of clinical Actinomyces species: Phenotype, source, and disease correlation among genospecies. *J Clin Microbiol*. 2002;40:3442–3448.

Colmegna I, Rodriguez-Barradas M, Rauch R, et al. Disseminated Actinomyces meyeri infection resembling lung cancer with brain metastases. *Am Med Sci*. 2003;326:152–155.

Lynch T, Gregson D, Church DL. Species-level identification of actinomyces isolates causing invasive infections: multiyear comparison of Vitek MS (matrix-assisted laser desorption ionization-time of flight mass spectrometry) to partial sequencing of the 16S rRNA Gene. *J Clin Microbiol*. 2016;54(3):712–717.

Naik NH, Russo TA. Bisphosphonate-related osteonecrosis of the jaw: The role of actinomyces. *Clin Infect Dis*. 2009;49(11):1729–1732.

Pulverer G, Schütt-Gerowitt H, Schaal KP. Human cervicofacial actinomycoses: Microbiologic data for 1997 cases. *Clin Infect Dis*. 2003;37:490–497.

Qiu L, Lan L, Feng Y, et al. Pulmonary actinomycosis imitating lung cancer on (18)F-FDG PET/CT: A case report and literature review. *Korean J Radiol*. 2015;16(6):1262–1265.

Smith AJ, Hall V, Thakker B, et al. Antimicrobial susceptibility testing of Actinomyces species with 12 antimicrobial agents. *J Antimicrob Chemother*. 2005;56:407–409.

Steininger C, Willinger B. Resistance patterns in clinical isolates of pathogenic Actinomyces species. *J Antimicrob Chemother*. 2016;71(2):422–427.

Sudhakar SS, Ross JJ. Short-term treatment of actinomycosis: two cases and a review. *Clin Infect Dis*. 2004;38:444–447.

Valour F, Sénéchal A, Dupieux C, et al. Actinomycosis: Etiology, clinical features, diagnosis, treatment, and management. *Infect Drug Resist*. 2014;7:183–197.

122

Anaerobic infections

Itzhak Brook

Introduction

Infections caused by anaerobic bacteria occur frequently and can be serious and life-threatening. Because anaerobes colonize the skin and are the main component of mucous membranes flora[1] they are endogenous in nature. Because of their fastidiousness, anaerobes are difficult to isolate and are often unrecognized. Delay in implementing appropriate therapy may lead to clinical failures. Their isolation requires proper methods of collection, transportation, and cultivation of specimens. Treatment is complicated by their slow in vitro growth, the infection's polymicrobial nature, and the organisms' mounting antimicrobial resistance.

Epidemiology

Most infections are caused by normal flora anaerobes that contaminate a previously sterile body site or gain access to the body from an external source of normal flora such as a bite. They also occur when the local defenses are decreased. Some infections are caused by wound contamination by soil anaerobes (i.e., Clostridia). *Clostridium difficile* can lead to hospital epidemics when these bacteria are transmitted from patient to patient. Toxin-producing *Clostridium botulinum* causes food poisoning.

Microbiology

The clinically important anaerobes accounting for >95% of infections are:

- Gram-negative rods (*Bacteroides, Prevotella, Porphyromonas, Fusobacterium, Bilophila,* and *Sutterella* spp.);
- Gram-positive cocci (mainly *Peptostreptococcus* spp.);
- Gram-positive spore-forming (*Clostridium* spp.) and non–spore-forming bacilli (*Actinomyces, Propionibacterium, Eubacterium, Lactobacillus,* and *Bifidobacterium* spp.);
- Gram-negative cocci (mainly *Veillonella* spp.) (Table 122.1).

The recovery of anaerobes differs in various infectious sites (Table 122.2) and is influenced by their presence in the adjacent endogenous mucus membranes and skin flora. Polymicrobial synergistic infections caused by aerobic and anaerobic organisms are common.

Anaerobes taxonomy has changed because of improved characterization methods using genetic studies. Recent advances in direct detection of anaerobes from clinical samples include 16rRNA gene-based methods, DNA hybridization, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

TABLE 122.1 **ANAEROBIC BACTERIA PREDOMINATING IN INFECTIONS**

Gram-positive cocci	*Peptostreptococcus* spp.: *P. magnus, P. asaccharolyticus, P. prevotii, P. intermedius, P. anaerobius, P. micros* Microaerophilic streptococci (not true anaerobes)
Gram-positive non–spore-forming bacilli	*Propionibacterium* spp.: *P. acnes, P. propionicum, P. granulosum, Eubacterium tentum* *Bifidobacterium* spp.: *B. eriksonii, B. dentium* *Actinomyces* spp.: *A. israelii, A. naestundii, A. viscosus, A. odontolyticus, A. meyerii*
Gram-positive spore-forming bacilli	*Clostridium* spp.: *C. perfringens, C. ramosum, C. septicum, C. novyi, C. histolytica, C. sporogenes, C. difficile, C. bifermentans, C. butyricum, C. innocuum, C. sordellii, C. botulinum, C. tetani*
Gram-negative bacilli	*Bacteroides fragilis* group: *B. fragilis, B. thetaiotaomicron, B. distasonis, B. vulgatus, B. ovatus, B. uniformis* Other *Bacteroides* spp.: *B. gracilis, B. ureolyticus, Bilophila wadsworthia, Sutterella* spp., Pigmented *Prevotella* spp.: *P. melaninogenica, P. intermedia, P. denticola, P. loescheii, P. corporis, P. nigrescens, Other Prevotella* spp.: *P. oris, P. buccae, P. oralis* group (*P. oralis, P. buccalis, P. veroralis*), *P. bivia, P. disiens, Porphyromonas* spp.: *P. asaccharolytica, P. gingivalis, P. endodontalis, Fusobacterium* spp.: *F. nucleatum, F. necrophorum, F. gonidiaformans, F. naviforme, F. mortiferum, F. varium*

(MALDI-TOF MS) Biotyper, multiplex polymerase chain reaction (PCR), and oligonucleotide array technologies.[5] The ability to differentiate between similar strains enables better characterization of types of infection and anticipation of antimicrobial susceptibility.

Anaerobic spore-forming bacilli belong to the genus *Clostridium*. They are highly pleomorphic, ranging from short, thick bacilli to long filamentous forms, and are either ramrod straight or slightly curved. The most frequent Clostridia in clinical infections are

TABLE 122.2 **ANAEROBIC BACTERIA MOST FREQUENTLY ENCOUNTERED IN SPECIFIC INFECTION SITES**

Organism		***Infection site***
Gram-positive cocci	*Peptostreptococcus* spp. Microaerophilic streptococci (not obligate anaerobes)	Respiratory tract, intra-abdominal and soft tissue infections Sinusitis, brain abscesses
Gram-positive bacilli	Non–spore-forming: *Actinomyces* spp.	Intracranial abscesses, chronic mastoiditis, aspiration pneumonia, head and neck infections
	Propionibacterium	Shunt infections (cardiac, intracranial), infections associated with foreign body
	Bifidobacterium spp. *Acnes*	Chronic otitis media, cervical lymphadenitis, abdominal infections
	Spore-forming: *Clostridium perfringens*	Soft tissue infection, sepsis, food poisoning
	Clostridium septicum	Sepsis, neutropenic enterocolitis
	Clostridium difficile	Colitis, antibiotic-associated diarrheal disease
	Clostridium botulinum	Botulism
	Clostridium tetani	Tetanus
	Clostridium ramosum	Soft tissue infections
Gram-negative bacilli	*Bacteroides fragilis* group	Intra-abdominal and female genital tract infections, sepsis, neonatal infections
	Pigmented *Prevotella* and *Porphyromonas* spp. *Prevotella oralis, Prevotella oris-buccae,*	Orofacial infections, aspiration pneumonia, periodontitis Orofacial infections Orofacial infections, intra-abdominal infections
	Prevotella bivia, Prevotella disiens, *Fusobacterium nucleatum*	Female genital tract infections Orofacial and respiratory tract infections, brain abscesses, bacteremia
	Fusobacterium necrophorum	Aspiration pneumonia, mastoiditis, Lemierre's Syndrome, bacteremia

Clostridium perfringens, C. septicum, C. ramosum, C. novyi, C. sordellii, C. histolyticum, C. fallax, C. bifermentans, and *C. innocuum.*

C. perfringens is an often encapsulated, stout gram-variable rods of varying length, found in soil and human and animal intestines. It is the most commonly isolated histotoxic clostridia and produces several necrotizing extracellular toxins. It can cause devastating illness with high mortality rates and bacteremia associated with extensive tissue necrosis, hemolytic anemia, and renal failure.

C. septicum infection (mostly blood and subcutaneous tissue) is often association with occult colonic malignancy. *C. sordellii* infections often follow abortion, childbirth, and injection drug use.

C. botulinum can cause four syndromes: foodborne, wound, infant botulism, and adult intestinal toxemia. All of these produce the same clinical syndrome of symmetrical cranial nerve palsies followed by descending, symmetric flaccid paralysis of voluntary muscles, which may progress to respiratory compromise and death. Proteolytic strains of types A and B have been reported from food poisoning and wound infections. Infant botulism occurs with types A, B, and F.7 Disease caused by *C. botulinum* is usually an intoxication produced by ingestion of contaminated food (uncooked meat, poorly processed fish, improperly canned vegetables) containing a highly potent neurotoxin. *C. difficile* causes antibiotic-associated and spontaneous diarrhea and colitis. *C. tetani* is found in soil and rarely human feces. Infections can result from wound contamination with soil containing *C. tetani* spores that germinate in devitalized tissue and produce a neurotoxin.

Anaerobic gram-positive, non–spore-forming rods are part of gingival crevices, gastrointestinal tract, and vaginal and skin flora. They include Propionibacterium, Eubacterium, Bifidobacterium, Lactobacillus. Actinomyces, Arcanobacterium, Atopobium, Mobiluncus, and Pseudoramibacter.

The *Actinomyces, Arcanobacterium,* and *Bifidobacterium* spp. are gram-positive, pleomorphic, anaerobic to microaerophilic bacilli. *Actinomyces israelii, Actinomyces naeslundii* and *Propionibacterium propionicum*, members of the oral and throat flora, are the most frequent cause of actinomycosis. They have been isolated from intracranial abscesses, chronic mastoiditis, aspiration pneumonia, and peritonitis. Actinomycosis usually occurs in the face, neck, lungs, pleura, and genital and urinary tracts. Bone, pericardial, and anorectal lesions and bacteremia are less common, but all tissues may be involved.

Eubacterium and anaerobic lactobacilli are part of the oral, vaginal, and gastrointestinal flora. They are common in infections associated with malignancy, surgery, immunodeficiency, diabetes mellitus, foreign bodies, dental extraction, and broad-spectrum antibiotic therapy.

Propionibacterium spp., ordinarily nonpathogens, can cause implanted prostheses or central nervous system (CNS) shunt infection and endocarditis in previously damaged heart valves. They have been recovered from parotid and dental infections, brain abscesses, conjunctivitis associated with contact lens, peritonitis, and foreign body and pulmonary infections. *Propionibacterium acnes*, the commonest species, can be isolated from blood but is associated only rarely with bacteremia or endocarditis. Because these organisms are part of the normal skin flora, they are often a contaminant. *P. acnes* can cause bacteremia, especially in association with shunt and infections, and it plays a role in acne vulgaris.

Among *gram-negative bacilli*, the *Bacteroides fragilis* group are the most recovered Bacteroidaceae in clinical specimens. They resist penicillins, mainly through the production of β-lactamase. They include several members—the most commonly isolated ones are *B. fragilis* (the most commonly recovered member), *B. thetaiotaomicron, B. distasonis, B. ovatus,* and *B. vulgatus*. They are part of the normal gastrointestinal flora1 and predominate in intra-abdominal infections and other infections that originate from gut flora (i.e., perirectal abscesses, decubitus ulcers). The newly defined *Bilophila wadsworthia* and *Centipeda periodontii* are found in abdominal and endodontic infections, respectively.

Pigmented *Prevotella* (*Prevotella melaninogenica, Prevotella intermedia*), *Porphyromonas* (*Porphyromonas asaccharolytica*), and nonpigmented Prevotella (*Prevotella oralis, Prevotella oris*) are part of the oral and vaginal flora and are the predominant anaerobic gram-negative bacilli (AGNB) isolated from respiratory infections and their complications, aspiration pneumonia, lung abscess, chronic otitis media, chronic sinusitis, abscesses around the oral cavity, bite infection, paronychia, brain abscesses, and osteomyelitis. *P. bivia* and *P. disiens* predominate in obstetric and gynecologic infections.

Fusobacterium species are fusiform, moderately long, and thin organisms with tapered ends. *F. nucleatum, F. necrophorum, F. mortiferum,* and *F. varium* predominant in oral, pulmonary and intracranial infections. *Fusobacterium* spp. are also isolated from abscesses, obstetric and gynecologic infections, blood, and wounds.

A growing resistance of AGNB to penicillins has been noted in recent years.[20] Resistance was observed in pigmented *Prevotella* and *Porphyromonas, P. oralis, P. disiens, P. bivia,* and *Fusobacterium* spp. The main mechanism of resistance is through β-lactamase production.

The recovery AGNB in infected sites is similar to their distributions in the normal flora.[4–6] The *B. fragilis* group was more often found in sites proximal to the gastrointestinal tract, pigmented *Prevotella* spp. were more prevalent in infections proximal to the oral cavity, and *P. bivia* and *P. disiens* were more often isolates in obstetric and gynecologic ones (Table 122.2). Familiarity with this mode of distribution enables logical choice of antimicrobials adequate for the treatment of infections in or proximal to these sites.

The *predominate gram-positive cocci* are *Peptostreptococcus magnus, P. asaccharolyticus, P. anaerobius, P. prevotii,* and *Parvimonas micra* (*P. micros*). Other anaerobic cocci include *Coprococcus, Peptococcus, Ruminococcus sarcina,* and *Staphylococcus saccharolyticus.* They are part of the oral, upper respiratory tract, intestinal tract, vagina, and skin flora.

These organisms can be isolated in all types of anaerobic infection including respiratory infection (chronic sinusitis, mastoiditis, acute and chronic otitis media, aspiration pneumonia and lung abscess) and necrotizing, subcutaneous, and soft tissue infections. They can be isolated alone or mixed with other aerobic or anaerobic organisms. Microaerophilic streptococci are not true anaerobes and can become aerotolerant after subculture. They include the *Streptococcus anginosus* group (previously *Streptococcus milleri* group, which includes *S. constellatus* and *S. intermedius*) and *Gemella morbillorum* (previously *S. morbillorum*). Microaerophilic streptococci are common in chronic sinusitis and brain abscesses, obstetric and gynecologic infections, and abscesses.

There are three anaerobic *gram-negative cocci* genera: *Veillonella, Acidaminococcus,* and *Megasphaera* spp. *Veillonella* spp., the commonest of the three, are members of the oral, vaginal, and small intestinal flora. They are rarely isolated from almost every type of anaerobic infection.

Collection and transportation of specimens for anaerobic bacteria

Collection of specimens for anaerobic bacteria is important because documentation of an anaerobic infection is through isolation of organisms from the infected site. Appropriate documentation of anaerobic infection requires proper collection of appropriate specimens, expeditious transportation, and careful laboratory processing. Inadequate techniques or media can lead to missing the presence of anaerobic bacteria or the assumption that only aerobic organisms are present in a mixed infection.

Because anaerobes are present on skin and mucous membranes, even minimal contamination with normal flora can be misleading. Unacceptable or inappropriate specimens can yield normal flora and can be misleading and have no or little diagnostic value. Appropriate materials should be obtained by using techniques that bypass the normal flora.

Acceptable specimens include those obtained from normally sterile sites, such as blood or spinal, joint, or peritoneal fluids, or are collected after thorough skin decontamination. Two approaches are used to culture the maxillary sinus by aspiration following sterilization of the canine fossa or the nasal vestibule, via either the canine fossa or the inferior meatus. Urine is collected by percutaneous suprapubic bladder aspiration. Specimens can be collected from abscess contents, from deep aspirates of wounds, and via special techniques such as transtracheal aspirates or direct lung puncture. Specimens of the lower respiratory tract are difficult to obtain without contamination with indigenous florae. Double-lumen catheter bronchial brushing and bronchoalveolar lavage, cultured quantitatively, can be useful. Culdocentesis fluid obtained after decontamination of the vagina is acceptable.

Prompt delivery of specimens to the laboratory to allow for microbiologic processing is essential. Transportation of specimens should be prompt unless anaerobic transport devices are available. Transport devices generally contain oxygen-free environments provided by a mixture of carbon dioxide, hydrogen, and nitrogen, plus an aerobic condition indicator. Specimens should be placed into an anaerobic transporter as soon as possible.

Liquid or tissue specimens are always preferred to swabs. Liquid specimens are inoculated into an anaerobic transport vial or collected in a syringe and a needle. All air bubbles are expelled from the syringe. Insertion of the needle tip into a sterile rubber stopper is no longer recommended. Because air gradually diffuses through the plastic syringe wall, specimens should be processed in <30 minutes.

Swabs are placed in sterilized tubes that contain carbon dioxide or prereduced anaerobically sterile Carey and Blair semisolid media. Tissue specimens can be transported in an anaerobic jar or in a sealed plastic bag rendered anaerobic.

Virulence factors

Anaerobes possess a number of virulence factors including synergistic capability and production of toxins, polysaccharide capsules, and lipopolysaccharides.

Anaerobes possess several virulence factors that assist them to adhere to and invade epithelial surfaces. These factors include the presence of surface structures (such as capsule polysaccharide or lipopolysaccharide), production of superoxide dismutase and catalase, immunoglobulin proteases, coagulation promoting, spreading factors (such as hyaluronidase, collagenase, and fibrinolysin), adherence factors, and the production of toxins. Other factors that enhance the virulence of anaerobes include mucosal damage, oxidation–reduction potential drop, and the presence of hemoglobin or blood in an infected site.

Anaerobes contribute to the severity of infection through their synergy with their aerobic counterparts and with each other. Anaerobes generally take longer than aerobic bacteria to become virulent. This is because some of the major virulence factors of certain anaerobic bacteria (i.e., the production of a capsule) are expressed only after the infection has become chronic.

Predisposing conditions

Predisposing conditions include exposure of a sterile body site to a high inoculum of indigenous mucosal membrane flora, poor blood supply, tissue necrosis favoring the growth of anaerobes, or any condition that lowers the blood supply to an affected area such as trauma, foreign body, malignancy, surgery, edema, shock, colitis, and vascular disease. Other conditions include diabetes mellitus, splenectomy, immunosuppression, hypogammaglobinemia, neutropenia, leukemia, collagen vascular disease, and cytotoxic drugs. Infection with aerobic or facultative bacteria can be favorable for the growth of anaerobes. Anaerobic conditions and anaerobic bacteria can impair phagocytosis and intracellular killing through production of succinic acid, inhibition of chemotaxis, degradation of serum proteins by proteases and production of leukotoxins.

Suppuration, abscess formation, thrombophlebitis, and gangrenous tissue destruction associated with gas formation are the hallmarks of anaerobic infection. Anaerobes are commonly recovered in chronic infections and after failure of antimicrobial therapy with ineffective agents.

Some infections are likely to include anaerobes. These include brain abscess, oral and dental infections, bites, aspiration pneumonia, lung abscesses, peritonitis after perforation, amnionitis, endometritis, septic abortions, tubo-ovarian abscess, abscesses in and around the oral and rectal areas, pus-forming necrotizing infections of soft tissue or muscle, and postsurgical infections. Some solid

tumors (i.e., colonic, uterine, bronchial, carcinomas, head and neck) can become infected with anaerobes.

Prevention

Prevention and early therapy of conditions that can lead to anaerobic infection can reduce their rate. Examples include preventing oral flora aspiration by improving neurologic status, suctioning oral secretions, improving oral hygiene, and maintaining lower stomach pH to reduce the risk of aspiration pneumonia and its complications. Irrigation and debridement of wounds and necrotic tissue, drainage of pus, and improvement of blood supply help prevent skin and soft tissue infections.

Prophylactic antimicrobial therapy is recommended before surgery when the operative field is expected to be contaminated by mucosal membrane flora. Cefoxitin or ertapenem are used in procedures that involve the oral, rectal, or vulvovaginal. Vaccination with tetanus toxin can prevent *C. tetani* infection.

Signs and symptoms associated with anaerobic infections

Suppuration, abscess formation, thrombophlebitis, and gangrenous destruction of tissue associated with gas formation are the hallmarks of anaerobic infection. Clinical signs of anaerobic infection include:

- Infection adjacent to a mucosal surface
- Foul-smelling discharge
- Necrotic gangrenous tissue and abscess formation
- Free gas in tissue
- Bacteremia or endocarditis with no growth on aerobic blood cultures
- Infection related to the use of antibiotics effective against aerobes only
- Infection related to tumors or other destructive processes
- Infected thrombophlebitis
- Infection after bites
- Black discoloration of exudates containing *P. melaninogenica*, which may fluoresce under ultraviolet light
- Sulfur granules in discharges caused by actinomycosis
- Clinical presentation of gas gangrene
- Clinical condition predisposing to anaerobic infection (after maternal amnionitis, perforation of bowel, etc.)

Anaerobes are especially common in chronic infections and are commonly seen after failure of therapy with antimicrobials that are not effective against them, such as aminoglycosides, trimethoprim-sulfamethoxazole (co-trimoxazole), and older quinolones.

Certain infections are very likely to involve anaerobes as important pathogens, and their presence should always be assumed. Such infections include brain abscess, oral and dental infections, human and animal bites, aspiration pneumonia and lung abscesses, peritonitis after perforation of viscus, amnionitis, endometritis, septic abortions, tubo-ovarian abscess, abscesses in and around the oral and rectal areas, pus-forming necrotizing infections of soft tissue or muscle, and postsurgical infections following procedures on the oral or gastrointestinal tract or female pelvic area. Certain solid malignant tumors, such as colon, uterine, and bronchogenic carcinomas, and necrotic tumors of the head and neck, can become infected with anaerobes. The anoxic conditions in the tumor and exposure to the endogenous adjacent mucous flora may predispose to these infections.

Clinical infections

Anaerobes have been isolated from infections at all sites. However, the frequency and types of isolates vary and depend on the microbial flora at their source or the adjacent mucocutaneous sites.

Central nervous system

These include brain abscess (brain abscess), subdural empyema, epidural abscess, and meningitis. Brain abscess often originate from ear, mastoid, sinus, oropharynx, dental, or lung infection.[10] Ear or mastoid infection tends to spread to the temporal lobe or cerebellum, whereas facial sinusitis often causes abscess of the frontal lobe. Hematogenous spread often occurs after dental, oropharyngeal, or pulmonary infections, and rarely from endocarditis.

Meningitis can follow respiratory or cerebrospinal fluid shunt infection. Shunt infections are generally caused by skin flora (i.e., *P. acnes*) and in ventriculoperitoneal shunts that perforate the gut by enteric organisms (i.e., *B. fragilis*). *C. perfringens* can cause brain abscess and meningitis after head injuries or after intracranial surgery.

The anaerobes generally recovered from brain abscesses complicating respiratory and dental infections include *Prevotella, Porphyromonas, Bacteroides, Fusobacterium*, and *Peptostreptococcus* spp. Microaerophilic and other streptococci are also often isolated.

Early administration of antimicrobials at the stage of encephalitis can prevent abscess formation. Once an abscess has formed, surgical excision or drainage may be needed, combined with a long course of antibiotics (4–8 weeks). Some recommend evacuation of the abscess, whereas others advocate repeated aspirations. The procedures used are aspiration through a burr hole and complete excision after craniotomy. In multiple abscesses or abscesses in essential brain areas, repeated aspirations are preferred. Open craniotomy with debridement, intraventricular lavage, and intraventricular as well as intravenous anti-bimicrobial(s) are recommended after intraventricular rupture of the abscess. Prolonged high-dose antibiotics is an alternative approach replacing surgical drainage. Antimicrobials with adequate intracranial penetration are advocated for these infections: metronidazole, penicillins, meropenem, and chloramphenicol.

Head and neck and upper respiratory tract

Anaerobes can be recovered from a variety of head, neck, and upper respiratory tract infections especially in their chronic forms (Table 122.3). These include chronic otitis media, sinusitis and mastoiditis, tonsillar, peritonsillar and retropharyngeal abscesses, deep neck space infections, parotitis, sialadenitis, thyroiditis, odontogenic infections, and postsurgical and nonsurgical head and neck wounds and abscesses. The predominant isolates are *Prevotella, Porphyromonas, Bacteroides, Fusobacterium,* and *Peptostreptococcus* spp.

Most dental infections involve anaerobes; these include endodontic (e.g., pulpitis) and periodontal (gingivitis, periodontitis, and peri-implant) infections, periapical and dental abscesses, perimandibular space infection, and postextraction infection. Microaerophilic streptococci and *Streptococcus salivarius* can also be involved in dental infections. *Vincent's angina* is a distinct form of ulcerative gingivitis; the causative organisms include *Fusobacterium* spp. and anaerobic spirochetes.

Ludwig's angina is a connective tissue infection of the floor of the mouth, and *Lemierre's syndrome* is characterized by thrombosis and suppurative thrombophlebitis of the internal jugular vein that is

TABLE 122.3 **AEROBIC AND ANAEROBIC BACTERIA ISOLATED IN HEAD AND NECK AND UPPER RESPIRATORY TRACT INFECTIONS**

Type of infection	Aerobic and facultative organisms	Anaerobic organism
Otitis media and mastoiditis: acute Chronic	*Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis*[a] *Staphylococcus aureus*[a] *Escherichia coli*[a] *Klebsiella pneumoniae*[a] *Pseudomonas aeruginosa*[a]	*Peptostreptococcus* spp., Pigmented *Prevotella* and *Porphyromonas* spp.[a] *Bacteroides* spp.[a] *Fusobacterium* spp.[a] *Peptostreptococcus* spp.
Peritonsillar and retropharyngeal abscess	*Streptococcus pyogenes* *Staphylococcus aureus*[a]	*Fusobacterium* spp.[a] Pigmented *Prevotella* and *Porphyromonas* spp.[a]
Recurrent tonsillitis	*Streptococcus pyogenes* *Haemophilus influenzae*[a] *Staphylococcus aureus*[a]	*Fusobacterium* spp.[a]
Suppurative thyroiditis	Streptococcus pyogenes Staphylococcus aureus[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a] *Peptostreptococcus* spp.
Sinusitis: acute chronic	*Haemophilus influenzae*[a] *Streptococcus pneumoniae* *Moraxella catarrhalis*[a] *Staphylococcus aureus*[a] *Streptococcus pneumonia* *Haemophilus influenzae*[a]	*Peptostreptococcus* spp. Pigmented *Prevotella* and *Porphyromonas* spp.[a] *Fusobacterium* spp.[a] *Bacteroides fragilis* group[a]
Cervical lymphadenitis	*Staphylococcus aureus*[a] *Mycobacterium* spp.	Pigmented *Prevotella* and *Porphyromonas* spp.[a] *Peptostreptococcus* spp.
Postoperative infection disrupting oral mucosa	*Staphylococcus* spp.[a] Enterobacteriaceae[a] *Streptococcus pyogenes*	*Fusobacterium* spp.[a] *Bacteroides* spp.[a] Pigmented *Prevotella* and *Porphyromonas* spp.[a] *Peptostreptococcus* spp.
Deep neck abscesses and parotitis	*Streptococcus* spp. *Staphylococcus* spp.[a]	*Bacteroides* spp.[a] *Fusobacterium* spp.[a] *Peptostreptococcus* spp.[a]
Odontogenic complications	*Streptococcus* spp. *Staphylococcus* spp.[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a] *Peptostreptococcus* spp.
Oropharyngeal: Vincent's angina and necrotizing	*Streptococcus* spp. *Staphylococcus* spp.[a]	*Fusobacterium necrophorum*[a]

[a]Organisms that have the potential of producing β-lactamase.

associated with spread of septic emboli to the lungs and other sites; *F. necrophorum* is the prevalent species.

Deep neck infections (e.g., mediastinitis following perforation of the esophagus, extension of retropharyngeal abscess or cellulitis, dental abscess) are usually polymicrobial.

Otitis media

Peptostreptococcus spp. and *P. acnes* were found in 5% to 15% of acute otitis media. These organism and AGNB were present in 42% of culture-positive aspirates of patients with serous otitis media.

Anaerobes were recovered in half of the patients with chronic suppurative otitis media, mastoiditis, and infected cholesteatomas. The infection is often polymicrobial; the main isolates were AGNB, peptostreptococci, *Pseudomonas aeruginosa,* and *Staphylococcus aureus*. Anaerobes were isolated from 23 out of 24 (96%) specimens of chronic mastoiditis and from most intracranial abscesses complicating chronic suppurative otitis media. *Fusobacterium* spp. were also isolated from children with acute and chronic mastoiditis. Many of these organisms can produce β-lactamase that may contribute to the high failure rate of β-lactam antibiotics.

Rhinosinusitis

Streptococcus pneumoniae, Haemophilus influenzae, and *Moraxella catarrhalis* predominate in acute sinusitis. The bacterial sinus flora transitions from aerobic to anaerobic when the infection becomes chronic and oxygen levels decline. An elevated serum antibody level to *Prevotella* and *Fusobacterium* was demonstrated in patients with chronic sinusitis. Although anaerobes are generally isolated from only about 7% of acute sinusitis (mostly secondary to dental infection), they can be recovered from up to 67% of chronic infections.

Sinus infection may spread via anastomosing veins or contiguously to the CNS. Complications include orbital cellulitis, meningitis, cavernous sinus thrombosis, and epidural, subdural, and brain abscesses.

Parotitis

Acute suppurative parotitis is caused by aerobic (*S. aureus*, streptococci, gram-negative bacteria) and anaerobic (*Peptostreptococcus*, *Bacteroides*, and pigmented *Prevotella* and *Porphyromonas* spp.) bacteria. Empiric therapy should be directed against both. Drainage may be indicated when pus has formed.

Cervical lymphadenitis

The organisms causing acute unilateral infection associated with facial trauma or impetigo are *S. aureus* and group A β-hemolytic streptococci (GABHS). *Bartonella henselae* and mycobacteria are important in chronic infections. Anaerobes (mostly *Fusobacterium* and *Peptostreptococcus* spp.) were isolated in 25% and were associated with dental, periodontal, or tonsillar infection.

Head and neck infection after surgery

Postoperative head and neck infections are caused by the surgical site exposure to the oropharyngeal flora. Surgical wounds are generally infected by polymicrobial aerobic and anaerobic flora; the number of isolates varies from one to nine. The commonest isolates are peptostreptococci, *S. aureus*, AGNB, fusobacteria, and Enterobacteriaceae.

Tonsillitis

Clinical and laboratory data support the role of anaerobes in acute and chronic tonsillitis. Anaerobes were isolated from 25% of suppurative cervical lymph nodes, dental and tonsillar infections,[31] and internal jugular veins thrombophlebitis causing postanginal sepsis. Fusobacteria, peptostreptococci, and AGNB play a major role in complications of tonsillitis (e.g., bacteremia, abscesses). Polymicrobial flora predominate in peritonsillar and retropharyngeal abscesses. Anaerobes were isolated from the cores of tonsils of children with recurrent GABHS and non-GABHS tonsillitis.

The pathogenic role of anaerobes in tonsillitis is supported by their recovery in tonsillar or retropharyngeal abscesses, often without any aerobic bacteria; isolation in Vincent's angina[5]; recovery of encapsulated *Prevotella* and *Porphyromonas* in inflamed tonsils; isolation from the core of recurrently inflamed non-GABHS tonsils; and response to antibiotics in non-GABHS tonsillitis.

Immune response against *P. intermedia* can be detected in non-GABHS tonsillitis patients and against *P. intermedia* and *F. nucleatum* after recovery from peritonsillar cellulitis or abscesses, and infectious mononucleosis.

Metronidazole alleviated the symptoms of tonsillar hypertrophy and reduced fever in infectious mononucleosis. Since metronidazole has no antiviral or aerobic antibacterial efficacy, its suppression of oral anaerobes may reduce their secondary inflammation. This is supported by the increased recovery of *P. intermedia* and *F. nucleatum* during acute phases of mononucleosis.

Recurrent pharyngotonsillitis and failure of penicillin to eradicate GABHS can be a serious clinical problem. Penicillin therapy can select β-lactamase-producing bacteria (BLPB; e.g., *Prevotella, Porphyromonas, Fusobacteria*, *H. influenza*, *S. aureus*) found in the tonsils of three-quarters of children with recurrent GABHS tonsillitis. The ability to detect β-lactamase in the tonsillar core and the response to antimicrobials effective against BLPB (i.e., clindamycin or amoxicillin/clavulanate), highlights the role of aerobic and anaerobic BLPB in the inability of penicillin to eradicate GABHS tonsillitis.

Pleuropulmonary

Aspiration of oropharyngeal or gastric content and severe periodontal or gingival disease predispose for anaerobic pleuropulmonary infection. The infection can progress from pneumonitis to necrotizing pneumonia, pulmonary abscess, and empyema. The infection is usually polymicrobial and includes *Prevotella, Porphyromonas, Fusobacterium,* and *Peptostreptococcus* spp.; GABHS; and microaerophilic streptococci (Table 122.4). Anaerobes were recovered in most community-acquired and in one-third of

TABLE 122.4 **AEROBIC AND ANAEROBIC BACTERIA ISOLATED IN VARIOUS TYPES OF INFECTION**

Type of infection	Aerobic and facultative organisms	Anaerobic organism
Pleuropulmonary	*Staphylococcus aureus*[a] viridans streptococci *Pseudomonas aeruginosa*[a] Enterobacteriaceae[a]	Pigmented *Prevotella* spp. (*P. denticola, P. melaninogenica, P. intermedia, P. nigrescens, P. loescheii*) Nonpigmented *Prevotella* spp. (*P. oris, P. buccae, P. oralis*) *Fusobacterium nucleatum* *Peptostreptococcus* spp. (*P. micros, P. anaerobius, P. magnus*) *Bacteroides fragilis* group Non–spore-forming gram-positive rods (*Actinomyces, Eubacterium, Lactobacillus* spp.)
Intra-abdominal	*Escherichia coli* *Enterococcus* spp. *Pseudomonas aeruginosa*[a]	*Bacteroides fragilis* group *Bilophila wadsworthia* *Peptostreptococcus* spp. (especially *P. micros*) *Clostridium* spp.
Female genital tract	*Streptococcus* (groups A, B, others) *Escherichia coli* *Klebsiella pneumonia, Neisseria gonorrhoeae* (in sexually active patients) *Chlamydia* spp. (in sexually active patients) *Mycoplasma hominis* (in postpartum patients)	*Peptostreptococcus* spp. *Prevotella* spp. (especially *P. bivia, P. disiens*) *Bacteroides fragilis* group *Clostridium* spp. (especially *C. perfringens*) *Actinomyces* *Eubacterium* spp. (in intrauterine contraceptive device–associated infections)
Skin and soft tissue	*Staphylococcus aureus* *Streptococcus* (*Strep. milleri group*, groups A and B, viridans group) *Enterococcus* spp. Enterobacteriaceae, *Pseudomonas aeruginosa*[a]	*Peptostreptococcus* spp. (*P. magnus, P. micros, P. asaccharolyticus*) Pigmented *Prevotella* spp., *Actinomyces* spp. Fusobacterium nucleatum *Bacteroides fragilis* group[‡] *Clostridium* spp.

[a] Organisms that have the potential of producing β-lactamase.

nosocomial-acquired aspiration pneumonia and pneumonia associated with tracheostomy with and without mechanical ventilation.

Adequate cultures should avoid oral flora contamination by using bronchoalveolar lavage, bronchoscopy via bronchial brush protected in a double-lumen plugged catheter (using quantitative cultures in the last two methods), percutaneous transtracheal aspiration, lung biopsy, or thoracentesis (of empyema fluid). Management includes drainage of empyema and antimicrobials effective against anticipated anaerobic and aerobic bacteria.

Intra-abdominal

Most visceral abscesses (e.g., hepatic, splenic); chronic cholecystitis; perforated and gangrenous appendicitis; perforations resulting from obstruction, inflammatory bowel disease, trauma, diverticulitis, or infarction; and postoperative abdominal surgery wound infections and abscesses are polymicrobial due to gastrointestinal aerobic and anaerobic bacteria.

The initial infection following perforation is peritonitis, a synergistic polymicrobial infection. The predominant aerobic and facultatives are *E. coli* and *Streptococcus* spp. (including *Enterococcus* spp.), and the anaerobes are the *B. fragilis* group, and *Peptostreptococcus, Clostridium, Fusobacterium,* and *Eubacterium* spp. (see Table 122.4).

Intra-abdominal infections are biphasic: an initial peritonitis associated with *E. coli* sepsis, followed by abscess formation due to anaerobes (mainly *B. fragilis*). Biliary tract infection is usually caused by *E. coli, Klebsiella*, and *Enterococcus* spp. Anaerobes (mainly *B. fragilis* group and rarely *C. perfringens*) can be isolated in infections associated with carcinoma, recurrence, obstruction, and bile tract surgery or manipulation.

Appropriate management of intra-abdominal infections requires administrating antimicrobials effective against both aerobic and anaerobic bacteria, as well as surgical correction and drainage of pus. Single and easily accessible abscesses can be drained percutaneously. The outcome of the infection depends on a variety of factors that include the general condition of the patient (as measured by the Apache score), site of perforation, bacteriology, and antimicrobials given.

Antimicrobials should cover Enterobacteriaceae and anaerobes (mainly *B. fragilis* group). For mild to moderate community-acquired

infections in adults, the agents recommended are ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin. Agents no longer recommended are cefotetan and clindamycin (because of *B. fragilis* group resistance), ampicillin-sulbactam (*E. coli* resistance), and aminoglycosides (toxicity). For high-risk community-acquired infections in adults, recommended agents are meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin, or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole. Quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones.

Female genital tract

These include soft tissue and perineal infections, bacterial vaginosis, vulvar and Bartholin gland abscesses, endometritis, pyometra, salpingitis, tubo-ovarian abscesses, adnexal abscess, pelvic inflammatory disease (including pelvic cellulitis and abscess), amnionitis, septic pelvic thrombophlebitis, intrauterine contraceptive device-associated infection, septic abortion, and postsurgical obstetric and gynecologic infections. Avoiding specimen contamination by normal genital flora can be achieved by use of culdocentesis, laparoscopy, or quantitative endometrial cultures of transcervical samples.

The predominant anaerobes in these polymicrobial infections include *P. bivia, P. disiens*, and *Peptostreptococcus, Porphyromonas,* and *Clostridium* spp. *Actinomyces* spp. and *Eubacterium nodatum* are isolated in infections associated with intrauterine devices. *Mobiluncus* spp. may be involved with bacterial vaginosis. The isolated aerobes include Enterobacteriaceae, *Streptococcus* spp., *Neisseria gonorrhoeae*, *Chlamydia* spp., and *Mycoplasma genitalium* (see Table 122.4).

Gas in the tissues, abscess formation, and foul-smelling discharge is often associated with the presence of anaerobes. Management includes administration of antimicrobials effective against potential aerobic, anaerobic, and sexually transmissible pathogens. Outpatient regimens include cefoxitin, ceftriaxone, or other parenteral third-generation cephalosporins plus doxycycline, with or without metronidazole. In-patient regimens include cefoxitin, cefotetan, or ampicillin-sulbactam plus doxycycline, and clindamycin or metronidazole plus doxycycline and gentamicin.

Skin and soft tissue infections

These include superficial infections, such as infected cutaneous ulcers, cellulitis, pyoderma, paronychia, hidradenitis suppurativa, and various secondary infected sites. Secondary sites include secondary infected diaper rash, gastrostomy or tracheostomy site, subcutaneous sebaceous or inclusion cysts, eczema, psoriasis, poison ivy, atopic dermatitis, eczema herpeticum, scabies, kerion, and postsurgical wound.

Subcutaneous tissue infections include cutaneous and subcutaneous abscesses, breast abscess, decubitus ulcers, diabetic (vascular or trophic) ulcers, bite wounds, anaerobic cellulitis, gas gangrene, bacterial synergistic gangrene, infected pilonidal cyst or sinus, Meleney's ulcer, and burns. Deeper soft tissue infections include necrotizing fasciitis, necrotizing synergistic cellulitis, gas gangrene, and crepitus cellulitis. These infections can involve the fascia and muscle, and cause myositis and myonecrosis. The isolated bacteria vary according to the type and circumstances leading to the infection and usually involve members of the normal flora of the region.

Aspirates from wounds and subcutaneous tissue infections and abscesses of the rectal area (i.e., decubitus ulcer, perirectal abscess) or those that originate from the gut flora (i.e., diabetic foot infection) often yield colonic flora. (i.e., *B. fragilis* group, *Clostridium* spp., Enterobacteriaceae, *Enterococcus* spp.). Infections in and around the oropharynx or that originate from that site (i.e., paronychia, bites, breast abscess) harbor oral flora. (i.e., *Prevotella*, *Porphyromonas, Fusobacterium*, and *Peptostreptococcus* spp.). Skin flora (i.e., *S. aureus*, *Streptococcus* spp.) and nosocomially acquired organisms can be found at all body sites (see Table 122.4). In addition to oral flora, human bite infections often contain *Eikenella* spp., and animal bites harbor *Pasteurella multocida*.

These infections are frequently polymicrobial and, in some (i.e., decubitus ulcers, diabetic foot ulcer), complicated by osteomyelitis or bacteremia. Deep tissue infections such as necrotizing cellulitis, fasciitis, and myositis often involve *Clostridium* spp., *S. pyogenes*, or polymicrobic aerobic and anaerobic bacteria. These often have gas in the tissues; putrid pus with a gray, thin quality; and are associated with a high rate of bacteremia and mortality.

Management includes surgical debridement and drainage; improving tissue oxygenation and administration of hyperbaric oxygen (HBO), especially in clostridial infection, may be helpful.

Osteomyelitis and septic arthritis

Anaerobes are notable in osteomyelitis of cranial and facial bones, long bones following trauma and fracture, osteomyelitis related to peripheral vascular disease, and decubitus ulcers. Cranial and facial bone osteomyelitis is usually caused by oral flora that spread from a contiguous soft tissue source or from sinus, ear, or dental infection. Intestinal anaerobes predominate in pelvic osteomyelitis that spreads from decubitus ulcers. Osteomyelitis of long bones is usually caused by hematogenic spread, trauma, or the presence of a prosthetic device.

Peptostreptococcus and *Bacteroides* spp. predominate at all sites; *Prevotella* and *Porphyromonas* spp. are prevalent in skull and bite infections, *B. fragilis* group is associated with vascular disease and neuropathy. Fusobacteria are often isolated from bites and cranial and facial infections. Clostridia are found in long bones, especially in association with wound contamination after trauma or exposure to gut flora.

Septic arthritis is rare and is frequently associated with hematogenous and contiguous spread, trauma, and prosthetic joints. Most infections are monomicrobial and the predominant isolates are peptostreptococci and *P. acnes* (often in prosthetic joint infection), *B. fragilis* and fusobacteria (often following hematogenic origin), and clostridia (associated with trauma).

Bacteremia

The incidence of anaerobes in bacteremia is 5% to 15%. Recent resurgence in anaerobic bacteremia is due to the greater incidence of anaerobic bacteremia in immunosuppressed and those with complex underlying disease. The common isolates are *B. fragilis* group (>75%), *Clostridium* (10–20%), *Peptostreptococcus* (10–15%), *Fusobacterium* spp. (10–15%), and *P. acnes* (2–5%).

B. fragilis group and clostridia are mostly associated with a gastrointestinal source; pigmented *Prevotella, Porphyromonas*, and *Fusobacteria* with oropharynx and pulmonary sources; fusobacteria with the female genital tract; *P. acnes* with foreign bodies; and peptostreptococci with all sources, but especially with oropharyngeal, pulmonary, and female genital tract sources.

Predisposing factors include malignancy; hematologic disorders; organ transplant; recent gastrointestinal, obstetric, or gynecologic surgery; intestinal obstruction; decubitus ulcers; dental extraction; the newborn; sickle cell disease; diabetes mellitus; splenectomy; and the use of cytotoxic agents or corticosteroids.

Typical features include metastatic lesions, hyperbilirubinemia, and suppurative thrombophlebitis. Mortality is 15% to 30% but improves with early and appropriate antimicrobials and resolution of the primary infection.

Management

Recovery depends on prompt and proper management. Treatment include neutralizing bacterial toxins produced and preventing local bacterial proliferation by changing the environment and hampering their spread.

Neutralization of toxins by specific antitoxins can be employed in clostridial infections (tetanus and botulism). Environmental control is achieved by debriding necrotic tissue, draining pus, improving circulation, alleviating obstructions, and increasing tissue oxygenation, sometimes by HBO. The primary role of antimicrobials is to limit local and systemic spread of the infection.

Hyperbaric oxygen

The use of HBO in gram-positive spore-forming anaerobic rods infection is controversial. Several uncontrolled reports demonstrated efficacy in individual cases,[3,5,74] however, since no controlled studies are available, HBO efficacy is unproved. Using HBO along with other therapeutic modalities is not contraindicated except when it delays other essential procedures.

Surgical therapy

Surgical therapy is often the most important and sometimes the only required treatment, whereas in others it is an important adjunct to antimicrobials. It is essential to drain abscesses, debride necrotic tissues, decompress closed space infections, and relieve obstructions. Without drainage the infection may persist and serious complications can arise.

Antimicrobial treatment

Appropriate management of mixed aerobic/anaerobic infection requires the administration of antimicrobials active against both components. A number of factors should be considered when choosing appropriate antimicrobials. They should be effective against all targeted organisms, induce minimal or no resistance, achieve adequate levels in the infected site, and induce minimal toxicity.

Antimicrobials may fail to clear the infection because of development of resistance, not achieving sufficient tissue levels, incompatible drug interaction, and development of an abscess. Antimicrobials are ineffective in treating abscesses. The abscess capsule reduces their penetration, and the low pH and the presence of binding proteins or inactivating enzymes (i.e., β-lactamase) can impair their activity. Low pH and the anaerobic conditions are detrimental for aminoglycosides and quinolones.

When choosing antimicrobials (see Table 122.5) for the therapy of polymicrobial infection, their aerobic and anaerobic spectrum and their availability in oral or parenteral form should be considered (Table 122.6). Some agents possess a limited range of efficacy. Metronidazole is effective only against anaerobes and therefore cannot be administered alone for mixed infections. Others (i.e., carbapenems) have broader spectra of activity.

Antimicrobials selection is easier when reliable culture results are available. However, this may be difficult to achieve, and most are treated empirically. Fortunately, the types of organism involved in many infections and their antimicrobial susceptibility patterns are predictable. However, antimicrobial resistance patterns may vary and may emerge during therapy.

B. fragilis group's susceptibility varies geographically and between institutions, and some antimicrobials used in the past are no longer adequate for empiric therapy. Many AGNB developed resistance to clindamycin, cefoxitin, and cefotetan, but most are uniformly susceptible to metronidazole, carbapenems, and chloramphenicol, and the combinations of a β-lactam/β-lactamase inhibitor. β-lactam/β-lactamase inhibitor combinations maintained good activity against the vast majority of anaerobes; 89% of *B. fragilis* strains are susceptible to ampicillin-sulbactam, 98% are susceptible to piperacillin-tazobactam.

Reports of a multidrug-resistant *B. fragilis* group underscores the importance of antibiotic stewardship. Clinicians can no longer rely on cumulative susceptibility data alone to select antimicrobials and should consider performing susceptibility testing when treating serious infections.

Additional factors influencing antimicrobial choice include drug pharmacology, toxicity, and effect on the flora. Although identification of the pathogen(s) and antimicrobial susceptibility may be required for selection of optimal therapy, the clinical setting and Gram stain of the specimen may suggest the types of organisms present.

Antimicrobials

Aminoglycosides, monobactams, and older quinolones possess poor activity against anaerobes. The agents adequate for treatment of anaerobic infections are discussed here.

TABLE 122.5 **ACTIVITY OF ANTIMICROBIAL AGENTS AGAINST ANAEROBES**

Agent	Comments
Nearly always active	
Metronidazole	Inactive versus microaerophilic streptococci (e.g., *Streptococcus milleri*), *Propionibacterium* and *Actinomyces* spp.; bactericidal versus most gram-negative anaerobic strains
Carbapenems	Resistant to most *Bacteroides* β-lactamases, although a novel β-lactamase that cleaves carbapenems was found in rare *B. fragilis* strains
β-Lactam plus β-lactamase inhibitors	The addition of a β-lactamase inhibitor to a β-lactam dramatically increases activity against anaerobes that produce a β-lactamase
Chloramphenicol	Good activity versus virtually all clinically significant anaerobes
Usually active	
Clindamycin	B. *fragilis* group: 15–40% of strains resistant; some clostridia other than *C. perfringens* are resistant
Cephamycins	B. *fragilis group*: 5–15% of strains resistant with considerable institutional variation at least partly reflecting use patterns; poor activity versus clostridia
Antipseudomonal	Relatively resistant to β-lactamases of *Bacteroides* spp; penicillins large doses usually employed
Variable activity	
Penicillin	Inactive versus some or most penicillinase-producing anaerobes, including most of the *B. fragilis* group and many strains of *Prevotella melaninogenica, P. intermedia, P. bivia, P. disiens,* and some clostridia
Cephalosporins	Less activity in vitro than penicillin G versus most anaerobes and limited other than cephamycins published clinical experience to document efficacy
Tetracycline	Inactive versus many anaerobes and most strains of *B. fragilis*; doxycycline and minocycline are somewhat more active than tetracycline
Vancomycin	Active against gram-positive anaerobes; inactive versus gram-negative anaerobes
Macrolides	Inactive versus many *Fusobacterium* spp. and some *B. fragilis* spp.; ketolides also show reduced activity versus fusobacteria
Fluoroquinolones	Third-generation (gatifloxacin, moxifloxacin, and gemifloxacin) show good in vitro activity; limited published data
Tigecycline	Active against nearly all anaerobes including strains of *B. fragilis* that are resistant to β-lactams, clindamycin, and quinolones. Minimum inhibitory concentrations are somewhat higher for clostridia
Poor activity	
Aminoglycosides	
Trimethoprim–sulfamethoxazole	
Monobactams (aztreonam)	

[†] While in vitro activity is excellent, clinical failures with chloramphenicol have been documented, rendering this drug less preferable to other active agents for the treatment of anaerobic infections.

Penicillins

Penicillin G is effective against *Peptostreptococcus* spp., most *Clostridium* spp., and nonsporulating anaerobic bacilli, and most non–β-lactamase-producing AGNB (i.e., *Bacteroides, Fusobacterium, Prevotella,* and *Porphyromonas* spp.). AGNB that exhibit increased resistance include *Fusobacterium*, *Prevotella*, and *Porphyromonas* spp., *P. bivia*, *P. disiens*, *Bilophila wadsworthia*, and *Bacteroides splanchnicus*. Resistance to penicillin by *C. ramosum, C. clostridioforme*, and *C. butyricum* through production of β-lactamase has also been observed.

Ampicillin and amoxicillin are equally effective to penicillin G, but the semisynthetic penicillins are less effective. Methicillin, nafcillin, and the isoxazolyl penicillins (oxacillin, cloxacillin, dicloxacillin) possess unpredictable activity and are inferior to penicillin G.

Penicillin therapy might be rendered ineffective by the presence of BLPB. The combinations of β-lactamase inhibitors (e.g., clavulanic acid, sulbactam, tazobactam) with a β-lactam antibiotic (ampicillin, amoxicillin, ticarcillin, or piperacillin) can overcome this phenomenon. Other mechanisms of resistance include

TABLE 122.6 **ANTIMICROBIAL DRUGS RECOMMENDED FOR THE THERAPY[A] OF SITE-SPECIFIC ANAEROBIC INFECTIONS**

	Parenteral	Oral
Intracranial	1. Metronidazole[4] 2. Chloramphenicol	1. Metronidazole[4] 2. Chloramphenicol
Dental	1. Clindamycin 2. Metronidazole,[4] Ticarcillin + CA, Ampicillin + SU[6]	1. Clindamycin, Amoxicillin + CA 2. Metronidazole[4]
Upper respiratory tract	1. Clindamycin 2. Ticarcillin + CA, Ampicillin + SU[6] 3. Metronidazole[4]	1. Clindamycin, Amoxicillin + CA 2. Metronidazole[5]
Pulmonary	1. Clindamycin[5] 2. Ticarcillin + CA, Ampicillin + SU,[6] Imipenem or Meropenem	1. Clindamycin[8] 2. Metronidazole,[5] Amoxicillin + CA
Abdominal	1. Metronidazole[3] 2. Imipenem or Meropenem Ertapenem, Piperacillin-Tazobactam, Tigecycline, Cefoxitin[3]	1. Metronidazole[8] 2. Amoxicillin + CA
Pelvic	1. Cefoxitin,[6] Clindamycin[3] 2. Piperacillin–Tazobactam,[6] Ampicillin + SU,[6], Metronidazole[6]	1. Clindamycin[6] 2. Amoxicillin + CA,[6] metronidazole[6]
Skin and soft tissue	1. Clindamycin, Cefoxitin 2. Metronidazole + Vancomycin 3. Tigecycline	1. Clindamycin, Amoxicillin + CA 2. Metronidazole + Linezolid
Bone and joint	1. Clindamycin, Imipenem, or Meropenem 2. Metronidazole + Vancomycin, Piperacillin-Tazobactam	1. Clindamycin 2. Metronidazole + Linezolid
Bacteremia with BLPB	1. Imipenem or Meropenem, Metronidazole 2. Cefoxitin, Ticarcillin + CA	1. Clindamycin, Metronidazole 2. Chloramphenicol, Amoxicillin + CA
Bacteremia with non-BLPB	1. Penicillin 2. Clindamycin, Metronidazole, Cefoxitin	1. Penicillin 2. Metronidazole, Chloramphenicol, Clindamycin

[a]Therapies are given as drug(s) of choice (alternative drugs). BLPB, β-lactamase-producing bacteria; CA, clavulanic acid; NA, not applicable; SU, sulbactam.
1, drug(s) of choice; 2, alternative drugs; 3, plus aminoglycoside; 4, plus a penicillin; 5, plus a macrolide (i.e., erythromycin); 6, plus doxycycline; 7, in location proximal to the rectal and oral areas use cefoxitin; 8, plus a quinolone (only in adults).

alteration in the porin canal and changes in the penicillin-binding protein.

In high concentrations, ticarcillin, piperacillin, and mezlocillin have good activity against Enterobacteriaceae and most anaerobes; however, about a third of *B. fragilis* group are resistant.

Cephalosporins

First-generation cephalosporins have similar activity against anaerobes similar to penicillin G. *B fragilis* group, *Prevotella*, and *Porphyromonas* are resistant to first-generation cephalosporins through cephalosporinase production. Cefoxitin is the most effective cephalosporin against the *B fragilis* group, although 5% to 15% may be resistant. It is not effective against clostridia, except *C. perfringens*. Cefotetan and cefmetazole (a second-generation cephalosporins) possess a longer half-life than cefoxitin. They are as effective against *B. fragilis*, but less efficacious against other members of the *B. fragilis* group. Consequently cefotetan is no longer recommended for treatment of intra-abdominal infections.

Carbapenems (imipenem, meropenem, doripenem, ertapenem)

Carbapenems possess excellent activity against aerobic and anaerobic bacteria and are often administered in serious infections. Resistance of the *B. fragilis* group is rare (<1%). Carbapenem resistance among anaerobes (1.1–2.5%) was found in a multicenter US survey. A higher rate (7–12%) was noted in a small number of isolates from Taiwan. Ertapenem has similar efficacy but is not active against *Pseudomonas* spp. and *Acinetobacter* spp.

Chloramphenicol

Chloramphenicol has excellent in vitro activity against most anaerobes, and resistance is uncommon. Its lipid solubility enables its penetration across lipid barriers, and it can gain high CNS concentrations. Its toxicity, the rare but fatal aplastic anemia, and the dose-dependent leukopenia, limit its use.

Clindamycin

B. fragilis resistance to clindamycin is increasing worldwide and reached about 40% in some locations. It is no longer recommended as empiric therapy for intra-abdominal infections. Up to 10% resistance was noted for *Prevotella*, *Fusobacterium*, *Porphyromonas*, and *Peptostreptococcus* spp., with higher rates for some *Clostridium* spp. (mostly *C. difficile*). Antibiotic-associated colitis due to *C. difficile,* although associated with most antimicrobials, was first described after clindamycin therapy.

Metronidazole and tinidazole

These nitroimidazoles possess excellent activity against anaerobes; however, they are ineffective against aerobes and facultatives. Microaerophilic streptococci, *P. acnes*, and *Actinomyces* spp. are often resistant, and adding antimicrobials effective against these organisms is often needed. Resistance among *B. fragilis* group is rare. Concern was raised about the carcinogenicity and mutagenicity of these drugs; however, these effects were found only in a single mice species and were never substantiated in other mammals or humans.

Macrolides (erythromycin, azithromycin, clarithromycin, fidaxomicin)

Macrolides have moderate to good activity against anaerobes other than *B. fragilis* group. They are active against pigmented *Prevotella* and *Porphyromonas* spp. and microaerophilic streptococci, gram-positive non–spore-forming anaerobic bacilli, and certain clostridia. They are less effective against *Fusobacterium* and *Peptostreptococcus* spp. They are active against *C. perfringens* and have poor or inconsistent activity against AGNB. Clarithromycin is the most active among macrolides against gram-positive anaerobes, including *Actinomyces, Propionibacterium,* and *Lactobacillus* spp. and *Bifidobacterium dentium*. Emergence of erythromycin-resistant isolates during therapy has been documented.

Fidaxomicin is a minimally absorbed narrow-spectrum macrolide effective against *C. difficile.*

Glycopeptides (vancomycin, teicoplanin)

Glycopeptides are effective against gram-positive anaerobes (including *C. difficile*) and inactive against AGNB.

Tetracyclines

Tetracycline is rarely used because of development of resistance by most anaerobes. Resistance in *P. acnes* has been related to previous use. The newer tetracycline analogues doxycycline and minocycline have better efficacy. Because of significant resistance, they can be used only when the isolates are susceptible or in less severe infections where a therapeutic trial is possible.

Tigecycline

This glycylcycline is active against aerobes and anaerobes and certain drug-resistant pathogens. It is active against *Streptococcus anginosus* group (includes *S. anginosus, S. intermedius*, and *S. constellatus*), *B. fragilis* group, *C. perfringens, C. difficile,* and *Parvimonas micra*. Resistance of members of the *B. fragilis* group is 3.3% to 7.2%.

Fluoroquinolones

Ciprofloxacin, ofloxacin, levofloxacin, fleroxacin, pefloxacin, enoxacin, and lomefloxacin are not very active against anaerobes; sparfloxacin, grepafloxacin. trovafloxacin, gatifloxacin, and moxifloxacin have considerable anti-anaerobic activity; and clinafloxacin and sitafloxacin have the greatest in vitro activity against anaerobes. Moxifloxacin monotherapy has been used in intra-abdominal infections in adults. However, concern over increasing resistance of *E. coli* and *B. fragilis* group has reduced its utilization. Quinolones use is restricted in growing children and during pregnancy because of their possible adverse effects on cartilage.

Other agents

Bacitracin is active against pigmented *Prevotella* and *Porphyromonas* spp. and is inactive against *B. fragilis* and Fusobacteria. Quinupristin-dalfopristin is active against *C. perfringens, Lactobacillus,* and *Peptostreptococcus* spp. Linezolid is active against *Fusobacterium, Porphyromonas, Prevotella,* and *Peptostreptococcus* spp.

Choice of antimicrobial agents

Parenteral antimicrobials (Tables 122.6 and 122.7) include metronidazole, a penicillin (i.e., ticarcillin, ampicillin, piperacillin) plus a β-lactamase inhibitor (i.e., clavulanic acid, sulbactam, tazobactam). Agents effective against gram-negative enteric bacilli (e.g., aminoglycoside, a fluoroquinolone) or an antipseudomonal cephalosporin (e.g., cefepime) are often added to metronidazole for treatment of intra-abdominal infection. Carbapenems (e.g., imipenem, meropenem, doripenem, ertapenem) are utilized as monotherapy.

Penicillin can be added to metronidazole in the therapy of intracranial, pulmonary, and dental infections to cover microaerophilic streptococci, *Actinomyces*, and *Arachnia* spp.; A macrolide can be added to penicillin to treat *S. aureus* and aerobic streptococci. Penicillin is added to clindamycin for supplemental coverage against *Peptostreptococcus* spp. and other gram-positive anaerobes.

Doxycycline is added to most regimens in pelvic infections to cover *Chlamydia* and *Mycoplasma*. Penicillin is still the drug of choice for bacteremia caused by susceptible non-BLPBs. However, other agents should be used for the therapy of bacteremia caused by BLPBs.

TABLE 122.7 **ANTIMICROBIAL DRUGS OF CHOICE FOR ANAEROBIC BACTERIA**

	Drug of choice	Alternative drugs
Peptostreptococcus spp.	Penicillin	Clindamycin, chloramphenicol, cephalosporins
Clostridium spp.	Penicillin	Metronidazole, chloramphenicol, cefoxitin, clindamycin
Clostridium difficile	Vancomycin, Fidaxomicin	Metronidazole, bacitracin
Fusobacterium spp.	Penicillin	Metronidazole, clindamycin, chloramphenicol
Bacteroides (BL-)	Penicillin	Metronidazole, clindamycin, chloramphenicol
Bacteroides (BL+)	Metronidazole, a carbapenem, a penicillin and β-lactamase inhibitor, clindamycin	Cefoxitin, chloramphenicol, piperacillin, tigecycline

Gram-negative bacilli include Bacteroides fragilis group and Prevotella, Porphyromonas, and Fusobacterium spp. BL, β-lactamase.

Because the duration of therapy is often longer than for infections caused by aerobic and facultative bacteria, oral therapy is often substituted for parenteral therapy. The available antimicrobials for oral therapy include amoxicillin plus clavulanic acid, clindamycin, chloramphenicol, and metronidazole. The duration of therapy of uncomplicated infection is generally 2 to 4 weeks. Some infections (i.e., osteomyelitis) require longer treatment. In some cases, such as lung abscesses, treatment may be required for as long as 6 to 8 weeks, but can often be shortened with proper surgical drainage.

Clinical judgment, personal experience, safety, and patient compliance should direct the physician in the choice of the appropriate antimicrobial agents.

Conclusion

Anaerobes are a frequent cause of endogenous infections in all body locations: the CNS, oral cavity, head and neck, chest, abdomen, pelvis, skin, and soft tissues. Management of these infection includes administration of effective antimicrobials, surgical drainage, and correction of the underlying pathology. Because these infections are often polymicrobial, the antimicrobial chosen should provide coverage of both the aerobic and anaerobic component of the infection. The most effective antimicrobials against anaerobes are metronidazole, the carbapenems (imipenem, meropenem, doripenem, ertapenem), chloramphenicol, the combinations of a penicillin and a β-lactamase inhibitor (ampicillin or ticarcillin plus clavulanate, amoxicillin plus sulbactam, and piperacillin plus tazobactam), tigecycline, cefoxitin, and clindamycin.

Suggested reading

Brook I. *Anaerobic infections diagnosis and management. A textbook*. New York: Informa Healthcare; 2007.

Brook I. The role of anaerobic bacteria in bacteremia. *Anaerobe*. 2010;16:183–189.

Brook I, Wexler HM, Goldstein EJ. Antianaerobic antimicrobials: spectrum and susceptibility testing. *Clin Microbiol Rev*. 2013;26:526–546.

Finegold SM. Anaerobic infections in humans: An overview. *Anaerobe*. 1995;1:3–9.

Hentges DJ. The anaerobic microflora of the human body. *Clin Infect Dis*. 1993;164:S175–180.

Jousimies H, Summanen P. Recent taxonomic changes and terminology update of clinically significant anaerobic gram-negative bacteria (excluding spirochetes). *Clin Infect Dis*. 2002;35(Suppl.1):S17–21.

Jousimies-Somer HR, Summanen P, Baron EJ, Citron DM, Wexler HM, Finegold SM, Wadsworth KTL. *Anaerobic bacteriology manual*, 6th ed. Belmont, CA: Star Publishing; 2002.

Nord CE. The role of anaerobic bacteria in recurrent episodes of sinusitis and tonsillitis. *Clin Infect Dis*. 1995;20:1512–1524.

Pieracci FM, Barie PS, Bartlett JG. Intra-abdominal infections. *Curr Opin Crit Care*. 2007;13:440–449.

Snydman DR, Jacobus NV, McDermott LA, et al. Update on resistance of Bacteroides fragilis group and related species with special attention to carbapenems 2006–2009. *Anaerobe*. 2011;17:147–151.

Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:133–164.

Stein GE, Goldstein EJ. Fluoroquinolones and anaerobes. *Clin Infect Dis* 2006;42:1598–16607.

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Anthrax

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Introduction

Anthrax is a disease caused by the gram-positive, aerobic bacterium *Bacillus anthracis* and was recognized in antiquity. The disease figures prominently in the history of modern medicine because it was the first bacterial illness for which successful vaccines were prepared, almost simultaneously by William Smith Greenfield in London and Louis Pasteur in Paris. Anthrax is a zoonosis of herbivores encountered worldwide (except for Antarctica), and human cases continue to be seen in southern Europe, Eurasia, south Asia, and sub-Saharan Africa. Grazing wild ruminants and cattle are very susceptible, and human disease in animal husbandmen and herders is closely tied to exposure to infected beasts. It is reported that in some areas of rural Kenya 26% of animal husbandmen are serologically positive for *B. anthracis*. Propagating the bacteria in the spore form is used in bioterrorism, a novel and more recent form of human exposure to anthrax, utilizing delivery systems such as the postal service.

To understand anthrax one must keep in mind the natural cycle of disease in animals: spores survive prolonged periods in alkaline soils, rainwater concentrates spores in low-lying depressions, and susceptible herbivores gather in these locales during dry periods and inhale aerosolized spores or swallow spores loosely attached to forage. These geographic and climatic factors are usually present prior to animal outbreaks and may culminate in humans being infected accidentally. Spores arise from bacilli exposed to ambient air when blood from dying animals reaches the soil or carcasses are torn apart by scavengers. When the bacilli are exposed to air, spores form in the central and subterminal part of the bacillus. Spores may survive for prolonged periods (~90 years) in soil rich with organic material, a pH greater than 6.1 (alkaline soils), and with high concentrations of calcium ions (Ca^{++}). This characterizes a wide geographic swathe in the middle United States from Texas to North Dakota. It is also true for soils in the steppes of Asia and in sub-Saharan Africa, where anthrax remains common in wildlife. Although anthrax is considered an obligate pathogen, it is likely that in some circumstances a vegetative bacillus-spore cycle occurs independent of infection in the soil alone.

Currently, human anthrax infections in the resource-rich countries occur as a result of animal infection occurring thousands of miles away from the victim. Due to the worldwide trade in hides and wool, occasional occupational/recreational anthrax infections occur. There have even been recent reports of anthrax among intravenous drug users in Great Britain, their heroin contaminated at the source in Afghanistan. The widespread use of animal vaccines has reduced the number of livestock infections and, secondarily, human infections, but epizootics continue to occur in wildlife, particularly in South Africa and even in the United States and Canada.

Epidemiology of anthrax

Human anthrax infections related to the pursuit of agriculture most commonly take the form of cutaneous anthrax. This has been the pattern in Turkey and Zimbabwe, where the disease is endemic. Occasionally

gastrointestinal anthrax occurs and is almost always secondary to consumption of an animal dead from anthrax and usually in rural areas. Inhalational anthrax and meningitis are rare in the agricultural setting. Other persons at risk, apart from the animal husbandmen/herders, are veterinarians, slaughterhouse workers, and individuals handling bone meal.

Although anthrax occurs among wild animals in many resource-rich countries, human disease is almost always due to importation of contaminated animal products from resource-poor, rural areas of the world. Within the latter countries there are more than 1 billion livestock and 60 million poor rural livestock owners at risk for disease. The United States, Canada, and Europe are considered countries with only sporadic disease, although wildlife and cattle in Montana and northwestern Canadian provinces are endemic for animal anthrax. Research is being conducted to develop oral vaccines that to provide protection for wildlife where epizootics continue to occur.

Industrial anthrax is related to the use of animal products such as hair, wool, bone meal, and hides that are contaminated with spores of *B. anthracis*. This form of disease may occur years after the animals are slaughtered. Individuals at risk include tannery and textile workers and anyone using imported wool or yarn, hair, and hides from endemic areas. Disease is usually cutaneous (Box 123.1). Differential diagnoses are listed in Table 123.1.

TABLE 123.1 **DIFFERENTIAL DIAGNOSIS OF CUTANEOUS LESION OF ANTHRAX**

Zoonotic disease	Differentiating points
Tularemia (*Francisella tularensis*)	Prominent lymphadenopathy
Orf	Painless bullae
Cat scratch	Fleeting eschar
Tick-borne *Rickettsia: R. africae*, STARI, RMSF	Small eschar, often with body rash
Plague	Lymphadenopathy; Four Corners area of the United States

Abbreviations: STARI = Southern tick-associated rash illness; RMSF = Rocky Mountain spotted fever.

Pathogenesis of anthrax

Animal studies demonstrate that spores introduced through the skin rapidly germinate, and, within hours the subcutaneous lesions swell and numerous encapsulated gram-positive rods, often "box-car" in shape, are present. The capsule is composed of poly-D-glutamic acid and probably protects the bacterium from host recognition and attack by neutrophils (it is thought to be antiphagocytic). It is a bona fide virulence factor carried on a plasmid, pX02, and loss of the plasmid renders the bacterium less virulent (Table 123.2). The successful animal vaccine developed by Max Sterne uses a strain cured of pX02. Wildtype *B. anthracis* possesses a second plasmid, pX01, that controls toxin production of the vegetative state in the host. The toxin consists of three proteins, protective antigen (PA), edema factor (EF), and lethal factor (LF), typical binary toxins with an enzymatic site and binding site. After proteolysis of a small fragment from PA, the protein binds to six other PA fragments forming a heptameric channel to which LF and EF competitively bind and are then endocytosed. EF leads to increased levels of cyclic AMP and swelling whereas LF leads to cell death (Figure 123.1).

Spores inhaled into the lung reach the alveoli, where they are phagocytosed by macrophages. Macrophages then transit through the lymphatic system. Germination of the spores may occur up to 60 days following inhalation, as shown in monkeys. In gastrointestinal anthrax, hemorrhage and edema are located in the intestinal wall. In some animals, the M cell in Peyer's patches may be the site of entry of the microorganism.

BOX 123.1

Clinical clues that one may be dealing with anthrax

Think anthrax:
Employment history: Herdsman, veterinarian, textile worker, hide/wool worker
Chest x-ray findings: Widened mediastinum; pleural effusion (hemorrhagic)
Cutaneous lesions: Necrotizing ulcer with bullae; eschar (bacteria present beneath lesion)
Hemorrhagic meningitis: Gram-positive bacteria present in CSF

Clinical manifestations of anthrax

The clinical presentation of anthrax is variable and depends on the route of exposure. Presentations include cutaneous, inhalational, and enteric (gastrointestinal and oropharyngeal) forms, which may result in disseminated disease involving the central nervous system (CNS) (meningitis) and secondary bacteremia leading to sepsis. The majority of infections are due to cutaneous disease, and these infections have the lowest mortality. Cutaneous lesions, referred to as *eschars,* develop as single or multiple lesions after exposure to *B.*

TABLE 123.2 **VIRULENCE FACTORS POSSESSED BY *BACILLUS ANTHRACIS***

Virulence factor	Contribution to disease
Plasmid X02	Encodes for poly-D-glutamic acid capsule which may mask bacterium from host defenses
Plasmid X01	Encodes for tripartite toxin complex: protective antigen, lethal factor and edema factor
Spore	Survival of infectious propagule for up to ~90 years in conducive soils; exosporium allows for delay of germination within alveolar macrophages

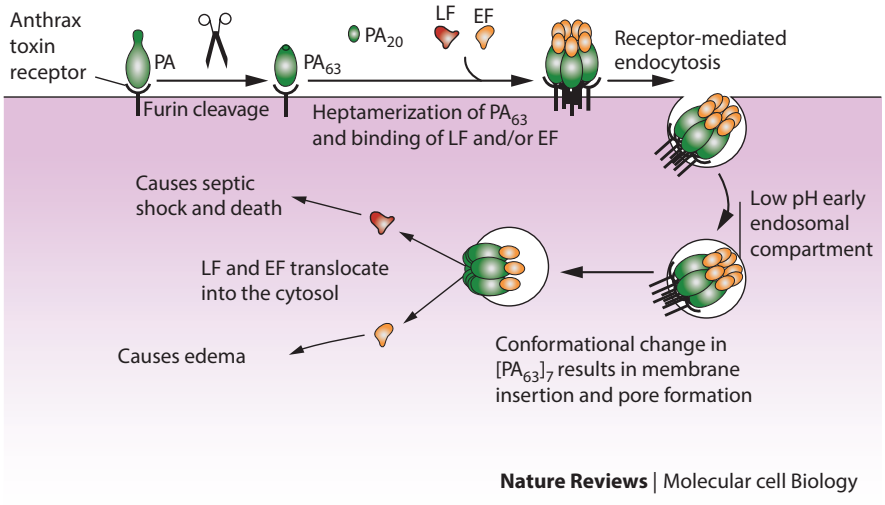

FIGURE 123.1

anthracis spores. Spores enter breaks in the skin, and, following an incubation period ranging from several hours to 3 weeks, the inoculum site develops into a papule followed by a ring of vesicles, accompanied by edema, regional lymphadenopathy, and necrosis. The lesion then forms the typical dark eschar, which is accompanied by profound edema usually from 5 to 7 days. Resolution occurs over a period of several weeks. Although the eschar is usually not painful most patients may experience constitutional symptoms or may present with sepsis, especially with lesions involving the face, neck, and upper chest. Infection involving the gastrointestinal tract occurs after ingestion of meat from animals dying of anthrax. The disease has an incubation period of 1 to 6 days and the presentation may initially include mild symptoms such as fever, nausea, vomiting, and mild diarrhea but then progresses to more severe symptoms of bloody diarrhea, acute abdominal pain, hematemesis, and ascites. Complications include obstruction, perforation, sepsis, and death. Pathologic evaluation demonstrates ulcerating, necrotizing lesions accompanied by regional lymphadenopathy. Inhalation anthrax is a rare but dangerous form of the disease with public health implications due to its association with bioterrorism. Infection involves lymph nodes rather than lung parenchyma, which makes the term "pulmonary" a misnomer since complications result from germinating spores transported to the lymphatic system by macrophages. The disease has a biphasic presentation with nonspecific initial symptoms of fever, headache, chills, malaise, and nonproductive cough followed by a more rapid progressive form when patients experience dyspnea, cyanosis, respiratory failure, sepsis, and death. The incubation period ranges from 4 to 11 days. The chest x-ray findings most consistent with inhalation anthrax include mediastinal widening, pleural effusions, and the presentation of hyperdense necrotic-appearing lymph nodes involving the mediastinum on CT. Infection of the CNS is a life-threatening complication of any of the major forms of anthrax and carries a poor prognosis. In contrast to common causes of bacterial meningitis, the cerebral spinal fluid contains large numbers of red blood cells, indicating a hemorrhagic component (Table 123.2).

Treatment of anthrax

Treatment for inhalational anthrax includes ciprofloxacin or doxycycline plus consideration of one or two other antimicrobials, such as rifampin, vancomycin, imipenem, chloramphenicol, penicillin or ampicillin, clindamycin, and clarithromycin. Doxycycline may be less optimal for cases with meningitis because of poor CNS penetration. For cutaneous anthrax, ciprofloxacin or doxycycline are recommended for initial therapy. Duration of combined intravenous and oral therapy should continue for 60 days for all anthrax cases because of the potential persistence of spores after an aerosol exposure. For additional details of antimicrobial regimens, see Chapter 120, "Bioterrorism." A new modality of therapy is the use of a monoclonal antibody (raxibacumab) that inhibits PA binding to anthrax toxin receptors.

However, reliance solely upon a monoclonal antibody against toxins in established anthrax bacteremia may not be efficacious. Animal studies show that antibodies to bacterial cell wall proteins may be needed in addition to anti-toxins to protect victims from the high-grade bacteremia that occurs in disseminated disease.

Bioterrorism and anthrax

The Working Group on Civilian Biodefense has identified *B. anthracis* as one of the most serious biologic weapon threats to cities or regions. Presentation of bioterrorism-related anthrax will typically result in inhalational and cutaneous cases. The sudden appearance of several cases of severe acute febrile illness with fulminant courses should prompt the clinician to consider anthrax—and therefore bioterrorism—as the etiology and delivery mechanism of the disease.

A cluster of cutaneous anthrax cases should also alert the clinician to the possibility of bioterrorism-associated anthrax. (See Chapter 120, "Bioterrorism.")

Prophylaxis of anthrax

Pre-exposure vaccination

An acellular vaccine against *B. anthracis* has been approved for human vaccination in the United States (anthrax vaccine absorbed or AVA, [BioThrax]). Pre-exposure vaccination is recommended by the Advisory Committee on Immunization Practices for adults, age 18–65 years, with specific occupational and laboratory exposures to *B. anthracis*. Laboratory personnel who work with high concentrations or pure cultures of *B. anthracis* spores, and/or with environmental samples associated with anthrax investigations, and/or in spore-contaminated areas or other settings with exposure to aerosolized *B. anthracis* are recommended to receive pre-exposure vaccination with AVA (BioThrax). Persons involved in environmental investigations or remediation efforts are also recommended to receive pre-exposure vaccination. Routine vaccination of those who handle animals or animal products in the United States is not recommended unless the person is handling potentially infected animals in research settings or in areas with a high incidence of enzootic anthrax or when standards and restrictions are insufficient to prevent exposure to *B. anthracis* spores. Pre-exposure AVA vaccination may be indicated for the military as recommended by the Department of Defense. Persons involved in emergency response activities are not routinely advised to receive pre-exposure vaccination but may be offered vaccine in specific circumstances. The recommended vaccination schedule includes five 0.5 mL doses administered intramuscularly at 0 weeks, 4 weeks, 6 months, 12 months, and 18 months; annual boosters are required every 3 years to maintain immunity.

Postexposure prophylaxis (PEP)

Those at risk for anthrax following a *B. anthracis* spore exposure are identified by public health officials depending on epidemiologic circumstances. Prophylaxis is indicated for those exposed to an airspace contaminated with aerosolized *B. anthracis*. Ciprofloxacin, doxycycline, and parenteral penicillin G procaine have been approved by the US Food and Drug Administration (FDA) for prophylaxis of inhalational *B. anthracis* infection. Although the optimal duration of prophylaxis is uncertain, antibiotics were recommended for 60 days for those exposed in the US anthrax attacks of 2001, based on animal studies of anthrax deaths and spore clearance after exposure, and the FDA has licensed a 60-day course for postexposure use. The Working Group on Civilian Biodefense recommends monotherapy with ciprofloxacin for adults, children, and pregnant women, recognizing that fluoroquinolones are not generally recommended for children or pregnant women because of risks of arthropathy in children. However, the working group determined that the risk of anthrax and its consequences outweighs the risks of fluoroquinolone use in these groups. Doxycycline is recommended as an alternative in all groups, with cautions and recommendations for its use in pregnant women and children similarly acknowledged. Amoxicillin is listed as an alternative 60-day prophylaxis option in pregnant women and children. The FDA has approved penicillin G, ciprofloxacin, levofloxacin, and doxycycline for antimicrobial posttexpoure prophylaxis of anthrax.

Postexposure vaccination of exposed persons is recommended in conjunction with a 42–60-day prophylactic antibiotic course (depending upon the demographics of those exposed) by the Advisory Committee on Immunization Practices. In contrast to pre-exposure vaccination, PEP vaccination is recommended as a three-dose subcutaneous series (at 0, 2, and 4 weeks) in conjunction with a 60-day course of appropriate antimicrobial agents. The vaccine is stored in the Strategic National Stockpile (SNS) to be used for postexposure prophylaxis in the event of a terrorist attack. In the event of a large-scale emergency response, in which the demand for vaccine exceeds the supply, dose-sparing regimens for AVA, and an alternative intramuscular administration route, have been shown to be protective and are available. PEP animal studies using monkeys support the use of vaccine *in conjunction* with antibiotics following exposure to aerosolized *B. anthracis* spores. Although 5 of 29 animals died after completing a 30-day course of antibiotics following *B. anthracis* spore exposure, none of 9 receiving doxycycline for 30 days plus vaccine at baseline and at day 14 following exposure died. However, 8 of 10 animals treated with vaccine only subsequent to aerosolized spore exposure died.

Laboratory diagnosis of anthrax

The most useful diagnostic laboratory test for anthrax is the blood culture. If drawn before antibiotics are started in those with inhalational anthrax, the standard blood culture may show growth of large gram-positive bacilli with preliminary identification of *Bacillus* species. During the US anthrax attacks, eight of eight case patients with inhalational anthrax who had blood cultures obtained prior to initiation of antibiotics had positive blood cultures for *B. anthracis*. *Bacillus* species are routinely identified in blood cultures within 24 hours following inoculation, but some laboratories do not further identify *Bacillus* species unless specifically requested because of the frequency of *Bacillus cereus* contaminants. If *B. anthracis* cannot be specifically excluded from cultures in a clinical laboratory, isolates can be transferred to a Laboratory Response Network (LRN) laboratory to identify or rule out *B. anthracis*. In specialized and LRN laboratories, other definitive diagnostic tests can be performed, such as immunohistochemical (IHC) staining or polymerase chain reaction (PCR) assays of biopsied tissue or body fluids. Cerebrospinal fluid (CSF) cultures may be useful for diagnosis.

For cutaneous anthrax, a Gram stain and culture of vesicular fluid should be obtained, and, if negative or if antibiotics were initiated prior to the sampling, a punch biopsy should be performed for IHC staining or PCR.

Nasal swabs are not used for diagnosis of inhalational anthrax since they may be negative in those with infection. However, they were useful as epidemiologic tools to identify the source and route of exposure and mechanism of release in the US anthrax attacks. A positive nasal swab indicates exposure to *B. anthracis* and is an indication for clinical or prophylactic treatment.

Sputum samples for Gram stain and culture are generally not helpful to diagnose inhalational anthrax due to the frequent lack of a pneumonic process. Antibody testing to the PA of *B. anthracis* has not been established as a diagnostic tool.

Non-*Anthrax bacillus* species and the diseases they cause

Bacillus cereus and other non–anthrax-related species are recognized contaminants but also clearly pathogenic. These bacteria, which are ubiquitous in the environment, are one of the most common microbes on the Earth's crust, present in wide diverse ecologic niches, and found in animal and plant food sources. Members of the genus are catalase-positive, spore-forming, aerobic or facultative anaerobic, gram-positive or gram-variable with close phenotypic and genetic similarities to one another, and they are easily grown on most culture media. Optimum temperature for growth is between 28°C/82°F and 35°C/95°F. The *B. cereus* group includes *B. cereus, B. anthracis, B. thuringiensis, B. mycoides, B. pseudomycoides*, and *B. weihenstephanesis*. The use of 16S rRNA for the comparison of the nucleotide sequences has highlighted the close relationship of *B. cereus, B. anthracis*, and *B. thuringiensis*. Other species, *B. subtilis*, *B. licheniformis*, *B. megaterium*, *B. pumilus*, and *B. sphaericus*, bear a more distant relationship and are clinically not as important in human infections. *B. cytotoxicus* belongs to the *B. cereus* group and was implicated in cases of severe food poisoning with a fatal diarrheal disease. It may have a lower cytotoxic potential than first reported. *B. cereus* has served as the model in several taxonomic studies and is the main focus of discussion in this section. *B. thuringiensis* is utilized as a biopesticide. *B. cereus* toxin is important in cases of foodborne illness. Additionally, intestinal and nonintestinal tissue destructive toxin production may occur secondary to hemolysins, phospholipases, emesis-inducing toxin, and pore-forming enterotoxins.

Recently anthrax-like infections affecting different wildlife species have been reported in several sub-Saharan African rainforests including the Taï National Park, Côte d'Ivoire, caused by *B. cereus* biovar *anthracis. B. cereus* biovar *anthracis* is a member of the *B. cereus* group and carries both *B. anthracis* virulence plasmids. *B. cereus* strain G9421, harboring two virulence plasmids, pBCXO1 and pBC210, has been linked to fatal anthrax-like pneumonias. The *B. cereus* isolate, BcFL2013, which is positive for the *B. anthracis* pXO1 toxin genes, has been associated with the development of lesions similar to the classic cutaneous anthrax eschar. (All three variants are discussed in the last reference of "Suggested reading"). *Bacillus cereus* harbouring *Ba813*, a chromosomal marker of *B. anthracis*, was reported to form a biofilm contributing to an outbreak of infections in patients with hematological malignancies.

Epidemiology of non-*Anthrax bacillus* species

Nosocomial infections include bacteremia and hospital-acquired pneumonias. These are usually due to microorganisms present in decaying organic matter, soil, fomites, water, and food sources. Foodborne outbreaks are due to the microorganism's presence in food sources and human intestinal flora. *B. cereus* species are often regarded as contaminants when recovered in blood cultures and have been implicated in cases of pseudo-outbreaks since the microorganism may survive usual disinfectants and inadequate sterilization techniques, and it has the capability to adhere to intravascular catheters. Populations at risk for disease include injection drug users, immunocompromised hosts, neonates, and long-term hospitalized critically ill patients with nosocomial infections.

Clinical manifestations of non-*Anthrax bacillus* infections

The clinical presentation of non-anthrax *Bacillus* infections is variable and includes wound and burn-related infections; endophthalmitis; bacteremia; CNS infections; intravascular infections including endocarditis; respiratory tract infections; complicated bone, skin and soft tissue infections; and toxin-mediated foodborne illnesses and chorioamnionitis with fetal demise. Most infections are due to *B. cereus*, but other species including *B. circulans, B. licheniformis, B. megaterium, B. pumilus, B. sphaericus*, and *B. subtilis* have been reported. While occupational exposure to *B. cereus* resulting in bacteremia and pneumonia has been reported, nosocomial infections such as ventilator-associated pneumonias, catheter-related bloodstream infections, and meningitis, through exposure to fomites, are increasingly being reported among immunocompromised hospitalized patients. Exotoxin-mediated tissue destructive ocular infections such as endophthalmitis resulting from exogenous (trauma) and endogenous (hematogenous) sources lead to rapid vision loss. These infections are typically more aggressive and rapid in nature in comparison to infections by other bacteria. CNS infections have been reported in immunocompromised patients who acquired the infections from hematogenous, intrathecal procedures, and possible gastrointestinal sources. Complicated skin and soft tissue infections due to penetrating trauma, surgery, injection drug use, or burns are associated with a high mortality, and, in some cases, have mimicked the eschars of *B. anthracis*. Cutaneous infections with necrotizing fasciitis and myonecrosis may resemble *Clostridium perfringens* gas gangrene infections. Intravascular infections including native valve and prosthetic valve endocarditis, and device-related infections, such as on pacemakers, have been described.

Gastrointestinal disease caused by *B. cereus* is due to the ability of the microorganism to survive heat and changes in environment and infiltrate human food sources. Its ability to cross-contaminate various food sources by spore formation indicates its ubiquitous presence in the food chain and opportunity for foodborne diseases. The most commonly reported clinical manifestations of foodborne illness with *B. cereus* are emetic and diarrheal syndromes mediated by various toxins. The presentations range from asymptomatic to mild to fatal cases. In emetic disease the incubation period ranges from 0.5 to 6 hours after ingestion of starchy foods such as rice contaminated by spores with an infective dose of 10^5 to 10^8 colony-forming units (CFU). Preformed toxins including cyclic peptide and cereulide mediate the disease process. The patients experience nausea, vomiting, and malaise with symptoms lasting from 6 to 24

hours. In diarrheal disease the incubation period ranges from 8 to 16 hours after ingestion of foods with high protein contents such as meat and milk products, mediated by hemolysin BL, nonhemolytic enterotoxin, and cytotoxin K enterotoxins in the small intestine. Patients often present with nausea, abdominal pain, and non-bloody diarrhea that lasts from 12 to 24 hours.

Treatment of non-*Anthrax bacillus* infections

Timely diagnosis and treatment of *B. cereus* infections is critical. Historically, culture methods are labor-intensive, costly and time-consuming. Recent advancements in the use of biosensors such as phage-based, cell-based, immunosensors and DNA biosensors allowTi for the rapid diagnosis of infections caused by *B. cereus* strains.

Through its production of β-lactamases, *B. cereus* is resistant to most β-lactam antibiotics including penicillins and cephalosporins. Reports of resistance to erythromycin, tetracycline, and carbapenems have created a problem for the clinician in choosing an initial treatment regimen. Some experts consider vancomycin the drug of choice, and there are multiple reports indicating that ciprofloxacin has been found to be effective in the treatment of skin and soft tissue infections. Antibiotic susceptibility methods should be performed to guide correct antibiotic selection even though studies have indicated uniform sensitivity to levofloxacin, moxifloxacin, rifampin, daptomycin, and linezolid. As is the case in most intravascular infections, removal of the source is key to achieving control of infection. Unfortunately, the reputation of *Bacillus* spp. as contaminants often leads to underrecognition, disregard of crucial information, and thus delay in treatment of severe, life-threatening infections. Treatment of gastrointestinal disease is supportive.

Suggested reading

Arensen LPS, Fagerlund A, Granum PE. From soil to gut: Bacillus cereus and its food poisoning toxins. *FEMS Microbiol Rev*. 2008;32:579–606.

Bottone E. Bacillus cereus, a volatile human pathogen. *Clin Microbiol Rev*. 2010;23(2):382–398.

Carlson CJ, Kracalik I, Ross N, et al. The global distribution of Bacillus anthracis and associated anthrax risk to humans, livestock, and wildlife. *Nat Microbiology*. 2018. doi.org/10.1101/394023.

Centers for Disease Control and Prevention. Use of anthrax vaccine in the United States. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2019. *MMWR*. 2019;68(No. RR-4).

Drobiniewski F. Bacillus cereus and related species. *Clin Microbiol Rev*. 1993;6(4):324–338.

Glinert I, Bar-David E, Sittner A, et al. Revisiting the concept of targeting only Bacillus anthracis toxins as a treatment for anthrax. *Antimicrob Agents Chem.* 2016;60:487–485.

Hugh-Jones M, Blackburn J. The ecology of Bacillus anthracis. *Mol Aspects Med*. 2009;30:356–367.

Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biologic weapon, 2002. *JAMA*. 2002;287:2236–2252.

Traeger MS, Wiersma ST, Rosenstein NE, et al. First case of bioterrorism-related inhalational anthrax in the United States, Palm Beach County, Florida, 2001. *Emerg Infect Dis*. 2002;10:1029–1034.

Vilas-Boas GT, Peruca APS, Arantes OMN. Biology and taxonomy of Bacillus cereus, Bacillus anthracis, and Bacillus thuringiensis. *Can J. Microbiol.* 2007;53:673–687.

Scarff JM, Seldina YI, Vergis JM, Ventura CL, O'Brien AD. Expression and contribution to virulence of each polysaccharide capsule of Bacillus cereus strain G9241. *PLoS One*. 2018 Aug 22;13(8):e0202701. doi:10.1371/journal.pone.0202701. eCollection 2018.

124

Bartonella bacilliformis

Nuria Sanchez Clemente

Introduction

Bartonella bacilliformis is a gram-negative, facultative intracellular, aerobic coccobacillus that is a member of the α-proteobacteria group along with *Rickettsia* and *Brucella*.

It is responsible for a spectrum of disease which, despite its limited distribution, have been given a multitude of names including *bartonellosis*, *Carrion's disease*, *Oroya fever*, and *verruga peruana*.

The disease is restricted to the Andean cordillera in Peru, Ecuador, and Colombia with sporadic cases being reported in Bolivia, Chile, and Guatemala. Classically, endemic areas are said to be confined to inter-Andean valleys at altitudes between 500 and 3,200 meters above sea level (Figure 124.1). This focality is mainly due to the characteristics of its putative principal sandfly vector, *Lutzomyia verrucarum*, which has a weak, hopping flight and is intolerant of extreme temperatures.

Young children under 10 are the most affected age group in endemic communities, partly because of a predominantly younger population but also due to the presumed protective immunity that develops with repeated infection.

B. bacilliformis is thought to be mainly transmitted to humans by sand flies belonging to the *Lutzomyia* genus. However, transmission via blood transfusion, tick bites, and vertical transmission have all been reported.

Clinical features

There are two well-described phases of the illness.

The initial intraerythrocytic acute stage, known as Oroya fever, occurs typically around 2 to 6 weeks after inoculation of the microorganism by the bite of an infected sandfly. It is characterized by fever, pallor, malaise, joint pain, headache, and anorexia. In severe cases, with high parasitemia, this progresses to severe hemolytic anemia.

High mortality rates of 44% to 88% have been reported in untreated individuals in endemic areas. Most deaths are associated with secondary bacterial infection, most commonly with *Salmonella* spp. but also with *Toxoplasma*, *Histoplasma*, mycobacteria, and fungi. Other complications include pericardial effusion, acute respiratory distress syndrome, hepatitis, convulsions, and coma. In pregnancy, infection can lead to miscarriage, premature labor, and maternal death.

Specific genetic variants of *B. bacilliformis* might account for the marked variability in mortality and morbidity observed in outbreaks.

B. bacilliformis may, in some cases, subsequently colonize the vascular bed of the skin, resulting in a chronic eruptive phase that can occur weeks to months after the acute illness. This stage is characterized by the eruption of crops of miliary, mular, or nodular verrugas or warts containing sero-sanguinous fluid. These occur mainly over the extremities but can also affect the face and trunk. Miliary lesions (Figure 124.2,

FIGURE 124.1

lower lesion) are the most common; occurring in the upper dermal layers they can crop in large numbers and can be pruritic. There may also be mucosal involvement. Mular lesions (Figure 124.2, upper lesion) are >5 mm in diameter and have an eroded center. Nodules are larger diffuse subdermal swellings. The latter two can be painful, especially if occurring over joints. Secondary bacterial infection is a recognized complication.

Due to the fact that *B. bacilliformis*, like all *Bartonella* spp., can circulate in the blood for the remaining life span of the infected erythrocyte, there is also a chronic and usually asymptomatic phase that can last several weeks or months.

The eponym Carrion's disease recognizes the contribution of Daniel Alcides Carrion, a Peruvian medical student who, in 1885, asked a fellow student to inoculate him with blood from a cutaneous lesion from a diseased patient in order to test his hypothesis that the two clinical entities were actually manifestations of the same disease. His hypothesis was proved tragically correct as he developed and soon after succumbed to the acute febrile form of the illness hitherto known as Carrion's disease, thus becoming a martyr of Peruvian medicine.

Diagnosis

In endemic areas, cases are treated empirically during outbreaks. However, the most frequently used diagnostic test is peripheral blood smear (Figure 124.3). When stained with Giemsa, the blue intra- and extraerythrocytic coccobacilli of *B. bacilliformis* can be seen microscopically. Few studies have looked at the sensitivity and specificity of this easy and affordable test. One study which used polymerase chain reaction (PCR) as a reference standard found a sensitivity of 36% and a specificity of 96% in patients with the acute form of the disease. In the chronic eruptive phase, the sensitivity of peripheral blood smear is even lower and therefore not usually carried out.

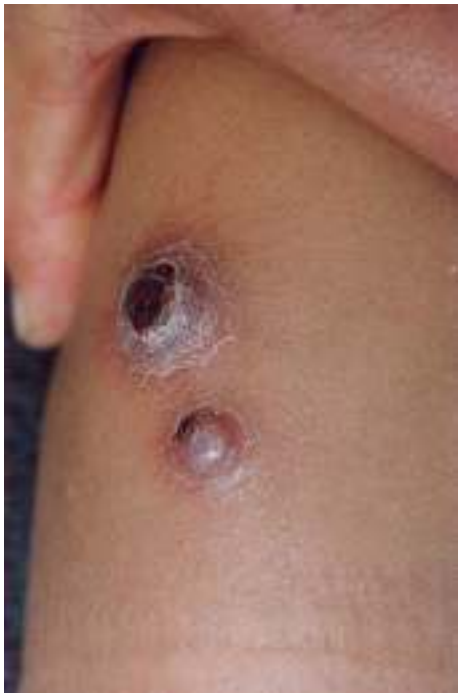

FIGURE 124.2

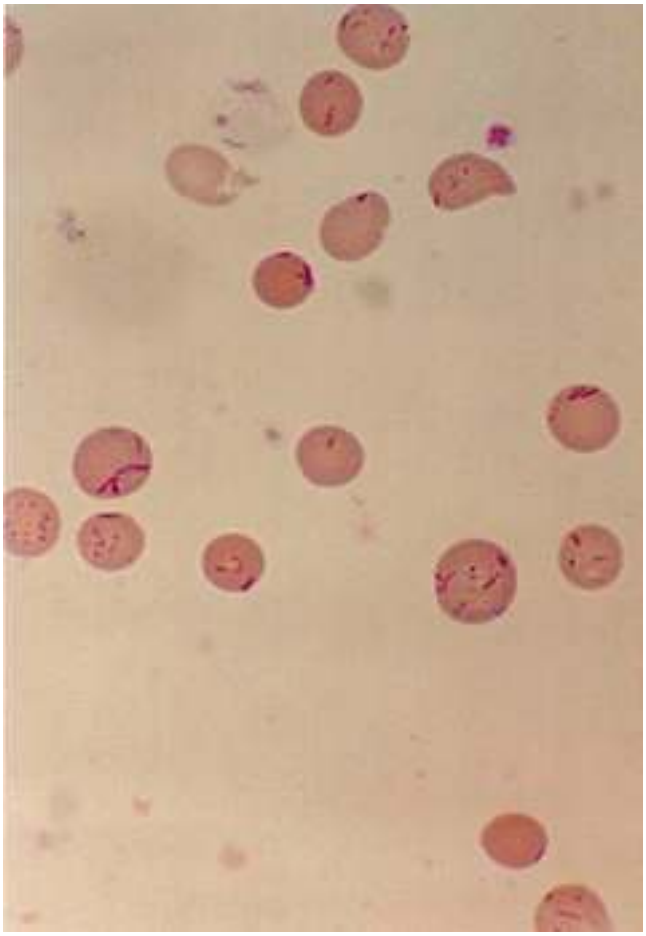

FIGURE 124.3

Blood cultures are rarely used as a diagnostic method as they require prolonged incubation for several weeks in blood-rich medium.

Histopathologic samples of the verrugas are rarely taken in the chronic eruptive phase if the diagnosis is unclear. Biopsy of the lesion classically shows angioblastic proliferation with copious macrophages and lymphocytes. Giemsa staining demonstrates *B. bacilliformis* in the endothelial cells and extracellular matrix.

Serologic methods such as indirect fluorescence antibody test (IFA) and enzyme-linked immunosorbent assay (ELISA) have been developed for use in both phases of the illness but are only available in tertiary centers away from endemic areas. Sensitivity using IgM is superior to IgG ELISA (85% vs. 70%); specificity has been quoted as 100% for both. IFA has a reported sensitivity of 85% and a specificity of 92%.

PCR tests also exist, and studies have shown 16S ribosomal RNA PCR tests to be superior in the detection of *B. bacilliformis* in peripheral blood samples and dried blood spots compared to other PCR techniques.

Management

There are no published controlled clinical trials of therapy for acute or chronic Carrion's disease. Treatment guidelines are based on observational studies and have not been updated since 2006 (Table 124.1).

Severe cases are those in which there are any of the following features: hemodynamic instability, metabolic acidosis, signs of cardiac failure, respiratory compromise, neurologic involvement, severe anemia, hepatitis, gastrointestinal involvement, renal failure, or raised inflammatory markers.

TABLE 124.1 **ANTIBIOTIC MANAGEMENT OF ACUTE AND CHRONIC BARTONELLOSIS ACCORDING TO SEVERITY**

Type of disease, severity	Antibiotic
Acute, mild to moderate	**Chloramphenicol** 50 mg/kg/d for first 3 d then 30 mg/kg to complete 14 d Ciprofloxacin 5 mg/kg BID for 14 d **Amoxicillin-clavulanate** 20 mg/kg BID for 14 d **Trimethoprim-sulfamethoxazole** 5 mg/kg BID for 14 d
Acute, severe	First line: ciprofloxacin 10–15 mg/kg BID for 14 d and ceftriaxone 70 mg/kg IV for 7–10 d Second line: ciprofloxacin (as above) and ceftazidime 30 mg/kg TID IV for 7–10 d or amikacin 7.5 mg/kg BID IV for 7–10 d
Chronic, all	**Azithromycin** 10 mg/kg/d for 7 d **Rifampin** 10 mg/kg/d for 21–28 d **Erythromycin** 12.5 mg/kg QID for 14 d **Ciprofloxacin** 5 mg/kg BID for 14 d

Prevention of the disease is mostly centered on vector control with the use of intra- and extradomiciliary DDT and pyrethroid sprays. Bed nets can also be efficacious but should be impregnated with insecticide as sandflies may penetrate the mesh due to their small size.

Due to its focal geographic nature and the fact that it affects small, isolated, rural communities, Carrion's disease has been truly neglected. Diagnostic and treatment guidelines are supported only by very low-evidence studies and expert opinion. Further research is needed to improve the understanding of this fascinating disease.

Suggested reading

Angelakis E, Raoult D. Pathogenicity and treatment of Bartonella infections. *Int J Antimicrob Agents*. 2014 Jul;44(1):16–25. doi:10.1016/j.ijantimicag.2014.04.006. Epub 2014 May 9.

Birtles RJ, Fry NK, Ventosilla P, et al. Identification of Bartonella bacilliformis genotypes and their relevance to epidemiological investigations of human bartonellosis. *J Clin Microbiol*, 2002;40: 3606–3612.

Chamberlin J, Laughlin L, Gordon S, et al. Serodiagnosis of *Bartonella bacilliformis* infection by indirect fluorescence antibody assay: Test development and application to a population in an area of bartonellosis endemicity. *J Clin Microbiol*. 2000;38:4269–4271.

Del Valle-Mendoza J, Rojas-Jaimes J, Vásquez-Achaya F, et al. Molecular identification of Bartonella bacilliformis in ticks collected from two species of wild mammals in Madre de Dios: Peru. *BMC Res Notes*. 2018 Jun 25;11(1):405. doi:10.1186/s13104-018-3518-z

Ellis BA, Rotz LD, Leake JAD, et al. An outbreak of acute bartonellosis (Oroya fever) in the Urubamba region of Peru, 1998. *Am J Trop Med Hyg*. 1999;61:344–349.

Gomes C, Ruiz J. 2018. Carrion's disease: the sound of silence. *Clin Microbiol Rev*. 31:e00056-17. https://doi.org/10–1128/CMR.00056-17

Gomes C, Martinez-Puchol S, Pons MJ, et al. Evaluation of PCR approaches for detection of Bartonella bacilliformis in blood samples. *PLoS Negl Trop Dis*. 2016;10(3);e0004529. https://doi.org/10.1371/journal.pntd.0004529

Maguiña C, Guerra H, Ventosilla P. Bartonellosis. *Clin Dermatol*. 2009;27:271–280.

Maguiña Vargas C, Ugarte-Gil C, Breña Chavez P, et al. Actualización de la enfermedad de Carrión. *Rev Med Hered*. 2008;19:36–41.

Peru Ministerio de Salud. *Norma Tecnica de Salud para atencion de la Bartonelosis o Enfermedad de Carrion en el Peru*. Lima: Ministerio de Salud; 2006.

Rolain JM, Brouqui P, Koehler JE, Maguina C, Dolan MJ, Raoult D. Recommendations for treatment of human infections caused by Bartonella species. *Antimicrob Agents Chemother*. May 2004;48(6):1921–1933; doi:10.1128/AAC.48.6.1921-1933.2004.

Sanchez Clemente N, Ugarte-Gil CA, Solórzano N, et al. *Bartonella bacilliformis*: A systematic review of the literature to guide the research agenda for elimination. *PLoS Negl Trop Dis*. 2012;6(10):e1819. doi:10.1371/journal.pntd.0001819

Sanchez Clemente N, Ugarte-Gil C, Solorzano N, Maguiña C, Moore D (2016) An Outbreak of Bartonella bacilliformis in an endemic Andean community. *PLoS ONE*. 11(3):e0150525. https://doi.org/10.1371/journal.pone.0150525

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Cat scratch disease and other *Bartonella* infections

William A. Schwartzman

Introduction

Cat scratch disease (CSD) was first described in 1950 by Rene Debré as "La Maladie de Griff de Chat." Its cause remained a mystery until the late twentieth century, when amplification and sequencing of 16S rRNA genes was introduced as a method of identifying organisms that had not been successfully cultured. In 1992, David Relman and co-workers used this technique to identify the agent of CSD, and bacillary angiomatosis and parenchymal bacillary peliosis (BAP). He found that the causative organism was a small gram-negative coccobacillus closely related to the agents causing trench fever, brucellosis, and crown gall disease in plants (*Agrobacterium tumefaciens*).

The organism was first named *Rochalimaea henselae*, and was subsequently grouped within the family Bartonellaceae, along with a number of other organisms, including the agents of trench fever, *Bartonella quintana* (formerly *Rochalimaea quintana*). *Bartonella bacilliformis*, the agent of acute and chronic Carrión's disease is a related ancestor of modern members of the family Bartonellaceae. Recent reports suggest that similar clinical syndromes in the Andean highlands may also be caused by *Bartonella rochalimae* and possibly *Candidatus* Bartonella ancashi 20.0. These organisms, and probably others of the genus, share the ability to invade vascular endothelial cells, bone marrow erythroblasts, and mature erythrocytes. They also share the ability to induce macrophage-mediated secretion of proinflammatory cytokines (notably interleukin-10 [IL-10]) andvascular endothelial cell growth factor (VEGF) and the ability to suppress vascular endothelial cell apoptosis. These virulence factors give them the ability to disseminate within the host, causing proliferative vascular lesions and prolonged bacteremia in humans and mammalian reservoirs.

Since the identification of *Bartonella henselae*, there has been an explosion of knowledge about the manifestations of CSD and those of the expanding roster of *Bartonella* species that populate their mammalian reservoirs; from small rodents to horses, cows, kangaroos, and, in one report, porpoises (Table 125.1).

The clinical spectrum of CSD in the immunocompetent host includes classic CSD as well as ophthalmologic, neurological, cardiovascular, parenchymal, musculoskeletal, and immune complex–mediated syndromes such as glomerulonephritis; as well as prolonged fever without adenopathy or focal lesions. Parenchymal masses associated with CSD have been mistaken for malignancies such as breast cancer or lymphoma.

In hosts with compromised cell-mediated immunity, including patients with acquired immunodeficiency syndrome (AIDS), solid organ transplant recipients, and patients with hematologic malignancies, *B. henselae* and *B. quintana* cause vascular tumors called bacillary angiomas (BA) and blood-filled cavities of liver and spleen, termed bacillary peliosis hepatis; these lesions are referred to collectively as "BAP."

TABLE 125.1 *BARTONELLA* SPECIES CURRENTLY REPORTED TO HAVE CAUSED ZOONOTIC INFECTIONS

Species	Reservoir	Vector	Human disease
B. henselae	Cat, dog, raccoon	Cat flea *(Ctenocephalides felis)*, other?	CSD, retinitis, IE, myocarditis, encephalopathy, aseptic meningitis, myelitis, neuropathy, osteomyelitis, BAP, glomerulonephritis, purpura, pseudomalignancy, prolonged asymptomatic bacteremia
B. quintana	Rat, human?	Louse	CSD, IE, trench fever, encephalopathy, BAP, osteomyelitis, prolonged asymptomatic bacteremia
B. vinsonii subsp. *berkhoffii*	Coyote, dog	Unknown	IE
B. vinsonii subsp. *arupensis*	White-footed mouse	Unknown	IE, neurologic disorders
B. koehlerae	Cat, raccoon	Flea, *C. felis*	IE
B. elizabethae	Rat	Oriental rat flea *Xenopsylla cheopsis*	IE
B. washoensis	California ground squirrel *(Spermophilus beecheyi)*	Unknown	Fever, myocarditis
B. alsatica	Rabbit	Unknown	IE
B. grahamii	Wild mice	Unknown	Neuroretinitis
B. clarridgeiae	Cat, raccoon	Flea, *C. felis*	Possible CSD

Abbreviations: CSD = cat scratch disease; IE = infective endocarditis; BAP = bacillary angiomatosis and parenchymal bacillary peliosis.

Classic cat scratch disease

CSD is the most common cause of regional lymphadenitis in children and young adults. Approximately 24 000 cases occur each year with a prevalence of roughly 9.3/10 000 ambulatory patients per year and a seroprevalence ranging from 3% to 6%. CSD tends to occur in late summer or fall and to vary in frequency with the geographic distribution of the cat flea, *Ctenocephalides felis*.

The first clinical manifestations of CSD appear 5 to 7 days after the scratch or bite from an infected cat, kitten, or cat flea, with the appearance of a small erythematous nodule at the site of bacterial entry. Although this inoculation papule may go unnoticed, it is said to be present in 70% of CSD cases. This nodule represents the initial host response to bartonella and is characterized by palisading macrophages, acute and chronic inflammatory cell infiltration, as well as activation and invasion of vascular endothelial cells. Painful swelling of the proximal lymph nodes follows the appearance of the inoculation papule by 7 to 14 days and may be accompanied by constitutional symptoms and fever. The histopathology of the lymph node is highly characteristic of CSD, involving both acute and chronic inflammatory cells and the presence of microabscesses that are described as "stellate." Aggregates of small coccobacilli may be identified in these abscesses using either silver impregnation stains such as Warthin–Starry and Steiner stains or by immunofluorescent staining with commercially available monoclonal antibodies specific for *B. henselae* or *B. quintana*. The clinical diagnosis of classic CSD can also be confirmed by PCR of tissue or the demonstration of elevated immunoglobulin G (IgG) and IgM antibodies to *B. henselae* or *B. quintana*. Classic CSD usually resolves over several weeks to months without treatment. Although one prospective randomized controlled trial indicated that a 5-day course of azithromycin might hasten the resolution of lymph node swelling, most experts do not recommend antimicrobial therapy for mild to moderately severe CSD. Where lymph nodes become fluctuant and painful, needle aspiration may be all that is required to relieve discomfort and hasten resolution. The syndrome of classic CSD in immunocompetent hosts is thought to be due to an exuberant host response to relatively few organisms, which is one possible explanation for the relatively minor impact of antimicrobials in this setting (Table 125.2).

Ophthalmologic CSD

Approximately 3% of CSD patients develop ocular pathology. These manifestations may be unilateral or bilateral and include conjunctivitis, retinitis, choroiditis, iridocyclitis, endophthalmitis, or orbital abscess with osteomyelitis.

Most frequently patients present with retinitis and vision loss in the context of classic CSD; however, this may also appear without adenopathy. CSD retinitis may be indicated by the presence of characteristic exudates radiating from the macula, the so-called "macular star" or stellate retinitis.

The diagnosis may be confirmed by demonstrating elevated IgG or IgM antibodies to *B. henselae* or PCR of tissue biopsy specimens.

TABLE 125.2 **TREATMENT RECOMMENDATIONS FOR *BARTONELLA* INFECTIONS**

Clinical presentation	Adult treatment recommendations
Mild to moderate classic CSD	No antimicrobials recommended
Severe CSD with large painful lymphadenopathy	Azithromycin, 500 mg PO, d 1, 250 mg d 2–5, aspiration if fluctuant
Retinitis	Doxycycline[a], 100 mg PO BID for 4–6 wk, + rifampin, 300 mg PO BID for 4–6 wk; consider topical corticosteroids
Encephalopathy	Doxycycline[a], 100 mg PO or IV for 6 wk, + rifampin, 300 mg PO BID for 4–6 wk; duration is not a matter of consensus at this time
Suspected *Bartonella* BCNE	Gentamicin, 3 mg/kg/d × 14 d, + ceftriaxone, 2 g/d IV or IM × 6 wk
Confirmed *Bartonella* BCNE	Gentamicin, 3 mg/kg/d IV × 14 d, + doxycycline[a], 100 mg BID × 6 wk
Trench fever, prolonged *B. quintana* bacteremia	Gentamicin, 3 mg/kg/d IV × 14 d, + doxycycline[a], 200 mg/d PO × 4 wk
BA	Erythromycin, 500 mg PO QID × 3 mo, or doxycycline, PO QID 100 mg BID × 3 mo
PH	Erythromycin, 500 mg PO QID × 4 mo, or doxycycline[a], PO QID 100 mg BID × 4 mo

[a] Substitution of minocycline for doxycycline has not been addressed in published reports.
Abbreviations: CSD = cat scratch disease; BCNE = culture-negative infectious endocarditis; BA = bacillary angioma; PH = peliosis hepatitis.
Adapted from Rolain JM, Brouqui P, Koehler JE, Maguina C, Dolan MJ, Raoult D. Recommendations for treatment of human infections caused by Bartonella species. *Antimicrob Agents Chemother*. 2004;48:1921–1933.

Parinaud's oculoglandular syndrome (POGS) is a nodular, or "cobblestone," conjunctivitis accompanied by reactive preauricular lymphadenopathy. This is thought to represent the ocular equivalent of classic CSD, secondary to conjunctival inoculation of *B. henselae*.

Resolution of ocular CSD may be spontaneous; however, treatment with 4 to 6 weeks of doxycycline, with rifampin, with or without topical corticosteroids is recommended.

Neurologic CSD

Neurologic manifestations of CSD are relatively rare, accounting for 0.17% to 2% of cases. These include encephalopathy involving cortex, internal capsule, or midbrain; myelopathy; granulomatous cerebral angiitis; vertebral osteomyelitis; and peripheral neuropathy.

This encephalopathy may present with agitation, delirium, or new onset of seizures, including status epilepticus, coma, cerebellar ataxia, and disruptions of basal ganglia or midbrain. Anecdotal reports of successful treatment have included supportive measures with antiepileptic medication, usually accompanied by intravenous antibiotics with or without high-dose corticosteroids. A combination of intravenous or oral doxycycline with rifampin for at least 14 days is recommended; however, the most appropriate choice of antimicrobials, optimum duration of therapy, and the role of corticosteroids in these cases have not been resolved.

A number of mechanisms have been proposed for CSD encephalopathy, including direct bacterial involvement of neurons, host inflammatory response, autoimmune disease, and toxin production.

In immunocompromised patients, an acute psychiatric syndrome similar to acute mania may occur, which improves rapidly with antimicrobial therapy directed against *B. henselae*. An association has been reported between intrathecal synthesis of *B. henselae* antibodies and human immunodeficiency virus (HIV)-associated encephalopathy; although there is no evidence that this improves with treatment for bartonella.

Cardiovascular infections

Bartonella quintana and *B. henselae* are significant causes of blood culture-negative infectious endocarditis (BCNE). Estimates of the relative contributions of *Bartonella* species to these infections are based on several large case series from reference centers equipped to diagnose these relatively fastidious organisms, including the agent of Q fever, *Coxiella burnettii, Legionella pneumophila, Brucella* species, *Chlamydia psittaci, Tropheryma whipplei, Mycoplasma hominis*, nutritionally deficient streptococci, and the fungal causes of BCNE.

In a series of 349 cases of BCNE reported by Houpikian and Raoult in 2005, *Bartonella* species accounted for 29% of all cases. *Bartonella quintana* represented 75% of these and *B. henselae* 25%. As reported in previous series, *B. quintana* endocarditis was associated with body louse infestation, immunodeficiency, and chronic alcoholism, whereas *B. henselae* endocarditis was associated with cat contact and pre-existing valvular disease. The overall mortality was 7% with no difference between the two species. The aortic valve was the predominant site for both species, and valve replacement was performed in 75% of cases. Several cases of renal failure secondary to necrotizing crescentic glomerulonephritis have been reported in the context of both *B. henselae* and *B. quintana* endocarditis.

To date, four additional *Bartonella* species have been reported to cause infective endocarditis (IE) in humans: *Bartonella vinsonii, Bartonella vinsonii* subsp. *berkhoffii*, *Bartonella elizabethae,*

Bartonella koehlerae, and *Bartonella alsatica*. The diagnosis of *Bartonella* endocarditis was made by culture in roughly 30% of cases, whereas PCR of valvular tissue yielded 67%. Serologic demonstration of anti-*Bartonella* antibody titers ≤1:800 by direct fluorescent antibody (DFA) provided an acceptable noninvasive method of diagnosis in this series.

Suspected *Bartonella* BCNE should be treated with gentamicin for 2 weeks, combined with 6 weeks of intravenous or intramuscular ceftriaxone, to cover other possible causes of BCNE, with or without oral or intravenous doxycycline for 6 weeks. For proven *Bartonella* endocarditis, a combination of gentamicin for 2 weeks plus intravenous or oral doxycycline for 6 weeks is recommended.

Although rare, myocarditis has been associated with *Bartonella* infections. *Bartonella washoensis*-associated myocarditis was reported in a 70-year-old immunocompetent man, presumably associated with the presence of a large reservoir of the organism in the California ground squirrels (*Spermophilus beecheyi*) in recreational areas near Reno, Nevada. *Bartonella henselae* has been associated with a case of chronic active myocarditis in a 43-year-old immunocompetent man with classic CSD. An autoimmune reaction triggered by the *B. henselae* infection was postulated.

Prolonged bacteremia without endocarditis

Prolonged symptomatic or asymptomatic bacteremia is more frequently caused by *B. quintana* but may also be caused by *B. henselae* as well as other less common members of the genus. When accompanied by fever and constitutional symptoms, prolonged, relapsing *B. quintana* bacteremia was called trench fever in World War I and was at first thought to be a variant of endemic typhus, until Dr. Henrique da Rocha Lima determined it to be a distinct louse-borne infection. Following World War II, trench fever was considered to be an historical relic, until its resurrection in the late twentieth century as a significant cause of illness among the world's growing population of urban homeless, so-called urban trench fever.

Although the relation of prolonged bacteremia to infectious endocarditis has not been established, it is assumed that antimicrobial treatment of *B. henselae* and *B. quintana* bacteremia may have a role in preventing endocarditis. The currently recommended therapy for *B. henselae* and *B. quintana* bacteremia is intravenous gentamicin for 14 days with oral or intravenous doxycycline for 28 days. A thorough search for evidence of endocarditis should accompany the treatment of *Bartonella* bacteremia.

Parenchymal CSD

CSD with or without regional lymphadenopathy may be accompanied by hepatic or splenic foci of infection. The clinical presentation of hepatosplenic bartonellosis includes chronic or subacute course characterized by fever and abdominal pain that may be accompanied by nausea and vomiting. Hepatic transaminases may be elevated and may demonstrate disproportionate elevations of hepatic alkaline phosphatase over aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Abdominal ultrasound or computerized axial tomography may demonstrate radiolucencies in liver and spleen. Histopathology of these lesions frequently demonstrates either necrotizing granulomas or stellate microabscesses similar to those described in the lymph nodes of classic CSD. Anecdotal reports suggest that doxycycline plus rifampin for periods of from 7 to 14 days may be effective in these cases, but spontaneous resolution has also been documented and there is currently no consensus favoring antimicrobial treatment.

Musculoskeletal

Bartonella henselae is a rare cause of osteomyelitis. *Bartonella quintana* has been linked to most bartonella-related cases, especially in children. Small case series describe typical presentations, including fever and bone pain in children or young adults with cat or kitten exposure, with or without associated lymphadenopathy. These may involve single or multiple foci of infection and frequently involve the axial skeleton or pelvic bones. The etiologic diagnosis in these cases was made by serology, histopathology, or PCR of bone biopsy specimens. There is no evidence beyond anecdotal reports that antimicrobial therapy is effective.

Bartonella in immunocompromised patients

Infections in immunocompetent hosts are characterized by an exuberant inflammatory response to relatively few organisms and a poor response to antimicrobial agents. However, in those with compromised cell-mediated immunity, such as individuals with AIDS or hematologic malignancies, organ transplant recipients, and those receiving immunomodulating agents for treatment of hepatitis C or rheumatologic diseases, the same organisms commonly cause systemic infections characterized by BAP lesions, which teem with organisms and respond dramatically to antimicrobial therapy.

BAP may develop in practically any anatomical site or organ, including skin, mucosa of the nasopharynx, gastrointestinal tract, central nervous system, bone, or lymph nodes. Cutaneous BA usually forms a 1-cm to 2-cm erythematous nodule with a surrounding collar of scaling skin (Figures 125.1 and 125.2). These are friable, bleed easily, and may itch.

The microscopic appearance of BA is of disorganized vascular channels, with prominent, rounded endothelial cells, projecting into irregular vascular lumens. These lesions are easily distinguished

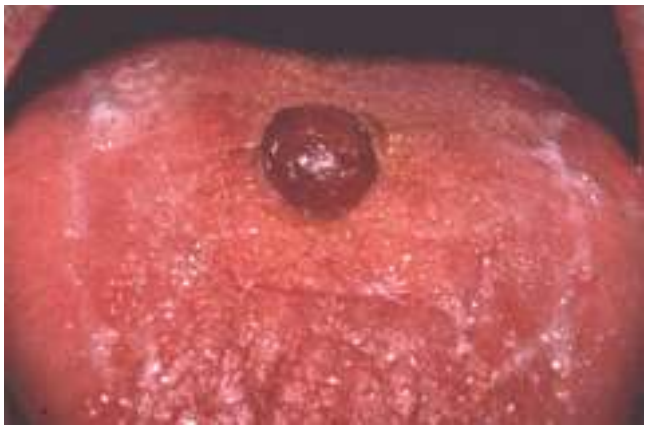

FIGURE 125.1

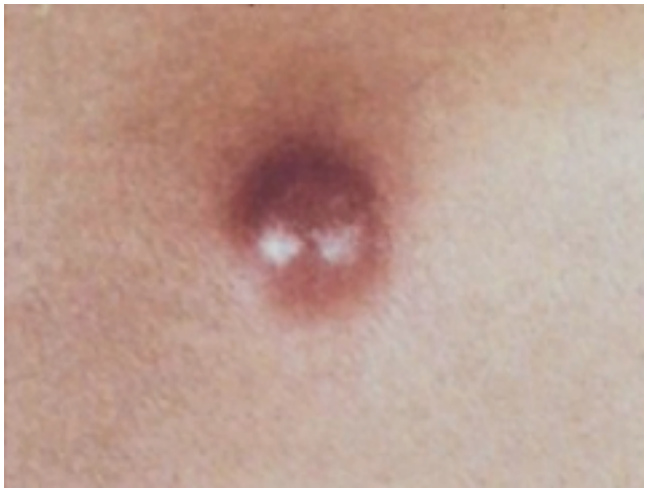

FIGURE 125.2

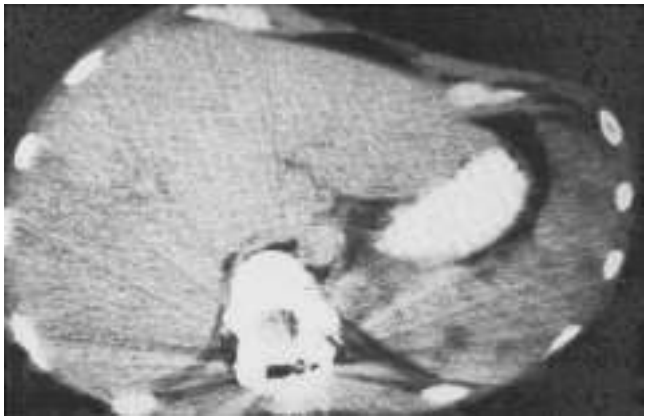

FIGURE 125.3

from the more organized spindle cells of Kaposi's sarcoma. When stained with hematoxylin and eosin, azurophilic granular material can be seen, representing clumps of bacteria. Although they may also be seen with Brown–Brenn tissue Gram stain or silver impregnation stains such as Steiner or Warthin–Starry, they are more easily visualized by immunofluorescent staining.

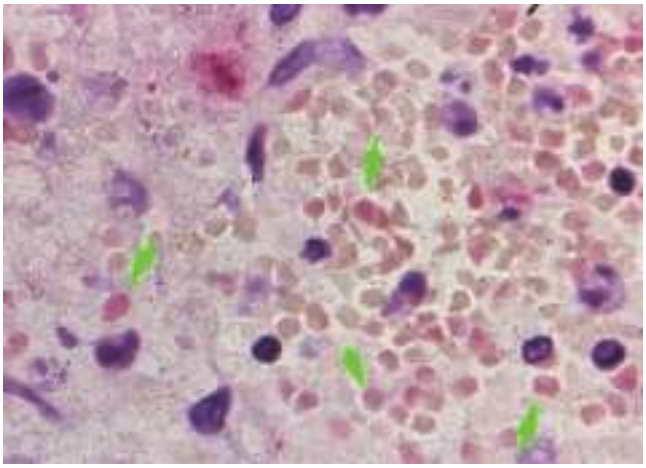

FIGURE 125.4

The second type of vascular lesion, bacillary parenchymal peliosis or peliosis hepatitis (PH), may involve liver or spleen. Computed tomography (CT) or magnetic resonance imaging may demonstrate hypodense lesions (Figure 125.3). Histologically, PH lesions are blood-filled cavities that appear to arise where normal sinusoidal endothelial cells have become disrupted by bartonella infection. The endothelial cells, erythrocytes, and macrophages of these lesions contain intracellular bacteria (Figures 125.4–125.6).

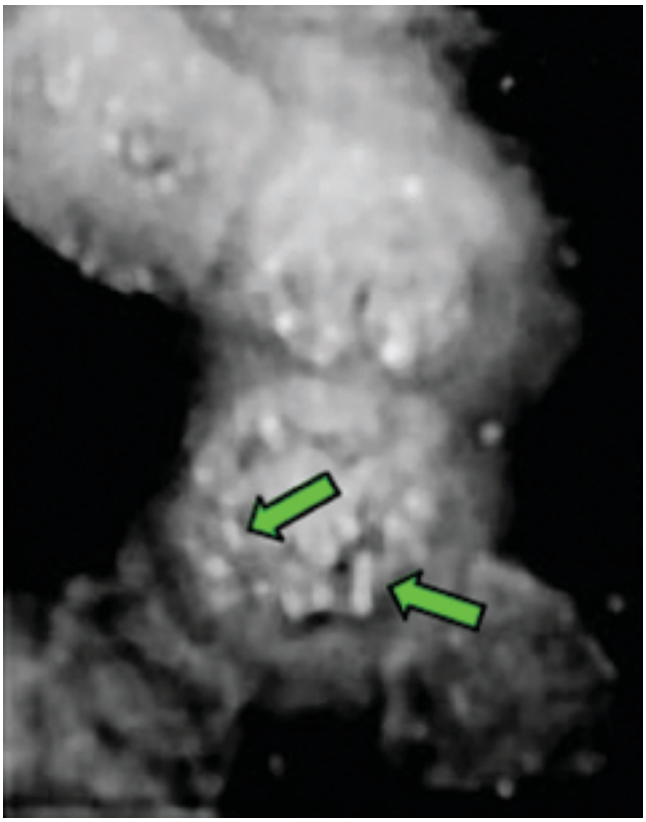

FIGURE 125.5

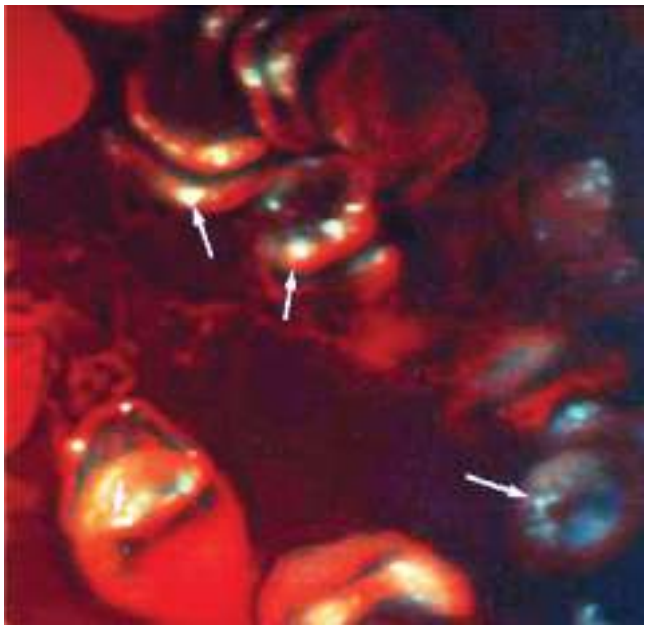

FIGURE 125.6

Treatment of patients with BAP usually results in a rapid clinical improvement. Treatment should continue for at least 3 months to avoid relapses. Although erythromycin is recommended, doxycycline appears to be as effective, with fewer gastrointestinal side effects.

Suggested reading

Bhatti Z, Berenson CS. Adult systemic cat scratch disease associated with therapy for hepatitis C. *BMC Infect Dis*. 2007;7:8.

Foucault C, Brouqui P, Raoult D. *Bartonella quintana* characteristics and clinical management. *Emerg Infect Dis*. 2006;12:217–223.

Harms A, Dehio C. Intruders below the radar: molecular pathogenesis of *Bartonella* spp. *Clin Microbiol Rev*. 2012;25:42–78.

Houpikian P, Raoult D. Blood culture-negative endocarditis in a reference center: etiologic

Koehler JE, Sanchez MA, Tye S, et al. Prevalence of *Bartonella* infection among human immunodeficiency virus-infected patients with fever. *Clin Infect Dis*. 2003;37:559–566.

Martinez-Osorio H, Calonge M, Torres J, et al. Cat-scratch disease (ocular bartonellosis) presenting as bilateral recurrent iridocyclitis. *Clin Infect Dis*. 2005;40:e43–e45.

Mathieu S, Vellin JF, Poujol D, et al. Cat scratch disease during etanercept therapy. *Joint Bone Spine*. 2007;74(2):184–186.

Ohl ME, Spach DH. *Bartonella quintana* and urban trench fever. *Clin Infect Dis*. 2000;31:131–135.

Relman DA, Loutit JS, Schmidt TM, et al. The agent of bacillary angiomatosis. An approach to the identification of uncultured pathogens. *N Engl J Med*. 1990;323:1573–1580.

Rolain JM, Brouqui P, Koehler JE, et al. Recommendations for treatment of human infections caused by *Bartonella* species. *Antimicrob Agents Chemother*. 2004;48:1921–1933.

Wheeler SW, Wolf SM, Steinberg EA. Cat-scratch encephalopathy. *Neurology*. 1997;49:876–878.

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Bordetella

Emily Souder and Sarah S. Long

Bordetellae are fastidious, non–carbohydrate-fermenting, tiny, gram-negative coccobacilli that grow aerobically on starch blood agar or synthetic medium supplemented with nicotinamide and amino acids for growth and charcoal or cyclodextrin resin for protection from fatty acids and other inhibitory substances. Bordetellae have multiple attachment proteins, including a 69-kDa outer membrane protein (pertactin), filamentous hemagglutinin, and fimbriae. *Bordetella pertussis* is the only species that expresses the major virulence protein, pertussis toxin. *B. pertussis* and *B. parapertussis* are exclusive human pathogens. *B. pertussis* is the cause of epidemic pertussis and the usual cause of endemic and sporadic pertussis. *B. parapertussis* is an infrequent cause of pertussis in the United States and is genetically more closely aligned with *B. bronchiseptica*, a common veterinary pathogen causing upper respiratory tract illnesses in animals. *B. holmesii*, first described as a cause of bronchitis, endocarditis, and septicemia in immunocompromised patients, infrequently can cause pertussis-like illness in otherwise healthy persons. Occasional case reports of *B. bronchiseptica* in humans include upper and lower respiratory tract illnesses, endocarditis, septicemia, posttraumatic meningitis, and peritonitis. *B. hinzii* has caused bloodstream infection in a handful of cases, usually associated with pulmonary symptoms. Asplenia or immunosuppression has been present in many adults infected with *Bordetella* non-*pertussis* and non-*parapertussis* species. Exposure to pets also is a factor.

Epidemiology and clinical manifestations

Pertussis is an unusual example among vaccine-preventable diseases for which universal immunization is given but for which incidence continues to be considerable. The >42,000 cases reported in the United States in 2012 were the highest number reported for any year in the past half-century. The actual number of cases likely is exponentially greater than that reported because pertussis is undersuspected, underdiagnosed, and underreported. During a prospective vaccine trial in adults, it was estimated that >600,000 cough illnesses due to *B. pertussis* likely occur in the United States annually. Age-related incidence of pertussis is highest in infants ≤2 months of age (~150 per 100,000), but the greatest number of cases and the reservoirs for *B. pertussis* are in school-aged children, adolescents, and adults who have waning vaccine immunity and lack the frequent natural subclinical reinfections that boosted immunity in a previous era. Additional factors in resurgence are speculated to include increased awareness, improved diagnostics, use of acellular vaccines for all doses, and pathogen adaptation.

Classic pertussis illness occurs almost exclusively in unimmunized older infants and children. It includes 2-week stages: an afebrile, upper respiratory tract illness with escalating cough (catarrhal stage) followed by paroxysms of machine-gun bursts of coughing, frequently with whoops and posttussive vomiting (paroxysmal stage), fading into fewer and less severe paroxysms (convalescent stage). Young infants have rapid onset of "fits" of gagging, gasping, and cyanotic or apneic episodes, with paroxysmal cough and whoop occurring only later, sometimes during convalescence. Adults do not have distinct stages, and at least one-third have only a prolonged nonspecific cough illness. Clues to pertussis in adolescents and adults are (1) pure or predominant cough illness that is escalating after 1 week, (2) cough illness in which there are sudden paroxysms

(repeated bursts of cough on one breath, bulging watery eyes, red face), or (3) cough illness associated with posttussive emesis. Several studies suggest that 13% to 32% of patients with this symptom complex have pertussis. Patients are afebrile, have few upper or lower respiratory tract signs or symptoms, do not have myalgia or malaise, and are well between paroxysms. Adults with pertussis describe a typical paroxysm as beginning with an aura of anxiety and fear to take a breath, followed by strangulating cough, feeling of suffocation, and posttussive exhaustion. Whoop is uncommon.

Diagnosis

Differential diagnosis predominantly includes other respiratory tract infection due to agents such as *Mycoplasma pneumoniae, Chlamydophila pneumoniae*, adenovirus, influenza, and parainfluenza. History of illness onset is most helpful. These other infections typically begin abruptly and include fever, systemic symptoms, multiple mucous membrane involvement, or rash—none of which is part of pertussis. Simple laboratory tests generally are not helpful in differentiating causes as only unimmunized persons with pertussis have remarkable lymphocytosis.

Current methods for confirmation of infection due to *B. pertussis* (i.e., culture, polymerase chain reaction [PCR], and serology) have limitations in sensitivity, specificity, or practicality; relative value depends on setting (sporadic vs. outbreak), phase of disease, and purpose of use (diagnostic vs. epidemiologic). Culture requires (1) collection of a posterior nasopharyngeal specimen obtained either by aspiration or with Dacron or calcium alginate swab, (2) use of Regan–Lowe transport medium, and (3) inoculation of specialized agar medium and incubation for up to 10 days. PCR is more sensitive than culture, averts difficulties of isolation, and has rapid result, but standardized validated primers should be used. Use of insertion sequence (IS) *481* increases sensitivity of PCR but does not distinguish between *B. pertussis* and *B. holmesii* nor will it detect *B. parapertussis* if used as the sole PCR target. Inclusion of multiple targets is necessary to detect and differentiate species. The PCR test is most sensitive during the first 2 weeks of cough illness, although some individuals may remain PCR positive for longer, and it requires similar collection of a posterior nasopharyngeal specimen using a Dacron swab (not a calcium alginate) or nasal wash technique. Serologic diagnosis is confirmed by an increase/seroconversion of immunoglobulin G (IgG) antibody to pertussis toxin (PT-IgG) between acute and convalescent samples in a previously unimmunized individual, or a single level in the second to third week of cough illness that is >2 standard deviations above the expected resting level in distantly immunized individuals. Generally, PT-IgG level >2 years after immunization of >90 EU/mL is highly suggestive, and levels >50 EU/mL are suggestive of symptomatic *B. pertussis* infection.

In unimmunized individuals, pertussis usually is confirmed easily by positive PCR and culture. However, these tests are positive in <20% of cough illnesses due to *B. pertussis* in adolescents and adults. A single elevated serum PT-IgG antibody level is the best diagnostic test in adolescents and adults.

Treatment

An antimicrobial agent is given when pertussis is suspected or confirmed, for potential clinical benefit and to limit the spread of infection to others (Table 126.1). In vitro, *B. pertussis* is susceptible to erythromycin, newer macrolides, fluoroquinolones, and third-generation cephalosporins. Ampicillin, rifampin, and trimethoprim-sulfamethoxazole have only modest activity, and first-and second-generation cephalosporins are not effective. In clinical studies, erythromycin is superior to amoxicillin for eradication of *B. pertussis*. Rare isolates resistant to erythromycin have been reported. Azithromycin is the drug of choice for all age groups. Idiopathic hypertrophic pyloric stenosis (IHPS) has been reported in up to 2% of neonates given azithromycin (this risk is less than that following erythromycin). The US Food and Drug Administration (FDA) also warns of risk of fatal heart rhythms with use of azithromycin in patients already at risk for cardiovascular events, especially prolongation of the QT interval. *B. parapertussis* is less susceptible in vitro to all agents except macrolides. *B. bronchiseptica* is susceptible in vitro to antipseudomonal penicillins, aminoglycosides, and fluoroquinolones but generally is not susceptible to cephalosporins; clinical failure has occurred with agents effective in vitro. *B. holmesii* has in vitro susceptibilities similar to *B. bronchiseptica*, but isolates have been susceptible to third-generation cephalosporins.

Secondary sinusitis, otitis media, bronchitis, or pneumonia can complicate *B. pertussis* infection, which denudes ciliated epithelium and inhibits local phagocytic function. Pathogens of secondary infections are *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae*, and *Moraxella catarrhalis*. Convalescence from uncomplicated pertussis is protracted, with exacerbations of paroxysmal cough during subsequent respiratory illnesses; these are not caused by reinfection or reactivation of *B. pertussis*.

Control and prevention

Postexposure prophylaxis (PEP) using the same agents, doses, and duration as for treatment (Table 126.1) should be given promptly to all household contacts and other close contacts regardless of their age or history of immunization. Benefits of PEP using azithromycin for infants far outweighs risk of IHPS. PEP of contacts has little effect if instituted ≥2 weeks after exposure to the index case. Healthcare personnel (HCP) not wearing a mask who were exposed at close range to an individual with pertussis before the fifth day of treatment should be given PEP promptly, especially if they have contact with young infants, regardless of receipt of Tdap (tetanus toxoid, reduced content diphtheria toxoid, and reduced content acellular pertussis vaccine). Cases and contacts with any respiratory tract illness should be excluded from high-risk settings (e.g., school, healthcare facilities) until the fifth day of treatment.

Five doses of DTaP vaccine should be given on the recommended schedule before 7 years of age. Since 2006, Tdap was recommended for universal immunization at 11 to 12 years of age (with catch-up of older adolescents), and for certain adults. By 2012, the Centers for Disease Control and Prevention (CDC) recommended a single

TABLE 126.1 **RECOMMENDED ANTIMICROBIAL AGENTS FOR TREATMENT AND POSTEXPOSURE PROPHYLAXIS OF PERTUSSIS[A]**

	Age group			
Agents	**≤1 Month**	**1–5 Months**	**≥6 Months and children**	**Adults**
Primary agents				
Azithromycin	Recommended agent 10 mg/kg/d, once daily ×5 d	10 mg/kg once daily ×5 d	10 mg/kg (max 500 mg) once on d 1; then 5 mg/kg (max 250 mg) once on d 2–5	500 mg once on d 1; then 250 mg once on d 2–5
Clarithromycin	Not recommended	15 mg/kg/d divided BID ×7 d	15 mg/kg/d (max 1 g/d) divided BID ×7 d	1 g/d divided BID ×7 d
Erythromycin	Not preferred Use if azithromycin unavailable; 40–50 mg/kg/d divided QID x 14 days	40–50 mg/kg/d divided QID ×14 d	40–50 mg/kg/d (max 2 g/d) divided QID × 14 d	2 g/d divided QID × 14 d
Alternate agent				
TMP–SMX	Contraindicated	Contraindicated at age <2 mo. At ≥2 mo, TMP 8 mg/kg/d–SMX 40 mg/kg/d divided BID ×14 d	TMP 8 mg/kg/d–SMX 40 mg/kg/d (max TMP 320 mg/d) divided BID ×14 d	TMP 320 mg-SMX 1,600 mg/d divided BID ×14 d

Abbreviations: TMP-SMX = trimethoprim–sulfamethoxazole; BID = twice a day; QID = four times a day; d=day.
[a] Recommendations of the Centers for Disease Control and Prevention and the American Academy of Pediatrics. *Morbid Mortal Weekly Rep*. 2005:54(RR-14):1–16.

dose of Tdap for *all* people 11 years of age and older (i.e., including those ≥65 years of age) regardless of time since Td and regardless of perceived risks of acquisition or transmission or the ages of likely contacts. Although Boostrix is the only licensed Tdap for use in those ≥65 years of age and is preferred, either Boostrix or Adacel can be used. In 2012, the CDC also recommended Tdap for pregnant women in the third trimester of *every* pregnancy (optimally early in the period between 27 and 36 weeks of gestation) to prevent infant deaths and severe morbidity by creating a passive antibody bridge until the infant can receive DTaP. When preparing for arrival of all newborns, and when pertussis is suspected or confirmed, immunization status of contacts should be sought and evaluated, and DTaP (for children ≤7 years) or Tdap (for people who have not previously received Tdap) should be given promptly if indicated. In 2018, Tdap (Adacel) was licensed for a second dose. However, because of rapid waning of protection following currently available acellular pertussis vaccines, there is no recommendation for Tdap revaccination for any age or risk group outside of pregnancy. However, when Td is indicated and only Tdap is available, Tdap can be given to a previously Tdap-immunized individual.

Suggested reading

American Academy of Pediatrics. Pertussis. In Pickering LK, ed. *2018–2021 Red Book: Report of the Committee on Infectious Diseases*, 31st ed. Elk Grove Village, IL: American Academy of Pediatrics. 2018–2021: 620–634.

Baughman AL, Bisgard KM, Edwards KM, et al. Establishment of diagnostic cutoff points for levels of serum antibodies to pertussis toxin, filamentous hemagglutinin, and fimbriae in adolescents and adults in the United States. *Clin Diagn Lab Immunol*. 2004;11:1045–1053.

Healy CM, Rench MA, Swaim LS, et al. Association between third-trimester Tdap immunization and neonatal pertussis antibody concentration. *JAMA* 2018;320:1464–1470.

Lee AD, Cassiday PK, Pawloski LC, et al. Clinical evaluation and validation of laboratory methods for the diagnosis of *Bordetella pertussis* infection: Culture, polymerase chain reaction (PCR) and anti-pertussis toxin IgG serology (IgG-PT). *PLoS One*. 2018;13:e0195979.

Liang JL, Tiwari T, Moro, P, et al. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2018;67:1–44.

McIntyre PB, Sintchenko V. The "how" of polymerase chain reaction testing for *Bordetella pertussis* depends on the "why." *Clin Infect Dis*. 2013;56:332–334.

Rodgers L, Martin SW, Cohn A, et al. Epidemiologic and laboratory features of a large outbreak of pertussis-like illnesses associated with cocirculating *Bordetella holmesii* and *Bordetella pertussis*—Ohio, 2010–2011. *Clin Infect Dis*. 2013;56:322–331.

Stone BL, Daly J, Srivastava R. Duration of *Bordetella pertussis* polymerase chain reaction positivity in confirmed pertussis illness. *J Peds Infec Dis Soc*. 2014;3:347–349.

Ward JI, Cherry JD, Chang S-J, et al. Efficacy of an acellular pertussis vaccine among adolescents and adults. *N Engl J Med*. 2005;353:1–9.

Witt MA, Arias L, Katz PH, et al. Reduced risk of pertussis among persons ever vaccinated with whole cell pertussis vaccine compared to recipients of acellular pertussis vaccines in a large US cohort. *Clin Infect Dis*. 2013; 56:1248–1254.

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Branhamella-Moraxella

Lisa S. Hodges and Joseph A. Bocchini, Jr.

Moraxella catarrhalis is an important etiologic agent of otitis media in children, sinusitis in children and adults, and bronchopulmonary infection in adults with chronic obstructive pulmonary disease (COPD) or impaired host defenses.

Moraxella catarrhalis is a gram-negative unencapsulated diplococcus similar in morphology to the *Neisseria*. The bacterium was first described by Ghon and Pfeiffer as *Micrococcus catarrhalis* in 1902 and has since undergone several reclassifications. In 1970 it was placed into the genus *Branhamella* based on fatty acid content and DNA homology. *Moraxella (Branhamella) catarrhalis* is the most widely accepted nomenclature at this time.

Epidemiology

Moraxella catarrhalis is a normal inhabitant of the upper respiratory tract, but can be a pathogen in susceptible hosts. Colonization is seasonal, with an increase in prevalence during winter and spring months. Age and comorbidity are the major determinants of colonization. The mode of transmission is assumed to be direct contact with respiratory secretions or droplet spread. Approximately two-thirds of children become colonized during the first year of life. One prevalence study demonstrated that colonization with *M. catarrhalis* in infants occurs earlier than with *Streptococcus pneumoniae* or *Haemophilus influenzae*, and persists longer. Infants who become colonized with *M. catarrhalis* before 3 months of age are more likely to develop an episode of acute otitis media (AOM) or otitis media with effusion (OME) by the time they are 6 months old. Carriage rates in healthy adults are only 3% to 5%. In contrast, *M. catarrhalis* has been recovered in 5% to 32% of adults with COPD. Approximately half of adults with COPD who are newly colonized will develop an acute exacerbation of COPD.

The pneumococcal conjugate vaccine has altered patterns of nasopharyngeal colonization, permitting replacement with nonvaccine pneumococcal serotypes, nontypeable *H. influenzae*, and *M. catarrhalis*.

Pathogenesis

The pathogenesis of infection is complex with both host and bacterial factors determining the evolution from colonization to clinical disease. *Moraxella catarrhalis* expresses adhesion factors and several outer membrane proteins that facilitate preferential binding to mucosal surfaces of the upper and lower respiratory tract and to middle ear epithelial cells. Biofilm formation in sequestered sites such as the middle ear suggest its potential role in the development of AOM with effusion.

Prior colonization of the nasopharynx by *M. catarrhalis* appears to enhance the adherence and invasion of human epithelial cells by *Streptococcus pyogenes*.

Following infection, the organism has the ability to act through Toll-like receptors to induce proinflammatory cytokines in the bronchial epithelium that, in addition to causing acute exacerbations of COPD, may also be responsible for its pathogenesis. *Moraxella catarrhalis* also has the ability to inhibit this proinflammatory process and evade the host immune response, allowing for persistent mucosal colonization.

Clinical syndromes

Moraxella catarrhalis is the third most common etiologic cause of AOM and sinusitis in infants and children after *S. pneumoniae* and *H. influenzae*. Cultures of middle ear fluid and of sinus aspirates reveal that 15% to 20% of these infections are caused by *M. catarrhalis*. Most are mixed infections that resolve spontaneously. Suppurative complications are uncommon. *Moraxella catarrhalis* has also been recovered from children with OME.

Acute exacerbations of chronic bronchitis in adults with COPD and other chronic lung diseases is the most common lower respiratory tract infection caused by this organism. *Moraxella catarrhalis* is responsible for 30% of acute exacerbations of COPD, second only to *H. influenzae*. Exacerbations are characterized by cough, purulent sputum production, shortness of breath, low-grade fever, and a lack of leukocytosis. It is usually mild to moderate in severity with either patchy or lobar alveolar infiltrates on chest radiograph. CT findings include ground-glass opacities, bronchial wall thickening, and centrilobular nodules. Bacteremia is rare, and pleural effusion and empyema are uncommon.

Less common clinical syndromes associated with *M. catarrhalis* include conjunctivitis in infants that mimics the opthalmia neonatorum of *Neisseria gonorrhoeae*. Bacteremia in children may present like occult pneumococcal bacteremia but has also been reported in association with focal infections such as preseptal cellulitis, septic arthritis, osteomyelitis, and prosthetic vascular graft infection, and a purpuric rash similar to that seen in meningococcemia has been reported. Bacteremia in adults has been reported as a consequence of pneumonia and sepsis has been reported in patients with leukemia, AIDS, and agammaglobulinemia. Pancreatitis, peritonitis, and ventriculitis have also been described. Meningitis, especially in children, has occurred as a result of hematogenous spread from the nasopharynx, or as a consequence of ventriculoperitoneal shunt placement or surgery.

Nosocomial outbreaks with a single strain of *M. catarrhalis* have been reported, in respiratory units and healthcare facilities.

Diagnosis

A presumptive diagnosis can be made from a sputum smear that demonstrates many polymorphonuclear leukocytes with intracellular and extracellular gram-negative diplococci. Because *M. catarrhalis* is somewhat resistant to decolorization, this step in the Gram-stain procedure requires special attention. *M. catarrhalis* can be isolated on blood or chocolate agar media with the addition of CO_2.

Therapy

In many cases of otitis media and mild to moderate exacerbations of COPD, spontaneous resolution of *M. catarrhalis* infection occurs with the development of strain-specific immunity, an important consideration in determining the need for antimicrobial therapy in an individual patient.

Virtually all strains of *M. catarrhalis* now produce β-lactamase and are resistant to penicillin, amoxicillin, and ampicillin. The addition of a β-lactamase inhibitor (clavulanate, sulbactam, or tazobactam) to a penicillin restores its bactericidal activity against *M. catarrhalis*.

In addition, *M. catarrhalis* is susceptible to amoxicillin–clavulanate, ampicillin–sulbactam, piperacillin–tazobactam, second- and third-generation cephalosporins (including the oral agents), aminoglycosides, aztreonam, and carbapenems. It is also sensitive to macrolides, tetracyclines, trimethoprim–sulfamethoxazole (TMP–SMX), and fluoroquinolones.

Most infections caused by *M. catarrhalis* can be treated with oral antibiotics. For AOM or sinusitis (documented by tympanocentesis or sinus aspiration), amoxicillin–clavulanate administered for 10 days (otitis media) or 2 weeks (sinusitis) is the drug of choice. In patients with known penicillin allergy, macrolides, TMP–SMX, or fluoroquinolones may be used where appropriate.

Acute exacerbations of chronic bronchitis caused by *M. catarrhalis* can also be treated with a variety of oral antibiotics, including amoxicillin–clavulanate, second- or third-generation cephalosporins, TMP–SMX, macrolides, doxycycline, or fluoroquinolones.

Parenteral antibiotics are preferred for more invasive disease. The drug of choice for *M. catarrhalis* pneumonia is ampicillin–sulbactam; however, ceftriaxone could also be used. In patients with known penicillin allergy, a macrolide or a fluoroquinolone is an acceptable alternative.

In most patients with otitis, sinusitis, or an acute exacerbation of chronic bronchitis, the etiologic agent will not be known. The decision to treat and the choice of empiric therapy should consider *M. catarrhalis* but include all common pathogens associated with the specific infection syndrome.

Suggested reading

de Vries SPW, Bootsma HJ, Hays JP, Hermans PWM. Molecular aspects of *Moraxella catarrhalis* pathogenesis. *Microbiol Mol Biol Rev*. 2009;73:389–406.

Faden H, Duffy L, Wasielewski R, et al. Relationship between nasopharyngeal colonization and the development of otitis media in children. *J Infect Dis*. 1997;175:140–145.

Hall-Stoodley L, Hu FZ, Gieseke A. Direct detection of bacterial biofilms on middle-ear mucosa of children with chronic otitis media. *JAMA*. 2006;296:202–211.

Lafontaine ER, Wall D, Vanlerberg SL, Donabedian H, Sledjeski DD. *Moraxella catarrhalis* coaggregates with *Streptococcus pyogenes* and modulates interactions of *S. pyogenes* with human epithelial cells. *Infect Immun*. 2004;72:6689–6693.

Leibovitz E, Greenberg D. *Moraxella* and *Psychrobacter* species. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practices of Pediatric Infectious Diseases*, 4th edn. Edinburgh: Elsevier Saunders; 2012:839–840.

Murphy TF. *Moraxella catarrhalis*, a human respiratory pathogen. *Clin Infect Dis*. 2009;49:124–131.

Murphy TF. *Moraxella catarrhalis*, *Kingella*, and other gram-negative cocci. In Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia, PA: Elsevier; 2010:2771–2776.

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Brucellosis

Carlo Carrillo and Eduardo Gotuzzo

Brucellosis is a zoonotic disease found in Latin America, Mediterranean countries (Spain, Italy, Greece), and Arabian countries (Iraq, Kuwait). According to the Centers for Disease Control and Prevention (CDC), the number of cases dropped from 6147 in 1947 to 104 in 1991 with modern bovine brucellosis eradication, mainly by pasteurization of milk or dairy products.

Most cases of brucellosis in the United States are related to occupational exposure to *Brucella abortus*. The affected are mainly men and occasionally laboratory and technical personnel. However, in Texas and Florida, the ingestion of unpasteurized dairy products is the common mechanism, and the pathogen responsible is *Brucella melitensis*, attacking men and women in equal proportion and sometimes children. *B. melitensis* produces a more severe clinical pattern and can even produce a chronic form. The attack rate is higher, especially in family outbreaks, with rare subclinical infections. *B. abortus* produces a mild disease with low attack rates (<10%) and more subclinical cases.

Clinical manifestations

Brucellosis is one of the most protean diseases because any system can be involved. We prefer to divide it into three forms.

Acute brucellosis

Usually, there is high fever, mainly in the evening, with malaise, headache, perspiration, arthralgias, and myalgias. In most cases, constipation, back pain, and loss of weight (as much as 20 pounds in 2 months) are found. Generally, granulomatous hepatitis, hematologic disorders, and articular compromise (especially, peripheral arthritis and sacroiliitis) are seen.

In this form of the disease, any of the routine agglutination assays produce an appropriate diagnosis (immunofluorescence [IF], enzyme-linked immunosorbent assay [ELISA], counterimmunoelectrophoresis [CIE], and Bengal rose test) with high specificity and sensitivity. Rarely, false-positive results may be caused by *Francisella tularensis* and *Yersinia enterocolitica*. With the epidemic of cholera in Latin America, the cross-reaction between *Vibrio cholerae* and *Brucella* is significant, producing false-positive serology to *Brucella* in patients with cholera. Even vaccines against cholera produce false-positive reactions transiently.

The medium Ruiz-Castañeda with Carrillo's modification (addition of 0.025% sodium phosphate sulfonate [SPS] and 0.05% of cysteine) increased the yield of *Brucella*. In the acute form, two blood cultures are as efficient as one bone marrow culture.

Subacute brucellosis (Figure 128.1)

Subacute form (undulant fever or Malta fever) is the typical and classic form described in endemic areas. There is intermittent low fever, often with articular compromise (peripheral arthritis, sacroiliitis, and/or

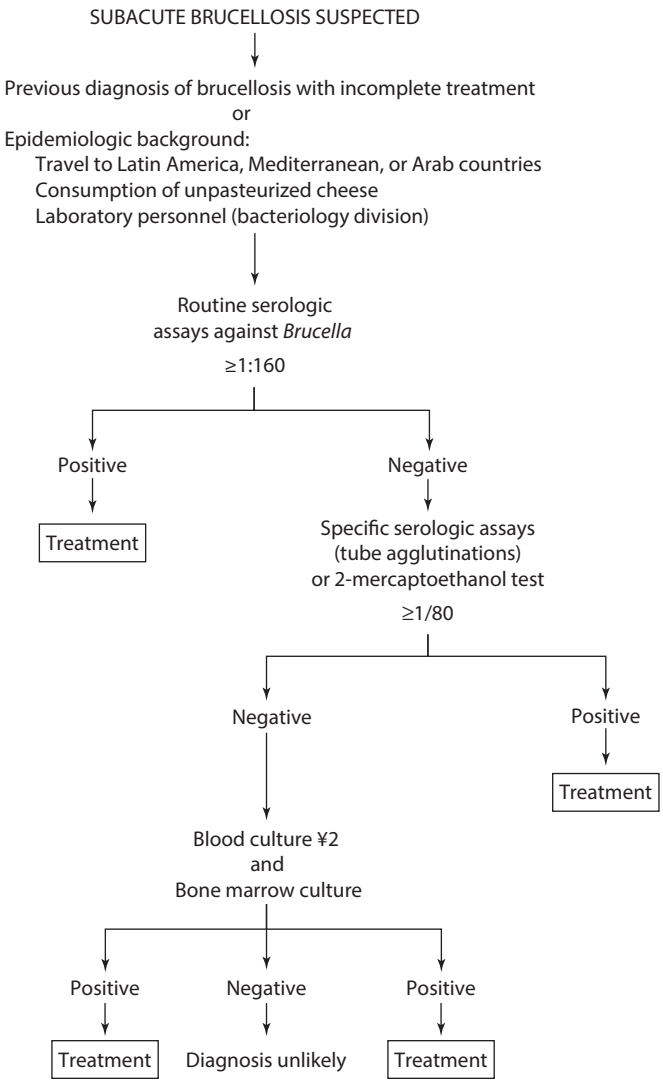

FIGURE 128.1 Algorithm for the evaluation and treatment of subacute brucellosis.

spondylitis), hematologic changes (e.g., pancytopenia, thrombocytopenia, hemolytic anemia), or hepatic damage (granulomatous hepatitis). Patients with incomplete treatment are also included in this form of brucellosis.

In this form of the disease, the 2-mercaptoethanol test detects IgG, and titer above 1:80 defines active infection. *Brucella* are isolated in 40% to 70% of serial blood cultures; the bone marrow culture (0.5 to 1 mL of aspirate from the iliac crest) permits isolation in 90% of these patients.

Chronic brucellosis (Figure 128.2)

In the chronic form with more than 1 year of illness, there usually is an afebrile pattern with myalgia, fatigue, depression, arthralgias, and so on. The most important differential diagnosis is chronic fatigue syndrome.

Other localized forms are granulomatous or recurrent uveitis and spondylitis. Peripheral arthritis and sacroiliitis are rare.

This form of disease is produced mainly by *B. melitensis*. It is found mainly in adults older than 30 years of age, especially older than 50 years old, and is rare in children.

The routine serologic tests and blood cultures give a diagnosis only 10% to 20% of the time. We recommend Coombs test specific for *Brucella* or blocking antibodies. The bone marrow in our experience produces a positive culture in 50% to 75% of patients.

Therapy

The intracellular character of *Brucella* results in an important therapeutic challenge, especially in subacute and chronic forms. Antibiotics should have in vitro activity, but the intracellular concentration must be adequate.

Tetracyclines have shown excellent in vitro activity throughout the world. The MIC90 (minimum inhibitory concentration required to inhibit growth of 90% of the organisms) was 2 μg/mL for tetracycline and 0.125 μg/mL for doxycycline in our surveillance in Peru. During the past 25 years, the antibiotic activity pattern of tetracycline against *B. melitensis* has not changed, which is remarkable because these are still our drugs of choice.

In addition, for oxytetracycline and doxycycline the minimal bactericidal concentration (MBC) was equal to MIC. All these features in conjunction with worldwide experience point to tetracyclines as the keystone of treatment.

The differences among tetracyclines are tolerance, dosage, and safety profile; however, the new ones have better tolerance and fewer side effects and can be used with meals without reducing efficacy. We prefer to use doxycycline or minocycline.

The other important aspect is the need to combine antibiotics to reduce the rate of relapse. Most antibiotics can reduce the fever, but recurrence is high.

Rifampin has been introduced as a preferential agent because of its excellent in vitro activity and intracellular concentration. The possibility of rapid resistance was shown in our strains when 5 of 10 strains exposed in vitro to rifampin developed resistance by the seventh day.

The third effective group of drugs against *Brucella* is the aminoglycosides, with good in vitro activity and good clinical response. The largest study was done with streptomycin; however, gentamicin, netilmicin, and amikacin showed the same and even better results in open trials.

Comparative studies have been done of doxycycline plus rifampin versus doxycycline plus streptomycin (D-S). Both schedules had a high cure rate (more than 95%); however, D-S had a lower relapse rate.

The doxycycline levels in the plasma of patients treated with rifampin were significantly lower than those of patients treated with D-S. Patients who were rapid acetylators had lower levels because they had higher clearance rates. In addition, the half-life

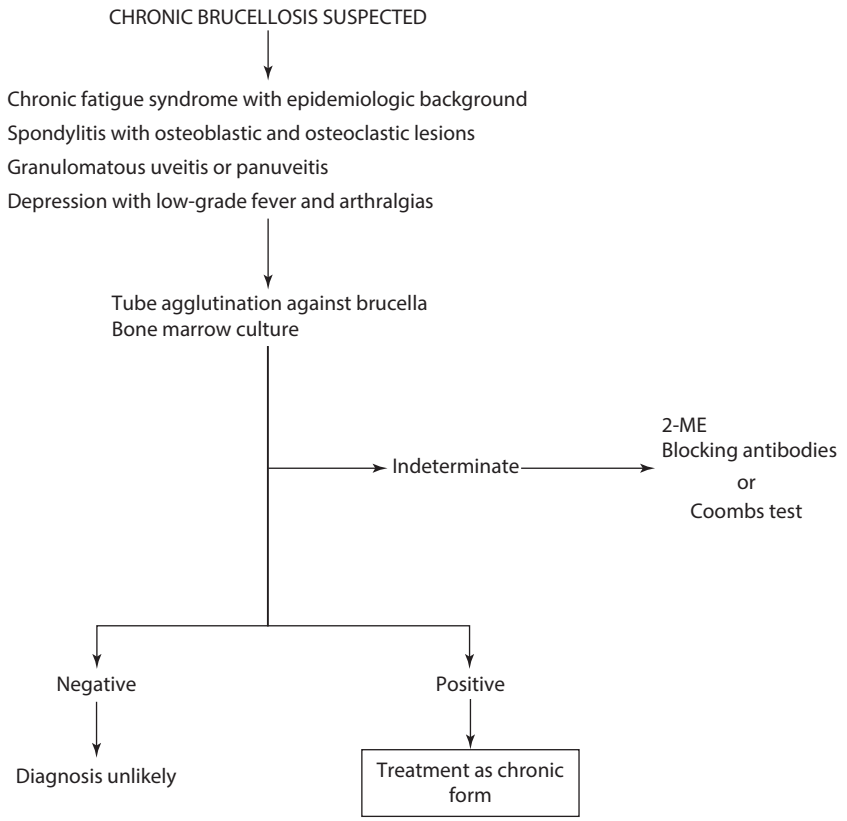

FIGURE 128.2 Algorithm for the evaluation and treatment of chronic brucellosis. 2-ME = 2-mercaptoethanol.

and the area under the curve were significantly lower in these patients. All these new data suggest that relapses may result from this interaction.

Adults

Our standard treatment for adult patients is oral doxycycline, 100 mg twice a day for 45 days, plus streptomycin, 1 g intramuscularly per day for 2 weeks (prolonging treatment with streptomycin for more than 2 weeks has not proved to be more effective); or doxycycline, 100 mg twice a day, plus rifampin, 600 mg once a day, both for 45 days. Only in a case of spondylitis, endocarditis, or brain abscess do we prolong treatment for 3 months.

In chronic brucellosis we prefer to use standard treatment for 45 days and then 3 months of doxycycline only. Some experts recommend adding levamisole for this special form during 3 months.

Children

In children younger than 8 years of age, tetracyclines cannot be used. The combination of rifampin, 15 to 20 mg/kg once a day for 4 weeks, and aminoglycosides at standard dose for 5 to 10 days is highly effective in children.

The use of trimethoprim–sulfamethoxazole (TMP–SMX) has also been recommended in children. TMP–SMX may be used at 240 mg for 4 weeks plus rifampin 20 mg/kg once a day for 4 weeks. This schedule has a high level of tolerance and few adverse effects; however, the efficacy is not as acceptable as with other schedules. Some report excellent results of TMP–SMX for 4 weeks plus gentamicin for 5 to 10 days.

Pregnancy and brucellosis

Brucellosis during pregnancy is a special problem because the best drug should be avoided and the clinical course and fetal prognosis are poor.

In our experience with more than 70% of women with brucellosis, early and adequate treatment showed excellent evolution of pregnancy, and the babies were normal. However, when antibiotic treatment is begun late, the prognosis is worse.

The best schedule is TMP–SMX plus rifampin for 6 weeks. Folic acid supplements should be given.

Another option is aminoglycoside for 10 days plus rifampin or TMP–SMX for 6 weeks.

Other antibiotics

Some drugs, such as chloramphenicol, erythromycin, ampicillin, and cephalosporins, showed moderate in vitro activity, but the clinical experience is not as good as with the other drugs.

Recently, the fluoroquinolones showed better in vitro activity, and they have good intracellular penetration. However, some trials showed that norfloxacin and ciprofloxacin had less clinical efficacy. Only ofloxacin in one trial showed good efficacy.

Steroids

We recommend corticosteroids only for 3 to 6 weeks for uveitis and for 2 to 10 weeks for severe thrombocytopenic purpura. If there is no response, we maintain steroids for 2 to 4 months. After this time if the thrombocytopenia is still evident, we recommend splenectomy.

Suggested reading

Colmenero JD, Fernández-Gallardo LC, Aqúndez JA, et al. Possible implication of doxycycline-rifampin interaction for treatment of brucellosis. Antimicrob Agent Chemother. 1994;38:2798–2802.

Dean AS, Crump L, Greter H, Hattendorf J, Schelling E, Zinsstag J. Clinical manifestations of human brucellosis: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2012;6(12): e1929. doi: 10.1371/journal.pntd.0001929.

Miguel PS, Fernandez G, Vasallo FJ, et al. Neurobrucellosis mimicking cerebral tumor: case report and literature review. Clin Neurol Neurosurg. 2006;108(4):404–406.

Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. N Engl J Med. 2005;352(22):2325–2336.

Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. The new global map of human brucellosis. Lancet Infect Dis. 2006;6(2):91–99.

Yousefi-Nooraie R, Mortaz-Hejri S, Mehrani M, Sadeghipour P. Antibiotics for treating human brucellosis. Cochrane Database Syst Rev. 2012;10:CD007179.

Campylobacter

David W. K. Acheson

Campylobacter (Greek *campylo*, curved; *bacter*, rod) are motile, non-spore-forming gram-negative rods. Today they are recognized as a very common cause of gastrointestinal (GI) infection in humans in many parts of the world. *Campylobacter* organisms were first isolated in the early 1900s from aborted sheep fetuses. However, it was not until the 1970s that *Campylobacter* were isolated from stool.

While there are many members of the genus *Campylobacter*, the major enteric pathogen for humans is *Campylobacter jejuni*, although *Campylobacter coli*, *Campylobacter fetus*, *Campylobacter upsaliensis*, and *Campylobacter lari* are also pathogenic to humans. *C. jejuni* is most frequently associated with GI disease, and *C. fetus* usually causes systemic infection, often in debilitated patients. *Campylobacter* are microaerophilic, and although all will grow at 37°C (98.6°F), *C. jejuni* grows best at 42°C (107.6°F). A number of selective media are in use for the detection of *Campylobacter* spp. and the organisms grow optimally in a gas mixture of 5% to 10% oxygen, 1% to 10% carbon dioxide, and some hydrogen. Growth may be present following overnight incubation, but 2 days are needed before a negative report can be issued.

Although several serotypes of *C. jejuni* have been reported, there are few data regarding the relative virulence of these different types, although some appear to be more closely associated with the development of Guillain–Barré syndrome (GBS) than others.

Epidemiology

Campylobacter is one of the most commonly diagnosed enteric bacterial infections in many parts of the United States and Europe. It is estimated that there are more than 2 million cases per year in the United States. It is especially common in children younger than 1 year of age and in young adults, and it occurs most often in the summer. *Campylobacter* species are found in fowl and many wild and domestic animals, and most human infections probably result from contamination of milk and other animal food sources, especially poultry. The recent increase in consumption of raw milk has led to illness associated with *Campylobacter*. The organisms can also be transmitted by direct contact with infected animals and contaminated water, and cross-contamination between infected poultry and other foods is probably one of the most frequent modes of transmission. Small numbers of organisms may cause disease; as few as 800 have been shown to cause infection in volunteer studies, but the infecting dose is usually about 10^4. Although asymptomatic carriage of *Campylobacter* is thought to be uncommon in developed countries, in less developed nations carriage rates as high as 37% have been reported among children.

Clinical features

The incubation period for *C. jejuni* infection varies and is typically between 1 and 7 days, with most cases occurring 2 to 4 days after exposure. Very short incubation periods of fewer than 12 hours have been reported.

Campylobacter jejuni illness typically presents with a prodrome of fever, headache, myalgia, and malaise for up to 24 hours before intestinal symptoms develop. The fever may be as high as 40°C (104°F), and the diarrhea varies from a few loose stools to copious watery discharge. Blood is often present in the stool but varies in amount. The illness usually lasts less than a week, but patients untreated with antibiotics often continue to excrete the organisms for several weeks. Documented bacteremia is thought to occur in the early stages of infection in up to 1% of cases. Routine surveillance of infection in England and Wales detected 394 cases of *Campylobacter* bacteremia in 11 years that increased with age, with a range of 0.3/1000 in children aged 1 to 4 years to 5.9/1000 in patients aged 65 years or more. Overall 89% of the identified isolates were *C. jejuni* or *C. coli*. This may explain why focal infections such as endocarditis, meningitis, septic abortion, acute cholecystitis, pancreatitis, and cystitis have all been documented. Postinfectious reactive arthritis may also occur, especially in human leukocyte antigen (HLA)-B27-positive individuals. One of the most serious consequences of infection with *C. jejuni* is the development of GBS. This is an autoimmune disorder of the peripheral nervous system resulting in an ascending flaccid paralysis that carries a mortality rate of up to 5%. GBS is thought to be caused by molecular mimicry between polysaccharides on the outer surface of *C. jejuni* and gangliosides in the myelin sheaths of peripheral nerves.

In contrast to *C. jejuni, C. fetus* commonly produces systemic disease, often in vascular sites: endocarditis, pericarditis, and mycotic aneurysms of the abdominal aorta. Central nervous system infections such as meningoencephalitis also occur with *C. fetus*, as do other localized infections, including septic arthritis, spontaneous bacterial peritonitis, salpingitis, lung abscess, empyema, cellulitis, urinary tract infection, vertebral osteomyelitis, and cholecystitis. In patients with acquired immunodeficiency syndrome (AIDS), *Campylobacter* species other than *C. fetus* and *C. jejuni* may also cause bacteremia.

Diagnosis

Campylobacter have a characteristic darting motility, and a presumptive diagnosis of *Campylobacter* infection may be made by examination of stool passed within 2 hours using direct dark-field or phase-contrast microscopy. Leukocytes and red cells are also often seen in stool samples, with 75% of patients having polymorphonuclear leukocytes in their stool. Confirmation of the diagnosis of *C. jejuni* infection is based on a positive stool or blood culture as noted above, although *Campylobacter* is fastidious and may die during transport to the laboratory. DNA probes, polymerase chain reaction, and serologic testing all have been used to confirm diagnosis but are not routinely available. Direct detection of *Campylobacter* antigens in stool using enzyme immunoassays is a relatively new approach that is now commercially available. This method has the attraction of not requiring live organisms but has the detraction of not producing an isolate that will be available for antimicrobial sensitivity testing. *Campylobacter fetus* may be isolated from blood held in culture up to 14 days. The fastidious nature of the organisms means that failure to culture *Campylobacter* does not rule them out as the cause of significant clinical disease.

Therapy

As with all diarrheal diseases, fluid replacement and attention to electrolyte balance is the most important therapy in *Campylobacter* diarrhea. Oral rehydration is usually adequate, but patients with severe dehydration should be given volume replacement with intravenous solutions of electrolytes and water.

Most *Campylobacter* infections are mild and self-limited and do not result in a visit to a physician. These mild infections do not usually require antimicrobial therapy. Antimicrobial therapy should be reserved for patients who are severely ill, elderly, pregnant, or immunocompromised but may on occasion also be indicated in patients with bloody stools, high fever, extraintestinal infection, worsening symptoms or relapses, and those with symptoms lasting longer than 1 week. Treating patients later in the course of the disease (after several days of symptoms) will remove *Campylobacter* from the stool, but it is not likely to have a dramatic effect on the duration of symptoms. Person-to-person spread generally is not considered a major concern with *Campylobacter*, so treating to prevent this is not generally recommended (except in the case of food handlers). However, there may be exceptions to this, for example, the reduction of spread in day-care settings. Antibiotic therapy can have a dramatic positive effect on symptoms of *C. jejuni* infection, justifying a trial of therapy in severe or persistent illness.

Campylobacter jejuni is usually susceptible to many antimicrobial agents in vitro, including macrolides, tetracyclines, aminoglycosides, chloramphenicol, quinolones, and nitrofurans. The clinically important antibiotics include the macrolides, fluoroquinolones, aminoglycosides, and carbapenems. They are inherently resistant to trimethoprim and most cephalosporins except cefotaxime, ceftazidime, and cefpirone.

Erythromycin was, for years, the first-line drug to treat *Campylobacter*. However today the first-line agents for *Campylobacter* gastroenteritis include fluoroquinolones (if sensitive) or azithromycin. In patients with uncomplicated *Campylobacter* infection a first-line treatment would be levofloxacin or azithromycin 500 mg PO daily for 3 days or until signs and symptoms of disease have improved. For those with complications or underlying immunosuppression, a longer course (7 to 14 days) may be warranted. If a patient is not able to tolerate oral treatment or if they are severely ill other options include the use of an aminoglycoside or a carbapenem but it is recommended that susceptibility testing should be performed prior to their use.

Campylobacter resistance has not become a huge issue but is certainly more of a concern than it used to be. Generally the rate of macrolide-resistance among *Campylobacter* has remained stable at <5% in most parts of the world—but has been reported to be higher in Thailand and in Ireland. The prevalence of fluoroquinolone-resistant *Campylobacter* is rising. Resistance rates of greater than 50% have been reported in Spain, Hungary, and several developing countries. The rate of fluoroquinolone resistance is also increasing

in Southeast Asia and in the United States; in the United States, resistance increased from 0% to 19% between 1989 and 2001. This growing level of resistance to fluoroquinolones is important in the context of treating infections that may have been acquired in areas of high resistance or if treatment is appearing to fail.

Prognosis and prevention

Most patients recover totally following infection with *C. jejuni*. Complications such as reactive arthritis and GBS are unusual. Systemic *C. fetus* infections have a significant mortality, especially in patients with underlying disease such as diabetes mellitus or cirrhosis or who are immunocompromised. Transmission of *Campylobacter* infection can be reduced by careful food handling, with special attention to cross-contamination from poultry products. Proper cooking of food, pasteurization of milk, and protection of water supplies are all critical in preventing infection with *Campylobacter*.

Suggested reading

Allos BM. Clinical features and treatment of *Campylobacter* infection. In: UpToDate 2013; UpToDate. Available at: http://www.uptodate.com/ (accessed September 30, 2013).

Allos BM. Microbiology, pathogenesis, and epidemiology of *Campylobacter* infection. In: UpToDate 2013; UpToDate. Available at: http://www.uptodate.com/ (accessed September 30, 2013)

Giesendorf BAJ, van Belkum A, Koeken A, et al. Development of species-specific DNA probes for *Campylobacter jejuni*, *Campylobacter coli*, and *Campylobacter lari* by polymerase chain reaction fingerprinting. *J Clin Microbiol*. 1993;31:1541–1546.

Nachamkin I, Allos B, Ho T. *Campylobacter* species and Guillain-Barré syndrome. *Clin Microbiol Rev*. 1998;11:555–567.

Skirrow MB. Campylobacter enteritis: a "new" disease. *Br Med J*. 1977;2(6078):9–11.

Skirrow MB, Blaser MJ. *Campylobacter jejuni*. In: Blaser MJ, Smith PD, Ravodom HB, Guerrant RL, eds. *Infections of the Gastrointestinal Tract*. New York: Raven Press; 1995:825–848.

Skirrow MB, Jones DM, Sutcliffe E, Benjamin J. *Campylobacter* bacteraemia in England and Wales, 1981–1991. *Epidemiol Infect*. 1993;110:567–573.

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Clostridium

Derek Forster

Introduction

The genus *Clostridium* contains many species of bacteria that cause human diseases. These bacteria produce some of the most deadly toxins ever discovered. Distinctive infections include botulism, tetanus, gas gangrene, and food poisoning from *Clostridium perfringens*. With few exceptions, clostridia are obligate, anaerobic, spore-forming bacilli that are ubiquitous in the environment, in soil and marine sediment. Although a member of the *Clostridium* genus, *Clostridium difficile* is discussed separately (Chapter 51, Antibiotic-associated diarrhea).

Botulism

Botulism is a rare but potentially fatal disease caused by *Clostridium botulinum* bacteria, which produce botulinum toxin, one of the most potent bacterial toxins ever described. It can be classified into four categories which reflect the mode of acquisition: foodborne botulism, infant and adult enteric botulism, wound botulism, and inhalational botulism. A recent category, iatrogenic botulism, has also been described in patients who have received botulinum toxin injections. All modes of acquisition can lead to the clinical syndrome of botulism, which manifests as symmetric flaccid paralysis of the voluntary musculature.

The word botulism is derived from the latin word *botulus*, which means sausage, and is a reference to an early investigation of "sausage poisoning" in a southern German town in which affected patients developed gastrointestinal and neuromuscular symptoms. This investigation is believed to be the first described outbreak of foodborne botulism.

There are eight strains of *C. botulinum* that are classified according to the type of toxin they produce. Of the eight toxin types, only types A, B, E, and occasionally F cause human disease. The spores are heat-resistant and able to survive at 100°C for several hours. In contrast to the spores, the toxins are heat-labile and are readily denatured by heating to temperatures above 80°C.

Epidemiology

Foodborne botulism

Foodborne botulism is caused by the ingestion of contaminated improperly cooked or raw foods containing preformed toxin. The toxin is absorbed in the small intestine whereby it enters the bloodstream and causes disease as it reaches the peripheral nervous system. The ingestion of spores alone does not cause botulism because the competitive environment of the gastrointestinal tract does not allow the spores to vegetate and produce toxin. The exceptions to this are infantile botulism and adult enteric botulism, which are discussed later.

Foodborne botulism represents the greatest public health concern related to botulism and is most frequently recognized in small outbreaks involving home-canned fruits and vegetables but has also been

associated with commercial products and restaurants. In the USA, 263 cases from 160 foodborne botulism events occurred between 1990 and 2000. Toxin type A was the most common, causing 51% of all cases. The highest percentage of cases occurred in Alaska where 103 (39% of cases) were due to ingestion of non-commercial fish and marine mammal products. Another study evaluated the epidemiology of endemic foodborne botulism among Alaskan natives from 1947 to 2007 and concluded that the incidence was decreasing but still remained >800 times the overall US rate.

Wound botulism

Wound botulism is caused by contamination of a wound with *C. botulinum* spores that germinate and produce toxin. Reported cases have increased dramatically over the last 20 years and are now mainly attributed to injection drug use. These cases have been associated with the use of "black tar" heroin administered subcutaneously or intramuscularly, a technique known as "skin popping." Wound botulism has also been described following open fractures and surgery.

Infant and adult enteric botulism

Infant botulism occurs when spores (not toxins) are ingested and then vegetate in the intestinal tract due to a lack of competing bacteria, producing toxin. It is the most common form of botulism in the United States with 2419 cases identified from 1976 to 2006. The main reservoir leading to infection is thought to be environmental dust containing spores. This correlates with the fact that states with high soil botulinum spore counts have the highest incidence of cases. California accounts for nearly 50% of all US cases. Honey remains the only identified food and the only avoidable source of infant botulism. Educational efforts have increased public awareness and ingestion of honey by infants has decreased markedly; however, significant decreases in cases have not been seen.

Adult enteric botulism, like infant botulism, occurs from infection of the intestinal tract with vegetative bacteria that leads to toxin production. It is considered rare in the adult but those at risk include patients with a disruption of their bowel flora due to anatomic abnormalities, functional disorders, or antibiotic use. Protracted symptoms and relapse due to persistent production of toxin may be seen.

Inhalational botulism

Inhalational botulism is not a naturally occurring disease. It has been described among users of intranasal cocaine, leading to a local wound infection in the sinuses where the bacteria ultimately germinate and produce toxin. This form also represents a potential route for bioterrorism attacks. A deliberate release of aerosolized toxin could produce an outbreak of botulism with considerable mortality.

Iatrogenic botulism

Iatrogenic botulism is a recently described entity that is caused by the direct injection of botulinum toxin for cosmetic purposes. In 2004, four cases of botulism were linked to the use of a highly concentrated, unlicensed botulinum toxin. These patients may have received doses nearly 3000 times the estimated human lethal dose by injection and had pretreatment serum toxin levels up to 43 times the estimated lethal human dose. All four patients survived but suffered a long hospital course.

Pathogenesis

Regardless of the mode of acquisition, once toxin has entered the bloodstream it reaches the peripheral cholinergic synapse where it eventually prevents the release of acetylcholine. It binds to a specific receptor called synaptotagmin on the pre-synaptic cleft of the synapse. Once bound, the toxin enters the cell via receptor-mediated endocytosis where it irreversibly disrupts the release of acetycholine. The exact mechanism of this action varies and depends on the type of toxin present. Return of function requires the formation of a new presynaptic terminal with a new synapse which generally takes 6 months or longer to occur. For this reason, clinical recovery is prolonged.

Clinical

The classic description of botulism is the acute onset of symmetric cranial nerve palsies with subsequent symmetrical descending flaccid paralysis that may progress to respiratory arrest. Fever is typically not present unless it is a component of a wound infection as with wound botulism. Sensory deficits are absent. Although botulinum toxin may be transported in a retrograde fashion via the nerves, central nervous system (CNS) involvement is rare and the patient almost always remains responsive.

As the disease progresses, descending paralysis of the neck, shoulders, upper extremities, and lower extremities can occur. Respiratory arrest can occur when the diaphragm and accessory breathing muscles become involved. Constipation is invariably present at later stages. The severity of disease ranges from mild involvement of the cranial nerves to full paralysis requiring mechanical ventilation and reflects the amount of toxin in the bloodstream.

Other symptoms depend on the mode of acquisition. With foodborne botulism, patients may have a prodrome of nausea, vomiting, abdominal pain, and dry mouth. In wound botulism, local wound infection with fever may be present. The incubation period is difficult to ascertain given the frequency of injection drug use but is generally longer than other forms of botulism (7 to 14 days) because of the time required for spores to vegetate, produce local infection, and generate toxin. At the time of evaluation, the local wound infection may have resolved, making history the key to diagnosis. The presentation of infantile botulism varies but may involve constipation, weakness, feeding difficulties, hypotonia, drooling, irritability, and a weak cry.

The major differential diagnoses are myasthenia gravis, Lambert–Eaton myasthenia syndrome, tick paralysis, Guillain–Barré syndrome and poliomyelitis. The edrophonium test may be positive in botulism and thus may not distinguish botulism from myasthenia gravis. Guillain–Barré syndrome frequently begins with sensory complaints and rarely as cranial nerve dysfunction. Fever is usually present in poliomyelitis but not in botulism. Cerebrospinal fluid (CSF) analysis is normal in botulism.

Diagnosis

The clinical syndrome of botulism is distinctive and thus a careful history and physical examination are essential to considering and making the diagnosis. Confirmation involves detection of the toxin in the patient's serum, gastric secretions, stool, or a food sample. This is done via mouse bioassay, which is performed in a limited number of public health laboratories.

Other diagnostic tools include anaerobic cultures of serum, stool, and implicated food if available; however, the strict anaerobic conditions needed for growth make isolation of *C. botulinum* difficult. Enzyme-linked immunosorbent assays and polymerase chain reaction have been used for detection in contaminated food samples but are not available for widespread use.

Treatment

The mainstay of therapy is supportive care with intubation and mechanical ventilation if necessary. The only specific therapy is botulinum antitoxin, which exists as two forms: equine serum heptavalent botulism antitoxin and human-derived botulism immune globulin. The equine antitoxin is used to treat adults and children > 1 year of age. Rates of hypersensitivity (including anaphylaxis) have been reported to be between 9% and 20% and thus a test dose is often given prior to administration. Human botulinum immune globulin (BabyBIG) is the recommended antitoxin for use in infantile botulism (children < 1 year of age). Antitoxin administration should not be delayed while awaiting the results of diagnostic testing. The antitoxin is available through the Centers for Disease Control and Prevention (CDC). A pentavalent antitoxin is only available through the department of defense.

Antibiotic therapy is often used for wound botulism. Penicillin G provides effective coverage of clostridial species with metronidazole a good alternative for penicillin-allergic patients. Wound debridement should be performed even if the wound appears unimpressive. A polymicrobial infection may be present, and thus broader coverage can be considered, but the use of aminoglycosides and clindamycin is contraindicated as they may induce neuromuscular blockade and thus worsen the effects of the toxin. Antibiotics are not recommended for infant botulism or adults with suspected enteric botulism as this may increase the toxin available for absorption. In the setting of foodborne botulism, laxatives, enemas, or other cathartics may be given if no significant ileus is present.

Prevention

A pentavalent botulinum toxoid vaccine was available for occupational exposure to botulinum toxins but was discontinued in 2011.

Tetanus

Tetanus is a neurologic disorder characterized by muscle spasms; it is caused by *Clostridium tetani*, an obligately anaerobic gram-positive bacillus found worldwide in soil. It has a characteristic "tennis racket" or "drumstick" appearance on Gram stain (Figure 130.1). Because of vaccination, the annual incidence of cases in the United States has decreased markedly from 1947 to 2008 (Figure 130.2). In the United States, there were 233 cases from 2001 to 2008. Most of the cases were in individuals over 65, reflecting waning immunity. In developing countries tetanus remains endemic with an estimated one million cases occurring worldwide annually with 300 000 to 500 000 deaths. Prevention of neonatal tetanus has been a target of the World Health Organization which has resulted in a decrease in the number of cases and deaths.

Pathogenesis

A wound infection with *C. tetani* is the first step of the disease process. Once the bacterium vegetates it produces tetanospasmin (tetanus toxin) and tetanolysin. Tetanospasmin enters the nervous system through presynaptic terminals and interrupts neuromuscular transmission whereby it can initially cause local paralysis. Once it enters the nervous system, retrograde transport facilitates its movement to the CNS where it prevents the release of inhibitory neurotransmitters, which results in an unopposed excitatory signal. This effect is also seen in the autonomic nervous system, causing a hypersympathetic state. Tetanospasmin binding is irreversible, and thus the effects last the lifetime of the neuron. The other toxin produced is tetanolysin, which causes tissue necrosis and thus a more favorable environment for growth of the bacterium.

Clinical

Tetanus exists in four clinical forms: generalized, local, cephalic, and neonatal. These forms reflect the location of initial involvement as well as the extent of disease. The incubation period is variable and can be as short as 1 day or as long as several months. The distance from the site of inoculation of the organism to the CNS is a major determinant of the incubation period, with longer distances resulting in a longer incubation period.

Generalized tetanus is the most commonly recognized form which often presents with trismus but later manifests as tonic contraction of skeletal muscles with intermittent muscular spasms.

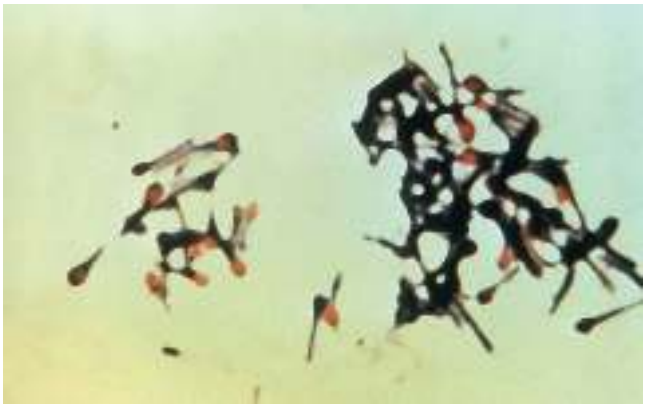

FIGURE 130.1 "Tennis racket" or "drumstick" appearance of Clostridum tetani. (http://www.cdc.gov/tetanus/about/photos.html)

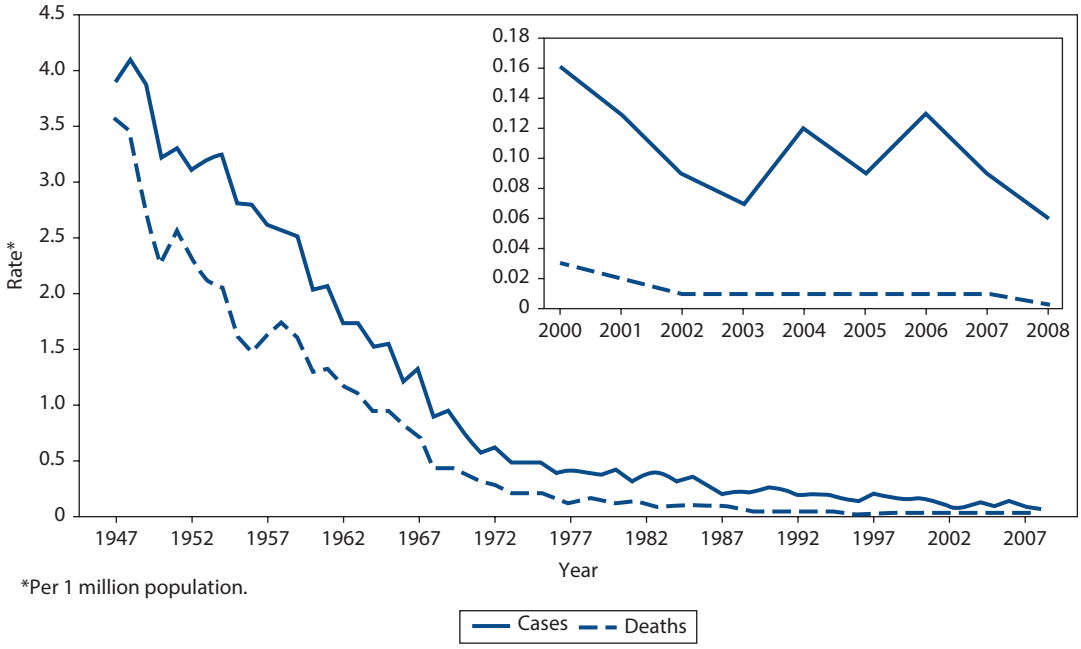

FIGURE 130.2 Annual rate of tetanus cases and tetanus deaths in the United States during 1947–2008, according to the National Notifiable Disease Surveillance System. From 1947–2008. (Centers for Disease Control and Prevention (CDC). Tetanus surveillance—United States, 2001–2008. MMWR Morb Mortal Wkly Rep. 2011;60 (12):365–369 available from: PM:21451446)

Decorticate posturing with flexion of the arms and extension of the legs is classically described with generalized spasms. There is no impairment in consciousness and thus the spasms are intensely painful. Symptoms of autonomic hyperactivity including irritability, restlessness, sweating, and tachycardia may be seen early in the course with progression to cardiac arrhythmias, labile blood pressures, and fevers in the later stages. This autonomic instability is the leading cause of death with a fatality rate of 11% to 28%.

Localized tetanus involves the muscles at the site of inoculation, presenting as tonic and spastic contractions. It may be mild and may persist for weeks to months. Although it may resolve spontaneously without long-term sequelae, it is often a prodrome of generalized tetanus. The reported incidence of localized tetanus is 13%.

Cephalic tetanus is a form of localized tetanus that involves the head or neck. Although it initially involves only the cranial nerves, it can be a prodrome of generalized tetanus. It can also spontaneously resolve without complications. The incubation period for progression to generalized tetanus is short due to its proximity to the CNS.

Neonatal tetanus typically occurs in the first 28 days of life. It develops in infants of unvaccinated mothers when infection of the umbilical stump with *C. tetani* occurs due to poor aseptic technique at delivery or contamination with dirt, straw, or other materials. Cultural practices involving the application of clarified butter, juices, and cow dung to the umbilical stump have also been implicated in the development of disease. It may manifest initially as general weakness and a failure to nurse but progresses to rigidity, spasms, trismus, and seizures. Sepsis, related to bacterial infection of the umbilical stump, occurs in about half of the patients and accounts for significant mortality which can exceed 90%.

Diagnosis

The diagnosis of tetanus is primarily based on the typical findings mentioned above. There is no definitive testing to confirm or exclude the diagnosis. Antitetanus antibodies are often undetectable in clinical disease. Culture for *C. tetani* is of little value because of poor sensitivity and specificity as positive cultures may be present without disease and represent colonization rather than true infection. Inadequate immunization and inadequate wound prophylaxis are important risk factors for the development of tetanus and thus, knowing a patient's prior vaccination status can be helpful when entertaining the diagnosis. Patients should also be questioned regarding prior tetanus prone injuries and physical exam should include evaluating for any possible inoculation sites.

There are several considerations in the differential diagnosis including drug-induced dystonia, trismus due to dental infections, strychnine poisoning, and neuroleptic malignant syndrome. Drug-induced dystonia, in contrast to tetanus, produces deviation of the eyes and an absence of tonic muscular contractions between spasms. Also, administration of anticholinergics will reverse the spasms in drug-induced dystonia but not in tetanus. Trismus due to dental infections is seen in the presence of an obvious dental abscess. Strychnine poisoning can cause a syndrome similar to tetanus. Testing of blood, urine, and tissue samples for strychnine can be done in settings when accidental or intentional poisoning is considered. Neuroleptic malignant syndrome can present with muscular rigidity and autonomic instability as well as fever and altered mental status, both of which are not seen in tetanus.

Treatment

The initial treatment of tetanus should include early and aggressive airway management. If endotracheal intubation is required, benzodiazepine sedation and neuromuscular blockade should be used because passage of the endotracheal tube can trigger spasms. Subsequent control of spasms requires the use of benzodiazepines at doses higher than typically required for sedation. Neuromuscular blockade may be required if adequate control is not achieved with benzodiazepines. Magnesium sulfate may be helpful as an adjunct to treatment. It blocks catecholamine release from nerves and reduces receptor responsiveness to catecholamines. It has been shown to reduce the use of other drugs for control of spasms and aid in the control of autonomic dysfunction but has not been shown to reduce mortality or the need for mechanical ventilation. Patients should be placed in darkened, quiet areas in the ICU to avoid triggering muscular spasms. This becomes more important in resource-limited settings where access to some medications and mechanical ventilation may not be available.

Passive immunization with human tetanus immune globulin (HTIG) to bind free toxin should be given as soon as the diagnosis of tetanus is considered. The dose for treating active tetanus is 3000 IU given intramuscularly. This shortens the course of tetanus and reduces the severity. Intrathecal administration may provide benefit when given in combination with intramuscular HTIG. Because infection does not confer immunity, active immunization with tetanus toxoid should also be initiated.

Antibiotics are generally recommended but their benefit is unclear. Antimicrobial susceptibilities demonstrate reliable sensitivity to penicillin and metronidazole as well as cephalosporins, imipenem, macrolides, and tetracycline. Favorable results with metronidazole compared to penicillin were described in one study with reduction in mortality and shorter hospitalization; however, subsequent studies have failed to show a difference. A possible explanation of poorer response to pencillin would be γ-aminobutyric acid (GABA) antagonism which is known to occur and results in CNS excitability. This effect is also seen with later-generation cephalosporins. Local wound management should be undertaken but surgical intervention, if necessary, should be performed after spasms are controlled.

Prevention

Tetanus is considered a preventable disease with vaccination. Current recommendations from the Advisory Committee on Immunization Practices (ACIP) include a combination vaccine containing diphtheria, tetanus, and pertussis (DTaP) as primary vaccination given at ages 2, 4, and 6 months, followed by a dose at age 15 to 18 months and again at age 4 to 6 years. A Tdap should be given for children ages 11 to 12. Adults should receive tetanus booster every 10 years with one booster being given as a Tdap to also provide boosted immunity for pertussis. Patients that sustain an unclean wound that is not considered minor should also receive a booster if more than 5 years has passed from their last immunization.

Clostridial myonecrosis (gas gangrene)

Clostridial myonecrosis is a deep space infection that results in destruction of healthy muscle tissue and causes systemic toxicity. It can result from trauma with direct inoculation or contamination and subsequent infection of a wound from *C. perfringens*. These account for about 70% of cases. It can also arise spontaneously from hematogenous seeding with *Clostridium septicum*. As with other species of clostridia, they are found commonly in soil. *Clostridium perfringens* is also found commonly in the intestines of humans and animals and requires a microaerophilic environment to thrive, which is in contrast to *C. septicum* which can grow in oxygen-rich environments. It is a life-threatening infection with mortality reported in 19% of traumatic cases and up to 81% of spontaneous cases. Other less common species that can cause disease include *C. sordelli*, *C. novyi*, *C. bifermentans*, and *C. histolyticum*.

Pathogenesis

Traumatic injury can result in vascular compromise to previously healthy tissue and provide an anaerobic environment which is ideal for the growth of *C. perfringens* as well as some other species listed above. Once the spores germinate, they produce alpha and theta toxin that cause tissue destruction, hemolysis, vasodilatation, and alterations in the extravascular migration of neutrophils. It is this alteration of neutrophil migration that accounts for the characteristic absence of purulence in the necrotic tissues. Alpha toxin can contribute to shock by suppressing myocardial contractility, which further compromises cardiac output in the setting of endothelial dysfunction and systemic vasodilatation.

Spontaneous clostridial myonecrosis is typically the result of hematogenous seeding from bacteria (usually *C. septicum*) that gain access to the bloodstream through the gastrointestinal tract. In stark contrast to *C. perfringens*, these bacteria do not require an anaerobic environment and thus can affect previously normal and healthy tissue. *C. septicum* also produces several toxins; however, their contribution to pathogenesis is less clearly known. As with *C. perfringens*, neutrophils are notably absent in the necrotic tissues. There are some predisposing factors which include colonic or hematologic malignancy, inflammatory bowel disease, recent gastrointestinal surgery, neutropenia, and acquired immunodeficiency syndrome.

Clinical

Severe pain is one of the hallmark findings in early disease and is present in both traumatic and spontaneous cases. In traumatic cases, erythema of the inoculation site may be seen. The classic skin findings include the rapid development of a bronze appearance, followed by purple or red discoloration with formation of fluid-filled blisters. As stated above, purulence is uncommon. The extremities become tense from progressive edema of the deeper structures and gas may be appreciated on palpation. Anemia may result from the hemolytic

effect of alpha toxin. Progression to sepsis and multiorgan failure may occur rapidly and can be seen within hours of the initial presentation.

Diagnosis and treatment

Early consideration of gas gangrene is critical to treatment success. The clinical signs mentioned above should point to the diagnosis. Gas in the tissues can be demonstrated by radiography, ultrasound, CT scan, or MRI; the latter two modalities also show deep structures in detail to determine if the infection is localized or if it is involving adjacent structures. Gram stain of involved tissue or fluid may demonstrate gram-positive or gram-variable rods with culture providing a definitive diagnosis.

The most essential component of therapy is early surgical debridement of the involved tissues. Antibiotics comprise another key component of therapy and reduce mortality when combined with early surgery. Penicillin remains one of the most widely used antibiotics to treat clostridial myonecrosis. The addition of clindamycin provides a highly active regimen and through its inhibition of protein synthesis may also decrease toxin production. Other antibiotics with activity include tetracyclines, metronidazole, erythromycin, and carbapenems. Hyperbaric oxygen has been used as an adjunct to therapy with reported improved survival rates; however, its use remains controversial. *Clostridum septicum* can survive and grow in an oxygen-rich environment and thus spontaneous cases caused by this organism would be unlikely to benefit from the use of hyperbaric oxygen.

Food poisoning caused by *clostridium perfringens*

C. perfringens is the second most common bacterial cause of foodborne illness in the United States, with one million cases each year. It results from the ingestion of a large inoculum of vegetative bacteria. Once ingested, the bacteria release an enterotoxin that causes watery diarrhea, abdominal cramping, vomiting, and fever. The incubation period is short, generally between 7 and 15 hours with spontaneous resolution of symptoms occurring at 24 to 48 hours. Meats are the most common contaminated foods with most cases occurring as a common source outbreak. Diagnosis requires the detection of bacterial toxin in stool or by detection of at least 10^6 *C. perfringens* spores per gram of stool in symptomatic patients. Therapy is supportive with hydration playing a major role. Of the five strains of *C. perfringens* (A through E) type A accounts for the majority of cases.

Other clostridial infections

Other clostridial infections may occur as part of a disease process described above or as part of a separate entity. For example, clostridial bacteremia may occur in the setting of clostridial myonecrosis, with *C. perfringens* and *C. septicum* accounting for the majority of cases. The association with *C. septicum* bacteremia and the presence of an underlying hematologic or colonic malignancy should be noted. Clostridia can also cause infections of the gallbladder with *C. perfringens* again accounting for the majority of cases. In this setting, gas may be demonstrated in the biliary tract and would be an indication for surgical intervention. Clostridia may be present as a component of polymicrobial abdominal infections that result from contamination of the peritoneum from intestinal contents. Although rare, they have also been described in anaerobic pulmonary infections.

Suggested reading

Alpern RJ, Dowell VR Jr. *Clostridium septicum* infections and malignancy. *JAMA*. 1969;209(3):385–388.

Centers for Disease Control and Prevention (CDC). Tetanus surveillance—United States, 2001–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(12):365–369.

Grass JE, Gould LH, Mahon BE. Epidemiology of foodborne disease outbreaks caused by *Clostridium perfringens*, United States, 1998–2010. *Foodborne Pathog Dis*. 2013;10(2) 131–136.

Hart GB, Lamb RC, Strauss MB. Gas gangrene. *J Trauma*. 1983;23(11):991–1000.

Koepke R, Sobel J, Arnon SS. Global occurrence of infant botulism, 1976–2006. *Pediatrics*. 2008;122(1):e73–e82.

Reddy P, Bleck T. "*Clostridium tetani* (Tetanus)." In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia: Churchill Livingstone; 2010:3091–3096.

Roper MH, Vandelaer JH, Gasse FL. Maternal and neonatal tetanus. *Lancet*. 2007;370(9603): 1947–1959.

Sobel J. Botulism. *Clin Infect Dis*. 2005; 41(8):1167–1173.

Sobel J, Tucker N, Sulka A, McLaughlin J, Maslanka S. Foodborne botulism in the United States, 1990–2000. *Emerg Infect Dis*. 2004;10(9):1606–1611.

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Corynebacteria

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Corynebacterium diphtheriae (diphtheria)

Diphtheria is an acute, infectious, preventable, and sometimes fatal disease caused by *Corynebacterium diphtheriae*. The infection is usually localized to the upper part of the respiratory tract and/or the skin; from here it gives rise to local and systemic signs or it can be an asymptomatic carrier state. These signs are the result of a toxin produced by the microorganisms multiplying at the site of infection. The systemic complications particularly affect the heart (22%), the peripheral nerves (5%), and/or the kidneys (renal failure in severe cases).

Cause

Diphtheria is distributed worldwide, there are four biotypes: gravis, intermedius, mitis, and belfanti. All are associated with epidemic and endemic diphtheria. The highest incidence occurs in temperate climates. It occurs predominantly under poor socioeconomic conditions, where crowding is common and where many persons are either not immunized or inadequately immunized. In the United States 20% to 60% of adults are susceptible to diphtheria since the immunity wanes and it is not customary to receive boosters. In the 1990s there were reports of diphtheria outbreaks in the newly independent states of the former Soviet Union. Outbreaks were also experienced in other European countries and were characterized by a high fatality rate, and a large number of complications and adult cases. Diphtheria is seen in developed countries in people that travel to and return from endemic areas as well as in immigrants from endemic areas.

The only significant reservoir of *C. diphtheriae* is the human host. The organism is transmitted directly from one person to another, and intimate contact is required. Transmission is usually by way of infected droplets of nasopharyngeal secretions. Infective skin exudate has been involved in human-to-human transmission. Transmission may also occur via animals, fomites, or milk. The infectious period is usually 2 weeks from onset of symptoms, as long as 6 weeks, and, if treated with antibiotics, to less than 4 days.

Immunity depends on antitoxin in the host's blood. Antitoxin is formed by immunization or by clinical or subclinical infection, including skin infections. Immunity does not prevent carriage. Since immunity varies the Centers for Disease Control and Prevention (CDC) recommends that adults receive a diphtheria-toxoid-containing vaccine (Tdap) every 10 years after completing a primary childhood vaccination series. Despite incomplete immunity the rate of clinical disease is low, US incidence of ~0.001 cases/100 000 population.

Clinical features

Diphtheria may be symptomless or rapidly fatal. The incubation period varies from 1 to 7 days but is most commonly 2 to 4 days.

Respiratory diphtheria

Diphtheria infection of the respiratory tract is usually caused by toxin-producing strains of *C. diphtheriae*, rarely by toxigenic strains of *Corynebacterium ulcerans*, *Corynebacterium pseudotuberculosis* or *Corynebacterium hemolyticum*.

Anterior nares diphtheria

The infection is localized to the anterior nasal area and is manifested by unilateral or bilateral serous or serosanguineous discharge that erodes the adjacent skin, resulting in small crusted lesions. The membrane may be seen in the nose.

Tonsillar (faucial) diphtheria

Tonsillar diphtheria is the most common presentation and the most toxic form. The onset is usually sudden, with fever rarely exceeding 38°C (100.4°F), malaise, and mild sore throat. The pharynx is moderately infected, and a thick, whitish-gray tonsillar exudate is often seen. The tonsillar and cervical lymph nodes are enlarged. The exudate may extend to other areas and result in nasopharyngeal diphtheria and massive cervical lymphadenopathy (bull neck appearance also called malignant diphtheria). The most common complaints are sore throat (85%), pain on swallowing (23%), nausea and vomiting (25%), and headache (18%).

Pharyngeal diphtheria

Pharyngeal diphtheria is diagnosed when the membrane extends from the tonsillar area to the pharynx.

Laryngeal and bronchial diphtheria

Laryngeal and bronchial diphtheria involves the larynx. The voice becomes hoarse and inspiratory and expiratory stridor may appear; dyspnea and cyanosis occur, and the accessory muscles of respiration are used. Tracheostomy or intubation is needed.

Cutaneous diphtheria

Classically described as diphtheria in tropical areas, cutaneous diphtheria now is seen in nontropical areas as well. It takes the form of a chronic nonhealing ulcer, sometimes covered with a grayish membranous exudate. Another form is secondary infection of a pre-existing wound. Finally, superinfection with *C. diphtheriae* may occur in a variety of primary skin lesions, such as impetigo, insect bites, ecthyma, and eczema.

Complications of diphtheria

Myocarditis

Although electrocardiographic (ECG) changes have been described in up to 66% of cases, overt clinical myocarditis is less common (10%–22%). The onset is insidious, occurring in the second or third week of the infection. The patient exhibits a weak, rising pulse; distant heart sounds; and profound weakness and lethargy. Overt signs of heart failure can occur. The most common ECG changes are flattening or inversion of T waves, bundle branch block or intraventricular block, and disorders of rhythm. Serial determination of cardiac enzyme concentrations identifies most patients with myocarditis. The prognosis is poor, especially when heart block supervenes.

Peripheral neuritis

Neurologic toxicity has been described in about 5% of patients with diphtheria, but in severe diphtheria up to 75% of patients develop neurologic complications. The most common form of cranial nerve palsy is paralysis of the soft palate. There may be nasal regurgitation and/or nasal speech. This condition is usually mild, and recovery occurs within 2 weeks. Ciliary paralysis and oculomotor paralysis are the next most common forms. Peripheral neuritis affecting the limbs may appear during the fourth to eighth week. It is usually manifested by weakness of the dorsiflexors and decreased or absent deep-tendon reflexes. Diphtheritic polyneuritis has been described after cutaneous diphtheria.

Diagnosis

Diagnosis is made on clinical grounds and can be confirmed by laboratory tests (Figure 131.1). The clinical features of a fully developed diphtheritic membrane, especially in the pharynx, are sufficiently characteristic to suggest diphtheria and for treatment to be started immediately.

Specific diagnosis of diphtheria depends completely on demonstration of the organism in stained smears and its recovery by culture. In experienced hands, methylene blue-stained preparations are positive in 75% to 85% of cases. The bacilli can be recovered by culture in Loeffler's or Tindale's medium within 8 to 12 hours if patients have not been receiving antimicrobial agents. *Corynebacterium diphtheriae* can be seen as gram-positive bacilli in a "Chinese letter" distribution pattern on Gram or methylene blue stain (Figure 131.2); one can find metachromatic granules on Loeffler's stain and black colonies with halos with growth on Tindale's medium. The presence of β-hemolytic streptococci does not rule out diphtheria because such streptococci are recovered in up to 20% to 30% of patients with diphtheria.

Toxin detection should be performed to differentiate toxigenic from nontoxigenic strains, but is not the reason not to administer antitoxin. Toxin production can be demonstrated by the ELEK test and or rapid enzyme immunoassay (ELISA).

The differential diagnosis of tonsillar-pharyngeal diphtheria should include streptococcal pharyngitis, adenoviral exudative pharyngitis, infectious mononucleosis, and Vincent's angina, among others (Table 131.1).

Therapy

The best and most effective treatment of diphtheria is prevention by immunization with diphtheria toxoid. The most important aspect

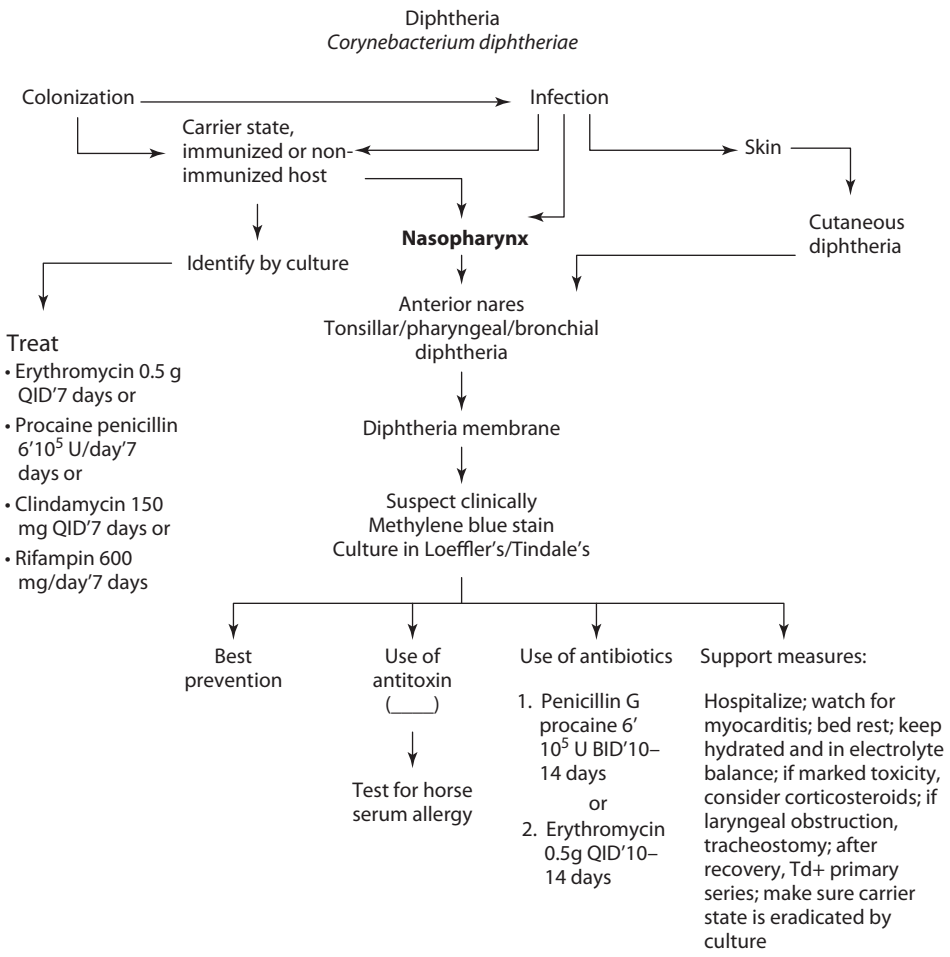

FIGURE 131.1 Diagnostic and treatment approach to diphtheria.

of treatment is to administer the antitoxin and antibiotics as soon as diphtheria is clinically suspected, without awaiting laboratory confirmation. The patient should be hospitalized, isolated, and kept in bed for 10 to 14 days (see Figures 131.1 and 131.3).

Use of antitoxin

The antitoxin is equine, and the minimal effective dose remains undefined; therefore, dosage is based on empiric judgment. It is usually accepted that for patients with mild or moderate cases, including those with tonsillar and pharyngeal membrane, 20 000 to 40 000 units for pharyngeal disease of <48 hours duration, 40 000 to 60

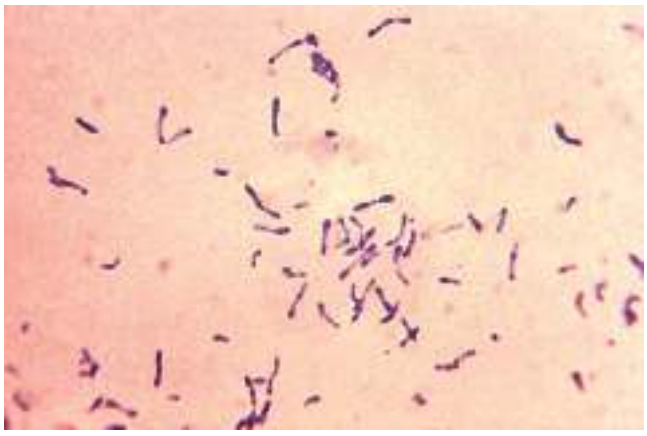

FIGURE 131.2 Gram-positive bacilli in a "Chinese letter" distribution pattern on Gram stain.

TABLE 131.1 **DIFFERENTIAL DIAGNOSIS OF DIPHTHERIA**

Affected area	Other conditions
Nose	Sinusitis, foreign body, snuffles of congenital syphilis, rhinitis
Fauces and pharynx	Streptococcal or adenoviral exudative pharyngitis, ulcerative pharyngitis (herpetic, Coxsackie-viral), infectious mononucleosis, oral thrush, peritonsillar abscess, retropharyngeal abscess, Vincent's angina, lesions associated with agranulocytosis or leukemia
Larynx	Laryngotracheobronchitis, epiglottitis
Skin	Impetigo, pyogenic ulcers, herpes simplex infection

000 units for nasopharyngeal disease, and 80 000 to 100 000 units for >3 days of illness or "bull neck" is appropriate. Doses should be given intravenously over 60 minutes as recommended by the American Academy of Pediatrics.

Before administration of the antitoxin, any history of allergy or reactions to horse serum or horse dander must be determined. All patients must be tested for antitoxin sensitivity with dilute horse antitoxin in saline 1:10 and an eye test. This is followed by a scratch test with a 1:100 dilution; if negative in half an hour, the scratch test is followed by an intradermal test, 1:100 dilution. If all tests are negative, antitoxin can be given. The intravenous route is recommended. A slow intravenous infusion of 0.5 mL antitoxin in 10 mL saline is followed in half an hour by the balance of the dose in a dilution of 1:20 with saline, infused at a rate not to exceed 1 mL/min. Others give the antitoxin dose intramuscularly in mild to moderate cases only.

If the patient is sensitive to horse serum, desensitization should be carried out with care, preferably in an intensive care unit. Epinephrine, intubation equipment, and respiratory assistance should be available. The following doses of horse serum antitoxin should be injected at 15-minute intervals if no reaction occurs:

1. 0.05 mL of 1:20 dilution subcutaneously
2. 0.10 mL of 1:10 dilution subcutaneously
3. 0.3 mL of 1:10 dilution subcutaneously
4. 0.1 mL of undiluted antitoxin subcutaneously
5. 0.2 mL of undiluted antitoxin subcutaneously
6. 0.5 mL of undiluted antitoxin subcutaneously
7. Remaining estimated therapeutic dose intramuscularly.

During all tests and on injection of antitoxin, a syringe containing epinephrine 1:1000 dilution in saline should be at hand to be used immediately in a dose of 0.01 mL/kg subcutaneously or intramuscularly at any sign of anaphylaxis. A good precaution is to have open venous access with normal saline prior to the test. If needed, a similar amount of epinephrine diluted to a final concentration of 1:10 000 in saline may be given slowly intravenously and repeated in 5 to 15 minutes. Other information and instructions in the package insert accompanying the antitoxin should be observed.

Antibiotics

Corynebacterium diphtheriae is susceptible to several antimicrobial agents. After cultures have been performed, antibiotics should be administered to prevent multiplication of the microorganism at the site of infection and to eliminate the carrier state. The antibiotics of choice are erythromycin (500 mg four times a day for 14 days) or penicillin G 25 000 to 50 000 units to a maximum of 1.2 million units IV every 12 hours until the patient can take oral penicillin V (250 mg QID) for a total of 14 days. Erythromycin has been favored since reports show greater efficacy than penicillin.

Supportive measures

Complications such as dehydration, malnutrition, and congestive heart failure should be diagnosed promptly and properly treated. In cases of severe laryngeal involvement, marked toxicity, or shock, corticosteroids (prednisone 3 to 5 mg/kg/day) have been advocated, but there are no hard data on their effectiveness. For laryngeal obstruction with respiratory stridor, a tracheotomy must be performed promptly.

Before the patient is discharged, specimens from throat and nose or suspected lesions should be cultured. At least two and preferably three consecutive negative cultures should be obtained.

After recovery, toxoid administration against tetanus and diphtheria (Td) should be administered to complete a primary immunization series if the patient has not been immunized.

Carriers

The chronic carrier state may occur despite immunity derived either from clinical disease or from immunization. The carrier state occasionally persists in the absence of antecedent disease. Erythromycin, 0.5 g orally four times a day for 7 days in adults, is the treatment of choice for the carrier state. Alternative antibiotics are procaine penicillin G, 600 000 U intramuscularly daily for 14 days, clindamycin, 150 mg orally four times a day for 7 days, or rifampin, 600 mg/day orally for 7 days.

Epidemics

The approach to epidemic disease is as follows:

1. Identify all primary cases, hospitalize, and treat.
2. Use toxoid in all the population at risk.
3. Culture all contacts for diphtheria, and treat all persons with *C. diphtheriae* in throat, nose, or skin lesions with erythromycin for 7 days to eliminate carrier state (Figure 131.3).
4. Watch primary contacts closely during the first week of exposure and treat at first signs or symptoms. Alternatively, all susceptible primary contacts can be given 1500 to 3000 U of diphtheria antitoxin, administered as previously described, in addition to toxoid. This low-level dose will boost them while they are forming their antibody.

Prevention

Children who have had a complete course of primary immunization with diphtheria–tetanus–pertussis (DTaP) vaccine may be given a booster injection on exposure to diphtheria. This is done in case of outbreaks but is not routine. Antibiotic prophylaxis is highly effective.

Household and other close contacts of a patient with diphtheria should be observed attentively for 7 days. They should receive either an intramuscular injection of 600 000 to 1.2 million units of benzathine penicillin or a 7- to 10-day course of erythromycin taken orally. Cultures should be performed before and after treatment. An injection of toxoid appropriate for age and immunization status can also be given. Susceptible close contacts who have had no (or only one) prior injections of toxoid should promptly be given 3000 to 10 000 units (depending on body size) of antitoxin, with the usual

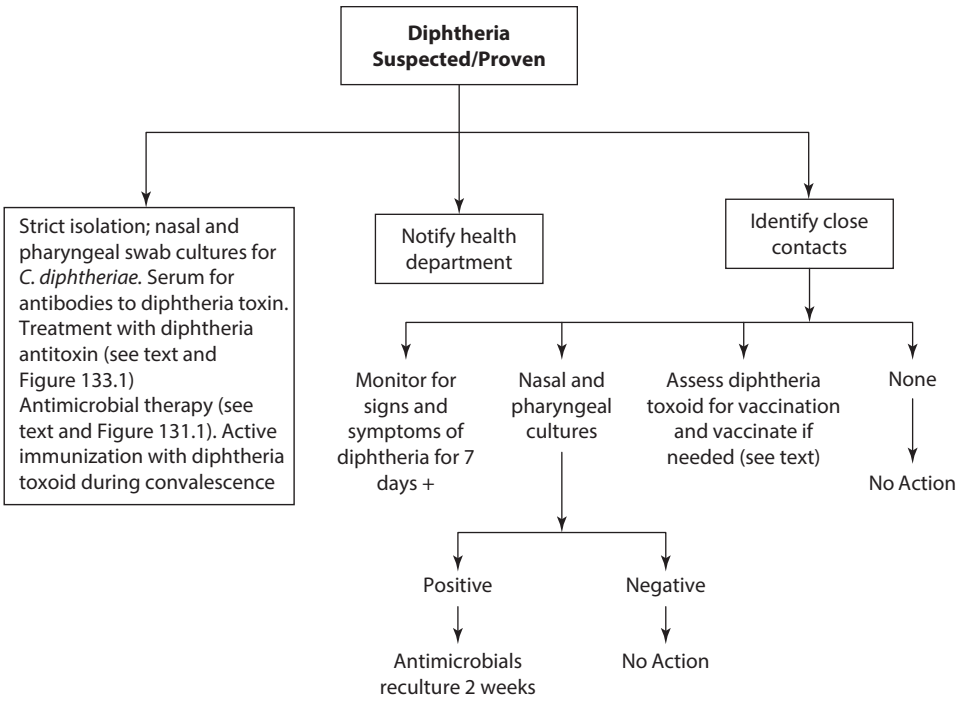

FIGURE 131.3 Public health management of diphtheria.[1]

precautions being followed. When indicated, active immunization with toxoid should be continued to completion. Routine immunization for diphtheria is discussed in Chapter 115, Immunizations.

Nondiphtheric corynebacteria

Nondiphtheric corynebacteria were once considered commensals. They are present in the skin and often are recovered from blood cultures. The presence of the microorganism in the blood has been considered contaminant, but there are many instances in which nondiphtheric corynebacteria are associated with bacteremias, sepsis, pneumonias, endocarditis, central nervous system infections, and intraocular infections, especially in immunocompromised patients and patients with vascular and central nervous system catheters and prosthetic devices. A common predisposing factor is neutropenia.

The diagnosis of infections with nondiphtheric corynebacteria usually involves their recovery from blood or other sterile body fluid. Corynebacteria can be identified by conventional methods; since 2000, a new system, the Rapid CORYNE System, was found to be excellent and an alternative to conventional methods.

Clinically, there are no specific findings that suggest nondiphtheric corynebacteria, but their association with central lines, skin, and subcutaneous infections in immunocompromised patients leads the clinician to associate a given infection with a gram-positive rod. Table 131.2 lists the epidemiology and clinical features of selected nondiphtheric corynebacteria.

TABLE 131.2 **EPIDEMIOLOGY AND CLINICAL FEATURES OF SELECTED NONDIPHTHERIC CORYNEBACTERIA**

Corynebacterium	Epidemiology	Clinical features
C. jeikeium	Skin, systemic	Soft-tissue, pneumonias, shunt infections; skin rash; endocarditis
C. minutissimum	Skin	Erythrasma, reddish-brown macular lesions, fluoresce under Wood's lamp
C. ulcerans	Skin, systemic	Cardiac and central nervous system involvement; diseases in horses and cattle
C. pseudotuberculosis	Skin exposure, farm animals, raw milk	Dermonecrotic toxin, suppurative granulomas, lymphadenitis, disease in farm animals
C. bovis	Shunts, skin	Meningitis, spinal epidural; abscess; ventriculoperitoneal or jugular shunts
C. pseudodiphtheriticum *C. striatum*	Systemic Immunosuppressed	Pneumonia endocarditis, tracheitis, urinary tract Pneumonias, meningitis, abscesses, bacteremias

Corynebacterium jeikeium

Corynebacterium jeikeium is a gram-positive coccobacillus or coccus resembling the streptococcus. Characteristically, it shows high-grade antibiotic resistance, being susceptible only to vancomycin in vitro and in vivo.

Clinical features

Diseases associated with *Corynebacterium jeikeium* include soft-tissue infections, pneumonitis with or without cavitation, continuous ambulatory peritoneal dialysis-related peritonitis, neurosurgical shunt infections, skin rash, catheter-related epicardial abscess, and endocarditis. It should always be considered a possible cause of sepsis in the neutropenic patient and in patients with prosthetic devices in place.

Therapy

Despite their high antibiotic resistance, these corynebacteria remain susceptible to vancomycin. Total effective duration of treatment has not been established. Clinical response must be followed, usually treating for 4 to 6 weeks. Newer fluoroquinolones, mainly ciprofloxacin, have also shown good results. Infected prosthetic material often requires removal.

Corynebacterium minutissimum

Infection with *C. minutissimum* usually involves the skin, and the classical disease entity is erythrasma. Erythrasma is a skin infection characterized by brownish-reddish macules that itch and when exposed to a Wood's lamp fluoresce. The most frequent location is the intertriginous areas.

Bacteremia with *C. minutissimum* has been described in patients with leukemia in blast crisis. There are also reports of trichomycosis axillaris associated with this corynebacterium.

Corynebacterium ulcerans

Corynebacterium ulcerans, like *C. diphtheriae*, produces diphtheria toxin by lysogeny but without apparent clinical consequences. However, there are documented reports of *C. ulcerans* bacteremias with cardiac and central nervous system involvement as well as pneumonia.

Corynebacterium pseudotuberculosis

Infection with *C. pseudotuberculosis* is associated with exposure to farm animals or consumption of raw milk. Clinically, it presents as a suppurative granulomatous lymphadenitis most likely related to the dermonecrotic toxin it produces. This organism responds to long-term treatment with erythromycin or tetracycline.

Corynebacterium bovis

Most infections reported with *C. bovis* are associated with central nervous system processes. There have been cases of meningitis, epidural abscesses, and shunt infections.

Corynebacterium pseudodiphtheriticum

Sites of infection caused by *C. pseudodiphtheriticum* include heart valves, wounds, urinary tract, and lungs, with pneumonia and necrotizing tracheitis. The susceptibilities of this microorganism are varied, with both susceptibility and resistance to erythromycin, clindamycin, and penicillin. There is a case of response to penicillin intravenously (12 million units daily for 14 days).

Corynebacterium striatum

Persons with an underlying immunosuppressive process are usually victims of *C. striatum*. There are reports of pneumonias, pulmonary abscesses, meningitis, and bacteremias with *C. striatum*. Most patients were treated with vancomycin.

Others

There have been reports of *Corynebacterium* CDC group A-4 associated with native valve endocarditis in immunocompetent patients as well as sepsis in immunocompromised hosts with infected Hickman catheters. *Corynebacterium aquaticum*, an environmental organism of fresh water, has been associated with septicemia in a neutropenic patient with an indwelling central venous catheter who used untreated stored rainwater to shower. *Corynebacterium afermentans* (CDC group ANF-1) was reported to cause endocarditis in a prosthetic valve.

Therapy

Some corynebacteria are susceptible to erythromycin, sulfonamides, chloramphenicol, gentamicin, imipenem, some of the newer fluoroquinolones, and vancomycin. For most serious and systemic infections, we prefer to use vancomycin at 1 g every 12 hours for at least 2 weeks in adults with normal renal function. In some patients, especially immunocompromised patients, combination therapy can be used with vancomycin plus imipenem at 500 mg intravenously every 6 hours, vancomycin plus rifampin at 600 mg daily orally, or vancomycin plus ciprofloxacin at 750 mg orally every 12 hours for 2 to 4 weeks. Erythromycin at a dosage of 2 to 4 g in divided doses can be used as an alternative regimen. The optimal effective therapy for these infections has not been determined, but 8 weeks of treatment are often required. For unresponsive cases, surgical consultation is recommended.

Suggested reading

Advisory Committee on Immunization Practices. Recommended adult immunization schedule: United States, 2010. *Ann Intern Med*. 2010;152:36–39.

American Academy of Pediatrics. Antibodies of animal origin (animal antisera). In: Pickering LK, ed. *Red Book: 2012 Report of the Committee on Infectious Diseases*, 29th edn, Elk Grove Village, IL: American Academy of Pediatrics; 2012:63–66.

Brooks GF, Bennett JV, Feldman RA. Diphtheria in the United States 1959–1970. *J Infect Dis*. 1974;129:172–178.

Halsey N, Bartlett JG. Corynebacteria. In: Gorbach SL, Barlett JG, Blacklow NR, eds. *Infectious Diseases*. Philadelphia: Lippincott Williams & Wilkins; 2004:1622.

Kneen R, Pham NG, Solomon T, et al. Penicillin vs. erythromycin in the treatment of diphtheria. *Clin Infect Dis*. 1998;27:845–850.

Lipsky BA, Goldberger AC, Tompkins LS, Plorde JJ. Infections caused by nondiphtheria corynebacteria. *Rev Infect Dis*. 1982;4:1220–1235.

Lowe CF, Bernard KA, Romney MG. Cutaneous diphtheria in the urban poor population of Vancouver, British Columbia, Canada: a 10-year review. *J Clin Microbiol*. 2011;49:2664–2666.

MacGregor RR. *Corynebacterium diphtheriae*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia: Churchill Livingstone; 2010:2687–2694.

Meyer DK, Rebou A. Other coryneform bacteria and rhodococci. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia: Churchill Livingstone; 2010:2695–2706.

Wagner KS, White JM, Crowcroft NS, et al. Diphtheria in the United Kingdom, 1986–2008: the increasing role of *Corynebacterium ulcerans*. *Epidemiol Infect*. 2010;138:1519–1530.

132

Enterobacteriaceae

Charles Stratton

The Enterobacteriaceae consist of a large, heterogeneous group of aerobic (facultatively anaerobic) gram-negative bacilli whose natural habitat is the gastrointestinal tract of animals and humans. Of the many members of the Enterobacteriaceae, there are three that are considered pathogens whenever they are isolated from humans. These three pathogens are *Salmonella*, *Shigella*, and *Yersinia*; their unique clinical features are considered in separate chapters. Many of the members of the Enterobacteriaceae are important causes of community- and hospital-acquired infections. Medically important Enterobacteriaceae are listed in Table 132.1.

Urinary tract infection

Members of the Enterobacteriaceae are the most important cause of both community- and hospital-acquired urinary tract infections (UTIs); *Escherichia coli* is the most frequently isolated pathogen and has been noted to have a unique pathogenesis in terms of its ability to cause UTIs. This pathogenesis involves adherent fimbriae and production of glycocalyx that allow it to adhere to normal bladder epithelium as well as the ability to invade bladder cells where this uropathogen is able to survive in biofilm colonies.

The symptoms of UTI are similar no matter which member of the Enterobacteriaceae is causing the infection; these symptoms can assist in differentiating upper UTI (i.e., pyelonephritis) from lower UTI (i.e., cystitis). Cystitis is characterized by frequency, urgency, dysuria, and suprapubic discomfort while pyelonephritis is characterized by fever, chills, nausea, vomiting, flank pain, and costovertebral angle tenderness. In male patients, involvement of the vesicles and/or prostate may occur with a UTI. Many of these symptoms may be absent in elderly patients or in patients with spinal cord injuries and/or indwelling urinary catheters. Perhaps the most distinct urinary tract pathogen is *Proteus* spp., which characteristically causes UTIs with an alkaline urine (pH of 8) and often is associated with the presence of staghorn calculi.

Asymptomatic bacteriuria is also important to understand when considering UTIs; asymptomatic bacteriuria is usually defined as $>10^5$ organisms/mL, with or without pyuria in the absence of symptoms. Asymptomatic bacteriuria infrequently results in symptomatic UTIs; treatment is indicated only in young children, pregnant women, or prior to instrumentation of the urinary tract, such as insertion of a Foley catheter.

The laboratory diagnosis of UTI typically involves a urine quantitative colony count, with 10^5 gram-negative (most often members of the Enterobacteriaceae) organisms/mL defining a UTI. However, as few as 10^2 gram-negative organisms/mL may be seen in symptomatic UTIs, particularly when the urine is collected by a suprapubic tap or by catheterization. It should be noted that quantitative colony counts have not been evaluated in a systematic manner for gram-positive organisms such as *Enterococcus* species, although 10^5

TABLE 132.1 **GENUS AND SPECIES COMMENTS**

Citrobacter diversus, *C. freundii, C. koseri*	Usually nosocomial, most frequently involving urinary tract, can cause neonatal meningitis and brain abscesses.
Cronobacter sakasakii	Causes meningitis and sepsis in neonates; associated with use of powdered infant formula.
Edwardsiella tarda	Associated with freshwater and fish; ingestion of fresh water can cause diarrhea. Soft tissue injuries while handling fish can lead to serious soft tissue infections.
Enterobacter cloacae	Colonizer of human colon, frequent cause of nosocomial infections, also noted for de-repression of AmpC beta-lactamase leading to high-level resistance to cephalosporins.
Escherichia coli	Most common cause of urinary tract infection. Six diarrheal pathotypes. Frequent cause of bacteremia related to urinary tract infection, ascending cholangitis, or intraabdominal infection. Cause of neonatal meningitis. Can cause pneumonia (both hospital-acquired and ventilator-associated). Important pathogen for community-acquired and hospital-acquired infections. Can have extended-spectrum β-lactamases.
Ewingella Americana	Rare cause of nosocomial infections.
Hafnia alvei	Rare cause of community-acquired and hospital-acquired infections.
Klebsiella pneumoniae, K. oxytoca, K. aerogenes	Common cause of community-acquired and hospital acquired infections. Urosepsis and bacteremia from ascending cholangitis are typical community-acquired infections. Can cause pneumonia. Hypermucoviscous strains associated with liver abscesses. High-level antimicrobial resistance possible due to extended-spectrum beta-lactamases, carbapenemases, or in the case of *K. aerogenes*, de-repressed AmpC β-lactamase.
Kluyvera ascorbate	Rare cause of nosocomial infections such as urinary tract infections.
Morganella morgani	Uncommon cause of community-acquired infections, more commonly seen in nosocomial infection, but still rarely seen causing infection.
Pantoea agglomerans	Plant pathogen that causes human infection after penetrating injuries with plant material such as wood splinters.
Plesiomonas shigelloides	Associated with fresh/brackish water as well as shellfish and oysters taken from brackish water; causes gastroenteritis in humans.
Proteus mirabilis, *P. vulgaris*	Common cause of urinary tract infections, particularly when renal calculi or indwelling catheters are involved. Also associated with fetid foot.
Providencia stuartii, *P. rettgeri*	Causes catheter-associated urinary tract infections.
Salmonella enterica	See Chapter 148, "Salmonella."
Serratia marcescens	Environmental pathogen associated with neonatal intensive care units and burn units, high-level resistance frequently seen.
Shigella species	See Chapter 153, "Shigella."
Yersinia species	See Chapter 158, "Yersinia."

gram-positive organisms/mL is often used as a definition of UTI. When in doubt, a repeat culture that grows the same organism can provide a clinically useful definition of UTI. When gram-positive organisms are suspected of causing a UTI, underlying urinary tract abnormalities should be considered and ruled out.

Gastrointestinal infections

Salmonella, *Shigella*, and *Yersinia* are considered pathogens whenever they are isolated from the human. These three pathogens often cause gastrointestinal infections and are discussed in separate

TABLE 132.2 **PATHOGENIC *ESCHERICHIA COLI* OF THE GASTROINTESTINAL TRACT**

Pathotype		Clinical illness	Comments
ETEC	Enterotoxigenic *E. coli*	Acute watery diarrhea, usually self-limited	Most common cause of travelers' diarrhea and in children worldwide
EAEC	Enteroaggregative *E. coli*	Mucoid diarrhea	May cause chronic diarrhea, emerging in travelers
EPEC	Enteropathogenic *E. coli*	Acute diarrhea and vomiting	Common in children in developing countries
EIEC	Enteroinvasive *E. coli*	Watery diarrhea or dysentery (fever, abdominal pain, tenesmus, blood)	Occurs in outbreaks
EHEC	Enterohemorrhagic *E. coli*	Watery and bloody diarrhea	Hemolytic-uremic syndrome

chapters. In addition, there are enteropathogenic forms of *E. coli* that can colonize the human gastrointestinal tract and cause diarrheal illnesses of the small and large intestines. These are listed in Table 132.2.

Given that *E. coli* is among the most common colonizers of the human gastrointestinal tract. It therefore is not surprisingly that there are five well-described mechanisms for enteropathogenic *E. coli* causing diarrheal illnesses. The most common of these mechanisms is enterotoxigenic *E. coli* (ETEC), which uses either a heat-labile toxin (LT) that interferes with cyclic adenosine monophosphate (AMP) or a heat-stable toxin (ST) that interferes with cyclic guanosine monophosphate (GMP). Both cholera-like toxins induce secretion of chloride anions into the small intestine and impede reabsorption of sodium chloride. The result is watery diarrhea that has been termed "traveler's diarrhea" or "Montezuma's revenge" and is the most common cause of diarrhea in children <2 years of age as well as in travelers to tropical regions where ETEC is commonly found in food and water supplies. ETEC is most easily diagnosed by molecular methods that detect the genes for LT or ST. The most serious of these five mechanisms is enterohemorrhagic *E. coli* (EHEC), which produce a Shiga toxin that inhibits host protein synthesis and induces apoptosis. This Shiga toxin also can be absorbed into the bloodstream and disseminated to other organs, causing acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia. This clinical constellation of organ dysfunction is collectively known as *hemolytic uremic syndrome* (HUS); treatment with antimicrobial agents is not indicated as this can make this syndrome worse.

Intra-abdominal infection

Because many of the Enterobacteriaceae are part of the normal gut flora, it is not surprising to find members of this group are the principal causes of intra-abdominal infections through a variety of different mechanisms. For example, obstruction of a diverticulum or of the appendix can lead to diverticulitis or appendicitis; both of these are polymicrobial infections in which members of the Enterobacteriaceae play an active role. Gut flora also plays an active role in peritonitis and/or abscesses anywhere in the abdominal or pelvic cavities when perforation of a viscus occurs. Members of the Enterobacteriaceae are commonly found in the biliary system, and, when obstruction by gall stones leads to cholecystitis, these gram-negative bacilli may cause ascending cholangitis or a liver abscess. Translocation of these gram-negative bacilli from the gut to the liver via the portal blood system also can result in a liver abscess. These biliary/liver infections are characterized by fever and abdominal pain that or may not be localized to the right upper quadrant. The likelihood of ascending cholangitis occurring with acute cholecystitis is roughly equal to the patient's age; if symptoms have been present for more that 3 days, then the likelihood of ascending cholangitis is almost 100%. Leukocytosis with a left shift is an important clue for the diagnosis of biliary/liver infections.

Cholecystitis and ascending cholangitis typically have an elevation of the total bilirubin if the common bile duct is involved and obstructed; if not obstructed, the total bilirubin is elevated 25% of the time. In two-thirds of liver abscesses, the alkaline phosphatase is elevated; usually there is little or no elevation of bilirubin or aminotransferases. Hypermucoviscous strains of *Klebsiella* spp. have been noted to cause liver abscesses; metastatic infections of the eye and central nervous system (CNS) also have been seen with these strains. The phenomenon was first described in East and Southeast Asia. More recently, this phenomenon has been reported from Europe and the United States.

Infection of the pancreas or of a pancreatic pseudocyst typically present with abdominal pain, nausea, vomiting, fever, and leukocytosis and can be difficult to diagnose; such pancreatic infections are often seen after pancreatic manipulations such as endoscopic retrograde cholangiopancreatography (ERCP). Suspicion of a possible pancreatic infection should result in serum amylase and serum lipase testing; if positive, these should be followed by appropriate imaging studies such as a CT or an MRI scan. Broad-spectrum empiric antimicrobial therapy should be directed at members of the Enterobacteriaceae as well as other gut flora such as anaerobes and enterococci.

Finally, members of the Enterobacteriaceae are the most common cause of *spontaneous bacterial peritonitis* (SBP), an infection of ascitic fluid without a concomitant intra-abdominal surgically treatable source of infection. Members of the Enterobacteriaceae are thought to cause 80% of SBP via bacterial translocation in which viable bacteria from the gastrointestinal lumen pass through the lumen to

extraintestinal sites. Nonenteric bacteria are the cause of SBP in about 20% and are thought to enter the peritoneal cavity from the bloodstream due to impaired liver function and altered portal circulation. Of these nonenteric bacteria, approximately 3% to 8% of culture-proven cases are caused by *Streptococcus pneumoniae*.

SBP is most often due to seeding of preexisting ascites, often in the setting of cirrhosis but occasionally in the setting of ascites due to nephritic syndrome or right-sided heart failure. Clinical manifestations include presence of ascites by physical exam or by imaging as well as fever, increasing abdominal girth, abdominal pain, and abdominal tenderness. Ascitic fluid should be obtained and the following tests done: aerobic and anaerobic cultures, cell count and differential, Gram stain, albumin, protein, glucose, lactate dehydrogenase, amylase, and bilirubin (if the fluid is dark orange or brown). If tuberculosis is suspected, a percutaneous biopsy of the peritoneum with a Cope needle should done.

Pneumonia and pleural space infections

Members of the Enterobacteriaceae cause between 5% and 15% of culture-proven pneumonias, regardless of whether the pneumonia is community-acquired or of nosocomial origin. Aspiration, older age, and comorbid conditions such as heart failure, renal disease, or diabetes tend to favor a gram-negative etiology; other clinical findings are not particularly useful in determining the etiological agent of bacterial pneumonia. Although production of dark-red mucoid sputum (termed "currant jelly sputum") has been associated with "Friedlander's bacillus" (i.e., *Klebsiella pneumoniae*), other clinical hallmarks of pneumonia caused by *K. pneumoniae* are nonspecific.

The imaging patterns from chest radiographs, CT scans, or MRI scans similarly are nonspecific and are not pathognomonic of gram-negative bacillary pneumonia, but this diagnosis should be considered whenever a necrotizing pneumonic process with pneumatoceles, cavitation, or empyema is noted. Gram-negative bacillary pneumonia is a well-recognized problem for patients with hospital-acquired and ventilator-associated pneumonia. The diagnosis should be made with Gram stains and cultures from expectorated sputum, deep lung suctioning via endotracheal tubes in intubated patients, or via bronchoscopy and bronchioalveolar lavage.

Skin and soft tissue infections

Although staphylococci and streptococci are the most common causes of skin and soft tissue infections, members of the Enterobacteriaceae are often involved in certain types of skin and soft tissue infections. Skin and soft tissue infections that typically involve members of the Enterobacteriaceae are surgical wound infections, particularly those involving abdominal or pelvic surgery. Such surgical wound infections are usually mixed infections and involve both gram-negative bacilli and anaerobic bacteria. Other skin and soft tissue infections that typically involve members of the Enterobacteriaceae include secondary infections of burns, infections of decubitus ulcers, the diabetic fetid foot, Fournier's gangrene, and other types of bacterial synergistic necrotizing fasciitis.

In general, these types of skin and soft tissue infections are complications arising from a preexisting wound or trauma, as well as arising from an enteric source such as a perforated intestine. Diabetes mellitus is a frequent comorbid factor, as exemplified by the fetid foot or Fournier's gangrene. Individuals with these types of skin and soft tissue infections are usually systemically ill-appearing with fever, leukocytosis, and often have accompanying bacteremia. These skin and soft tissue infections are characterized by moderate to severe pain, erythema, edema, crepitus on exam, tissue gas per radiographic, CT scan or MRI imaging, malodorous wound discharge, and evidence of skin/tissue necrosis. Empiric antimicrobial therapy along with surgical debridement is required for most of these types of skin and soft tissue infections.

Bone and joint infections

Septic arthritis, osteomyelitis, and prosthetic joint infections caused by members of the Enterobacteriaceae are well described in the medical literature. Overall, the involvement of gram-negative bacilli in these bone and joint infections is less frequent than is the involvement of gram-positive cocci and account for 5% to 25% of these infections. Osteomyelitis caused by a gram-negative bacillus may result from a focal soft tissue infection that has extended to involve the bone, as seen with the diabetic fetid foot. *E. coli, K. pneumoniae*, and *Proteus* spp. are the most common gram-negative bacilli involved in osteomyelitis of the diabetic foot. Seeding from the prostate or the bladder may lead to lumbar vertebral osteomyelitis; *E. coli* and *Proteus mirabilis* are the most common gram-negative bacilli involved in vertebral osteomyelitis. Hematogenous seeding of gram-negative bacilli can infect any bone or joint and are most often seen in septic arthritis and prosthetic joint infections in the elderly. The most common gram-negative bacillus isolated from such joint infections is *E. coli*.

The clinical presentations of gram-negative bacillary bone and joint infections is similar to that seen with bone and joint infections caused by gram-positive cocci. Joint infections are characterized by localized pain in the infected joint, joint swelling, joint erythema, and fever. Wound dehiscence and draining sinuses often are noted in cases of infections involving a recently implanted prosthetic joint. Vertebral infections typically have localized back pain with a radicular pattern; focal neurologic signs suggest an epidural abscess, which is a neurologic emergency requiring rapid diagnosis and appropriate decompressive surgery.

The clinical diagnosis of bone and joint infections relies on clinical suspicion that is usually strengthened by imaging studies such as radiographic studies, CT scans, MRI scans, and radionuclide white cell scans. The definitive diagnosis usually requires sterilely obtained cultures of joint fluid or bone; blood cultures should be done because approximately 50% of joint or bone infections will have an

accompanying bacteremia. Chronic draining sinuses are not appropriate sources for cultures as these sinus tracts may be colonized and not reveal the agents of deep infection.

Central nervous system infections

E. coli causes the majority of gram-negative bacillary meningitis due to members of the Enterobacteriaceae, although other members such as *Klebsiella pneumoniae*, *Citrobacter koseri*, *Enterobacter cloacae,* and *Cronobacter sakazakii* are occasionally seen. The majority of these gram-negative bacillary meningitis cases are seen in infants within the first weeks of life. Gram-negative bacillary infections of the CNS in adults are seen in the elderly or in patients with trauma, parenteral drug use, or neurosurgical procedures. Disseminated strongyloidiasis also may result in gram-negative bacillary meningitis when migrating *Strongyloides* larva bring colonic bacilli with them as they invade brain tissue. Due to the types of host that typically have gram-negative bacillary meningitis, the classic signs of fever and nuchal rigidity may not be seen. Analysis of cerebrospinal fluid (CSF) is needed to diagnose these cases of meningitis; the Gram stain may be difficult to read due to cellular and protein debris in the CSF. Blood culture should be done because >50% of these cases of gram-negative bacillary meningitis will have an accompanying bacteremia.

Focal suppurative gram-negative bacillary infections of the CNS, including brain abscesses, subdural empyema, and spinal epidural abscesses, are occasionally caused by members of the Enterobacteriaceae. In particular, ventriculitis and ventricular shunt infections can be seen and are difficult to treat because they act like abscesses. In addition, some of the gram-negative bacilli such as *Enterobacter* spp. that cause these infections have both intrinsic and acquired resistance to newer β-lactam agents. Indeed, members of the Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs), inducible AmpC-β-lactamases, and carbapenemases have become an increasing issue and have been seen in nosocomial infections such as ventriculitis and ventricular shunt infections.

Bacteremia, endovascular infection, and sepsis

A bacteremia caused by a member of the Enterobacteriaceae always should be considered a true-positive result, and a source of this bacteremia should be aggressively pursued. Most community-acquired infections with bacteremia caused by members of the Enterobacteriaceae will be due to pyelonephritis, ascending cholangitis, or diverticulitis. Hospital-acquired infections with bacteremia caused by members of the Enterobacteriaceae will be due to intravascular catheters, hospital-acquired pneumonia, or ventilator-assisted pneumonia. Intravascular catheters are particularly important causes of gram-negative bacteremia for patients receiving parenteral nutrition, hemodialysis, and chemotherapy for cancer, as well as for patients with long-term central venous catheters.

Infections caused by members of the Enterobacteriaceae can be seen with other intravascular devices such as vascular stints, prosthetic vascular grafts, and implanted transvenous pacemakers and defibrillators (automatic implantable cardioverter defibrillators; AICDs). The morbidity associated with infected intravascular devices is considerable, as is the morbidity of the intervention; this makes it imperative to establish a diagnosis. Unfortunately, the diagnosis of infections associated with these intravascular devices can be difficult; a tagged white blood cell (WBC) scan or the ^{18}F-FDG-PET/CT scan may be useful. The limited spatial resolution of the tagged WBC scan may decrease its sensitivity for low-grade infections; thus, a negative WBC scan does not rule out the possibility of this diagnosis.

Given the frequency of bacteremia due to members of the Enterobacteriaceae, a high percentage of native valve and prosthetic valve endocarditis would be expected to be seen yet only 2% to 5% of bacterial endocarditis are caused by gram-negative bacteria. *Salmonella* spp. and *Yersinia* spp. are the most common causes of Enterobacteriaceae endocarditis reported in the medical literature. Most members of the Enterobacteriaceae do not produce biofilm and are unable to adhere to damaged endothelium. *Salmonella* spp. seem to be an exception and are well-known causative agents of intravascular infections.

Bacteremia caused by members of the Enterobacteriaceae may rapidly progress to sepsis or septic shock. Sepsis is defined as "life threatening organ dysfunction caused by dysregulated host response to infection." Septic shock is defined as a "subset of sepsis with particular profound circulatory, cellular, and metabolic abnormalities associated with a greater risk of mortality than sepsis alone." Septic shock is usually accompanied by evidence of tissue hypoperfusion such as lactic acidosis, oliguria, or acute lung injury. Septic shock with fever and refractory hypotension may lead to organ failures. Therefore, the diagnosis of septic shock must be made in a timely manner.

The diagnostic criteria of septic shock are a "vasopressor requirement required to maintain a mean arterial pressure (MAP) of >65 mm Hg and a serum lactate level >2 mmol/L in the absence of hypovolemia." A qSOFA (quick SOFA) has been developed as a bedside tool to rapidly identify adult patients who are more likely to have a poor outcome; a qSOFA is considered to be positive if the patient has two of the following clinical criteria:

- Respiratory rate of 22/min or greater,
- Altered mentation (Glasgow Coma Scale of <15), or
- Systolic blood pressure of ≤100 mm Hg.

The qSOFA is also used to prompt clinicians to further investigate for organ dysfunction, initiate or escalate therapy as appropriate, and consider referral to critical care or increase monitoring frequency.
In addition, there are six management steps to be implemented within 1 hour of the onset of sepsis:

- Administer oxygen to maintain SpO_2 at >94%.
- Obtain blood cultures and consider infective source.
- Administer intravenous (IV) antibiotics.

- Consider IV crystalloid fluids.
- Check serial lactates.
- Commence hourly urine output measurement.

The window between the actual onset of sepsis and the clinical recognition of sepsis is often where significant delays in the management of sepsis occur; this time frame is also a critical time for appropriate management of sepsis. For example, IV antimicrobial agents (at least two classes of antimicrobial agents to cover known or suspected pathogens) should be started within 1 hour of recognition of sepsis. Patients who need vasopressors should receive norepinephrine as the first choice; vasopressin or epinephrine can be added. For patients who remain unstable, dobutamine is recommended. Finally, patients with hypoperfusion should receive 30 mL/kg of IV crystalloid, such as Ringer's lactate. All of these management steps hinge on the rapid recognition of sepsis and septic shock.

Principles of antimicrobial therapy

The principles of antimicrobial therapy, in part, require an understanding of the difference between empiric and definitive therapy, an appreciation of the role of the clinical microbiology laboratory in definitive therapy, acknowledging the importance of antimicrobial stewardship, and (most importantly) recognizing when to consult an infectious diseases specialist.

Under most circumstances, definitive antimicrobial therapy should be determined by the results of culture and susceptibility testing along with an appreciation of the pharmacokinetics and pharmacodynamics of the antimicrobial agents on the particular host to be treated. Factors such as allergies and toxicities, tissue penetration, presence of co-pathogens, renal and hepatic function, possible drug–drug interactions, dosing and ease of administration, and cost all must be considered. Empiric antimicrobial therapy must be guided by the clinical presentation, severity of illness, type and source of the infection, and local resistance patterns and/or available antibiograms that would predict potential resistance issues.

Unfortunately, increasing resistance found in members of the Enterobacteriaceae have made both empiric and definitive antimicrobial therapy more difficult in the 21st century. The successful development of novel antimicrobial agents, as well as novel β-lactamase inhibitors, has been impressive. These recent and future antimicrobial therapy options will be discussed in more detail in the next section. However, one of the major challenges of antimicrobial therapy is that many clinical microbiology laboratories do not have the technology to provide real-time information on the identification of bacteria as well as their susceptibility to antimicrobial agents and the presence of resistance markers. Susceptibility testing of these Enterobacteriaceae isolates often requires a send-out test to a reference laboratory, which may take several days. Finally, drug acquisition and costs must also be considered when adding new antimicrobial agents to the hospital formulary.

These issues addressed have greatly complicated empiric antimicrobial therapy in most hospitals in the United States because multidrug-resistant isolates of Enterobacteriaceae have a wide variety of resistance mechanisms. In particular, many different classes of β-lactamases may be seen in members of the Enterobacteriaceae. A brief review of these β-lactamase classes is found in Table 132.3. These multidrug isolates in the recent past often have been resistant to β-lactam agents due to ESBLs as well as the induction of chromosomal Class C (AmpC) β-lactamases. More recently, plasmid-borne Class C (Act1) β-lactamases have emerged in members of the Enterobacteriaceae, as have carbapenemase-producing strains. Carbapenemase-producing carbapenem-resistant Enterobacteriaceae are typically resistant due to the production of β-lactamases, such as Class A serine carbapenemases, Class D oxacillinases (OXA-48), or Class B metallo-β-lactamases. Non–carbapenemase-producing carbapenem-resistant Enterobacteriaceae have resistance mechanisms that include alterations in membrane permeability, development of drug efflux pumps, or alteration in binding site targets for antimicrobial agents. Moreover, resistance to aminoglycosides may be seen due to aminoglycoside-modifying enzymes.

Simple outpatient UTIs respond well to a short-course (3 days) of oral antimicrobial agents. The choice of therapy should be made on the basis of local susceptibility patterns for *E. coli*. Cultures often are not required unless the patient has a history of UTIs. Complicated UTIs (including pyelonephritis) often can be treated with an oral antimicrobial agent such as levofloxacin provided that nausea and vomiting do not prevent their use. Healthcare-associated or catheter-related UTIs may be caused by multidrug-resistant isolates of the Enterobacteriaceae, and cultures should be done. These patients often require hospitalization, and parenteral therapy is generally preferred.

Antimicrobial therapy for enteric infections caused by members of the Enterobacteriaceae is controversial. For patients with moderate to severe diarrhea, the most immediate goal of treatment is to restore and maintain electrolyte and fluid balance; this alone can be life-saving in elderly patients and infants. Empiric antimicrobial therapy is generally recommended for acute febrile dysentery; such therapy is clearly indicated in cases of bacteremic salmonellosis. However, antimicrobial therapy is indicated in only a small percentage of patients who have an established infectious cause of acute diarrhea. Most diarrheal illnesses caused by enteropathogenic *E. coli* are self-limited; cases of EHEC are thought to have a greater risk of HUS with antimicrobial administration.

The treatment of community-acquired gram-negative pneumonia caused by members of the Enterobacteriaceae has generally included β-lactam agents given for ≥3 weeks. Recent studies have demonstrated equivalent results with 8 days of therapy. Lung abscesses or empyema may require longer therapy as well as surgical intervention. Hospital-acquired and ventilator-associated gram-negative pneumonia may be caused by multidrug-resistant strains of Enterobacteriaceae; treatment of these pulmonary infections may be problematic and could require newer antimicrobial agents briefly reviewed in the following section.

TABLE 132.3 **SUGGESTED ANTIMICROBIAL REGIMENS FOR SELECTED INFECTIONS**

Infection	Typical pathogens	Recommended antibiotics	Alternatives	Treatment duration (days)
Urinary tract infection, uncomplicated	*E. coli, Klebsiella, Proteus*	Oral TMP–SMX, FQ	Ampicillin, cephalexin, nitrofurantoin	3
Urinary tract infection, complicated (including pyelonephritis, male UTI)	*E. coli, Klebsiella, Proteus*	Ceftriaxone, FQ	Pip/tazo, aminoglycosides, carbapenems, aztreonam	7–14
Urinary tract infection, recurrent catheter associated	All	Carbapenems, cefepime	Aminoglycosides	14
Diarrhea	*E. coli*	None	FQ, rifaximin, azithromycin	3–5
Spontaneous bacterial peritonitis	*E. coli, Klebsiella*	Cefotaxime	FQ, moxi, pip/tazo, ceph3, cefepime, carbapenems	10–14
Diverticulitis	*E. coli* + anaerobes	FQ or TMP–SMX + metronidazole, moxi	Pip/tazo, ceph3 + metronidazole	7–10
Cholangitis, cholecystitis, pancreatitis, other abdominal abscesses	All	Pip/tazo, cefepime + metronidazole, carbapenems	FQ + metronidazole, moxi, tigecycline	To resolution
Complicated skin/soft tissue	All	Pip/tazo, carbapenems	Tigecycline, FQ, moxi	To resolution + 2 days
Pneumonia, community acquired	*E. coli, Klebsiella*	Ceftriaxone, cefepime, FQ, moxi	Pip/tazo, carbapenems	≤21
Pneumonia, hospital or ventilator acquired	*E. coli, Klebsiella, Enterobacter, Serratia*	Carbapenems, cefepime, pip/tazo (usually with aminoglycoside or FQ as initial therapy)	Tigecycline	8
Meningitis	*E. coli*	Cefepime, ceftriaxone, meropenem		14
Meningitis/ventriculitis, shunt associated	*Enterobacter*	Cefepime or meropenem ± aminoglycoside	Ceph3	To normalization of CSF
Osteomyelitis, prosthetic joint infection	All	Ceftriaxone, cefepime	FQ, carbapenem, tigecycline	≥42
Bacteremia (line)	All	Cefepime	Carbapenem, pip/tazo,	10–14
Endocarditis, intravascular device	All	Cefepime or ceftriaxone ± aminoglycoside	FQ, moxi Pip/tazo ± aminoglycoside	42

Abbreviations: FQ = ciprofloxacin or levofloxacin; moxi = moxifloxacin; pip/tazo = piperacillin–tazobactam; ceph3 = ceftriaxone, cefotaxime, ceftazidime; TMP-SMX = trimethoprim–sulfamethoxazole; UTI = urinary tract infection; CSF = cerebrospinal fluid.

Therapy of gram-negative osteomyelitis and gram-negative infections involving orthopedic hardware generally requires 6 weeks of antimicrobial agents for acute infections and longer durations for chronic infections. The hardware should be removed if possible; if not possible, prolonged oral suppressive therapy may be needed. Parenteral cephalosporins with a long half-life may be preferable for these infections in comparison with fluoroquinolones or aminoglycosides. Fluoroquinolones may impede fracture healing, while aminoglycosides have toxicity issues when used for ≥6 weeks.

Suggested antimicrobial regimens for the infection discussed in this chapter are outlined in Table 132.4.

Recent and future antimicrobial therapy options

The antimicrobial management of serious infections caused by multidrug-resistant members of the Enterobacteriaceae has been improved in the past several years and promises to improve further because of the addition of new antimicrobial agents and/or β-lactamase inhibitors as therapeutic options. However, use of these newer antimicrobial agents against Enterobacteriaceae isolates in clinical practice requires a high level of antimicrobial stewardship so as to not promote overuse of these agents. These recent and

TABLE 132.4 **REVIEW OF B-LACTAMASE CLASSES THAT MAY BE FOUND IN ENTEROBACTERIACEAE ISOLATES**

Class	Examples with clinical relevance
Class A	TEM, SHV, CTX-M: ESBLs that hydrolyze β-lactam agents.
	KPC: Serine β-lactamase that hydrolyzes carbapenems.
Class B	IMP, VIM, SPM, NDM: Metallo-β-lactamases that require zinc for hydrolysis and hydrolyze both β-lactam agents and carbapenems.
	Metallo-β-lactamases are very resistant to β-lactamase inhibitors.
Class C	AmpC: Inducible chromosomal β-lactamases found in *Enterobacter*, *Serratia*, *Proteus*, and *Citrobacter*.
	Act1: Inducible plasmid-borne β-lactamases that produce AmpC β-lactamase.
Class D	OXA-48: Plasmid-borne β-lactamase found in some Enterobacteriaceae.

These β-lactamases have variable activity and may be able to hydrolyze carbapenems.

new antimicrobial agents/antimicrobial combinations are briefly reviewed.

Ceftolozane-tazobactam is a novel cephalosporin combined with a classic β-lactamase inhibitor (tazobactam). Ceftolozane, like other β-lactam agents, inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins, while tazobactam extends the activity of ceftolozane to include the majority of Class A ESBL-producing Enterobacteriaceae as well as most *Bacteroides fragilis* isolates. Ceftolozane-tazobactam (ZERBAXA) was approved in the United States in 2014 for use in adults with complicated UTIs (including pyelonephritis) as well as for use in adults with complicated intra-abdominal infections (in combination with metronidazole). Ceftolozane-tazobactam is not active against gram-negative bacteria that produce Class B metallo-β-lactamases or Class A serine carbapenemases. Ceftolozane-tazobactam has limited activity against methicillin-susceptible *Staphylococcus aureus* (MSSA) and no activity against methicillin-resistant *S. aureus* (MRSA).

Ceftazidime-avibactam is a combination of the third-generation cephalosporin ceftazidime and a novel (non-β-lactam) β-lactamase inhibitor, avibactam. Ceftazidime, like other β-lactam agents, inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins, while avibactam extends the activity of ceftazidime to include Class A ESBL-producing Enterobacteriaceae, Class A serine carbapenemase-producing Enterobacteriaceae, Class C (AmpC and Act1) β-lactamases, and some OXA-48 β-lactamase-producing Enterobacteriaceae. Ceftazidime-avibactam (AVYCAZ) was approved in the United States in 2015 for use in adults with complicated intra-abdominal infections (in combination with metronidazole) and in 2017 for complicated UTIs (including pyelonephritis). Ceftazidime-avibactam is not active against gram-negative bacteria that produce Class B metallo-β-lactamases and may not have activity against non–carbapenemase-producing carbapenem-resistant Enterobacteriaceae. Ceftazidume-avibactam has limited activity against gram-positive pathogens (e.g., MSSA and MRSA, as well as enterococci).

Meropenem-vaborbactam is a combination of the carbapenem meropenem and a novel boron-containing serine-β-lactamase inhibitor, vaborbactam. Meropenem, like other β-lactam agents, inhibits gram-negative bacterial cell wall synthesis by binding to penicillin-binding proteins, while vaborbactam extends the activity of meropenem to include Class A ESBL-producing and Class A serine carbapenemase-producing Enterobacteriaceae as well as Class C (AmpC and Act1) β-lactamase-producing Enterobacteriaceae. Meropenem-vaborbactam (VABOMERE) was approved in the United States in 2017 for use in adults with complicated UTIs (including pyelonephritis). Meropenem-vaborbactam has no activity against gram-negative bacteria that produce Class B metallo-β-lactamases or Class D OXA-48 β-lactamases. Meropenem-vaborbactam may not have activity against non–carbapenemase-producing carbapenem-resistant Enterobacteriaceae and has no activity against MRSA.

Plazomicin (Zemdri) is a novel semisynthetic parenteral aminoglycoside that, like other members of the aminoglycoside class, binds to the bacterial 30S ribosomal subunit and inhibits proteins synthesis. Plazomicin was approved in the United States in 2018 for once-daily use in adults with complicated UTIs (including pyelonephritis). Plazomicin was developed from sisomycin and is commonly referred to as a "next-generation" aminoglycoside. The enhanced activity of plazomicin against members of the Enterobacteriaceae is due to its being engineered to overcome the most commonly encountered aminoglycoside-modifying enzymes. However, plazomicin is not active against the less common 16S ribosomal RNA methyltransferases (16S-RMTase), which also modify the aminoglycoside target site. On occasion, plasmids carrying other resistant genes such as metallo-β-lactamases (MBL) will also carry the 16S-RMTase gene; because of this, there are some reports that plazomicin has no activity against some MBL producers. In summary, plazomicin displays potent in vitro activity against members of the Enterobacteriaceae, including both Class A ESBL-producing and Class A serine carbapenemase-producing isolates. Plazomicin does not offer improved activity over older aminoglycosides against *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Susceptibility testing is required for Class A serine carbapenemase-producing members of the Enterobacteriaceae to determine if these isolates are susceptible to plazomicin or resistant due to the plasmid carrying both the MLB gene and the 16S-RMTase gene.

Aztreonam-avibactam is a combination of the monobactam aztreonam with a novel (non–β-lactam) β-lactamase inhibitor avibactam. Aztreonam, like other β-lactam agents, inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins, while avibactam extends the activity of aztreonam to include Class A ESBL-producing Enterobacteriaceae, Class A serine carbapenemase-producing Enterobacteriaceae, Class C (AmpC and Act1) β-lactamases, Class B metallo-β-lactamases, and some OXA-48 β-lactamase-producing Enterobacteriaceae. Aztreonam-avibactam is not active against gram-positive pathogens (e.g., MSSA and MRSA, as well as enterococci).

Imipenem-relebactam is a combination of the carbapenem imipenem-cilastatin with a novel (non–β-lactam) β-lactamase inhibitor, relebactam. The chemical structure of relebactam resembles that of avibactam; like avibactam, relebactam binds Class A and C β-lactamases. However, relebactam does not inhibit Class D OXA-48 β-lactamases, although avibactam does inhibit these OXA β-lactamases. Imipenem-cilastatin, like other β-lactam agents, inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins, while relebactam extends the activity of imipenem-cilastatin to include Class A ESBL-producing- and Class A serine carbapenemase-producing Enterobacteriaceae as well as Class C (AmpC and Act1) β-lactamase-producing Enterobacteriaceae. Imipenem-relebactam has no activity against gram-negative bacteria that produce Class B metallo-β-lactamases or Class D OXA-48 β-lactamases. Imipenem-relebactam has no activity against MRSA.

Cefiderocol is an IV siderophore cephalosporin that inhibits gram-negative bacterial growth by both binding to PBP-3 as well as chelating iron ions within that organism that are essential to its survival. This unique property of cefiderocol is due to its catechol side chain that binds to ferric acid, which then allows the complex to be actively transported into the bacterium by bacterial iron transporters. The siderophore-like property results in chelation of iron ions that are essential to the cell's survival. Cepiderocol's chemical structure is similar to that of both ceftazidime and cefepime, but cefiderocol also has high stability to many β-lactamases, including extended-spectrum β-lactamases, AmpC-β-lactamases, and carbapenemases. In early clinical trials, cefiderocol has performed similarly to or has been superior to comparator agents in adults with complicated UTIs as well as in adults with hospital-acquired and ventilator-associated gram-negative bacillary pneumonia.

Eravacycline is a synthetic fluorocycline antimicrobial agent of the tetracycline class that structurally resembles tigecycline. Eravacycline has two modifications to the D-ring of its tetracycline core: a fluorine atom replaces the dimethylamine moiety at C-7, and a pyrrolidinoacetamido group replaces the 2-tertiary-butyl glycylamido at C-9. Like tigecycline, eravacycline binds to the 30S ribosome subunit and has activity against both clinically relevant gram-positive and gram-negative pathogens (except *Pseudomonas aeruginosa*), including anaerobes, as well as carbapenemase-producing members of the Enterobacteriaceae. Initial clinical studies investigating eravacycline in complicated intra-abdominal infections in adults have shown excellent efficacy. Eravacycline is available in IV and oral forms and should offer an alternate treatment option for adult patients with complicated intra-abdominal infections caused by multidrug-resistant gram-negative pathogens.

Conclusion

Clearly, the members of the Enterobacteriaceae cause a wide variety of infections and play a prominent role in UTIs, enteropathogenic *E. coli* diarrheal illnesses, gram-negative bacillary pneumonia, postoperative skin and soft tissue infections, and complicated intra-abdominal infections. These gram-negative bacilli play a lesser role in bone and joint infections and in CNS infections but are still important due to increasing resistance. The emergence of members of Enterobacteriaceae producing ESBLs, inducible AmpC-β-lactamases, and carbapenemases is a global problem that requires appropriate molecular and phenotypic methods for susceptibility testing and also may require the use of newer antimicrobial agents/antimicrobial combinations. These complex resistance mechanisms increasingly found in nosocomial gram-negative bacillary infections have created a challenge in selecting appropriate empiric antimicrobial therapy. Comprehensive microbial identification/antimicrobial susceptibility testing as well as a targeted approach to antimicrobial usage remain the keys to successful management of these infections.

Suggested reading

Ahmed M. Acute cholangitis: An update. *World J Gastroenterol Pathophysiol*. 2018;9:1–7.

Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376:2367–2375.

Aubron C, Charpentier J, Trouillet JL, et al. Native-valve infective endocarditis caused by Enterobacteriaceae: Report on 9 cases and literature review. *Scand J Infect Dis*. 2006;38:873–881.

Azzopardi EA, Azzopardi E, Camilleri L, et al. Gram-negative wound infection in hospitalised adult burn patients: Systematic review and metanalysis. *PLoS One*. 2014;9:e95042.

Basmaci R, Bonacorsi S, Bidet P, et al. *Escherichia coli* meningitis features in 325 children from 2001 to 2013 in France. *Clin Infect Dis*. 2015;61:779–786.

Bassetti M, Peghin M, Pecori D. The management of multidrug-resistant Enterobacteriaceae. *Curr Opin Infect Dis*. 2016;29:583–594.

Bonomo RA, Burd EM, Conly J, et al. Carbapenemase-producing organisms: A global scourge. *Clin Infect Dis*. 2018;66:1290–1297.

Bradley N, Lee Y. Practical implications of new antibiotic agents for the treatment of carbapenem-resistant *Enterobacteriaceae*. *Microbiol Insights*. 2019:12:1178636119840367.

Brook I. Microbiology and treatment of brain abscess. *J Clin Neurosci*. 2017;38:8–12.

Bush K, Jacoby GA. Updated functional classification of β-lactamases. *Antimicrob Agents Chemother*. 2010;54:969–976.

Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. *Lancet*. 2018;392:75–87.

Censullo A, Vijayan T. Using nuclear medicine imaging wisely in diagnosing infectious diseases. *Open Forum Infect Dis*. 2017;4:ofx011.

Cerceo E, Deitelzweig SB, Sherman BM, Amin AN. Multidrug-resistant gram-negative bacterial infections in the hospital setting: Overview, implications for clinical practice, and emerging treatment options. *Microb Drug Resist*. 2016;22:412–431.

Chew KL, Tay MKL, Cheng B, et al. Aztreonam-avibactam combination restores susceptibility of aztreonam in dual-carbapenemase-producing Enterobacteriaceae. *Antimicrob Agents Chemother*. 2018;62:e00414–18.

Cho JC, Fiorenza MA, Estrada SJ. Ceftolozane/tazobactam: A novel cephalosporin/β-lactamse inhibitor combination. *Pharmacotherapy*. 2015;35:701–715.

Cunha CB, Opal SM. Antibiotic stewardship: Strategies to minimize antibiotic resistance while maximizing antibiotic effectiveness. *Med Clin North Am*. 2018;102:831–845.

Dana AN, Bauman WA. Bacteriology of pressure ulcers in individuals with spinal cord injury: What we know and what we should know. *J Spinal Cord Med*. 2015;38:147–160.

Dando SJ, Mackay-Sim A, Norton R, et al. Pathogens penetrating the central nervous system: Infection pathways and the cellular and molecular mechanisms of invasion. *Clin Microbiol Rev*. 2014;27:691–726.

De Waele JJ, Dhaese S. Antibiotic stewardship in sepsis management: Toward a balanced use of antibiotics for the severely ill patients. *Expert Rev Anti Infect Ther*. 2019;17:89–97.

DuPont HL. Acute infectious diarrhea in immunocompetent adults. *N Engl J Med*. 2014;370:1532–1540.

Eljaaly K, Alharbi A, Alshehri S, et al. Plazomicin: A novel aminoglycoside for the treatment of resistant gram-negative bacterial infections. *Drugs*. 2019;79:242–269.

Evans BA, Amyes SGB. OXA β-Lactamases. *Clin Microbiol Rev*. 2014;27:241–263.

Fantoni M, Borre S, Rostagno R, et al. Epidemiological and clinical features of prosthetic joint infections caused by gram-negative bacteria. *Eur Rev Med Phamacol Sci*. 2019;23(Suppl 2):187–194.

Finer SR, Vincent JL. Severe sepsis and septic shock. *N Engl J Med*. 2013;369:840–851.

Gauthier L, Bonnin RA, Dortet L, Naas T. Retrospective and prospective evaluation of the carbapenem inactivation method for the detection of carbapenemase-producing *Enterobacteriaceae*. *PLoS ONE*. 2017;12:e0170769.

Gazin M, Paasch F, Goossens H, et al. Current trends in culture-based and molecular detection of extended-spectrum-β-lactamse-harboring and carbapenem-resistant Enterobacteriaceae. *J Clin Microbiol*. 2012;50:1140–1146.

Giurato L, Meloni M, Izzo V, Uccioli L. Osteomyelitis in diabetic foot: A comprehensive overview. *World J Diabetes*. 2017;8:135–142.

Goodman KE, Lessler J, Cosgrove SE, et al. A clinical decision tree to predict whether a bacteremic patient is infected with an extended-spectrum β-lactamse-producing organism. *Clin Infect Dis*. 2016;63:896–903.

Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52:e103–120.

Hodges K, Gill R. Infectious diarrhea: Cellular and molecular mechanisms. *Gut Microbes* 2010;1:4–21.

Honda H, Higuchi N, Shintani K, et al. Inadequate empiric antimicrobial therapy and mortality in geriatric patients with bloodstream infection: A target for antimicrobial stewardship. *J Infect Chemother*. 2018;24:807–811.

Hooton TM, Roberts MS, Cox ME, et al. Voided midstream urine culture and acute cystitis in premenopausal women. *New Engl J Med*. 2013;369:1883–1891.

Hu J, Torres AG. Enteropathogenic *Escherichia coli*: Foe or innocent bystander? *Clin Microbiol Infect*. 2015;21:729–734.

Hunstad DA, Justice SS. Intracellular lifestyles and immune evasion strategies of uropathogenic *Escherichia coli*. *Annu Rev Microbiol* 2010;64:203–221.

Iredell J, Brown J, Tagg K. Antibiotic resistance in Enterobacteriaceae: Mechanisms and clinical implications. *BMJ*. 2016;352:h6420.

Jacoby GA. AmpC β-Lactamases. *Clin Microbiol Rev*. 2009;22:161–182.

Jean SS, Gould IM, Lee WS, Hsueh PR. New drugs for multidrug-resistant gram-negative organisms: Time for stewardship. *Drugs*. 2019. doi:1007/s40265-019001112-1.

Johnson JR, Russo TA. Molecular epidemiology of extraintestinal pathogenic *Escherichia coli*. *EcoSal Plus*. 2018;8. doi:10.1128/ecosalplus.ESP-0004-2017.

Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–e111.

Keeley A, Hine P, Nsutebu E. The recognition and management of sepsis and septic shock: A guide for non-intensivists. *Postgrad Med J*. 2017;93:626–634.

Lee DS, Lee SJ, Choe HS. Community-acquired urinary tract infection by *Escherichia coli* in the era of antibiotic resistance. *Biomed Res Infect*. 2018;26:2018:7656752.

Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. *Mayo Clin Proc*. 2011;86:156–167.

Luyt CE, Hekimian G, Kouulenti D, Chastre J. Microbial cause of ICU-acquired pneumonia: Hospital-acquired pneumonia versus ventilator-associated pneumonia. *Curr Opin Crit Care*. 2018;24:332–338.

Mazuski JE, Tessier JM, May AK, et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. *Surg Infect*. 2017;18:1–76.

May AK. Skin and soft tissue infections. *Surg Clin N Am*. 2009;89:403–420.

Moxon CA, Paulus S. β-Lactamases in *Enterobacteriaceae* infections in children. *J Infect*. 2016;72:S41–S49.

Muresan MG, Balmos IA, Badea I, Santini A. Abdominal sepsis: An update. *J Crit Care Med*. 2018;4:120–125.

Nair R, Schweizer ML, Singh N. Septic arthritis and prosthetic joint infections in older adults. *Infect Dis Clin N Am*. 2017;31:715–729.

Nickerson EK, Sinha R. Vertebral osteomyelitis in adults: An update. *Br Med Bull*. 2016;117:121–138.

Ouchenir L, Renaud C, Khan S, et al. The epidemiology, management, and outcomes of bacterial meningitis in infants. *Pediatrics*. 2017;140:e20170476.

Peri AM, Potoski BA, Harris PNA, et al. Antimicrobial treatment challenges in the era of carbapenem resistance. *Diagn Microbiol Infect Dis*. 2019. doi:10.1016/j.diagmicrobio.2019.01.020.

Petty LA, Henig O, Patel TS, et al. Overview of meropenem-vaborbactam and newer antimicrobial agents for the treatment of carbapenem-resistant *Enterobacteriaceae*. *Infect Drug Resist*. 2018;11:1461–1472.

Philippon A, Slama P, Deny P, Labia R. A structure-based classification of Class A β-lactamases, a broadly diverse family of enzymes. *Clin Microbiol Rev*. 2016;29:29–57.

Pien BC, Sundaram P, Raoof N, et al. The clinical and prognostic importance of positive blood cultures in adults. *Am J Med*. 2010;123:819–828.

Poirel L, Madec JY, Lupo A, et al. Antimicrobial resistance in *Escherichia coli*. *Microbiol Spectr*. 2018;6. doi:10.1128/microbiolspec.ARBA-0026-2017.

Queenan AM, Bush K. Carbapenemases: The versatile β-lactamases. *Clin Microbiol Rev*. 2007;20:440–458.

Ramsey C, MacGowan AP. A review of the pharmacokinetics and pharmacodynamics of aztreonam. *J Antimicrob Chemother*. 2016;71:2704–2712.

Rennert-May E, Chew DS, Conly J, et al. Clinical practice guidelines for creating an acute care hospital-based antimicrobial stewardship program: A systematic review. *Am J Infect Control*. 2019. doi:10.1016/j.ajic.2019.02.010.

Rodriguez-Bano J, Gutierrez-Gutierrez B, Machuca I, Pascual A. Treatment of infections caused by extended-spectrum-β-, AmpC-,

and carbapenemase-producing *Enterobacteriaceae*. *Clin Micro Rev*. 2018;31:e00079–17.

Sader HS, Mendes RE, Pfaller MA, et al. Antimicrobial activities of aztreonam-avibactam and comparator agents against contemporary (2016) clinical Enterobacteriaceae isolates. *Antimicrob Agents Chemother*. 2017;62:e01856–17.

Sartelli M. A focus on intra-abdominal infections. *World J Emerg Surg*. 2010;5:9.

Scott LJ. Eravacycline: A review in complicated intra-abdominal infections. *Drugs*. 2019;79:315–324.

Serio AW, Keepers T, Krause KM. Plazomicin is active against metallo-β-lactamse-producing *Enterobacteriaceae*. *Open Forum Infect Dis*. 2019;6:0fz123.

Shaeer KM, Zmarlicka MT, Chahine EB, et al. Plasomicin: A next-generation aminoglycoside. *Pharmacotherapy*. 2019;39:77–93.

Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65:e45–e80.

Sheu CC, Chang YT, Lin SY, et al. Infections caused by carbapenemase-resistant *Enterobacteriaceae*: An update on therapeutic options. *Front Microbiol*. 2019. doi:10.3389/fmicb.2019.00080.

Shirley M. Ceftazidime-avibactam: A review in the treatment of serious gram-negative bacterial infections. *Drugs*. 2018;78:675–692.

Shon AS, Bajwa R, Russo TA. Hypervirulent (hypermicoviscous) *Klebsiella pneumoniae*: A new and dangerous breed. *Virulence*. 2013;4:107–118.

Sonnerville R, Ruimy R, Benzonana N, et al. An update on bacterial brain abscess in immunocompetent patients. *Clin Microbiol Infect*. 2017;23:614–621.

Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59:147–159.

Tangden T, Enblad P, Ullberg M, Sjolin J. Neurosurgical gram-negative bacillary ventriculitis and meningitis: A retrospective study evaluation the efficacy of intraventricular gentamicin therapy in 31 consecutive cases. *Clin Infect Dis*. 2010;52:1310–1316.

Temkin E, Torre-Cisneros J, Beovic B, et al. Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms. *Antimicrob Agents Chemother*. 2016;61:e01964–16.

Thomas KS. Extended-spectrum-β-lactamse, AmpC, and carbapenemase issues. *J Clin Microbiol*. 2010;48:1019–1025.

Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis*. 2017;64:701–706.

van Loon K, Voor In't Holt AF, Vos MC. A systematic review and meta-analysis of the clinical epidemiology of carbapenem-resistant Enterobacteriaceae. *Antimicrob Agents Chemother* 2017;62:e01730–1717.

Wagenlehner FME, Cloutier DJ, Komirenko AS, et al. Once-daily plazomycin for complicated urinary tract infections. *N Engl J Med*. 2019;380:729–740.

Wiest R, Krag A, Gerbes A. Spontaneous bacterial peritonitis: Recent guidelines and beyond. *Gut*. 2012;61:297–310.

Wilson WR, Bower TC, Creager MA, et al. Vascular graft infections, mycotic aneurysms, and endovascular infections: A scientific statement from the American Heart Association. *Circulation*. 2016;134:e412–e460.

Yahav D, Duskin-Bitan H, Eliakim-Raz N, et al. Monomicrobial necrotizing fasciitis in a single center: The emergence of gram-negative bacteria as a common pathogen. *Int J Infect Dis*. 2014;28:13–16.

Yahav D, Franceschini E, Koppel F, et al. Seven versus fourteen days of antibiotic therapy for uncomplicated gram-negative bacteremia: A non-inferiority randomized controlled trial. *Clin Infect Dis*. 2018. doi:10.1093/cid/ciy1054.

Yamaga S, Shime N. Association between appropriate empiric antimicrobial therapy and mortality from bloodstream infections in the intensive care unit. *J Infect Chemother*. 2018;24:267–271.

Yilmaziar T, Gulcu B, Isik O, Ozturk E. Microbiological aspects of Forunier's gangrene. *Int J Surg*. 2017;40:135–138.

Zhanel GG, Cheung D, Adam H, et al. Review of eravacycline, a novel fluorocycline antibiotic agents. *Drugs*. 2016;76:567–588.

Zhanel GG, Chung P, Adam H, et al. Ceftolozane/tazobactam: A novel cephalosporin/β-lactamse inhibitor combination with activity against multidrug-resistant gram-negative bacilli. *Drugs*. 2014;74:31–51.

Zhanel GG, Golden AR, Zelenitsky S, et al. Cefiderocol: A siderophore cephalosporin with activity against carbapenem-resistant and multidrug-resistant gram-negative bacilli. *Drugs*. 2019;79:271–289.

Zhanel GG, Lawrence CK, Adam H, et al. Imipenem-relebactam and meropenem-vaborbacctam: Two novel carbapenem-β-lactamase inhibitor combinations. *Drugs*. 2018;78:65–98.

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Enterococcus

Ronald N. Jones and Rodrigo E. Mendes

Since the early 1970s, the enterococci have steadily emerged as important hospital-acquired (nosocomial) pathogens. In statistics from the National Nosocomial Infections Surveillance System (NNISS) and subsequent Centers for Disease Control and Prevention (CDC) programs (National Healthcare Safety Network), enterococci are the second most common gram-positive cause of nosocomial infections overall, and gram-positive isolates causing bloodstream infections. Data from the SENTRY Antimicrobial Surveillance Program also confirmed enterococci as the second most common gram-positive organisms responsible for bloodstream infections in US hospitals. In addition, enterococci rank first among gram-positive cocci in producing urinary tract infections (see Table 133.1). Increases in occurrence of this genus since the mid-1970s are related to patterns of general antimicrobial use in the hospital and in particular to widespread use of extended-spectrum cephalosporins, penicillin-β-lactamase inhibitor combinations, fluoroquinolones, and carbapenems, as well as the emergence of resistances in the genus. Cephalosporins are generally not active or bactericidal against enterococci, as are not fluoroquinolones, and they may promote a selective pressure advantage for this organism thereby contributing to the increased prevalence. However, recent evidence reported by Mendes et al. has demonstrated that the occurrence of enterococci overall, and *Enterococcus faecalis* and *E. faecium* causing bloodstream infections in US hospitals, are in decline.

According to the SENTRY Program, *E. faecalis* is responsible for approximately 65% of all human enterococcal infections, and *E. faecium* accounts for most (~29%) of the remainder. However, *E. faecium* may account for a greater proportion (>30%) of enterococcal bacteremias (see Table 133.2). Antimicrobial resistance is a particular problem among *E. faecium* isolates. Other species of interest are *E. casseliflavus* and *E. gallinarum*, not because of the frequency with which they are isolated (<5%), but because of the intrinsic low-level resistance to vancomycin (i.e., the *vanC* genotype and resultant generally intermediate susceptibility phenotype; minimum inhibitory concentrations [MICs], 4–8 μg/mL).

The therapy of enterococcal infections challenges the healthcare practitioners as resistance to ampicillin, high-level aminoglycosides resistance (HLAR; compromising bacteriocidal combination therapy), and glycopeptides (vancomycin and others) have occurred; emerging linezolid and tedizolid (oxazolidinones), daptomycin (a lipopeptide), tigecycline (a glycylcycline), and quinupristin-dalfopristin resistance have also narrowed the number of therapeutic options. In addition, the risk of failure of trimethoprim-sulfamethoxazole (TMP-SMX) in therapy for urinary tract infection has become widely recognized regardless of in vitro susceptibility, where some standard organizations recommend *not* testing TMP-SMX.

All enterococci are intrinsically resistant to achievable in vivo levels of aminoglycosides; however, synergic killing can occur when aminoglycosides are combined with a cell wall–active agent such as a penicillin or a glycopeptide. HLAR strains are not susceptible to the synergic co-drug effects of the aminoglycosides. It is clinically significant that cross-resistance to the synergic activity of the aminoglycosides is *not* complete between gentamicin (and the related compounds tobramycin, netilmicin, amikacin, kanamycin, and isepamicin) and streptomycin. Streptomycin may be used successfully in combination to treat some HLAR strains. The selection of the appropriate aminoglycoside co-drug should be directed by validated in vitro susceptibility tests and the availability of streptomycin for clinical use and testing for monitoring drug levels.

TABLE 133.1 **PERCENTAGE OF VARIOUS GRAM-POSITIVE PATHOGENS CAUSING NOSOCOMIAL INFECTIONS IN THE NNISS/NHSN (CDC) COMPARING 1975, 2003, 2008, AND 2013**

	Percentage for 1975/2003/2008/2013 by infection site			
Pathogen	**Bloodstream**	**Wounds**[a]	**Pneumonia**	**Urine**
Enterococci	8.1/14.5/16.0/18.1	11.9/13.9/11.2/11.6	3.0/1.3/1.3/0.9	14.2/17.4/14.9/15.1
S. aureus	16.5/14.3/9.9/12.3	18.5/22.5/30.0/30.4	13.4/27.8/24.4/24.1	1.9/3.6/2.2/2.1
CoNS	10.3/42.9/34.1/20.5	7.4/15.9/13.7/11.7	2.6/1.8/1.3/0.9	3.2/4.9/2.5/2.2

[a] Skin and skin structure infections (SSSI).
Abbreviations: CoNS = coagulase-negative staphylococci; NNISS = National Nosocomial Infections Surveillance System; NHSN = National Healthcare Safety Network; CDC = Centers for Disease Control and Prevention.

Resistance to vancomycin is much more common among *E. faecium* isolates than with *E. faecalis*. Reports in the United States in the late 1990s suggested that the overall vancomycin-resistant rate for enterococci was approximately 20% among isolates causing bloodstream infections and higher resistance rates for some other drugs and species limited therapeutic choices. These resistance rates have escalated through 2010–2012, and decreased afterward (Table 133.2). It was reported by Willems and colleagues that the high prevalence of vancomycin-resistant *E. faecium* in US hospitals were due the spread of a successful hospital-adapted clonal complex lineage (CC-17), which has evolved ampicillin-, vancomycin-, and fluoroquinolone-resistance phenotypes. Acquired vancomycin resistance is often associated with resistance to teicoplanin (Van A phenotype or *vanA* gene) or may occur in the absence of cross-resistance to teicoplanin (Van B phenotype or *vanB* gene). This difference can be clinically significant in nations where teicoplanin has been clinically available for >30 years and could also be relevant in the United States because telavancin and dalbavancin (long-acting lipoglycopeptide) are marketed and active against isolates exhibiting a VanB phenotype. Also, another lipoglycopeptide, oritavancin, retains activity against both VanA and VanB resistance phenotypes, as does daptomycin and the oxazolidinones.

For the clinician, the problems posed by the emergence of resistance have been exacerbated by the technical difficulties in reliable detection of these antimicrobial resistances. In vitro resistance to TMP-SMX as a result of the ability of the most prevalent enterococci to use thymidine or thymine in the susceptibility test medium (escapes bactericidal action) has been addressed by use of media free of or low in concentration for these antagonists. However, there can be significant amounts of antagonists in the urine, and therefore the meaning of in vitro test results performed in these "improved" standardized test conditions remains compromised. Routine testing against ampicillin without testing for organism β-lactamase production may result in false-susceptible results. However, β-lactamase production continues to be an exceedingly rare mechanism of resistance (≤0.1%) among *E. faecalis*. A number of problems with the detection of HLAR using the most prevalent automated and commercial broth microdilution susceptibility test systems (Vitek 2, MicroScan, BD Phoenix) have been reported, although these appear to have been resolved in recent years. Similarly, with vancomycin and other newer agent resistances reported from both automated susceptibility test systems, Etest and disk diffusion test interpretive criteria may continue to require modifications over time to enable

TABLE 133.2 **TRENDS IN VANCOMYCIN-RESISTANT ENTEROCOCCI (VRE) BACTEREMIA RATES IN THE SENTRY ANTIMICROBIAL SURVEILLANCE PROGRAM (USA; 2000–2019) HOSPITALS, QUANTITATING VANCOMYCIN RESISTANCE (VANA) PATTERNS**

	Vancomycin nonsusceptible rate (%VanA)[a]	
Surveillance year	***E. faecium***	***E. faecalis***
(no. tested)	(3,743)	(6,871)
2000	57.1 (84.2)	4.0 (42.5)
2001	60.0 (88.2)	1.4 (35.7)
2002	70.7 (86.4)	2.9 (55.2)
2003	70.5 (88.5)	4.6 (34.8)
2004	68.6 (94.9)	2.6 (50.0)
2005	70.5 (95.6)	4.3 (51.2)
2006	69.7 (99.0)	4.8 (87.5)
2007	71.6 (97.6)	3.9 (89.7)
2008	75.3 (97.9)	6.5 (75.4)
2009	76.3 (97.6)	3.2 (65.6)
2010	80.7 (97.0)	5.3 (77.4)
2011	77.7 (96.6)	4.1 (82.9)
2012	78.2 (97.1)	2.9 (66.7)
2013	71.6 (98.4)	3.1 (100.0)
2014	68.4 (92.3)	1.9 (50.0)
2015	68.0 (98.6)	3.6 (66.7)
2016	66.0 (98.4)	4.8 (100.0)
2017	67.0 (95.1)	3.5 (100.0)
2018	67.4 (91.9)	3.4 (100.0)
2019	58.7 (96.3)	1.1 (100.0)

[a] A total of 753 other *Enterococcus* spp. were tested (data not shown) for a total of 11,092 US enterococcemia.
Modified from Arias et al., *Clin Infect Dis*. 2012;54(Suppl 3):S233–238 (data for 2000–2011) and Mendes et al., *J Chemoth*. 2018;30(5):280–289 (data for 2012–2016). Data on file (2017-2019), SENTRY Antimicrobial Surveillance Program (JMI Laboratories, North Liberty, IA). VanA phenotype defined as isolates displaying vancomycin and teicoplanin MICs of >4 μg/mL >8 μg/mL, respectively.

consistent, accurate detection of resistant strains. Lipoglycopeptide agents necessitate testing with surfactants (polysorbate-80) to prevent binding to reference test plastic labware and generally cannot be tested in widely available commercial testing systems.

Highly reliable, empiric therapy of enterococcal infection is not consistently satisfactory given the complexity and variability of resistance patterns, and therefore availability of prompt, reliable susceptibility test results is critical. At present, disk diffusion susceptibility testing, Etest, Vitek, or BD Phoenix Systems, and the reference broth microdilution or agar dilution methods are reliable methods for detection of important resistances. However, recent reports of false resistance have been reported for some newer agents, including oxazolidinones, caused by fuzzy zone diameter edges and trailing broth microdilution end points causing reading difficulties.

Enterococcal bloodstream infection

Isolation of enterococci from blood cultures may occur with or without endocarditis. In community-acquired enterococcal bloodstream infection approximately one-third of cases are concurrent with endocarditis, compared with fewer than 5% of nosocomial enterococcal bacteremias. These nosocomial infections are usually associated with urinary tract disease or instrumentation, intra-abdominal infection, infected intravascular devices, neoplastic disease, and significant neutropenia.

Infective endocarditis, even when caused by more susceptible strains of enterococci, tends to be more difficult to achieve clinical cure than those due to viridans group streptococci. Only two-thirds of patients will have favorable outcomes if a penicillin is used alone. Penicillin agents are not bactericidal, and a combination of a cell wall–active agent (a penicillin, usually ampicillin, or a glycopeptide) with an aminoglycoside for 4 to 6 weeks continues to be a recommended guideline for infections caused by *E. faecalis*. In general, ampicillin (two- or fourfold more active) is used in preference to penicillin. High-dose penicillin (ampicillin, 1-2 g q4-6h, or penicillin G, 18 to 30 million U/d) are considered appropriate, combined with gentamicin, 1 mg/kg every 8 hours or the use of the less toxic infusion pattern of 3 mg/kg once-daily dosing (Table 133.3). However, limited clinical information supports the use of once-daily aminoglycosides for endocarditis. Monitoring of aminoglycoside serum concentrations is essential to ensure adequate therapeutic levels and to minimize toxicity during the extended therapeutic course, as are vancomycin monitoring and stewardship if used (see also Chapter 37, "Endocarditis"). The choice of an aminoglycoside for combination therapy is between gentamicin and streptomycin (limited availability). Gentamicin is generally preferred because synergic killing is more consistent (see Table 133.4), ototoxicity is less frequent, and facilities to measure serum levels are more easily available. Enterococcal strains resistant to high levels of aminoglycoside in vitro are not susceptible to enhanced (synergistic) killing with a penicillin or vancomycin-like agents, and, in such patients, use of aminoglycosides constitutes exposure to potential toxicity (otic and renal) without apparent clinical benefit.

More recently, combinations of ampicillin and ceftriaxone to minimize gentamicin-caused renal toxicity and preserve higher cure rates have been successful for infections caused by *E. faecalis* (Table 133.3). In fact, the ampicillin and ceftriaxone combination therapy is the only option for the treatment of infective endocarditis and bacteremia due to HLAR *E. faecalis* with supportive clinical data. However, several clinical and observational studies implicated ceftriaxone as a major risk factor for occurrence of vancomycin-resistant *E. faecium* infection, including bacteremia. In addition, ceftriaxone is an independent risk factor for *Clostridium difficile* infections. Therefore, other alternative treatment options for *E. faecalis*, particularly combinations with newer cephalosporins (ceftaroline, ceftobiprole), as well as daptomycin, tigecycline, and fosfomycin have been suggested.

Unlike, ceftriaxone, other cephalosporins, such as cefepime and ceftaroline, do not appear to promote vancomycin-resistant enterococci (VRE) colonization/infection. Ampicillin plus ceftaroline demonstrated efficacy similar to ampicillin and ceftriaxone against *E. faecalis* in several in vitro pharmacodynamic studies. Other in vitro studies reported that the ampicillin-ceftriaxone activity was similar to ampicillin-ceftaroline and ampicillin-cefepime against *E. faecalis*. Daptomycin remains a very potent bactericidal agent against enterococci and is the treatment of choice for infections caused by *E. faecium*, where the majority of isolates in the United States are vancomycin-resistant (Table 133.2). Several studies have indicated that the daptomycin plus ceftaroline combination has been successful against *E. faecalis* and *E. faecium*, including isolates resistant to vancomycin. Although many studies reported success using a daptomycin dose of 6 mg/kg/d, there is evidence that higher doses of 8 to 12 mg/kg/d are associated with better clinical outcome and are recommended for serious and/or high-inoculum infections. The Clinical Laboratory Standards Institute (CLSI) MIC interpretative criteria for daptomycin was revised and published in May 2019 to include breakpoints for *E. faecium* and *Enterococcus* species other than *E. faecium*, and respective dosage regimens (Tables 133.4 and 133.5).

In serious infections caused by daptomycin-nonsusceptible *E. faecium*, linezolid has been recommended or daptomycin (high-dose) plus a β-lactam and another agent with in vitro activity, such as oritavancin, or an aminoglycoside if not a HLAR strain. Linezolid possesses US Food and Drug Administration (FDA) approval for treating VRE; however, this bacteriostatic agent offers a less desirable pathway for treating endovascular or serious infections. Tedizolid is a second-generation oxazolidinone recently approved for acute bacterial skin and skin structure infections, and clinical trial data indicate that tedizolid possesses an improved safety profile over linezolid (at the approved dose) with less likelihood of hematological and neurological toxicities and fewer drug–drug interactions. The use of this newest oxazolidinone for treating serious enterococci infections remains to be determined.

Older drugs such as chloramphenicol and doxycycline have demonstrated a variable degree of in vitro activity (<50% susceptible by CLSI criteria; data not shown) against the multidrug-resistant enterococci. Case reports indicate that these drugs used alone or with co-drugs can be successful in some cases, but each agent is

TABLE 133.3 **SUMMARY OF RECOMMENDED ANTIMICROBIAL TREATMENTS FOR INVASIVE ENTEROCOCCAL INFECTIONS**

Uncomplicated bacteremia			***E. faecium***	
		E. faecalis	**Vancomycin-susceptible**	**Vancomycin-resistant**
	1st options	Ampicillin	Vancomycin	Daptomycin or linezolid
	Alternatives	Piperacillin	Daptomycin	Daptomycin + β-lactams
		Imipenem	Linezolid	
		Vancomycin		
		Daptomycin		
		Linezolid		
Endorcaditis	1st options	Ampicillin + ceftriaxone	Vancomycin + gentamicin	Daptomycin or linezolid
		Ampicillin/penicillin + gentamicin		(Consider to add gentamicin or a β-lactam)
	Alternatives	Vancomicin + gentamicin	Linezolid	
		Daptomycin + β-lactams	Daptomycin + gentamicin	
			Daptomycin + β-lactams	

Table Modified from E. Rosselli Del Turco et al., *Clin Microbiol Infect*. 2021;27:364–371.
Dosages for the recommended antibiotics (all doses should be adjusted by kidney function):
Ampicillin: 1–2 g IV every 4 to 6 hours.
Piperacillin: 4 g IV every 8 hours.
Imipenem: 15–25 mg/kg IV every 6 hours.
Vancomycin: 25–30 mg/kg IV loading dose followed by 15 mg/kg every 8 hours.
Daptomycin: 6–8 mg/kg IV daily for uncomplicated non-vancomycin resistant enterococcal bacteraemia. At least 9 mg/kg IV daily for vancomycin-resistant enterococci.
Linezolid: 600 mg IV every 12 hours.
Ceftriaxone: 2 g IV every 12 hours.
Aqueous penicillin G sodium: 18–30 million U/24 h IV either continuously or in 6 equally divided doses.
Gentamicin: 3 mg/kg ideal body weight in 2–3 equally divided doses.

only bacteriostatic. Even with eradication of enterococci from the bloodstream, mortality remains high (30–50%). Furthermore, fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) may have limited value for strains tested as susceptible (see Tables 133.4 and 133.5) because resistance may emerge rapidly when these drugs are used alone. Combinations of ampicillin and a fluoroquinolone or a cephalosporin have been found bactericidal for some strains in vitro. Quinupristin-dalfopristin is a generally bacteriostatic option available for use in therapy of *E. faecium* infection only (not *E. faecalis*).

A variety of other agents (see Tables 133.4 and 133.5) with activity against enterococci may have the potential to expand the enterococcal treatment. Dalbavancin and telavancin are active in vitro against vancomycin-susceptible *E. faecalis.* Oritavancin is active against both *E. faecium* and *E. faecalis*, regardless of vancomycin susceptibility, and single and case reports have documented the clinical experiences of oritavancin (see Table 133.5). New generation tetracycline agents, such as tigecycline, omadacycline, and eravacycline were designed to retain activity against common tetracycline resistance determinants, and offer potential options for the treatment of VRE infections. The agent with the most clinical experience, tigecycline, is approved for use in intra-abdominal and skin and soft tissue infections for vancomycin-susceptible *E faecalis*, and shows *in vitro* activity against VRE of both species. However, owing to low serum concentrations, tigecycline has been used only for intra-abdominal infections or as a part of combination therapy in recalcitrant enterococcal bacteremia and infective endocarditis. Omadacycline and eravacycline are the two most recent new generation tetracycline agents approved by the FDA with antimicrobial activity that includes enterococci (Table 133.5). However, several of these drugs demonstrate little bactericidal action against multidrug-resistant enterococci, and experience with their use alone or in combination awaits reports from structured clinical studies.

Therapy with dalbavancin or telavancin is not an option for VanA vancomycin-resistant *E. faecium* strains, which is the predominant pattern (>70% strains) among clinical isolates in the United States (Table 133.2). Some experimental and clinical experiences with lipoglycopeptides for treating gram-positive infections are starting to emerge. Bouza et al. showed successful clinical outcomes with dalbavancin in 72.7% patients having a variety of enterococcal infections, including endocarditis during an observational and retrospective study in 29 hospitals in Spain. Jones et al. also reported favorable outcome when treating an ampicillin- and

TABLE 133.4 **SUSCEPTIBILITY RATES OF ALL ENTEROCOCCAL STRAINS FROM THE SENTRY ANTIMICROBIAL SURVEILLANCE PROGRAM, HOSPITAL PATIENTS IN 2015–2019 (50–77 MEDICAL CENTERS IN THE UNITED STATES/YEAR)**[a]

	Percentage susceptible[a]		
Antimicrobial agent	**All enterococci (*n* = 4,744)**	***E. faecalis* (*n* = 3,291)**	***E. faecium* (*n* = 1,321)**
Ampicillin	77.0	100.0	18.2
Levofloxacin	59.2	77.1	12.4
Daptomycin	99.6	99.7	99.5
Linezolid	99.7	99.9	99.2
Tetracycline	26.9	26.2	25.5
Minocycline	44.5	37.3	57.8
Teicoplanin	80.1	97.0	36.1
Tigecycline	99.5	99.8	98.8
Vancomycin	78.5	96.8	32.0
Gentamicin (HL)[b]	76.1	70.6	88.7
Streptomycin (HL)[b]	80.3	83.6	71.6

Abbreviation: HL = high-level resistance screen.
[a] Data on file, SENTRY Antimicrobial Surveillance Program (JMI Laboratories, North Liberty, IA). Categorical criteria per Clinical Laboratory Standards Institute (CLSI, 2021). Daptomycin percentage susceptible results for *Enterococcus* spp. other than *E. faecium* were obtained according to a breakpoint of ≤2 μg/mL, which is based on a dosage regimen of 6 mg/kg/d. The daptomycin percentage susceptible results for *E. faecium* were obtained according to a breakpoint of ≤4 μg/mL, which is based on a dosage regimen of 8–12 mg/kg/d for serious infections.
[b] Gentamicin and streptomycin HL data from 1,628 and 3,170 isolates, respectively, collected during 2016–2017.

vancomycin-susceptible *E. faecalis* bacteremia case with dalbavancin. Similarly, Thompson et al. also reported successful telavancin treatment of endocarditis caused by vancomycin-susceptible *E. faecalis*. Animal model study results described by Tran et al. indicated that telavancin could be an alternative for deep-seated infections caused by vancomycin-susceptible *E. faecalis*.

Therapy for enterococcal bloodstream infection in the absence of endocarditis follows the same general principles as for endocarditis except that bactericidal therapy may not be required. Bactericidal effect should be sought in the immunocompromised patient, and empiric therapy for such patients should be initiated with the broadest spectrum anti–gram-positive agents (vancomycin or daptomycin) because patients likely to develop nosocomial enterococcal infection are also at risk for infection with methicillin-resistant staphylococci. As with all other pathogens, removal of potential foci of infection, such as an indwelling vascular device, and drainage of an abscess as source control is essential for successful therapy.

Therapy of nonsevere infections and urinary tract disease

In the absence of immediate susceptibility test results, ampicillin is still a reasonable option for therapy of mild to moderate infections and particularly for urinary tract infections, given the high levels of ampicillin achieved in the urine. Nitrofurantoin is also active against most enterococci (>90%; data not shown including VRE) but is useful in therapy of urinary tract infection only.

Clearly, these approaches must be modified in the context of local epidemiology (antibiogram) and emergence of resistant strains. In centers with very high incidence of infection with ampicillin-resistant enterococci, usually *E. faecium*, this may not be appropriate empiric therapy. For infection with drug-resistant organisms, the options are similar to those discussed for bloodstream infection except that synergic combinations are usually not advised.

Enterococcal carriage

There is no general acceptance that fecal carriage or colonization by multidrug-resistant enterococci is an indication for therapy; however, given the risk to the patient of subsequent disseminated infection, there is high epidemiologic interest in this issue. Studies of the intestinal tract reservoir/source of VRE have greatly increased our knowledge of colonization and factors leading to persisting carriage. The third-generation cephalosporins, but not all cephalosporins or β-lactams, have clearly been implicated in promoting enterococcal colonization, possibly due to the high biliary excretion of some third-generation cephalosporins, with levels that exceed concentrations of 5,000 μg/mL. Examples

TABLE 133.5 **IN VITRO SUSCEPTIBILITY OF ALTERNATIVE ANTIMICROBIAL AGENTS FOR US ENTEROCOCCAL ISOLATES WITH RESISTANCE TO GLYCOPEPTIDES (1106 VANCOMYCIN-NONSUSCEPTIBLE ENTEROCOCCI [VANCOMYCIN MIC, ≥8 MG/ML] IN 2015–2019 SENTRY PROGRAM)**[a]

	Percentage by	Category[b]	
Antimicrobial agent	**Susceptible**	**Intermediate**	**Resistant**
Lipoglycopeptide			
Dalbavancin	5.7		
Oritavancin	93.7		
Telavancin	3.9		
Oxazolidinones			
Linezolid	99.3	0.4	0.3
Tedizolid	99.7		
Lipopeptide			
Daptomycin	68.7 (99.4)		0.6
Glycylcyclines			
Tigecycline	98.9		1.1
Aminomethylcycline			
Omadacycline	95.1	3.9	1.0
Fluoroquinolones			
Levofloxacin	1.2	0.7	98.1
Cephalosporins			
Ceftaroline	7.0		
Ceftobiprole	12.0		
Others			
Tetracycline	15.3	4.0	80.7
Minocycline	52.5	22.6	24.9

[a] Modified from results of the SENTRY Antimicrobial Surveillance Program (JMI Laboratories, North Liberty, IA).
[b] Categorical criteria per Clinical Laboratory Standards Institute (CLSI, 2021) or ≤0.25 μg/mL (susceptible) for dalbavancin and telavancin (vancomycin-susceptible *E. faecalis* breakpoint), and ≤0.12 μg/mL for oritavancin (vancomycin-susceptible *E. faecalis* breakpoint), ≤0.5 μg/mL for tedizolid (*E. faecalis* breakpoint), ≤2 μg/mL for daptomycin against *Enterococcus* spp. other than *E. faecium* when using a dosage regimen of 6 mg/kg/d and ≤4 μg/mL for daptomycin against *E. faecium* when using a dosage regimen of 8–12 mg/kg/d for serious infections, ≤0.25 μg/mL for tigecycline (vancomycin-susceptible *E. faecalis* breakpoint from the FDA package insert), ≤0.25 μg/mL for omadacycline (*E. faecalis* breakpoint from the FDA package insert), ≤4 μg/mL for ceftobiprole and ceftaroline.

of low-risk agents are aztreonam and cefepime, in contrast to cefoxitin, ceftriaxone, and clindamycin that have promoted VRE colonization. Some antimicrobials such as piperacillin-tazobactam inhibit establishment of VRE in the gut during therapy but promote overgrowth and persistence when exposed to VRE in the period of post-therapy recovery of normal flora. Data from clinical trials continue to be necessary to more adequately understand these complex interactions of antimicrobials, indigenous bowel flora, and colonizing resistant enterococci.

It seems reasonable to review the patient's therapy with a view toward discontinuation of any nonessential antimicrobials that might confer a selective advantage for the enterococci. However, relapses after discontinuation of selective intestinal tract decontamination remain high. The implications for infection control focus on (1) gastrointestinal selective decontamination; (2) antimicrobial use strategies (limit or restriction of selecting agents); (3) assuring persistence of the gastric acid barrier; (4) restoring indigenous colonic microflora; (5) assuring, where possible, decontamination of the hospital environment or patient's cutaneous surfaces; and (6) preventing patient-to-patient transmission via promoting handwashing/gloving by healthcare workers.

Conclusion

Therapy of enterococcal infections is one of the most challenging areas in the contemporary treatment of infectious disease. Quality laboratory support is essential to the management of these infections in the most appropriate manner while minimizing toxicity. Given the emerging inadequacies of our therapeutic armamentarium (ampicillin and glycopeptides) and the clear evidence that nosocomial spread of this pathogen can occur, an aggressive position with respect to hospital environment surveillance and infection control remains of critical importance. Also, more studies will be required to develop new, safe therapeutic agents and to focus our treatments on existing or newer antimicrobial agents (daptomycin, oxazolidinones, lipoglycopetides, tetracycline derivatives) used alone or in proven combinations that achieve acceptable enterococcus infection eradication with clinical safety.

Suggested reading

Arias CA, Mendes RE, Stilwell MG, Jones RN, Murray BE. Unmet needs and prospects for oritavancin in the management of vancomycin-resistant enterococcal infections. *Clin Infect Dis*. 2012;54:S233–S38.

Beganovic M, Luther MK, Rice LB, Arias CA, Rybak MJ, LaPlante KL. A review of combination antimicrobial therapy for *Enterococcus faecalis* bloodstream infections and infective endocarditis. *Clin Infect Dis*. 2018;67:303–309.

Bouza E, Valerio M, Soriano A, et al. Dalbavancin in the treatment of different gram-positive infections: A real-life experience. *Int J Antimicrob Agents*. 2018;51:571–77.

Carvalhaes CG, Huband MD, Reinhart HH, Flamm RK, Sader HS. Antimicrobial activity of omadacycline tested against clinical bacterial isolates from hospitals in China (Including Hong Kong) and Taiwan: Results from the Sentry Antimicrobial Surveillance Program (2013–2016). *Antimicrob Agents Chemother*. 2019;63:e02262–18.

Casapao AM, Kullar R, Davis SL, et al. Multicenter study of high-dose daptomycin for treatment of enterococcal infections. *Antimicrob Agents Chemother*. 2013;57:190–196.

Deshpande LM, Castanheira M, Flamm RK, Mendes RE. Evolving oxazolidinone resistance mechanisms in a worldwide collection of enterococcal clinical isolates: Results from the Sentry Antimicrobial Surveillance Program. *J Antimicrob Chemother*. 2018;73:2314–2322.

Eliopoulos GM. Quinupristin-dalfopristin and linezolid: Evidence and opinion. *Clin Infect Dis*. 2003;36:473–481.

Frampton JE, Curran MP. Tigecycline. *Drugs*. 2005;65:2623–2625; discussion 36–37.

Gaynes R, Edwards JR. Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis*. 2005;41:848–854.

Jones BM, Keedy C, Wynn M. Successful treatment of *Enterococcus faecalis* bacteremia with dalbavancin as an outpatient in an intravenous drug user. *Int J Infect Dis*. 2018;76:4–5.

Jones RN. Global epidemiology of antimicrobial resistance among community-acquired and nosocomial pathogens: A five-year summary from the Sentry Antimicrobial Surveillance Program (1997–2001). *Semin Respir Crit Care Med*. 2003;24:121–134.

Jones RN, Flamm RK, Sader HS. Surveillance of dalbavancin potency and spectrum in the United States (2012). *Diagn Microbiol Infect Dis*. 2013;76:122–123.

Mendes RE, Sader HS, Castanheira M, Flamm RK. Distribution of main gram-positive pathogens causing bloodstream infections in the United States and European hospitals during the Sentry Antimicrobial Surveillance Program (2010–2016): Concomitant analysis of oritavancin *in vitro* activity. *J Chemother*. 2018;30:280–289.

Mendes RE, Sader HS, Farrell DJ, Jones RN. Worldwide appraisal and update (2010) of telavancin activity tested against a collection of gram-positive clinical pathogens from five continents. *Antimicrob Agents Chemother*. 2012;56:3999–4004.

Moellering RC, Jr. The Garrod Lecture. The enterococcus: A classic example of the impact of antimicrobial resistance on therapeutic options. *J Antimicrob Chemother*. 1991;28:1–12.

Munita JM, Arias CA, Murray BE. *Enterococcus faecalis* infective endocarditis: Is it time to abandon aminoglycosides? *Clin Infect Dis*. 2013;56:1269–1272.

Rice LB, Hutton-Thomas R, Lakticova V, Helfand MS, Donskey CJ. Beta-lactam antibiotics and gastrointestinal colonization with vancomycin-resistant enterococci. *J Infect Dis*. 2004;189:1113–1118.

Rosselli Del Turco E, Bartoletti M, Dahl A, Cervera C, Pericàs JM. How do I manage a patient with enterococcal bacteraemia? *Clin Microbiol Infect*. 2021 Mar;27(3):364–371. doi:10.1016/j.cmi.2020.10.029. Epub 2020 Nov 2. PMID: 33152537.

Sakoulas G, Nonejuie P, Nizet V, Pogliano J, Crum-Cianflone N, Haddad F. Treatment of high-level gentamicin-resistant *Enterococcus Faecalis* endocarditis with daptomycin plus ceftaroline. *Antimicrob Agents Chemother*. 2013;57:4042–4045.

Tran TT, Tam VH, Murray BE, Arias CA, Singh KV. Efficacy of telavancin alone and in combination with ampicillin in a rat model of *Enterococcus faecalis* endocarditis. *Antimicrob Agents Chemother*. 2017;61:e02489.

Willems RJ, Top J, van Santen M, et al. Global spread of vancomycin-resistant *Enterococcus faecium* from distinct nosocomial genetic complex. *Emerg Infect Dis*. 2005;11:821–828.

Zhanel GG, Baxter MR, Adam HJ, Sutcliffe J, Karlowsky JA. In vitro activity of eravacycline against 2213 gram-negative and 2424 gram-positive bacterial pathogens isolated in Canadian hospital laboratories: Canward Surveillance Study 2014–2015. *Diagn Microbiol Infect Dis*. 2018;91:55–62.

134

Erysipelothrix

W. Lee Hand

Erysipelothrix rhusiopathiae is a pleomorphic, non-spore-forming, gram-positive bacillus. This organism causes both a self-limited soft-tissue infection (erysipeloid) and serious systemic disease. *Erysipelothrix rhusiopathiae* is widespread in nature and infects many domestic animals. Swine are probably the major reservoir of *E. rhusiopathiae*. The microorganism is also found in sheep, cattle, horses, chickens, and dogs, as well as in birds, fish, crustaceans, seals, and dolphins. Infection in humans is usually due to occupational exposure. Butchers, abattoir workers, fishermen, farmers, and veterinarians are at risk for *Erysipelothrix* infections. The clinical spectrum of human infection includes localized cutaneous infection, diffuse cutaneous disease, and systemic bloodstream infection.

Localized cutaneous infection

Erysipeloid of Rosenbach, the localized cutaneous form of illness, is the most common type of human infection caused by *E. rhusiopathiae* (Figure 134.1). Fingers and/or hands (sites of exposure) are almost always involved in this soft-tissue infection.

Mild pain may occur at the site of inoculation, followed by itching, throbbing pain, burning, and tingling. The characteristic skin lesion slowly progresses from a small red dot at the site of inoculation to a fully developed erysipeloid skin lesion, consisting of a well-developed purplish center with an elevated border. Patients often complain of joint stiffness and pain in the involved fingers, but swelling is minimal or absent. Small hemorrhagic, vesicular lesions may be present at the site of inoculation. Erysipeloid lesions do not resemble true cellulitis, as opposed to erysipelas, which is due to group A streptococcal infection. Thus, Rosenbach introduced the term *erysipeloid* for the human cutaneous disease caused by *Erysipelothrix*. Pain may be disproportionate to the degree of apparent involvement. Local lymphangitis and adenitis develop in 30% of patients. However, systemic symptoms such as high fever or chills are uncommon.

A provisional diagnosis is based on a history of contact with potentially contaminated materials or occupational exposure, plus compatible physical findings. Gram-stained smears and cultures of aspirated material from skin lesions are often negative because the organism is deep within the dermis.

Diffuse cutaneous disease

Most erysipeloid skin lesions resolve even without specific treatment. However, erysipeloid occasionally will progress to the diffuse cutaneous form in untreated patients. Eating of contaminated meat has also been reported as a cause of this clinical entity. The characteristic purplish skin lesions expand with gradual clearing of the center. Bullous lesions may appear at the primary site or at distant locations. These patients often have systemic symptoms such as high fever, chills, and arthralgias. Blood cultures are invariably negative.

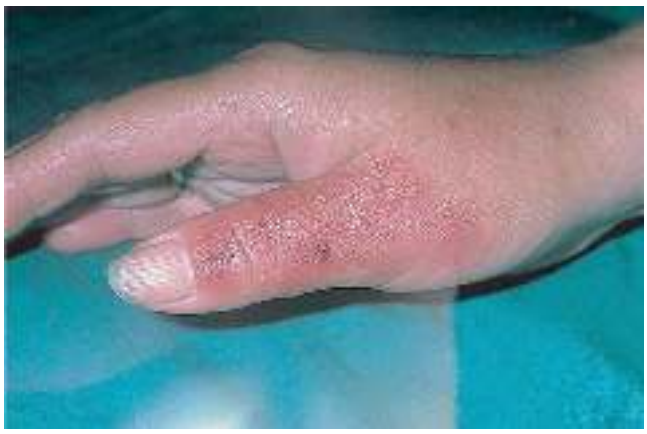

FIGURE 134.1 Erysipeloid.
(From Gary M. White and Neil H. Cox, Diseases of the Skin, Philadelphia: WB Saunders; 1995.)

Systemic infection (bacteremia and/or endocarditis)

Bacteremic infection caused by *E. rhusiopathiae* is generally a primary infection and not the result of dissemination from localized cutaneous disease. Nevertheless, one-third of patients with bloodstream infection have skin lesions suggestive of erysipeloid. Persistent bacteremia with *E. rhusiopathiae* has been reported after eating contaminated seafood. Cutaneous serpiginous lesions or multiple bullous lesions over the trunk and extremities may be seen. Many patients have fever for 2 to 3 weeks before presentation. Fever and chills may resolve spontaneously, but relapse is to be expected.

Patients with severe underlying heart disease or liver disease may present with a clinical picture resembling gram-negative sepsis. More than one-third of patients with disseminated infection are alcoholics, and chronic liver disease is a major predisposing factor. Bacteremia has also been reported in immunocompromised individuals, who often are receiving corticosteroid and/or cytotoxic drug treatment for collagen vascular disease or malignancy.

Erysipelothrix rhusiopathiae bacteremia is usually associated with a severe clinical course and is frequently complicated by endocarditis. *Erysipelothrix* endocarditis often results in extensive destruction of cardiac valves, especially the aortic valve. Previous reports were that approximately one-third of endocarditis patients die, and an additional one-third require cardiac valve replacement. However, there are no recent data on mortality. Absence of typical findings of endocarditis on initial physical examination or echocardiography does not exclude this diagnosis in patients with positive blood cultures. Reported complications of endocarditis have included proliferative glomerulonephritis with acute renal failure and visceral botryomycosis.

Earlier publications indicated that 90% of bacteremic infections were associated with endocarditis. This perceived high frequency may, at least in part, be a result of reporting bias because a number of bacteremic cases without endocarditis have been reported more recently.

Unusual reported infections due to *Erysipelothrix* include necrotizing fasciitis (after local inoculation), septic arthritis of native and prosthetic knees, peritoneal dialysis-associated peritonitis, acute and chronic meningitis, intra-abdominal abscesses, and empyema in the spinal canal with paravertebral abscesses.

The diagnosis of disseminated *E. rhusiopathiae* infection depends on identification of this organism in blood cultures. Commercial media are satisfactory for isolation from blood, and growth is usually recognized in 2 or 3 days. The organism may initially be misidentified as a *Lactobacillus* species.

TABLE 134.1 **ANTIBIOTIC THERAPY FOR *ERYSIPELOTHRIX RHUSIOPATHIAE* INFECTION**

	Antibiotics of choice		
Type of *Erysipelothrix* infection	**Drug**	**Dose and route**	**Duration**
Localized cutaneous			
Primary	Penicillin V	500 mg q6h PO	7 d
Alternatives	Ciprofloxacin (other fluoroquinolones may be used)	250 mg q12h PO	7 d
	Clindamycin	300 mg q8h PO	7 d
	Erythromycin (other macrolides may be used)	500 mg q6h PO	7 d
Severe bacteremic or endocarditis			
Primary	Penicillin G	2–4 million units q4h IV	4 wk
Alternatives	Ceftriaxone	2 g q24h IV	4 wk
	Imipenem	500 mg q6h IV	4 wk
	Ciprofloxacin (other IV fluoroquinolones may be used)	400 mg q12h IV	4 wk

Therapy

Erysipeloid may resolve spontaneously within 3 weeks, but treatment with appropriate antibiotic therapy hastens the healing process and prevents relapse. Local therapy with rest and heat is helpful for patients with painful, swollen lesions or arthritis. The involved hand or finger should be carried in a sling or splint. Surgical incision or debridement of local lesions is not necessary.

Penicillin and imipenem are the most active antibiotics against *Erysipelothrix* with in vitro testing. Penicillin is a time-tested, effective agent for treatment of all forms of *E. rhusiopathiae* infection. Other β-lactam antibiotics are also active against this organism. Fluoroquinolones and clindamycin demonstrate good in vitro activity. Macrolides, tetracyclines, and chloramphenicol have less predictable activity against *Erysipelothrix* and should not be used in the treatment of disseminated infection. *Erysipelothrix rhusiopathiae* is resistant to sulfonamides, trimethoprim–sulfamethoxazole, aminoglycosides, and vancomycin. Limited data indicated that daptomycin has good in vitro activity.

Antibiotic therapy should be based upon the clinical picture and results of blood cultures (Table 134.1). Oral antibiotic therapy is appropriate for localized cutaneous infection. Parenteral antibiotic treatment is indicated if patients have systemic infection or severe diffuse cutaneous disease. Penicillin G has been the historic drug of choice. Alternatives include ceftriaxone, imipenem, and fluoroquinolones. Patients with bacteremia or endocarditis should receive at least 4 weeks of intravenous antibiotic therapy.

Suggested reading

Campbell D, Cowan M. Septicemia and aortic valve endocarditis due to *Erysipelothrix rhusiopathiae* in a homeless man. *Case Rep Infect Dis*. 2013;2013:923034.

Dunbar SA, Clarridge JE III. Potential errors in recognition of *Erysipelothrix rhusiopathiae*. *J Clin Microbiol*. 2000;38:1302–1304.

Garcia-Restoy E, Espejo E, Bella F, Llebot J. Bacteremia due to *Erysipelothrix rhusiopathiae* in immunocompromised hosts without endocarditis. *Rev Infect Dis*. 1991;13:1252–1253.

Gorby GL, Peacock JE, Jr. *Erysipelothrix rhusiopathiae* endocarditis: microbiologic, epidemiologic, and clinical features of an occupational disease. *Rev Infect Dis*. 1988;10:317–325.

Klauder JV. Erysipeloid as an occupational disease. *JAMA*. 1938;111:15.

McNamara DR, Zitterkopf NL, Baddour LM. Photoquiz: a woman with a lesion on her finger and bacteremia. *Clin Infect Dis*. 2005;41:1005–1006, 1057–1058.

Ognibene FP, Cunnion RE, Gill V, et al. *Erysipelothrix rhusiopathiae* bacteremia presenting as septic shock. *Am J Med*. 1985;78:861–864.

Reboli AC, Farrar WE. *Erysipelothrix rhusiopathiae*: an occupational pathogen. *Clin Microbiol Rev*. 1989;2:354–359.

Soriano F, Fernandez-Roblas R, Calvo R, et al. In vitro susceptibilities of aerobic and facultative non-spore-forming gram-positive bacilli to HMR 3647 (RU 66647) and 14 other antimicrobials. *Antimicrob Agents Chemother*. 1998;42:1028–1033.

Venditti M, Gelfusa V, Terasi A, et al. Antimicrobial susceptibilities of *Erysipelothrix rhusiopathiae*. *Antimicrob Agents Chemother*. 1990;34:2038–2040.

Wang Q, Chang BJ, Riley TV. Erysipelothrix rhusiopathiae. *Vet Microbiol*. 2010;140: 405–417.

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HACEK

Vivian H. Chu

The acronym HACEK describes a heterogeneous group of organisms that share three major characteristics. First, they are small gram-negative rods that are commonly present as part of normal oral–pharyngeal or respiratory flora. Second, they are relatively fastidious microorganisms. Third, they have a predilection to infect heart valves. The HACEK group includes *Haemophilus* species (except *Haemophilus influenzae*), *Aggregatibacter* (formerly *Actinobacillus*) species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species. These organisms are infamous for their ability to cause endocarditis although, rarely, they can also cause a variety of other infections (Table 135.1). For example, human bites can result in cellulitis or abscess formation resulting from HACEK organisms, especially *Eikenella* species, and various *Haemophilus* species can cause epiglottitis or brain abscesses.

Members of the HACEK group are normal indigenous flora of the oral cavity. Hematogenous seeding of the bloodstream may occur after dental manipulation, but is more likely to occur in the setting of ordinary daily activities, particularly among individuals with periodontal disease. Transient or sustained bacteremia puts individuals with underlying valvular heart disease at risk for developing infective endocarditis (IE). Antibiotic prophylaxis (AP) prior to dental manipulation has not been shown to protect against IE, therefore the guidelines for AP have been modified to include only individuals in the highest risk group. While millions of patients undergo dental procedures annually, cases of IE caused by HACEK group organisms are rare.

Diagnosis

Bacteria in the HACEK group are commonly but often erroneously considered in the differential diagnosis for culture-negative endocarditis. In the past the traditional method of increasing the recovery of HACEK bacteria was to extend the incubation of blood culture bottles from 5 to 7 days to 2 to 3 weeks. However, with improvements in blood culture methods, this practice is no longer recommended. A recent multicenter study showed that the mean and median times to detection of HACEK isolates using current laboratory methods and media were 3 and 3.4 days, respectively. In addition, none of the cultures that were held for prolonged incubation and terminal subculturing yielded additional growth. Several other studies have demonstrated that isolation of HACEK organisms usually occurs within 5 days, suggesting that prolonged incubation is no longer needed to detect HACEK bacteria.

HACEK organisms typically grow on 5% sheep blood and chocolate agar but not on Mac-Conkey's agar. Because growth is often poor or absent in an unenhanced atmosphere, incubation in 5% to 10% carbon dioxide (CO_2) is recommended. After growth is observed, standard biochemical tests will identify individual HACEK species. The use of 16S ribosomal RNA (rRNA) gene analysis may be useful for HACEK organisms that are not readily identified with standard biochemical tests.

TABLE 135.1 **HACEK-ASSOCIATED INFECTIONS**

Haemophilus aphrophilus, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus parainfluenzae, Haemophilus paraphrophilus, Haemophilus segnis	Brain abscess, endocarditis, endophthalmitis, epiglottitis, hepatic abscess, intra-abdominal infection, meningitis, neonatal sepsis, necrotizing fasciitis, otitis media, pneumonia, sinusitis, septic arthritis, urinary tract infection
Aggregatibacter actinomycetemcomitans	Brain abscess, cellulitis, empyema, endocarditis, endophthalmitis, osteomyelitis, periodontal infection, parotitis, pericarditis, pneumonia, synovitis, thyroid abscess, urinary tract infection
Cardiobacterium hominis	Endocarditis, meningitis
Eikenella corrodens	Abscessed tooth, Bartholin's gland abscess, brain abscess, cellulitis, conjunctivitis, dacryocystitis, empyema, endocarditis, endometritis, gingivitis, intra-abdominal abscess, intravascular space infections, keratitis, liver abscess, mediastinitis, meningitis, mycotic aneurysm, otitis externa, parotitis, pericarditis, pneumonia, septic pulmonary emboli, subdural empyema, thyroid abscess, thyroiditis
Kingella dentrificens, Kingella indologenes, Kingella kingae	Abscess, endocarditis, epiglottitis, intervertebral diskitis, meningitis, oropharyngeal infections, osteomyelitis, septic arthritis

Clinical features

Endocarditis caused by members of the HACEK group typically occurs in individuals with pre-existing valvular abnormalities and/or prosthetic valves. The results of a recent large, multicenter cohort showed that individuals with HACEK IE tend to be younger than those with non-HACEK IE with a median age of 47 years vs. 60 years, respectively. According to the afore-mentioned study, the most common members of the HACEK group identified were *Haemophilus* spp. (40%) followed by *Aggregatibacter* spp. (34%), *Cardiobacterium* spp. (14%), *Eikenella corrodens* (5%), and *Kingella* spp. (5%).

Endocarditis due to members of the HACEK group usually has a subacute course that may include frequent embolization due to the presence of large valvular vegetations. In the aforementioned cohort, stroke occurred in a significantly higher proportion of patients with HACEK IE compared to non-HACEK IE (25% vs. 17%, respectively; $p = 0.05$); however, the rates of in-hospital mortality (4% vs. 18%, respectively; $p < 0.01$) and 1-year mortality (11% vs. 39%, respectively; $p < 0.01$) were low. The high rate of stroke and paradoxically low rate of death is unique to HACEK IE.

Therapy

There have been no large trials to evaluate the best therapy for IE caused by HACEK group organisms. Currently available information on treatment is derived from in vitro susceptibility testing and the results of small case series or individual case reports. In the past, ampicillin plus an aminoglycoside was widely recommended as the therapy of choice. This treatment was advocated because synergy between β-lactams and aminoglycosides could often be demonstrated in vitro, but such synergy has not been conclusively proven to occur in vivo. Moreover, a number of case reports have documented therapeutic failures of combined therapy with ampicillin and gentamicin in the treatment of infections caused by *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans* and *Haemophilus*. In addition, authors of several recent reports have described β-lactamase production by numerous strains of HACEK group organisms. Because of their fastidious growth requirements, susceptibility testing for many members of the HACEK group is often difficult to obtain in routine microbiology laboratories. Taken together, HACEK group organisms should be considered ampicillin resistant unless proved otherwise; and the use of ampicillin as empiric or initial therapy for infections due to HACEK group organisms is not advised.

Most HACEK organisms, with the notable exceptions of *A. actinomycetemcomitans* and *E. corrodens*, are susceptible to first- and second-generation cephalosporins, and virtually all species are susceptible to third-generation cephalosporins. Therefore, cefotaxime or ceftriaxone is generally considered to be the best therapy for IE caused by HACEK group bacteria. The use of ceftriaxone, 2 g intravenously (IV) or intramuscularly (IM) once daily, is recommended because of its convenience and suitability for outpatient parenteral therapy (Table 135.2). The duration of therapy for native valve endocarditis should be at least 4 weeks; at least 6 weeks of therapy is recommended for prosthetic valve endocarditis.

TABLE 135.2 **ANTIBIOTICS RECOMMENDED FOR SERIOUS INFECTIONS**

	Antibiotic	Dosage and route	Length of therapy
First choice	Ceftriaxone	2 g IV or IM daily	4–6 wk
Alternative	Ciprofloxacin	750 mg PO every 12 h	4–6 wk

HACEK group organisms are also susceptible in vitro to most fluoroquinolones and aztreonam. Thus one of these agents may be used in the β-lactam-intolerant patient. There is a growing body of evidence to support the use of ciprofloxacin as outpatient therapy for HACEK endocarditis.

A number of investigators advocate empirical therapy with either ceftriaxone along with an aminoglycoside or ciprofloxacin until sensitivities return. A fluoroquinolone such as ciprofloxacin is the preferred alternative for patients who are allergic to a β-lactam. Ciprofloxacin is an appropriate choice for the outpatient segment of therapy because of its high bioavailability after oral ingestion and excellent safety profile. However, because of the lack of published data about fluoroquinolone therapy for HACEK group bacterial infections, ceftriaxone would still be considered first-line therapy. Careful follow-up of all patients undergoing treatment is also recommended, including periodic assessment of clinical and microbiologic response using careful examinations and follow-up blood cultures. Careful monitoring for compliance is advised for all patients treated with oral therapy.

HACEK group organisms are usually susceptible to tetracycline and chloramphenicol; however, both of these agents are bacteriostatic and thus are poor choices for endovascular infections. Most HACEK group members are resistant to metronidazole, vancomycin, erythromycin, and clindamycin.

Prognosis

Endocarditis caused by HACEK group organisms is associated with a favorable prognosis. Most infections can be cured with medical therapy or a combination of medical and surgical therapy.

Nonendocardial infections

Nonendocardial infections caused by HACEK group organisms are rare. Such infections are usually responsive to short courses of antibiotic therapy. Surgical drainage is indicated for abscesses. Most authorities recommend 3 to 4 weeks of parenteral therapy followed by an additional 3 weeks of antibiotics by mouth for treatment of septic arthritis caused by *Kingella kingae* and other HACEK group organisms. Two to four weeks of parenteral therapy followed by 1 to 6 months of oral therapy is recommended for the treatment of osteomyelitis caused by HACEK organisms. Management plans should include a careful assessment of the need for surgical debridement and monitoring for clinical response.

Suggested reading

Babinchak TJ. Oral ciprofloxacin therapy for prosthetic valve endocarditis due to *Actinobacillus actinomycetemcomitans*. *Clin Infect Dis*. 1995;21:1517–1518.

Baron EJ, Scott JD, Tompkins LS. Prolonged incubation and extensive subculturing do not increase recovery of clinically significant microorganisms from standard automated blood cultures. *Clin Infect Dis*. 2005;41:1677–1680.

Chambers ST, Murdoch D, Morris A, et al. HACEK infective endocarditis: characteristics and outcomes from a large, multi-national cohort. *PLoS One*. 2013;8(5): e63181.

Coburn B, Baldwin T, Prasad R, et al. Antimicrobial susceptibilities of clinical isolates of HACEK organisms. *Antimicrob Agents Chemother*. 2013;57:1989–1991.

Das M, Badley AD, Cockerill FR, et al. Infective endocarditis caused by HACEK microorganisms. *Annu Rev Med*. 1997;48:25–33.

Kaplan AH, Weber DJ, Oddone EZ, et al. Infection due to *Actinobacillus actinomycetemcomitans*: 15 cases and review. *Rev Infect Dis*. 1989;11:46–63.

Nishimura RA, Carabello BA, Faxon DP, et al. ACC/AHA 2008 Guideline update on valvular heart disease: focused update on infective endocarditis. *J Am Coll Cardiol*. 2008;52:676–685.

Petti CA, Bhally HS, Weinstein MP, et al. Utility of extended blood culture incubation for isolation of *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* organisms: a retrospective multicenter evaluation. *J Clin Microbiol*. 2006;44:257–259.

Wilson WR, Karchmer AW, Dajani AS, et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. *JAMA*. 1995;274:1706–1713.

Helicobacter pylori

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Introduction

Helicobacter pylori are gram-negative spiral shaped-bacteria that infect more than 50% of humans globally. *H. pylori* infection is a serious, chronic, transmissible infectious disease that causes progressive, destructive inflammation (e.g., gastritis) of the stomach. The infection is etiologically related to a number of important diseases including gastric and duodenal ulcer disease, gastric cancer, primary B-cell gastric lymphoma, atrophic gastritis, vitamin B_{12} malabsorption (pernicious anemia), iron deficiency anemia, idiopathic thrombocytopenia, and dyspepsia (i.e., *H. pylori* is a major cause of morbidity and mortality worldwide). The prevalence of *H. pylori* infection is inversely related to the general health, well-being, and degree of development of a society. Acquisition of the infection is often associated with transient symptoms that resolve. The process then becomes clinically latent; approximately 20% of infected individuals eventually develop clinically recognizable diseases.

Discovery of *H. pylori*

In the early 1980s, Robin Warren, a pathologist in Perth, Western Australia, teamed up with a young trainee in internal medicine, Barry Marshall, to investigate small curved bacteria seen on gastric biopsies from patients with gastritis. In 1982, the organism was eventually cultured and is now known as *Helicobacter pylori. H. pylori* is a microaerophilic, gram-negative, spiral rod approximately 0.6 × 3.5 μm with approximately seven unipolar flagellae. Biochemical features that help identify it are the presence of urease, oxidase, and catalase.

Warren and Marshall were able to prove that the organism was etiologically involved in gastritis and suggested it might also cause peptic ulcer and gastric cancer, which were both already established to be tightly associated with gastritis. In 2005, the Nobel Prize for Physiology and Medicine was awarded to Warren and Marshall for culture of the organism and proof of its relation to peptic ulcer disease. In 1994, the International Agency for Cancer Research defined *H. pylori* as a Class I carcinogen for gastric cancer, and the infection is now recognized as the primary etiologic factor for gastric cancer. Before 1950, gastric cancer was the most common cause of cancer deaths in most countries, and it still ranks as fifth most common with approximately 1 million deaths worldwide annually.

Epidemiology and transmission

H. pylori infection is typically acquired in childhood. It can be considered a situational opportunist as transmission can involve any route that allows bacteria from one person's stomach to gain access to another's.

H. pylori has also been cultured from stools and from vomit obtained from both infected young children and adults and from contaminated water and food. Most often transmission is person-to-person and tends to be transmitted within families. In countries with generally poor sanitation and unclean water supplies, waterborne transmission may also be important. Oral–oral transmission is unlikely except related to premastication of infant foods, which is still practiced in some societies. Overall, the major risk factors for *H. pylori* infection generally fall under the category of poor household hygiene and include birth in a developing country, low socioeconomic status, crowded living conditions, large family size, unsanitary living conditions, unclean food or water, presence of infants in the home, and exposure to gastric contents of infected individuals.

The prevalence of *H. pylori* infections varies by geographic location, ethnic background, and socioeconomic condition. As countries develop economically and sanitation improves, the incidence of *H. pylori* acquisition falls. For example, in the past 30 year *H. pylori* has almost disappeared from children in Japan (e.g., prevalence of ≤4%), and, except among the socially disadvantaged, this same process is occurring or has occurred in most developed countries. This change in *H. pylori* acquisition has resulted in an epidemiologic pattern of decreasing prevalence among successive birth cohorts. As a generalization, the prevalence in a birth cohort at about age 20 generally identifies the prevalence of *H. pylori* infections maintained by that birth cohort throughout life. In developing countries this is typically between 60% and 90%. In contrast, the *H. pylori* prevalence among middle-class white Americans born in the United States and whose parents were also born in the United States is now <15%, except in the elderly where the higher prevalence reflects the lower standards of living during their childhood. The general phenomenon of a declining prevalence of *H. pylori* infection in the United States is, however, now being offset by increasing immigration from high *H. pylori* prevalence regions.

Worldwide, improvements in sanitation and standards of living have resulted in a decline in the incidence of *H. pylori* infection and consequently of *H. pylori*-related diseases. However immigrants from developing countries will likely continue to provide a pool of *H. pylori*-related diseases even in the most advanced societies.

Pathogenesis of infection

After gaining access to the stomach, *H. pylori* urease helps protect the organisms from gastric acid while they use their flagella to "swim" to reach the mucus layer, which they burrow through to reach the mucosal surface where their adhesins attach, often at intercellular junctions. Here, they are protected both from acidic gastric contents and from being emptied from the stomach with meals. *H. pylori* possess many tools needed to evade host defenses, such as catalase, superoxide dismutase, and a poorly reactive lipopolysaccharide. Small numbers of *H. pylori* are also found within gastric epithelial cells, which may serve as a sanctuary to evade host defenses and may in part be responsible for the failure of topical antibiotic therapy. Attachment of *H. pylori* to the gastric mucosa is associated with local production of proinflammatory cytokines (e.g., interleukin-8), which induces infiltration of polymorphonuclear leukocytes and ultimately leads to the characteristic histologic pattern of an acute inflammatory reaction superimposed upon chronic inflammation which also includes organized lymphoid follicles.

The clinical outcome of *H. pylori* infection is determined by a complex interaction of the host, bacterium, and environmental factors. A number of putative *H. pylori* virulence factors have been described, including the *cag* pathogenicity island (PAI), the outer membrane inflammatory protein (OipA), a vacuolating cytotoxin (VacA), and a host of adhesins. The *cag* PAI region encodes a type IV bacterial secretion apparatus, which translocates or injects the CagA protein and possibly other proteins into host target cells. Phosphorylation of CagA activates a number of host signaling pathways that can subsequently influence host cellular functions, including proliferation, apoptosis, cytokine release, and cell motility. VacA is present in nearly all *H. pylori* strains but only about half of the *H. pylori* strains produce VacA toxin in vitro. Although VacA induces epithelial vacuolation in vitro, its function in vivo remains unclear; recent evidence suggests it may be critically involved in the intracellular survival of *H. pylori*.

A large number of descriptive epidemiologic studies have been done attempting to correlate specific *H. pylori* virulence factor genotypes and clinical outcome, especially in relation to *cagA* status and to genotypic variations in the *vacA* signal sequence (s1a, s1b, s1c) and mid-region of the *vacA* (m1, m2) gene. The presence of the putative virulence factors is typically linked (i.e., CagA positive strains also typically possess vacA m1,s1, OipA "on," etc.), but attempts to establish region-specific associations using samples of convenience produce confusing, conflicting, and inconsistent putative disease. It is important to note that *H. pylori* that lack all of the currently recognized putative virulence factors also result in increased mucosal inflammation, which in turn increases the risk of peptic ulcer disease and gastric cancer. No clinically avirulent *H. pylori* have been identified, and the risk of developing gastric cancer with the most virulent strains is only about twice that of infection with the least virulent strains. As such, testing for putative virulence factors has not proved to have clinical utility and is not clinically recommended.

Pattern of gastritis and clinical outcomes of *H. pylori* infection

The clinical outcome of an *H. pylori* infection is closely related to the anatomic pattern and severity of *H. pylori*-induced gastritis. The stomach is divided into two basic regions, an acid-secreting proximal portion, the corpus, and a distal non–acid-secreting region, the antrum. Although *H. pylori* colonizes the entire surface of the stomach, the acid-secreting corpus is relatively resistant, such that infection and inflammation in the corpus tends to be superficial. This pattern is because the organism is repelled from the gastric pits in the proximal stomach by the highly acidic fluid (pH <1) secreted from parietal cells, which is injected into the lumen through these pits and restricts *H. pylori* to the surface mucosa where they can

"hide" under the mucus layer. Inhibition of acid secretion, whether by highly selective vagotomy, use of an antisecretory drug, or during febrile episodes, allows the bacteria to invade into the pits and interact with the mucosa to produce inflammation deeper within the mucosa where the stem cells are located. Interleukin-1β, a potent natural antisecretory agent, is also produced in response to attachment of the bacteria and further reduces acid secretion, which may eventually allow the infection to become established in the depths of the corpus and result in pangastritis.

Antral inflammation affects the neuroendocrine G- and D-cells that affect acid secretion. Antral inflammation causes up-regulation of the gastrin-producing G-cells as well as inhibition of somatostatin secretion by D-cells resulting in deregulated acid secretion characterized by an increase in the amount and duration of gastric acid secretion in response to meals. In patients with antral-predominant gastritis, acid secretion from the corpus is relatively unpaired and sustained high acid secretion makes these patients at markedly increased risk of developing a duodenal ulcer. In contrast, hosts with low acid secretory capacity due to a low number of parietal cells or whose parietal cells are being inhibited (e.g., by antisecretory drugs) allow the organism to colonize a wider niche, producing pangastritis which may become corpus-predominant. The combination of both chronic and active inflammation of the corpus mucosa can eventuate in oxyntic gland atrophy, with the normal corpus mucosa being replaced by atrophy characterized by pseudopyloric metaplasia (spasmolytic polypeptide expressing mucosa) within which islands of intestinal metaplasia may develop, thus producing the characteristic phenotype of chronic atrophic gastritis. This low acid-secreting state is the phenotype associated with an increased risk of gastric cancer.

The rate and odds of progression from *H. pylori*-related chronic gastritis to gastric cancer is modulated by interactions between bacterial, environmental, and host factors. For example, and as noted earlier, the presence of the *cag* PAI signifies the presence of an infection associated with increased levels of inflammation and a corresponding increased risk of atrophy, genetic instability, and subsequently cancer. Diets high in salt and low in fresh fruits and vegetables accelerate the progression of mucosal damage and an earlier transformation from non-atrophic to atrophic gastritis. A number of host genetic factors, especially polymorphisms in the genes regulating the intensity of the inflammatory response to the infection, also influence outcome. For example, single-nucleotide polymorphisms in the genes encoding interleukin-1 are associated with an increased inflammatory response and an increased risk of developing gastric atrophy and gastric cancer. Environmental factors also play a key role. For example, in Japan, when the population experienced changes in diet and a decrease in smoking this resulted in a marked fall in the age-related incidence of gastric atrophy despite no change in the prevalence of CagA-positive infections or host genetics.

H. pylori infection is a necessary but not sufficient cause of gastric cancer. Eradication of the infection before the development of irreversible change can prevent development of gastric cancer despite the presence of the environmental and host risk factors that promote the disease. Even after atrophic gastritis develops, *H. pylori* eradication prevents further damage and prevents further increases in cancer risk but cannot return the risk to zero.

Gastric atrophy/atrophic gastritis also result in hypochlorhydria or achlorhydria which promote gastric colonization by enteric bacteria that produce carcinogenic substances (e.g., nitrosamines) from dietary and other sources. If some parietal cells remain intact or regenerate following *H. pylori* eradication, the patient can experience the return of at least partial acid secretion, which can either eliminate or reduce bacterial overgrowth and its associated production of carcinogens.

Diagnosis of *H. pylori* infection

H. pylori infection can be reliably diagnosed by a variety of tests including noninvasive assays (i.e., those not requiring obtaining gastric juice or a mucosal biopsy) and by those requiring a sample of the gastric mucosa or contents, which can be considered invasive or minimally invasive tests (Box 136.1). The noninvasive methods include detection of an immune response to the infection (e.g., IgG serologic tests), urea breath tests, and stool antigen assays. Invasive methods include rapid urease tests, histology, and culture. In addition, a number of tests currently used for research purposes, such as detection of the presence of *H. pylori* or its antimicrobial resistance using polymerase chain reaction on gastric biopsies or stools, are in trial for clinical use.

The method of choice clinically depends on availability, cost, and whether endoscopy is otherwise indicated. It is now agreed

BOX 136.1

Indications for testing for *Helicobacter pylori* infection[a]

Duodenal or gastric ulcer (present or history of)
Evaluate success of eradication therapy
Gastric low-grade MALT lymphoma
Atrophic gastritis
After endoscopic resection of early gastric cancer
Uninvestigated dyspepsia
Non-ulcer dyspepsia
Chronic NSAID/aspirin therapy[b]
Need for chronic proton pump inhibitor therapy
Relatives of patients with gastric cancer patients
Relatives of patients with duodenal ulcer
Relatives of patients with *H. pylori* infection
Patient desires to be tested
Individual from high-risk populations based on place of birth or groups locally recognized to have a high prevalence of the infection

[a] All proved to have an active *H. pylori* infection should be treated.

[b] When planning long-term therapy.

[c] When planning long-term antisecretory therapy.

Abbreviations: MALT = mucosa-associated lymphoid tissue, NSAID = nonsteroidal anti-inflammatory drug.

that the diagnosis of an active *H. pylori* infection should prompt eradication therapy, making a willingness to treat the infection if present the primary consideration for testing. Currently, testing for *H. pylori* infection is indicated in patients with a wide variety of conditions (Box 136.1).

Whenever possible noninvasive testing (e.g., the urea breath or stool antigen test) is preferred. Stool antigen tests using monoclonal antibodies are superior to stool antigen tests using polyclonal antibodies. While serologic testing is often the least expensive test, the sensitivity and specificity of serologic tests, particularly in-the-office tests, is typically lower than that of the urea breath test or stool antigen test. Because antibody titers fall slowly after *H. pylori* eradication, a fall in titer cannot be relied on to reliably assess post-eradication status of *H. pylori* infection. IgA and IgM *H. pylori* serologic tests are offered but are typically neither approved by the US Food and Drug Administration (FDA) nor accurate and are not recommended. Although IgG serology is no longer recommended as a single test, it can still be useful in conditions with high or low pretest probability. For example, a positive test in a patient with a known high-probability condition such as peptic ulcer disease would be considered indicative of an *H. pylori* infection, as would a negative test in a low *H. pylori* prevalence region in a patient with a low-probability condition such as gastroesophageal reflux disease. However, if one obtains a negative test in a high pretest probability situation, it would be prudent to retest using a test for active infection. In asymptomatic individuals and in the general population of most Western countries, most positive serologic tests will be false-positives, thus the admonition that treatment is not indicated unless the results are confirmed by a second test using different methodology and preferably one for active infection.

TABLE 136.1 **SUMMARY OF DIAGNOSTIC TESTS**

Test	Sensitivity (%)	Specificity (%)	Cost
Noninvasive tests			
Serology			
Laboratory, serum, ELISA	86–95	78–95	$$
In-office, serum	88–94	74–88	$
In-office, whole blood	67–88	75–91	$
Urea breath test			
^{13}C-urea breath test[a]	90–96	88–98	$$$
^{14}C-urea breath test[b]	90–95	90–95	$$
Stool antigen test	83–98	81–95	$$
Invasive tests			
Rapid urease test	88–95	93–100	$
Histology	93–98	95–99	$$$
Culture	77–98	100	$$$

[a] No radiation exposure.
[b] Low radiation exposure.

When endoscopy is clinically indicated, a rapid biopsy urease test, preferably using two specimens, one from the antrum and one from the corpus, can be used. Biopsy urease testing provides both a high sensitivity and specificity for the diagnosis of *H. pylori* infection but false-negatives are especially likely to occur if the patient is taking proton pump inhibitors (PPIs) or has atrophic gastritis with intestinal metaplasia. The result of the rapid urease test is generally not available during endoscopy and because false-negative biopsy urease tests occur, histology is generally obtained to confirm the results. Increasing antimicrobial resistance has reduced the interest in and use of rapid urease testing because the desire for rapid knowledge is now offset by the need for additional information, such as the results of susceptibility testing to choose the best therapy. Histology has the additional advantage of providing a permanent record and allowing identification and scoring of the pattern and severity of gastritis, which in turn allows risk stratification for gastric cancer using the Operative Link on Gastritis Assessment (OLGA) or OLGA for intestinal metaplasia (OLGIM) histologic cancer risk scoring systems.

Prospective studies have consistently shown that hematoxylin and eosin (H&E) staining of gastric mucosal biopsies has a relatively poor sensitivity and specificity for diagnosis of active *H. pylori* infections. The hallmark of *H. pylori* infection is mucosal inflammation, which should prompt a search for *H. pylori*. While organisms can be visualized with special stains such as the Genta or El-Zimaity triple stains, or the combination of H&E and the Diff-Quik stains, many patients are taking PPIs that allow some overgrowth and cause false-positive results. Currently, the best test to confirm the presence of *H. pylori* is by specific immunohistochemistry.

Culture of mucosal biopsies to establish antimicrobial susceptibility is extremely helpful in choosing an effective therapy and is clearly indicated in patients who failed to eradicate *H. pylori* using standard antimicrobial regimens. Cultures can also be obtained using minimally invasive methods with a brush or string test. Potentially, molecular testing of gastric juice, mucus, biopsies, or stool samples may allow rapid susceptibility testing but current methods have shown limited applicability.

Cautions about false-negative diagnostic tests

False-negative results are especially likely if the patient has taken drugs that reduce the bacterial load such as antibiotics, bismuth, or PPIs. In general, one should stop these drugs for 1 to 2 weeks before testing. H_2-receptor antagonists do not adversely affect any of these tests (although they may adversely affect the ^{14}C-urea breath test unless the test is administered along with citric acid) and can be used if needed to control symptoms. In clinical practice, post-eradication assessment for *H. pylori* infection should be routinely done but should be delayed at least 4 weeks following the completion of eradication therapy to avoid false-negative results. A 6-week delay is probably best when using the stool antigen test to confirm cure.

TABLE 136.2 **RECOMMENDED ANTIBIOTIC COMBINATIONS FOR *H. PYLORI* INFECTIONS**

Treatment	Drugs, dosages, and duration
Susceptibility-based	**No drug allergies**
Clarithromycin triple therapy (susceptible to clarithromycin)	Amoxicillin (1 g) and clarithromycin (500 mg) plus a PPI (40 mg omeprazole equivalent per dose) all given BID for 14 days
Metronidazole triple therapy (susceptible to metronidazole)	Amoxicillin (1 g) and metronidazole or tinidazole (500 mg) plus a PPI (40 mg omeprazole equivalent per dose) all given BID for 14 days
Fluoroquinolone triple therapy (susceptible to fluoroquinolones)	Fluoroquinolone (e.g., levofloxacin 500 mg once daily), plus a PPI (40 mg omeprazole equivalent per dose) and amoxicillin 1 g BID for 14 days
Susceptibility-based	**Allergic to penicillin**
Susceptible to clarithromycin and metronidazole	Clarithromycin (500 mg), and metronidazole or tinidazole (500 mg) plus a PPI (40 mg omeprazole equivalent per dose) all given BID for 14 days
Resistant to clarithromycin and/or metronidazole	Bismuth quadruple therapy (see **Susceptibility testing unavailable**)
Empiric therapies	**Susceptibility testing unavailable**
Bismuth quadruple therapy	Bismuth subsalicylate or bismuth subcitrate 2 tablets 2 or 4 times daily after meals plus tetracycline hydrochloride (500 mg) 4 times daily with meals and at bedtime plus metronidazole (400 or 500 mg) 4 times daily with meals and a PPI (40 mg omeprazole equivalent per dose) BID for 14 days
Prepackaged bismuth quadruple therapy	Pylera for 14 days; add a PPI twice daily (20–40 mg omeprazole equivalent BID)
New bismuth quadruple therapy (amoxicillin replaces tetracycline)	Bismuth 2 tablets 2 or 4 times daily after meals plus metronidazole (400 or 500 mg) four times daily with meals and amoxicillin 1 gm TID along with a PPI (40 mg omeprazole equivalent or more BID) for 14 days
New bismuth quadruple therapy (amoxicillin replaces metronidazole)	Bismuth 2 tablets 2 or 4 times daily after meals plus tetracycline HCl 500 mg four times daily with meals and amoxicillin 1 g TID along with a PPI (40 mg omeprazole equivalent or more BID) for 14 days
Furazolidone quadruple therapy	Furazolidone therapies are obtained by replacing metronidazole in bismuth quadruple therapies with furazolidone 100 mg TID
Empiric likely effective regimens	
Rifabutin triple therapy	Rifabutin (150 mg once or twice daily), amoxicillin (1 g TID and omeprazole 40 mg (or an equivalent PPI) q8h for 14 days
Rifabutin bismuth therapy	Add bismuth subcitrate or subsalicylate 2 tablets BID to preceding therapy
Experimental regimens	
High-dose PPI-amoxicillin dual therapy	PPI (e.g., rabeprazole 40 mg, esomeprazole 40 mg) plus amoxicillin (500–750 mg) all four times daily at approximately 6-hour intervals for 14 days (can use 8-hour interval at night)
Vonoprazan-amoxicillin dual therapy	Vonoprazan (the potassium competitive acid blocker) 20 mg BID plus 500–750 mg amoxicillin q6h for 14 days is recommended
Obsolete regimens	Sequential, hybrid, concomitant therapies, empiric use of triple therapies

Preferred PPIs: 40 mg omeprazole, 60 mg lansoprazole, 20 mg rabeprazole or esomeprazole, pantoprazole not recommended as 40 mg = 9 mg omeprazole.

Indications for *H. pylori* eradication

In developed countries, the recommendation is to treat and confirm cure for all diagnosed active *H. pylori* infections. Box 136.1 lists indications for testing for *H. pylori* in the United States and other developed countries. *H. pylori* causes gastric cancer and universally causes progressive damage to the structure and functions of the stomach. As with smallpox, polio, and syphilis, humans are the natural host; the world will be better off when all these diseases have been eradicated. In March 2013, Japan approved universal *H. pylori* eradication and is leading the way toward population-wide *H. pylori* eradication. However, developing countries with poor sanitation remain a challenge because of the high prevalence of the infection and the high rate of reinfection after eradication therapy. Elimination of this important pathogen will likely require an effective vaccine. However, progress in vaccine development has remained slow.

Gastroesophageal reflux disease, Barrett's esophagus, and adenocarcinoma of the esophagus

One source of early confusion and uncertainty regarding whom to treat was related to an early hypothesis that *H. pylori* infection might have beneficial effects. For example, soon after the discovery of *H. pylori* it was noted that those least likely to be infected in Western countries (e.g., white men) were also the group most likely to develop Barrett's esophagus and esophageal carcinoma, resulting in a suggestion that *H. pylori* might be protective. Barrett's esophagus occurs as a complication of the acid-related disease reflux esophagitis. Reflux esophagitis and Barrett's esophagus are rare wherever atrophic gastritis and gastric cancer are common. Those living in developed areas have experienced a marked decline in *H. pylori* infections, atrophic gastritis, and gastric cancer and an increase in symptomatic reflux esophagitis, Barrett's esophagus, and adenocarcinoma of the esophagus. The odds of developing gastric cancer by age 74 have been calculated for men worldwide and ranges from 0.6% in the United States to 22% in Yangcheng County, China. The increased risk of adenocarcinoma of the esophagus might be considered a tradeoff for the fall in gastric cancer, which resulted in the most common cause of cancer deaths becoming a rare disease while a heretofore very rare disease increased. The increase has now plateaued such that overall it remains an uncommon cause of cancer deaths.

It was also suggested that *H. pylori* infection in childhood might protect against atopy and asthma in children. In this scenario, *H. pylori* infection was related to the hygiene hypothesis, in which early exposure to antigens that regulate the immune response set the stage for subsequent development of allergic diseases. The protective role of *H. pylori* in atopic disease has not survived testing. While *H. pylori* infection is a surrogate for poor household hygiene, it is not directly involved in the development of or protection from atopic diseases. Of interest, and contrary to predictions from the *H. pylori* protective hypothesis, countries like Malaysia, where *H. pylori* was naturally absent, have not been plagued by any of the dire consequences predicted by those proposing that *H. pylori* eradication would result in a variety of new problems. The hypotheses regarding putative protective effects of *H. pylori* have all been falsified, with current evidence supporting the notion that *H. pylori* infection provides no meaningful benefits and should be eradicated.

Treatment of *H. pylori* infection

H. pylori infection has proved more difficult to cure than many other common bacterial infections. *H. pylori* occupy a number of niches and widely different environments in the stomach, including being intracellular. The gastric contents are highly acidic whereas most antibiotics function best at neutral or near-neutral pH. However, there are a number of therapeutic regimens that will reliably cure 95% of more susceptible infections in treatment-adherent patients. The main impediments to successful treatment has been lack of regional, local, or patient-specific *H. pylori* susceptibility data coupled with poorly designed antimicrobial regimens, poor patient adherence to complicated regimens, increasing antimicrobial resistance, and poor treatment recommendations. The history of the development of antimicrobial therapies for *H. pylori* is unique because it has largely been based on results of trial-and-error rather than a traditional susceptibility-based approach. Treatment trials and subsequent meta-analyses have usually involved populations uncharacterized in terms of the proportion with infections resistant to the antibiotics being tested. Because the proportions with resistance has varied and has not been assessed, the results of any study are at best population-specific and thus neither generalizable nor comparable. The focus has been on superiority trials, which were often done in populations where the results of the so-called standard therapy was known to be poor because local resistance ensured that the test regimen which contained drugs not affected by resistance that undermined standard therapy would be equal or superior. In addition, there was no defined clinically acceptable (e.g., ≥95%) result allowing low and clinically unacceptable treatment results to be compared and the winner chosen. Such studies were then combined in meta-analyses and used to produce consensus guidelines, as if meta-analysis was somehow able to transform uninterpretable studies with clinically unacceptable results into clinically meaningful treatment guidelines. The concepts and principles of antimicrobial stewardship so loved and respected by specialists in infectious disease have yet to take hold in the gastroenterology community and have resulted in guidelines based on experience rather than susceptibility data. As such, clinicians are required to make empiric choices regarding antibiotics, doses, and durations of therapy.

The *H. pylori*-infected stomach typically contains vast numbers of *H. pylori,* making it likely that a population of resistant strains is also present (the inoculum effect) especially with macrolides, nitroimidazoles, and fluoroquinolones. Worldwide, the unrestricted use of macrolides and fluoroquinolones resulted in a rapid increase in resistance among *H. pylori* so that now a relatively high proportion of treatment-naïve patients will have resistance to at least one

of these three antibiotics and thus the current recommendation to avoid regimens that use those drugs empirically (i.e., unless susceptibility has been confirmed). Molecular tests for susceptibility for clarithromycin and fluoroquinolones have been developed but are currently not reimbursed in the United States. Resistance to amoxicillin, tetracycline, bismuth, furazolidone, and rifabutin have remained rare, allowing continued use of these drugs. In contrast to macrolides and fluoroquinolones, metronidazole resistance is not all-or-none, so that resistance can often be overcome by adding bismuth and increasing the daily metronidazole/tinidazole dose to 1,500 to 2,000 mg and the duration of therapy to 14 days. As a general rule *H. pylori* therapy should be for 14 days, in part because of the presence of persistently resistant populations. The organism only replicates when the pH is 6 or 7, and this is difficult to achieve in vivo. PPIs are typically administered to reduce acid secretion and improve the effectiveness of most antimicrobials. They also reduce antibiotic washout from the stomach, increase the concentration of intragastric antibiotics, and promote *H. pylori* replication. In promoting the use of PPIs, the pharmaceutical industry used a shorter duration of treatment as a marketing point. However, PPIs require ≥3 days to reach full effectiveness, which hampers the effectiveness of these short-term therapies. Most regimens contain amoxicillin, and effectiveness is dose- and pH-dependent. The relative effectiveness of PPIs is measured as omeprazole equivalents, and best results with all therapies containing amoxicillin require 40 mg of omeprazole equivalent twice a day (i.e., 40 mg omeprazole, 20 mg esomeprazole, 20 mg rabeprazole, 45 mg lansoprazole, 180 mg of pantoprazole all BID) or more. The new class of PPI, the *potassium competitive acid blockers* (vonoprazan; P-CABs), is more potent than traditional PPIs and obtains full effectiveness on the first day of therapy. When these become widely available, this class of PPIs will likely supplant traditional PPIs whenever acid-sensitive antimicrobials are used, which may also allow shorter duration therapy while retaining high cure rates.

The lack of susceptibility data has resulted in consensus-based treatment guidelines that neither reflect local resistance patterns nor provide guidance to reliably and consistently achieve high cure rates. All recent guidelines also promote antimicrobial misuse. For example, they recommend a four-drug combination consisting of a PPI, amoxicillin, and clarithromycin plus metronidazole, called *concomitant therapy*. This regime effectively gives two triple therapies simultaneously (clarithromycin and metronidazole triple therapy) and is based on the hope that the infection will be susceptible to either clarithromycin or metronidazole. It is thus designed to, at a minimum, provide one unnecessary antibiotic, and, if dual clarithromycin and metronidazole resistance is present, it provides two unnecessary antibiotics. It has been calculated that each 1 million prescriptions results in a minimum of approximately 14,000 kilograms of unnecessary clarithromycin or metronidazole (a class I carcinogen). A similar pattern of antibiotic misuse was produced by the most commonly prescribed regimen in Japan (vonoprazan, amoxicillin, and clarithromycin). The cure rate with vonoprazan and amoxicillin alone for 7 days is approximately 80% and could be further improved by increasing the duration of therapy. Each year, more than 1 million prescriptions are given resulting in thousands of kilograms of unnecessary clarithromycin being prescribed. The rising concern regarding antimicrobial resistance related to excessive and inappropriate antibiotic use resulted in the World Health Organization in 2017 publishing a list of 16 antibiotic-resistant bacteria that pose the greatest threat to human health. *H. pylori*

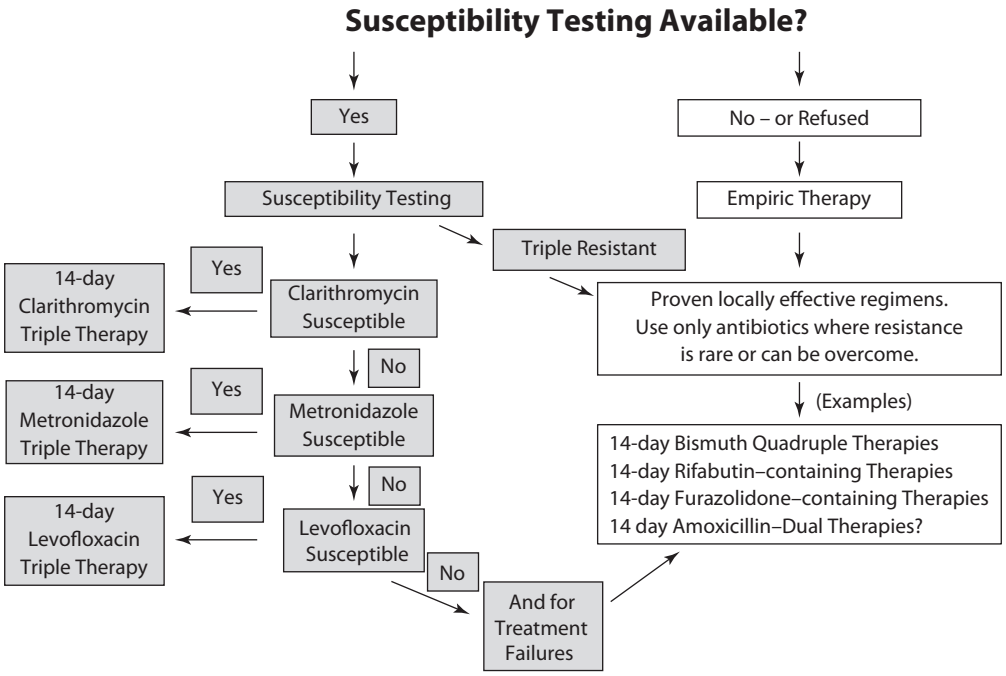

FIGURE 136.1 Algorithm showing idealized treatment scheme where local resistance patterns are known or patient-specific susceptibility is available. The concept is to either use susceptibility data or locally proven highly effective empiric regimens.

was categorized as a high-priority bacteria in the same tier as vancomycin-intermediate or –resistant bacteria and methicillin-resistant *Staphylococcus aureus*. Clearly, current recommendations for antimicrobial therapy of *H. pylori* contribute to the problem of antimicrobial resistance.

Which *H. pylori* therapies are best?

A successful regimen is defined as one that will reliably cure at least 95% of infections of susceptible strains in treatment-adherent patients. With susceptibility-based therapy this can easily be achieved, usually with a triple therapy. Clinically, it is prudent to use the regimen with highest patient acceptance and highest cure rates first (Figure 136.1). Levofloxacin has achieved black box status because of side effects by the FDA, moving it to third in the treatment order. For patients in whom susceptibility testing is unavailable, culture has failed, or multidrug resistance is present a four-drug bismuth-containing therapy is recommended (i.e., a triple therapy plus bismuth). Traditional bismuth quadruple therapy employs high doses of both tetracycline and metronidazole and has a high rate of side effects such that extra efforts in patient education are required to obtain adequate adherence. In the absence of metronidazole resistance, shorter duration therapy (e.g., 7 days) is sufficient. However, 14-day metronidazole triple therapy would be a better choice because it is better tolerated. A combination capsule formulation of bismuth quadruple therapy (Pylera) as been introduced but packaging was changed to a 10-day dose pack, requiring the patient to purchase two packages to obtain sufficient drug for the recommended 14-day therapy. This may be an example of the pharmaceutical industry rather than science deciding what is studied and what is offered. It is also an example of the failure of the regulatory agencies and opinion leaders to provide appropriate endpoints or advice.

The major issue with bismuth quadruple therapy is compliance because side effects are common and should be discussed (including the likelihood of black stools) before use. Studies are needed to test simplified bismuth-containing regimens, such as twice-a-day therapy instead of more frequent dosing.

Multiple treatment failures or salvage therapies

The best approach is to choose a regimen based on susceptibility testing, which currently may require referral to a *H. pylori* treatment specialist. Furazolidone is not widely available but, where available, is most often used as part of a 14-day bismuth-containing regimen (i.e., replacing the metronidazole) and given as 100 mg three times daily. It is highly effective but side effects are common, as are drug–drug interactions.

Confirmation of cure

Because the reasons that *H. pylori* was treated remain if therapy fails, it is important to confirm treatment success (i.e., therapy should always be followed by confirmation of cure). The confirmatory test should be delayed 4 to 6 weeks after the end of antimicrobial therapy to allow the bacteria, if still present, an opportunity to repopulate the stomach. Drugs that inhibit *H. pylori*, such as PPIs, should not be allowed for 1 and preferably 2 weeks prior to testing. The urea breath test is the ideal method of evaluating the outcome of therapy for those in whom follow-up endoscopy is not needed. An alternate approach would be to use the stool antigen test, but, in that case, testing should be delayed for 6 to 8 weeks.

Acknowledgments

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Suggesting reading

El-Serag HB, Kao JY, Kanwal F, et al. Houston Consensus Conference on testing for *Helicobacter pylori* infection in the United States. *Clin Gastroenterol Hepatol*. 2018;16:992–1002.

Graham DY. *Helicobacter pylori* update: Gastric cancer, reliable therapy, and possible benefits. *Gastroenterology*. 2015;148:719–731.

Graham DY. Illusions regarding *Helicobacter pylori* clinical trials and treatment guidelines. *Gut*. 2017;66:2043–2046.

Graham DY, Lu H, Dore MP. Relative potency of proton-pump inhibitors, *Helicobacter pylori* therapy cure rates, and meaning of double-dose PPI. *Helicobacter*. 2018;e12554.

Lee YC, Chiang TH, Chou CK, et al. Association between *Helicobacter pylori* eradication and gastric cancer incidence: A systematic review and meta-analysis. *Gastroenterology*. 2016;150:1113–1124.

Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection: The Maastricht V/Florence Consensus Report. *Gut*. 2017;66:6–30.

Rugge M, Genta RM, Di Mario F, et al. Gastric cancer as preventable disease. *Clin Gastroenterol Hepatol*. 2017;15:1833–1843.

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Neisseria gonorrhoeae

Amy J. Mathers and Michael F. Rein

In 2018, *Neisseria gonorrhoeae* reportedly caused 583,405 infections in the United States, an increase of 63% since 2014. The gonococcus attaches primarily to columnar or cuboidal epithelial cells (Box 137.1) via pili and outer membrane proteins. It then penetrates between and through the cells to submucosal areas, where it elicits a neutrophilic host response. The clinical spectrum of primary infection with *N. gonorrhoeae* mirrors that of *Chlamydia trachomatis*.

Acute urethritis, manifesting as some combination of urethral discharge and dysuria, is the most common presentation of disease in men, although some infected men are asymptomatic. Epididymitis, usually unilateral and accompanied by urethral disease, sometimes occurs. Gram stain of urethral discharge may be used for presumptive diagnosis of gonococcal urethritis. Polymorphonuclear neutrophils (PMNs) with gram-negative, intracellular diplococci (GNID; Figure 137.1) are observed in 95% of infected, symptomatic men, and the finding is 98% specific. Observing PMN without GNID supports a diagnosis of nongonococcal urethritis (see Chapter 59, "Urethritis"), but the sensitivity of GNID in asymptomatic men is only about 75%, and Gram stain should not be used to screen such patients for gonorrhea.

In women, the primary site of infection is the endocervix, although the organism can be recovered from the urethra and periurethral (Skene's) and Bartholin's glands in adults and from the vagina itself in prepubescent girls. Asymptomatic infection is more common in women than men. Gram stains of cervical smears are insensitive. Untreated endocervical infection may ascend to the Fallopian tubes, causing pelvic inflammatory disease and perihepatitis (see Chapter 64). Gestational gonorrhea may result in ophthalmia neonatorum and, very rarely, neonatal gonococcal pneumonia.

Anorectal gonorrhea occurs in up to 40% of women with endocervical disease. It can also be an isolated finding in homosexual men or heterosexual women who practice receptive anal intercourse and in whom it may be the only infected site in about 20%. Most patients are asymptomatic, but some present with acute proctitis. Patients with pharyngeal infection acquired from fellatio are also typically asymptomatic, but pharyngitis may occur. Gonococcal conjunctivitis in adults, usually acquired by autoinoculation from a genital focus, produces varying degrees of inflammation.

Disseminated gonococcal infection occurs historically in perhaps 0.5% to 3% of infected patients. It usually presents as the arthritis–dermatitis syndrome, manifesting as asymmetric, migratory polyarthritis, arthralgias, or tenosynovitis. In 75% of cases, disseminated disease is accompanied by small papules or by vesicles with an erythematous base. Hereditary or chemotherapy-induced deficiency of the terminal components of complement or infection with organisms resistant to the bactericidal activity of serum predisposes to dissemination. Endocarditis and meningitis are very rare complications.

Diagnosis

Definitive diagnosis requires demonstrating the presence of the organism. Culture has been largely supplanted by molecular techniques. Nucleic acid amplification tests (NAATs) are those most widely used clinically in the United States and have high sensitivity and specificity. Performing a NAAT on urine has

BOX 137.1

Sites of primary infection by *Neisseria gonorrhoeae*

Urethra
Pharynx
Cervix
Conjunctiva
Rectum
Vagina (in prepubescent girls)

adequate sensitivity in males and females, so a urethral swab or endocervical swab is no longer necessary. There have been some historic reports of decreased sensitivity in urine from women, and a vaginal swab, which can be self-collected, may be preferred in some settings. Although many NAATs are approved for urogenital specimens, only certain commercial laboratories are validated to test rectal or pharyngeal specimens. Clinicians should consult their local health departments regarding the current workup of extragenital sites. NAATs can detect free DNA from dead organisms for perhaps as long as 2 weeks after successful treatment and do not provide a specimen for testing antimicrobial sensitivity. Thus, in treatment failures, culture specimens should be obtained along with antimicrobial susceptibility testing. As the gonococcus is relatively unstable outside humans, one should contact the clinical laboratory for proper collection and transport procedures.

Therapy

There are several important and unique general principles to consider regarding treatment of gonococcal infections. Ideal treatment of uncomplicated infection should be single-dose, affordable, possessing a low side-effect profile, and, when possible, oral. Unfortunately, due to increases in antimicrobial resistance, there is no longer a first-line oral option for therapy. The treatment of uncomplicated infection is almost always performed without knowledge of antimicrobial susceptibility. There are few bacterial infections for which in vitro resistance correlates so tightly with clinical treatment failure. Resistance has emerged to all antimicrobial classes used to treat gonorrhea, and it is now considered one of the most urgent threats of antimicrobial resistance by the Centers for Disease Control and Prevention (CDC). Historically, one can follow the rapid appearance and dissemination of organisms resistant to penicillins, sulfonamides, tetracyclines, fluoroquinolones (FQ) and, most recently, cephalosporins. Gonococcal resistance is mediated by multiple chromosomal mutations and by acquisition of readily disseminated plasmids. This has now given rise to a handful of reports which describe isolates resistant to all recommended therapies.

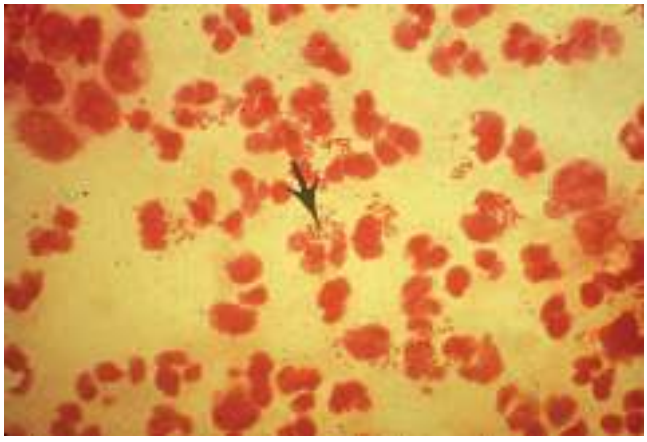

FIGURE 137.1 Gram stain of urethral discharge, showing gram-negative intracellular diplococci diagnostic of gonorrhea. Coincident nongonococcal urethritis cannot be ruled out.
Courtesy of Centers for Disease Control and Prevention.

The rapid rise of penicillin and tetracycline resistance was first identified in the 1970s. Resistance to both classes has been driven by chromosomal mutations and dissemination of plasmids carrying genes that encode for a β-lactamase and a protein that modifies the ribosomal target of tetracycline. By 2014, the Gonococcal Isolate Surveillance Project, which performed sensitivity testing on about 3% of male urethral isolates from around the United States (n = 5,093), found resistance rates of 25% for tetracycline and 16% for penicillin.

In the mid-1980s a single oral dose of a FQ successfully treated gonococcal urethritis in men. However, as early as 1990, resistance to ciprofloxacin was detected in *N. gonorrhoeae*. The prevalence of FQ resistance and the incidence of treatment failures continued to rise throughout the 1990s, and, in 2018, 31.2% of isolates from the CDC surveillance program harbored FQ resistance. *N. gonorrhoeae* has many mechanisms which may contribute to FQ resistance, but the primary mechanism is mutation in one or both genes (*parC* or *gyrA*) encoding differing topoisomerases. Fluoroquinolones are no longer recommended for the treatment of gonorrhea in the United States.

Due to increasing resistance to other drug classes, late-generation cephalosporins have become the mainstay of first-line treatment for gonococcal infection. Cephalosporin resistance is mediated through accumulation of chromosomal mutations that alter binding to the drug's target. Although cephalosporin resistance remains at a relativity low level, the steep rise in the rate of decreased cefixime susceptibility, which peaked in 2011 at 1.4%, does cause concern, as this class is the last reliable group of agents. During 2009–2018, the percentage of isolates with reduced ceftriaxone susceptibility (defined as an MIC of ≥0.125 μg/mL) fluctuated between 0.1% and 0.4% and was 0.2% in 2018. Because of the dramatic difference in bioavailability between oral and intramuscular dosing, the only recommended therapy is intramuscular ceftriaxone (Table 137.1). When coinfection with *C. trachomatis* is present or has not been ruled out, doxycycline should be added. Doxycycline (see Chapter 59, "Urethritis") is superior to azithromycin, especially in extragenital (e.g. rectal) sites. Azithromycin is preferred over doxycycline as a second agent only if coinfection with *Mycoplasma genitalium* (see Chapter 165, Mycoplasmas) has been diagnosed.

TABLE 137.1 **REGIMENS FOR UNCOMPLICATED GONORRHEA (URETHRITIS, CERVICITIS, PROCTITIS)**

Drug	Dose	CDC recommended	Safe in pregnancy	Effective in pharynx	Comments
Ceftriaxone	500 mg IM	Yes	Yes	Yes	Most effective
Plus Doxycycline	100 mg po, bid x 7 days	Yes	No	Yes	If coincident chlamydial infection is present or cannot be ruled out
Cefixime	400 mg PO	Secondary	Yes	Uncertain	Resistance developing and needs to be combined with azithromycin 1 g
Ciprofloxacin	500 mg PO	No	No	Uncertain	Significant resistance, not recommended, see text
Other fluoroquinolones	Various	No	No	Uncertain	Significant resistance, not recommended, see text
Spectinomycin	2 g IM	No	Yes	No	Unavailable in USA
Gentamicin	240 mg IM	No	Yes	No	Second-line and use with 2 g azithromycin. Severe penicillin allergy

In the face of rapidly increasing resistance, the recommended dose of ceftriaxone have been increased to 500 mg i.m., and further increases may be required in the future. Several new drugs are undergoing evaluation. Most are variants on fluoroquinolones (e.g., zoliflodaxin, delafloxacin, spiropyrimidinetriones, geptodidacin) or macrolides (e.g., solithromycin). The clinician should remain alert for such possible future developments.

Management of sexual partners should probably extend back for 60 days prior to the onset of symptoms or date of diagnosis. All patients with gonorrhea should be advised to undergo testing for infection with HIV. The recommended antigonococcal regimen is sufficiently effective that test of cure is not necessary, but retesting at 3 months should be encouraged to detect reinfection.

In some settings, expedited patient therapy—medication or prescriptions provided for patients to deliver to their sexual partners—is allowable. Since such therapies must be oral, they can no longer be considered first-line, and partners so treated should be advised to present for test of cure. Many medicolegal restrictions (e.g., CDC-recommended regimens, the need to call sexual partners) vary from state to state, and the clinician is advised to consult the local health department to receive current information.

Standard therapy

Intramuscular ceftriaxone is highly effective, and a 500 mg i.m. regimen is currently recommended by the CDC for the treatment of uncomplicated gonorrhea. Ceftriaxone is often diluted in 1% lidocaine to reduce discomfort. Other single-dose parenteral regimens (ceftizoxime or cefotaxime, 500 mg IM) offer no advantage over ceftriaxone. Resistance to cefoxitin, often in association with high-level tetracycline resistance, mandates that this drug should no longer be used in the treatment of uncomplicated gonorrhea.

Oral cephalosporins are less effective, and failure is associated with relative increases in *in vitro* resistance. Due to this increase in resistance, any oral cephalosporin should not be used unless ceftriaxone is unavailable. If an oral cephalosporin must be used, a single oral dose of cefixime 400 mg in combination with doxycycline 100 mg orally, twice daily for seven days seems reasonable. Fluoroquinolones should no longer be used to treat uncomplicated gonorrhea (see earlier discussion). However, for penicillin-allergic patients with severe (IgE-medicated) β-lactam allergy dual treatment with single doses of intramuscular gentamicin 240 mg plus a single dose of oral azithromycin 2 g is the only recommended therapy which is widely available in the United States. Earlier data supported the use of gentamicin (see Table 137.1), which may be effective in the same settings, but a meta-analysis found a 92% cure rate with this drug alone, which does not meet the criterion for cure rate of ≥95% required for CDC approval. Spectinomycin is no longer available in the United States. The use of any of these alternative agents mandates a test of cure 1 week after treatment.

Nonstandard therapy

The monobactam aztreonam and the carbapenems imipenem-cilastatin, meropenem, and ertapenem are uniformly effective against *N. gonorrhoeae* but are costly and available only in intravenous form. These drugs are never primary therapy for gonorrhea. Gentamicin 240 mg IM plus azithromycin 2 g PO or gemifloxacin 320 mg PO plus azithromycin 2 g PO demonstrated excellent efficacy against uncomplicated anogenital and pharyngeal gonorrhea. These regimens might be useful in the salvage treatment of infection with cephalosporin-resistant infections or in β-lactam-allergic patients.

Extragenital disease

A single dose of ceftriaxone, 1 g IM, in adults apparently cures gonococcal conjunctivitis, but clinical data are extremely limited. A single saline flush of the conjunctiva should be considered, but topical antibiotics have no proven additional benefit.

TABLE 137.2 **INITIAL REGIMENS FOR DISSEMINATED GONOCOCCAL INFECTION**[a]

Drug	Dose	CDC recommended	Safe in pregnancy	Comments
Ceftriaxone	1 g IV q24h	Yes	Yes	Most effective
Plus Doxycycline	100 mg po, bid x 7 days	Yes	No	If coincident chlamydial infection is present or cannot be ruled out
Ceftizoxime	1 g IV q8h	Secondary	Yes	No advantage over ceftriaxone
Plus Doxycycline	100 mg po, bid x 7 days		Yes	If coincident chlamydial infection is present or cannot be ruled out

[a] Intravenous therapy should be continued for 24 to 48 hours after improvement begins. Thereafter, the patient can be switched to an oral regimen based on susceptibility testing.

Elimination of *N. gonorrhoeae* from the oropharynx is particularly challenging. Some regimens successfully treating uncomplicated genital infection are not reliably effective for pharyngeal disease. The oropharynx is often where treatment failures from resistance will first be described.

No prospective studies on the treatment of disseminated gonococcal infection have been performed since 1976; hence, recommendations are empiric because the worldwide spread of resistant gonococci occurred after that time. The gonococcal arthritis–dermatitis syndrome should be treated with ceftriaxone (Table 137.2). Regimens employing other third-generation cephalosporins were equally effective in the past; however, this has not been examined in the more recent era of increasing cephalosporin resistance. If frank septic arthritis is not present, the patient can be switched to an oral regimen (Table 137.3), preferably with a cephalosporin, to complete 7 to 10 days of therapy. Prior to transition to oral therapy susceptibility testing of isolates is strongly recommended. The optimal duration of therapy is unknown. Gonococcal endocarditis should be treated with 4 weeks and meningitis with 2 weeks of an appropriate parenteral regimen, preferably ceftriaxone or another third-generation cephalosporin. There are no current studies of extended courses of FQ as treatment for extragenital disease, and, in the face of recent increases in resistance, these drugs should not be used.

TABLE 137.3 **FOLLOW-UP REGIMENS FOR DISSEMINATED GONOCOCCAL INFECTION**

Drug	Dosage	CDC recommended	Comments
Cefixime	400 mg PO, 2× daily	Yes	No data

Suggested reading

St. Cyr S, Barbe L, Workowski KA, et al. Update to CDC's treatment guidelines for gonococcal infection. *MMWR*. 2020;69:1911–1916.

Centers for Disease Control and Prevention (CDC). Sexually transmitted disease treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;649(No. RR–3):1–137.

Centers for Disease Control and Prevention (CDC). Sexually transmitted disease surveillance 2017. 2018. https://www.cdc.gov/std/.../2017-STD-Surveillance-Report_CDC-clearance-9.10.18.pdf

Centers for Disease Control and Prevention (CDC). Expedited partner therapy. 2016. https://www.cdc.gov/std/ept/default.htm?s_CID=tw_STDFB019005

Consentino LA, Danby CS, Rabe LK, et al. Use of nucleic acid amplification testing for diagnosis of extragenital sexually transmitted infections. *J Clin Microbiol*. 2017;55:2801–2807.

Kirkcaldy RD, Weinstock HS, Moore PC, et al. The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea. *Clin Infect Dis*. 2014;59:1083–1094.

Papp JR, Schachter J, Gaydos CA, et al. Recommendations for the laboratory-based detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*—2014. *MMWR*. 2014;63 (RR02):1–19.

Haemophilus

Amy Spallone and Daniel Musher

Haemophilus influenzae

General description and microbiology

Haemophilus influenzae is an extracellular, fastidious, small (1 × 0.3 μ), nonmotile, gram-negative bacterium, typically described as a coccobacillus; it is a pathogen of humans found primarily in the upper respiratory tract. Variable morphologic appearance and inconsistent retention of dyes may result in describer variability on stained smears. Colonies typically appear translucent, and encapsulated strains are mucoid and appear iridescent when grown on transparent media.

This organism was first isolated by Pfeiffer from the lungs of persons who died in 1892 during an influenza pandemic. Because it only grew on agar that contained blood cells and it was thought to be the causative agent of influenza, it was named *Haemophilus influenzae* (blood-loving [cause] of influenza). *H. influenzae* is a common cause of respiratory tract infections, including otitis media, sinusitis, bronchitis, and pneumonia.

Haemophilus requires growth factors supplied by erythrocytes. *H. influenzae* requires two supplements known as X factor and V factor. X factor comes from heat-stable iron-containing pigments that must be released from broken-up red blood cells to provide protoporphyrins; thus, porphyrin-based assays represent the most reliable method for identifying *Haemophilus influenzae* spp. V factor (nicotinamide adenine dinucleotide) diffuses from intact erythrocytes. The requirement for X factor renders blood agar unsuitable for culturing *H. influenzae,* although colonies may appear on blood agar around colonies that hemolyze blood, such as *Staphylococcus aureus*. Enriched CO_2 greatly facilitates its growth and sometimes is necessary to grow *H. influenzae. H. parainfluenzae* requires only V factor and therefore grows readily on blood agar plates. Inoculation onto appropriate media must be done without delay as *H. influenzae* rapidly degrades in clinical specimens.

Serotypes

H. influenzae species can be typeable (i.e., encapsulated) or n*ontypeable* (i.e., unencapsulated). Typeable *H. influenzae* has six serotypes (a to f) that contain antigenically distinct capsular polysaccharides. Nontypeable *H. influenzae* are genetically distinct from encapsulated strains and lack this polysaccharide capsule, but they exhibit substantial genetic diversity within their population structure. They are genetically distinct from encapsulated strains.

Nontypeable *H. influenzae* is most frequently implicated in inflammatory diseases of mucosal surfaces, such as otitis media, sinusitis, and exacerbation of inflammation or infection in patients who have structural lung disease. These strains are usually noninvasive (i.e., does not enter the bloodstream), but may, on occasion, cause invasive disease.

Serotype b strains of encapsulated *H. influenzae* represent the most medically significant strain because they represent an invasive pathogen in humans. Other serotypes of *H. influenzae* have invasive capacity that is intermediate, between nontypeable and type b isolates

Colonization

With no other known natural host, *H. influenzae* is recovered exclusively from humans, nearly always from the respiratory tract. Organisms bind to mucin or directly to epithelial cells, and person-to-person spread occurs via airborne respiratory droplets or direct contact. Colonization with *H. influenzae* begins after birth with frequent acquisition and clearance of new nontypeable strains in the respiratory tract, and recurrent otitis media has been associated with this course of nasopharyngeal colonization during the first years of life.

Depending on how frequently and carefully one attempts to detect it, *H. influenzae* can be found in the upper airways of about 25% of healthy adults, 50% of adults with chronic lung disease, and 50% to 75% of toddlers.

Colonization has important medical implications in patients with structural lung diseases, such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF). Multiple nontypeable strains of *H. influenzae* are often found in the lower respiratory tract in CF or in exacerbations of chronic obstructive lung disease. Clinically recognizable infections are often associated with acquisition of a new strains.

Type b strains of *H. influenzae* colonized the nasopharynx of 2–3% of healthy children, prior to the widespread use of conjugate vaccine. This colonization is regularly followed by clinically significant infection.

Disease/Immunity

Pathogenesis begins with colonization of the respiratory tract by expression of adhesin molecules on *H. influenzae*. These adhesin molecules vary in prevalence and distribution among nontypeable strains and have their own specificities for host mucosal cell receptors. Nontypeable strains cause disease by local invasion of mucosal surfaces inducing host inflammation, and nontypeable strains have different genetically based pathogenic potential. For example, strains capable of causing otitis media have different genes capable of producing the disease state compared to strains that are found in asymptomatic colonizers. This is also true in the setting of structural lung disease.

Immunity to infection by nontypeable *H. influenzae* is not completely understood, but a well observed trait of noninvasive infections with these strains is their tendency toward recurrence (i.e., chronic otitis media, COPD exacerbations). This suggests that strain-specific immune response still leaves susceptibility to infection by other strains. Because nontypeable strains cause mucosal infections, mucosal immunity likely plays an important role in host defense, but this remains an area of active research.

Type b strains of *H. influenzae* can gain access to the bloodstream and cause invasive disease. Antibody directed at the type b capsular polysaccharide protects against invasive infections via complement-mediated bactericidal and opsonic activity. Studies from the pre-vaccine era showed that systemic disease in the human population most commonly occurred before 4 years of age, by which time most children had acquired lifelong immunity due to naturally acquired antibodies.

Clinical manifestations of nontypeable *H. influenzae* infection

Otitis media

Approximately 25% to 35% of all acute otitis media cases are caused by nontypeable *H. influenzae* although definitive diagnosis with tympanocentesis is not routinely performed due to its invasive nature. Acute otitis media is most common among children and infants. The classic clinical presentation of acute otitis media includes fever, ear pain, and irritability. Antecedent viral respiratory infection is very common. Since 2000, most infants in developed countries have received pneumococcal protein-conjugate vaccine, which coincides with an increased proportion of acute otitis media being attributed to nontypeable *H. influenzae*.

Features specific to nontypeable *H. influenzae* as the cause of acute otitis media demonstrate less virulence when compared to pneumococcal otitis media, such as a lower frequency of fevers and otorrhea. However, a history of recurrent episodes, treatment failure, conjunctivitis, and bilateral otitis media typically indicates nontypeable *H. influenzae* as the causative agent.

Recurrent, chronic otitis media has been associated with nontypeable *H. influenzae* forming biofilms, which represents a community of bacteria intertwined in a matrix attached to a surface. Biofilms are more resistant to clearance either by host mechanisms of defense or antibiotics.

Chronic obstructive pulmonary disease and exacerbation

H. influenzae is the most commonly implicated bacterial cause of exacerbations in COPD, as demonstrated through bronchoscopic sampling of the lower respiratory tract, analysis of immune response to *H. influenzae* insolated in cases of exacerbations, and correlation of airway inflammation with sputum bacteriology analysis. COPD exacerbations are often the result of newly acquired strains of nontypeable *H. influenzae* which reach the lower airways by aspiration, causing a vigorous inflammatory response. This interaction includes factors such as the virulence of the new strain, degree of host inflammatory response, and pulmonary function.

Community-acquired pneumonia

In older adults, especially those with structural lung disease or immunodeficiencies, nontypeable *H. influenzae* is an important cause of community-acquired pneumonia. With the high rate of vaccination against pneumococcal infection in both children and adults, *H. influenzae* may now appear in some settings to be the most commonly identified cause of bacterial pneumonia. Clinical features of *H. influenzae* pneumonia are indistinguishable from

other bacterial causes of pneumonia. Chest x-ray often reveals patchy or lobar infiltrates and sputum Gram stains typically show a predominance of small gram-negative coccobacilli.

Sinusitis

Previous studies have used sinus aspirate cultures to show that nontypeable *H. influenzae* is a common cause of maxillary sinusitis. Clinical features include fever, purulent nasal discharge, headache, and facial pain (or tooth pain in the upper molars in the case of maxillary sinusitis).

Neonatal and postpartum sepsis

Invasive biotype IV, nontypeable (unencapsulated) strains have been identified as a common cause of neonatal sepsis, postpartum sepsis, or both. These organisms are genetically similar to *H. haemolyticus,* and some authorities believe that they should be removed from the group of nontypeable *H. influenzae* and placed in their own species. Biotype IV, nontypeable strains have also been implicated in causing postpartum endometritis and tubo-ovarian abscesses.

Bacteremia (invasive disease)

The incidence of *H. influenzae* type b bacteremia has declined dramatically since the introduction of the protein conjugate *H. influenzae* type b vaccine, but the incidence of invasive disease with other serotypes of *H. influenzae* and nontypeable *H. influenzae* has increased. Nontypeable *H. influenzae* has occasionally been implicated in invasive disease, primarily in older adults with underlying conditions such as alcohol use disorder, cardiac disease, structural lung disease, HIV infection, and cancers. In such cases, morbidity and mortality are substantial. The source of infection in *H. influenzae* bacteremia is typically the respiratory tract.

Conjunctivitis

The most common bacterial cause of conjunctivitis in children is nontypeable *H. influenzae*, which can occur in outbreaks at schools and daycare centers. *H. influenzae* conjunctivitis is marked by purulent discharge and conjunctival hyperemia, which can occasionally become severe with copious purulent discharge, lid edema, chemosis, and keratitis.

Clinical manifestations of type b *H. influenzae* infection

Meningitis

Often preceded by an upper respiratory infection, meningitis represents the most serious manifestation of invasive infection with *H. influenzae* type b. Clinically, its presentation resembles other common causes of bacterial meningitis with fever and nuchal rigidity that, if untreated, rapidly progresses to encephalopathy, seizures, and coma. Infection occurs in children who have not been vaccinated or who cannot make IgG. Adult cases have always been rare because antibody to other bacteria, for example, encapsulated Enterobactereaceae, cross reacts with type b polysaccharide and are even more rare now because the organism is no longer commonly found in the population. But meningitis with non-typable *H. influenzae* serotypes can occur in adults with a history of head trauma, cerebrospinal fluid leak, neurosurgery, paranasal sinusitis, and otitis.

Meningitis in neonates has always been uncommon because maternal antibody is still present. When it occurs, it resembles group B streptococcal infection. Nuchal rigidity is often absent. The developemtn of a subdural effusion is a common complication that is often marked by a tense anterior fontanelle, seizures, hemiparesis, and neurologic deterioration. These symptoms typically develop despite adequate antibiotic therapy. In older children, papilledema and encephalopathy occur.

Even with appropriate management, permanent neurologic sequelae, especially deafness, occur in many survivors of *H. influenzae* meningitis.

Epiglottitis

Rapidly progressive cellulitis of the epiglottis with *H. influenzae* and subsequent acute respiratory obstruction of the supraglottic tissue is a medical emergency and a potentially lethal disease. Clinical features include sore throat, fever, dyspnea, dysphagia, pooling of oral secretions, and drooling from the mouth. A classic presentation is based on the patient's posturing with an upright position, extended neck, and chin protrusion in an attempt to reduce airway obstruction. Examination of the larynx should only be performed in a setting in which a secure airway can be achieved as examination maneuvers can lead to fatal respiratory obstruction.

Pneumonia/Empyema

Primary lung infection with *H. influenzae* type b occurs most frequently in children between ages 4 months and 4 years in either the winter or spring months. They often present with a consolidative pneumonia with occasional pleural involvement. A rare but important complication of *H. influenzae* type b pneumonia is the development of pericarditis, which can present as severe dyspnea, tachycardia, and cardiovascular failure.

Cellulitis

Cellulitis due to *H. influenzae* type b is most common among young children and is seen often in the periorbital region or on the cheek. Clinically, it is distinguished by fever, signs of inflammation, and a distinctive red-blue coloration with rapid progression over hours. Accompanying bacteremia is very common and secondary septic foci can develop.

Septic arthritis

Septic arthritis in children <2 years old can occur with *H. influenzae* type b and is seen most often in a single, large, weight-bearing joint. Decreased mobility, pain, and swelling are typical symptoms, and

positive blood and synovial cultures are common. Typically, response to antibiotics is rapid and curative, but residual joint dysfunction has been documented to occur in a subset of children.

Septic arthritis due to *H. influenzae* type b also occurs in adults and can occur in the setting of extra-articular infection, such as meningitis, pneumonia, sinusitis, and cellulitis. Alcohol abuse, underlying joint disease, lupus, diabetes mellitus, splenectomy, multiple myeloma, lymphoma, and common variable hypogammaglobulinemia have been identified as predisposing factors for the development of *H. influenzae* septic arthritis in adults.

It must be noted that all these diseases are now rare in developed countries because of the widespread adoption of conjugate vaccine in infants and toddlers.

Clinical manifestations of other typeable *H. influenzae*

Although type b *H. influenzae* has always been the best recognized and the most virulent of the *H. influenzae* isolates, non-b types a through f occasionally infect children and adults. Types a, e and f have been most commonly implicated. These non-b typeable strains cause the same range of infections as caused by *H. influenzae* type b. Disease affects seemingly immunologically normal hosts and, when it occurs, is of severity similar to that caused by *H. influenzae* type b.

Diagnosis

Nontypeable *H. influenzae*

Since nontypeable *H. influenzae* is a common colonizer of the human upper respiratory tract, determining its role as a pathogen can be challenging. Means of diagnosing otitis media, for example, typically involves invasive diagnostic measures with tympanocentesis. Because this procedure is reserved for difficult or treatment-refractory cases, treatment of otitis media is empiric, based on research studies that have implicated *Streptococcus pneumoniae*, nontypeable *H. influenzae*, and *Moraxella catarrhalis* as the most common pathogens isolated in middle ear fluid cultures.

In cases of COPD exacerbations and community-acquired pneumonia, the presence of numerous small Gram negative coccobacilli on microscopic examination of Gram-stained sputum, supported by isolation of *H. influenzae* by culture suggests the diagnosis.

Isolation of nontypeable *H. influenzae* in blood cultures indisputably signifies its presence as a pathogen and agent of invasive disease, but bacteremia is uncommon in patients with these infections.

Type b *H. influenzae*

Cultures from blood, cerebrospinal fluid, and other sterile fluids are typically diagnostic for invasive disease with *H. influenzae* type b and are confirmatory in a number of conditions, including meningitis, epiglottitis, cellulitis, and septic arthritis.

Detection of *H. influenzae* type b capsular antigen by immunoelectrophoresis, latex agglutination, or enzyme-linked immunosorbent assay can be diagnostic in serum, CSF, and urine. Antigen can also be found in pleural, pericardial, and joint fluid in the setting of infection with *H. influenzae* and can assist in diagnosis as it often persists even after antibiotic therapy has been initiated.

Treatment

Nontypeable *H. influenzae*

An important consideration in the treatment of suspected *H. influenzae* infections is that about 30% of nontypeable strains are β-lactamase producers. A recently recognized mechanism of resistance in *H. influenzae* is a mutation in the gene (fts 1 gene) coding for penicillin-binding protein 3. β-lactam penicillins, such as amoxicillin and ampicillin, should only be used in cases of confirmed susceptible isolates. Clinicians starting empiric treatment for conditions such as otitis media and exacerbation of COPD should select antimicrobial agents with activity against β-lactamase producing nontypeable *H. influenzae*, *Streptococcus pneumoniae,* and *Moraxella catarrhalis*. These include amoxicillin-clavulanate, third-generation cephalosporins, fluoroquinolones, macrolides (e.g., azithromycin), and tetracyclines.

Type b *H. influenzae*

Infection with *H. influenzae* type b can be rapidly fatal, and it requires swift diagnosis and treatment initiation. The favored regimen for *H. influenzae* type b infections in children and adults is cefotaxime or ceftriaxone. Treatment should be continued until the patient is afebrile and has resolution of signs and symptoms for 3 to 5 days with a total duration of treatment not exceeding 7 to 10 days. Complications of metastatic infection (e.g., pericarditis, endocarditis, osteomyelitis) will require more prolonged therapy.

In addition to antimicrobials and supportive care, corticosteroids are administered to patients diagnosed with *H. influenzae* type b meningitis for the first four days of treatment to reduce inflammation and subsequent neurologic sequelae resulting from the release of bacterial cell wall components during microbial killing.

Chemoprophylaxis for type b H. influenzae

Secondary cases (illness occurring within 60 days of contact with an infected patients) of *H. influenzae* type b disease are uncommon, but rates are highest among household contacts aged <12 months (6%), <24 months (3%), and <48 months (2.1%). Chemoprophylaxis with rifampin is recommended for index patients who did not receive cefotaxime or ceftriaxone as part of the treatment and all household contacts (except pregnant women) of an invasive *H. influenzae* type b case who live in a household with a child <4 years of age who has not received their age-appropriate number of *H. influenzae* type b vaccines or a child <18 years of age, regardless of their immunization status, who is immunocompromised.

Rifampin prophylaxis, given for 4 days, has been shown to eradicate the carrier state and significantly reduce secondary

cases in household members and close contacts. Sufficient exposure to warrant prophylaxis is defined as a susceptible host who is a household member or who has spent at least 4 hours each day with the index patient for at least 5 days within the week preceding hospitalization.

In a daycare or classroom setting, chemoprophylaxis is recommended when unimmunized or incompletely immunized children attend the facility and two or more cases of invasive *H. influenzae* type b have occurred within 60 days.

Chemoprophylaxis can be given in conjunction with treatment barring any drug–drug interactions. Chemoprophylaxis is not generally indicated for contacts of patients with invasive disease caused by nontypeable *H. influenzae*.

Vaccine

The primary strategy for preventing disease with type b *H. influenzae* is immunization. The vaccine is composed of type b capsular polysaccharide conjugated to a carrier protein, which induces serum antibody production against the capsule, provoking bactericidal activity against the organism. This vaccine is widely available and considered highly effective in reducing the circulation of type b strains and preventing nasopharyngeal colonization and invasive disease in infants and children. The widespread use of the conjugated vaccine has almost eradicated invasive *H. influenzae* type b disease among children <5 years of age in the United States.

Two conjugated vaccines are currently available in the United States, and all children should be immunized with a conjugated vaccine beginning at 2 months of age. After the series is completed, an additional booster dose is indicated between 12 and 15 months of age due to declining antibody titers. The most common adverse reactions are pain and swelling at the injection site. Serious adverse reaction to the vaccines are rare.

Localized populations with low vaccination rates facilitate the continued circulation of *H. influenzae* type b strains and thus careful surveillance in these populations remains important.

At this time, there are no available vaccines for nontypeable *H. influenzae* in the United States. However, studies in Europe are under way and a vaccine containing a conserved surface protein has shown partial efficacy in prevention of otitis media.

There are no vaccines available or under study for typeable strains other than type b due to the rarity of infection caused by these organisms.

Suggested reading

Agrawal A, Murphy TF. Haemophilus influenzae infections in the H. influenzae type b conjugate vaccine era. *J Clin Microbiol*. 2011;49:3728–3732.

Briere EC, Rubin L, Moro P, et al. Prevention and control of *Haemophilus influenzae* type b disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention. *MMWR*. 2014 28 Feb. https://www.cdc.gov/mmwr/pdf/rr/rr6301.pdf

Campos J, Hernando M, Roman F, et al. Analysis of invasive Haemophilus influenzae infections after extensive vaccination against H. influenzae type b. *J Clin Microbiol*. 2004;42(2):524–529.

Eskola J, Kayhty H, Takala AK, et al. A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive Haemophilus influenzae type b disease. *N Engl J Med*. 1990;323(20):1381–1387.

Langereis J, De Jonge M. Invasive disease caused by nontypeable *Haemophilus influenzae*. *Emerg Infect Dis*. 2015;21:1711–1718.

Murphy TF, Faden H, Bakaletz LO, et al. Nontypeable Haemophilus influenzae as pathogen in children. *Pediatr Infect Dis J*. 2009;28:43–48.

Musher DM, Kubitschek KR, Crennan J, Baughn RE. Pneumonia and acute febrile tracheobronchitis due to *Haemophilus influenzae*. *Ann Intern Med*. 1983;99(4):444–450.

Peltola H. Worldwide Haemophilus influenzae type b disease at the beginning of the 21st century: Global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. *Clin Microbiol Rev*. 2000;13(2):302–317.

Robbins JB, Schneerson R, Argaman M, Handzel ZT. Haemophilus influenzae type b: Disease and immunity in humans. *Ann Intern Med*. 1973;78:259–269.

Sethi S, Evans N, Grant BJ, Murphy TF. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 2002;347(7):465–471.

Urwin G, Krohn JA, Deaver-Robinson K, Wenger JD, Farley MM. Invasive disease due to Haemophilus influenzae serotype f: Clinical and epidemiologic characteristics in the H. influenzae serotype b vaccine era. The Haemophilus influenzae Study Group. Clin Infect Dis. 1996;22(6):1069–1076.

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Legionellosis

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Etiologic agents

The Order Legionellales includes the family *Legionellaceae* which, in turn, includes the genera *Legionella, Berkiella, Occultobacter*, and *Nucleophilum*, among others. Of these, members of the genus *Legionella* are the predominant human pathogens. The genus name *Legionella* ("body of soldiers") was derived from the fact that the first recognized outbreak of infection due to these microorganisms affected members of the American Legion in 1976. *Pneumophila* ("lung loving") was the species designation for the first isolate, given its predilection for pulmonary infection. There are now >60 species and >70 serogroups in the family *Legionellaceae*, and about half of these are known to be pathogenic in humans. The predominant pathogen in this family is *L. pneumophila serogroup 1* which accounts for 80% to 90% of cases of Legionnaires' disease (LD) worldwide (Box 139.1). However, *L. pneumophila* includes 16 serogroups in total, and a degree of regional variation is observed. Additionally, in Australia and New Zealand, *L. longbeachae* accounts for 30% of the cases. Legionellaceae are gram-negative, aerobic, non–spore-forming bacilli that measure 0.3 to 0.9 μm wide and 2 to 20 μm long. These organisms require special media for growth. Charcoal yeast extract agar buffered to pH 6.9 and containing α-ketoglutarate along with cefamandole, polymyxin B, and anisomycin to prevent growth of other microorganisms is the primary medium used for isolation of these organisms. Addition of α-ketoglutaric acid to the medium promotes growth of *Legionella* likely by stimulation of oxygen-scavenging enzymes.

These organisms are visualized poorly, if at all, by Gram stain. In tissue, silver impregnation stains such as the Dieterle or Warthin–Starry method allow visualization of the organisms.

The genome of *L. pneumophila* ranges in size from 3.34 to 2.52 MB. The GC content ranges from 86% to 88%, and 86% to 87% of the genes are coding genes. Three hundred virulence proteins, termed "effectors" are active in infection with this microorganism. Currently, the genomes of 38 *Legionella* spp. have been sequenced.

Epidemiology and pathogenesis

Legionellae are aquatic microorganisms and thus the epidemiology of infections due to these microorganisms is linked to water systems that are contaminated with these bacteria, with optimal water temperature for growth being 25°C/77°F to 42°C/107°F. Growth is supported by biofilm formation as well as symbiotic relationships with water-dwelling amoebae and other organisms. The earliest known outbreak of LD occurred in 1965, at St. Elizabeth's Hospital in Washington, DC. The outbreak that gave this illness its name and led to the isolation of the causative microorganism was associated with the 58th Annual Convention of the American Legion held at a hotel in Philadelphia from July 21 to July 24, 1976. One hundred and eighty-two of the attendees at the convention developed pneumonia. One hundred and forty-seven (81%) were hospitalized, and 29 (16%) died. This outbreak of pneumonia of apparent unknown cause triggered an

BOX 139.1

Legionellaceae that have been reported as causing pneumonia

Legionella pneumophila serogroups 1–15 (serogroup 1 most commonly; also 3, 4, 6, 13)
Legionella micdadei
Legionella bozemanii
Legionella dumoffi
Legionella sainthelensi
Legionella longbeachae
Legionella anisa
Legionella maceachernii
Legionella waltersii
Legionella feelei
Legionella wadsworthii
Legionella parisiensis
Legionella hackeliae
Legionella jordanis
Legionella lansingensis
Legionella cincinnatiensis

extensive epidemiologic and microbiologic investigation by the US Centers for Disease Control and Prevention (CDC), culminating in the isolation of a new microorganism, *L. pneumophila*, about 6 months later.

Legionellosis can occur as sporadic (endemic) cases or as outbreaks in the community or in healthcare facilities, and much has been learned about legionellosis through outbreak investigations. Outbreaks have varied in size from a few cases to the largest outbreak yet reported of 800 suspected and 449 confirmed cases in Murcia, Spain, in July 2001.

A study from Europe, from 2011 to 2015, indicated that there were 30,532 cases of LD there, with the majority of cases arising from France, Germany, Italy, and Spain. For cases with a reported probable setting of acquisition, 70.7% were reported as community-acquired, 19.9% as travel-related, and 7.3% as healthcare-related. The vast majority (90.1%) were reported as sporadic cases while 9.9% were cluster-related, with the largest clusters occurring in Portugal (433 cases), Spain (57 cases), and the United Kingdom (23 cases). The case fatality ratio decreased from 10.5% in 2011 to 8.1% in 2015, while the annual incidence increased from 0.97 cases/100,000 population in 2011 to 1.3 cases/100,000 population in 2015.

With the use of geographic information systems it has been shown that the dispersion distance of *Legionella* from a contaminated cooling tower is about 11.6 km. When data on 3,254 patients with LD reported to the CDC in the United States from 1980 through 1989 were analyzed, investigators found that disease rates were higher in northern states and during the summer. The mean age of patients with LD was 52.7 years compared with 34.7 years for the US population. In contrast to earlier reports, persons with LD were now more likely to be black. They were also more likely to be smokers, or have diabetes, cancer, AIDS, or end-stage renal disease. Indeed, the observed number of cases among patients with AIDS was 42-fold higher than expected. Twenty-three percent of the cases were nosocomially acquired. However the number of reported cases of LD in the United States increased 4.5-fold from 2000 to 2016. The reasons for this increase are multifactorial including increased testing and reporting. Climate change and an aging population likely play a role as well. The highest rates continue to be in Mid-Atlantic States, lowest in the western and south-central states. The rate of LD is higher in males than in females and higher in African Americans. The highest rates were in those ≥80 years of age at 4.7/100 000 compared with 0.4/100 000 for those <50 years of age.

Other risk factors for LD in the setting of an outbreak are cigarette smoking (relative risk 1.7 to 3.4) (smoking cannabis and tobacco may be a risk factor for severe LD) and consumption of three or more drinks of alcohol per day (confers a relative risk of 3.5). More recently investigators have begun to combine studies of traditional risk factors with a dissection of host susceptibility using molecular biology tools. A mutation leading to a stop codon at position 392 results in a dysfunctional Toll-like receptor (TLR) 5 protein unable to recognize flagellin and is a risk factor for *L. pneumophila* infection in nonsmokers. Reduced interferon-γ release has been noted in patients who have recovered from LD. A number of biological modifying agents used to treat cancer, autoimmune disease, and multiple sclerosis seem to increase the risk of LD. For example, treatment with infliximab results in a 15-fold increase in risk and adalimumab a 38-fold increase.

It is interesting in light of the preceding information about the role of cell-mediated immunity in LD that patients with HIV infection who have a defect in cell-mediated immunity are relatively infrequently infected with *Legionella* spp. This may be partially related to the efficacy of trimethoprim-sulfamethoxazole prophylaxis administered for *Pneumocystis* prophylaxis in the subset of patients with CD4 counts <200/mm^3 providing protection against *Legionella* as well. Recent prospective case-control studies have shown no differences in disease severity or outcome of LD in those with HIV infection compared to control populations.

Outbreaks provide an opportunity to learn about the mechanisms of transmission of LD. In most instances, *Legionella* is transmitted to humans by inhalation of aerosols containing the bacteria. Outbreaks have been associated with exposure to a variety of aerosol-producing devices, including showers, a grocery store mist machine, cooling towers, whirlpool spas, decorative fountains, and evaporative condensers. Other water sources implicated in transmission of LD include showers and spas in wellness centers, water on trains, birthing pools, dental units, asphalt paving machines, and windscreen wiper fluid without added screen wash. New reservoirs for *Legionella* continue to be identified, such as compost facilities. It is also likely that aspiration of contaminated potable water by immunosuppressed patients is a mechanism whereby infection with *Legionella* is acquired. Legionellosis is believed to occur worldwide, but data are limited or nonexistent for many countries. Legionellosis is uncommon in areas without hot water heaters and complex water distribution systems. However, even in these areas, aspiration of contaminated natural water, as, for example, following boating accidents, can result in LD. Contrary to popular belief

that person-to-person transmission does not represent a route of transmission for *Legionella*, a recent case report involving such a mechanism has been presented.

Pathogenesis

Our knowledge of the pathogenesis of *Legionella* infections in humans is still incomplete. The alveolar macrophage is the target cell for *Legionella* in the lower airways. Both E-cadherin and b_1 integrin receptors mediate filamentous *L. pneumophila* attachment to lung epithelial cells. Only virulent strains of *Legionella* are capable of initiating parasite-directed endocytosis. Following phagocytosis or endocytosis, there is abrogation of phagosome–lysosome fusion, which is essential for the intracellular growth of this microorganism. The replicative phagosome becomes associated with the endoplasmic reticulum.

Following a latent period of about 12 hours, the bacteria start dividing. During this latent period, there is synthesis of up to 35 proteins and repression of 32 proteins. Iron must be available in the phagosome for growth. Virulent *L. pneumophila* strains are sensitive to sodium chloride.

Once the replicative phagosome has been established, the bacteria begin to multiply with a doubling time of 2 hours. Heat shock protein 60 (Hsp 60), a chaperone protein, is a dominant protein during this intracellular phase, suggesting that it has an essential role in the viability of the microorganism. Several morphologic changes occur as the number of bacteria increase: they become shorter and accumulate intracytoplasmic membranes and vesicles.

It is likely that *Legionella* behave differently while multiplying in macrophages than they do while multiplying in amebae, their natural hosts. Because airborne amebae have been found in water aerosols, this finding may have implications for LD in humans.

Infectious syndromes

Pneumonia is the most common manifestation of infection with *Legionella* spp. It may occur in the community as sporadic cases or as outbreaks. Epidemiological studies have estimated that Legionella accounts for <10% of cases of community-acquired pneumonia. In addition, *Legionella* is one of the agents of healthcare-associated pneumonia, particularly in hospitals with known water colonization and in patients with various medical and surgical risk factors for microaspiration. There may be a variety of extrapulmonary manifestations, and sometimes the clinical picture is dominated by these.

In the Philadelphia outbreak, fever was present in 97% of the patients, malaise in 89%, cough in 86%, chills in 74%, dyspnea in 59%, myalgias in 55%, headache in 53%, chest pain in 52%, sputum production in 50%, and diarrhea in 41% at presentation. Sixty percent had a white blood cell count >10,000/mm^3, and 34% had bilateral pulmonary opacities on chest radiograph.

When patients with LD are compared with those with community-acquired pneumonia due to other agents, the patients with LD are more likely to have myalgias, headache, diarrhea, and a higher mean oral temperature at the time of presentation. They also present to hospital sooner after the onset of symptoms—4.7 days vs. 7.7 days (P = 0.02). When patients with LD were compared with patients with bacteremic pneumococcal pneumonia, the following features were associated with *Legionella* pneumonia: male sex (odds ratio [OR] 4.6; 95% confidence interval [CI] [1.48, 14.5]); heavy alcohol consumption (OR 4.8; 95% CI [1.39, 16.42]); previous β-lactam therapy (OR 19.9; 95% CI [3.47, 114.2]); axillary temperature >39°C (OR 10.3; 95% CI [2.71, 38.84]); myalgias (OR 8.5; 95% CI [2.35, 30.74]); gastrointestinal symptoms (OR 3.5; 95% CI [1.01–12.18]). Negative associations included pleuritic chest pain, previous upper respiratory tract infection, and purulent sputum.

In a study comparing the radiographic features of LD, pneumococcal pneumonia, mycoplasma pneumonia, and psittacosis, it was noted that radiographic deterioration following diagnosis was a particular feature of LD, occurring in 30/46 (65%) compared with 14/27 (52%) patients with bacteremic pneumococcal pneumonia. It should be pointed out that this study was done at a time when erythromycin was the standard therapy for LD. In general, several days were required before a therapeutic effect was evident with this agent. With current therapies the same degree of radiographic deterioration is unlikely. About half the patients with LD have unilateral pneumonic involvement throughout the course of their illness. The lower lobes are involved most commonly, and pleural effusions are seen in about 35% of cases. The severity of the radiographic findings correlated significantly with the presence of *L. pneumophila* in sputum by direct fluorescent antibody. Lung abscess, empyema, and bulging fissure sign are other radiographic features that are occasionally seen in patients with LD.

Relative bradycardia is seen in about two-thirds of patients with LD. Most patients appear acutely ill. Crackles are generally present on auscultation of the chest. Many experts feel that LD cannot be distinguished from other causes of pneumonia on the basis of clinical features. However, recent attempts at creating diagnostic scoring systems have shown promising results, although prospective validation is required prior to widespread clinical application

One of the remarkable things about LD is the range of extrapulmonary manifestations, which primarily reflect metastatic spread although cases of primary extrapulmonary infection have been reported. Although they occur in about 30% of patients, they can dominate the clinical picture and determine the outcome: there can be a variety of central nervous system manifestations. These include lethargy, confusion, delirium, stupor, coma, seizures, hallucinations, slurred speech, fine or coarse tremors, hyperactive reflexes, absence of deep tendon reflexes, and signs of cerebellar dysfunction, including nystagmus and gait disturbance. There is some evidence that the central nervous system manifestations of legionellosis are due to an autoimmune mechanism, and case reports indicate that treatment with high-dosage intravenous immunoglobulin is of benefit. Peripheral neuropathy and cranial nerve palsies, incontinence, or urinary retention are other manifestations. Myocarditis, pericarditis, and endocarditis have all been reported, albeit uncommonly, as extrapulmonary manifestations of LD. Acute

renal failure, tubulointerstitial nephritis, tubular necrosis, and rapidly progressive glomerulonephritis are renal manifestations of LD. Gastrointestinal manifestations include peritonitis, hepatitis, and pancreatitis. Rhabdomyolysis, reactive arthritis, septic arthritis, and osteomyelitis are uncommon musculoskeletal manifestations.

The clinical course of LD with currently available treatments seems to be different now than when erythromycin was the treatment of choice. This is exemplified by a study of 25 patients with LD who were treated with azithromycin. These patients were all diagnosed using an assay for *Legionella* urinary antigen, and thus early diagnosis (results are available in a few hours in contrast to several days for culture of the microorganism or weeks for a serologic diagnosis) may have accounted for the very favorable outcomes. Twenty-two of twenty-three evaluable patients were cured. At the 10-day follow-up, 45% had signs and symptoms, whereas at the 4- to 6-week follow-up period 35% had signs and symptoms. It is also apparent that different strains of *Legionella* may vary in virulence. Thus in the Murcia, Spain, outbreak involving 800 suspect and definite cases, the mortality was 1.1% for definite and 0.9% for suspect cases.

Pontiac fever

In July 1968, an explosive epidemic of acute febrile illness occurred at a county health department facility in Pontiac, Michigan. This self-limiting illness of 2 to 5 days' duration was characterized by fever, headache, myalgia, and malaise. It affected 144 persons. The mean incubation period was approximately 36 hours. Later it was shown that Pontiac fever was due to *L. pneumophila* endotoxin. There has been speculation that Pontiac fever is due to inhalation of free-living amebae that are commonly present in environmental sites containing *Legionella*. Subsequently many outbreaks of Pontiac fever have occurred. It has been associated with exposure to *L. pneumophila* serogroups 1, 6, and 7; *L. feelei*; *L. micdadei*; and *L. anisa*. Most commonly, exposure to contaminated whirlpools, cleaning evaporative condensers, and water fountains has resulted in Pontiac fever. The pathogenesis is still incompletely understood, although some investigators feel it is exposure to *Legionella* endotoxin that results in the symptoms. In support of this is the finding of high concentrations of *Legionella* endotoxin in contaminated water associated with Pontiac fever. One hundred and seventy people who had visited a hotel and leisure complex in Lochgoilhead, a village on the west coast of Scotland, became ill with headache, fever, arthralgia, myalgia, cough, and breathlessness. This illness was initially labeled "Lochgoilhead fever" but because *L. micdadei* was isolated from the whirlpool spa and 60 of 72 persons with symptoms seroconverted to *L. micdadei*, this likely represented Pontiac fever. An outbreak of Pontiac fever and legionellosis at a hotel in Oklahoma from March 15 to March 21, 2004, is instructive because the sensitivity and specificity of the *Legionella* urinary antigen test were 35.7% and 100%, respectively, and for serology 46.4% and 90%. Because the urinary antigen test detects *L. pneumophila* serogroup 1 lipopolysaccharide (endotoxin), this outbreak adds to the evidence that *Legionella* endotoxin is the cause of Pontiac fever. In the Oklahoma outbreak, 3 of 101 (2.9%) persons with Pontiac fever were hospitalized.

Nosocomial (healthcare-associated) Legionnaires' disease

Nosocomial LD continues to occur. In a 20 US state and large metropolitan area surveillance study there were 2,809 cases of LD, 553 (20%), of which were nosocomial. Sixteen of the 21 (76%) jurisdictions reported nosocomial cases which occurred at 72 facilities (15 hospitals and 58 long-term care facilities). The case fatality rate was 25% for definite cases and 10% for possible cases.

The clinical features of nosocomial LD are not different from those of nosocomial pneumonia due to any bacterium. Immunocompromised patients, especially those receiving corticosteroid therapy, are most susceptible to *Legionella* if it is contaminating the hospital water supply. Indeed, nosocomial LD is all about contamination of the hospital's potable water: if there is no *Legionella* in the potable water there are usually no cases of nosocomial LD. This has led to a debate about whether to conduct routine surveillance for *Legionella* in the potable water and, if it is found, eradicate it. However, there are those who maintain that if you do not have a problem with nosocomial LD you should not do routine surveillance. Having battled nosocomial LD for many years, my opinion (TM) is that all hospitals should carry out routine surveillance of their water for *Legionella*. If it is present, all cases of nosocomial pneumonia should be investigated for *Legionella*, and, if found, measures to control or eradicate *Legionella* from the hospital water supply should be taken (Box 139.2).

More recently some investigators have proposed that there is a risk of nosocomial LD if ≥30% of water samples are positive for *Legionella* spp. A review of available data suggests that this number has sensitivity of 59% and a specificity of 74%.

Immunocompromised patients should not drink the hospital water (if it is contaminated with *Legionella*) nor should they shower in it. Only sterile water should be used to flush nasogastric tubes. Occasionally unusual sources of nosocomial LD such as

BOX 139.2

Control of *Legionella* in hot water systems

1. **Physical measures**
   Maintain water temperature above 55°C
   Ultraviolet irradiation
   Sonication
   Terminal tap water filters
2. **Chemical measures**
   Prevent scale formation in the pipes
   Biocides: sodium hypochlorite, ozone
   Charcoal filters
   Copper–silver ionization
3. **Maintain good plumbing practices**
   Dead spaces in calorifiers should be removed
   Dead legs should be removed
   Regular flushing of outlets
   Pumps and calorifiers should be in series not in parallel

contaminated esophageal probes are found. The CDC has issued guidelines for the prevention of healthcare-associated pneumonia but has not made any firm recommendations on the measures outlined in Box 139.2 for eradication or control of *Legionella* in potable water. Copper–silver disinfection and point-of-use filters have proved effective in control of nosocomial LD in some institutions.

Diagnosis

A high index of suspicion is necessary for the diagnosis of sporadic cases of LD. Outbreaks of pneumonia usually trigger a workup for *Legionella* so these are easier to diagnose.

Isolation of the organism from respiratory secretions or other specimens is the definitive diagnostic test. Detection of *Legionella* antigen in urine by enzyme-linked immunosorbent assay is about 80% sensitive and >95% specific. This test is readily available for *L. pneumophila* serogroup 1. Diagnostic kits are also available for detection of antigens of *L. pneumophila* 1 to 6. Legionella antigen is excreted in the urine for days to weeks (rarely up to 1 year) after the onset of pneumonia. It should be noted that the antigen test positivity rate varies with the severity of the disease, being positive in 40% to 53% of mild cases and in 88% to 100% of severe cases. Despite these performance characteristics, diagnosis remains difficult as appropriate testing indications remain poorly established despite guidance being provided in the most recent Infectious Diseases Society of America (IDSA) community-acquired pneumonia guidelines. In fact, studies using the IDSA recommended testing indications showed that only 1.6% of indicated samples were positive for an overall sensitivity of 63% (95% CI [44%, 79%]) and specificity of 35% (95% CI [33%, 37%]), thus a high degree of clinical suspicion is needed for accurate diagnosis.

Demonstration of a fourfold rise in antibody titer between acute and convalescent serum samples using an indirect immunofluorescence whole-cell assay can also be used to diagnose LD. Up to 12 weeks may be required to demonstrate a fourfold rise in antibody, so serology is not useful for the acute management of this disease. A single or static titer of ≥1:256 is no longer considered satisfactory for the diagnosis of LD. Polymerase chain reaction (PCR) applied to respiratory secretions, pulmonary tissue, or pleural fluid is also useful and has a sensitivity of 83% (95% CI [79%, 87%]) and a specificity of 90% (95% CI [88%, 92%]). Culture has a sensitivity of 60%, and the direct fluorescent antibody test on a sputum specimen has a sensitivity of 67% (95% CI [30%, 91%]) and a specificity of 100% (95% CI [91%, 100%]). Loop-mediated isothermal amplification (LAMP) is a process similar to PCR but requires less equipment and shorter time for processing specimens. To date its use has been confined to environmental samples

Treatment

In the original outbreak of LD, it was observed that those who were treated with the macrolide erythromycin had a lower mortality rate than individuals who were treated with other antibiotics. Subsequently a newer macrolide, azithromycin, was shown to have a bactericidal effect in the guinea pig alveolar macrophage model, and it had a 5-day post-antibacterial effect when it was removed from the system, whereas erythromycin in the same model was bacteriostatic and had no post-antibacterial effect. These observations have been confirmed in clinical trials wherein 20 of 21 patients treated with azithromycin were cured (see Box 139.3).

It is noteworthy that because β-lactam antibiotics do not penetrate host cells they are ineffective in LD even though they show activity in vitro. Data from a prospective, nonrandomized study indicate that levofloxacin is superior to older generation macrolides for the treatment of severe LD. In this study carried out in Murcia, Spain, 3.4% of the patients receiving levofloxacin had complications compared with 27.2% of those receiving macrolides; the levofloxacin patients had a shorter length of stay (5.5 vs. 11.3 days). Addition of rifampin to levofloxacin provided no additional benefit. However,

BOX 139.3

Antibiotic treatment of Legionnaires' disease

1. Fluoroquinolones
   - Levofloxacin, 750 mg IV (PO for mild cases) once daily
   - Moxifloxacin, 400 mg IV or PO once daily (only available PO in most countries)
   - Ciprofloxacin, 750 mg IV or PO q12h
2. Macrolides
   - Azithromycin, 1 g IV or PO, as a loading dose and then 500 mg IV or
   - PO (due to the long half-life) of azithromycin; only 5 days necessary for treatment of mild cases; 7–10 days for more severe cases
   - Erythromycin, 1 g q6h IV; phlebitis is problematic at this dosage (unless infused through a central line); transient deafness, especially in patients who are receiving treatment with diuretics, also occurs at this dosage level
   - Clarithromycin, 500 mg q12h IV or PO (IV formulation not available in all countries)
3. Doxycycline, 200 mg loading dose, and then 100 mg q12h IV or PO
4. Rifampin, 300–600 mg q12h PO (IV formulation available in some countries). Rifampin should only be used in combination with a macrolide. There are no data supporting a synergistic role when it is used with other classes of antimicrobials. Recent data indicate that treatment with rifampin is associated with longer length of stay and higher bilirubin levels

For cases of mild to moderately severe disease in immunocompetent patients treatment for 7 days is usually sufficient. For immunocompromised patients, treatment for 21 days or longer may be necessary. In these instances individual decisions are necessary and are based on the underlying process that requires the immunosuppression, degree of immunosuppression, and response to therapy. Close follow-up is necessary once treatment is discontinued because relapse is not infrequent.

it should be noted that 33/76 of patients receiving a macrolide were treated with erythromycin; the remaining 43/76 were treated with clarithromycin, and none was treated with azithromycin. In a study of 139 cases of *L. pneumophila* pneumonia from a prospective series of 1,934 consecutive cases of community-acquired pneumonia, the overall mortality rate was 5%. Eighty patients received initial therapy with a macrolide and 40 with levofloxacin. Patients who received levofloxacin had a shorter time to defervescence (2 vs. 4.5 days) and to clinical stability (3 vs. 5 days). The complication rates were the same in both groups at 25%. The case fatality rate for those treated with levofloxacin was 2.5% versus 5% for those treated with macrolides ($p = 0.906$). The median length of stay was 8 days for the levofloxacin-treated group and 10 days for those who received macrolides ($p = 0.014$). Alternatively, two more recent retrospective cohort analyses which excluded patients receiving erythromycin, one with 410 and one with 3,152 adult patients with LD, found no differences between fluoroquinolones and azithromycin or clarithromycin in terms of mortality, length of stay, rates of *Clostridium difficile* infection, or total hospitalization cost. In a study of 33 patients admitted to an intensive care unit with LD, fluoroquinolone administration within 8 hours of intensive care unit arrival was associated with decreased mortality.

In a recent study from Spain, the authors compared monotherapy (11 patients treated with clarithromycin) to combination therapy with clarithromycin and rifampin (21 patients). All patients were cured; however, the patients who received rifampin had a 50% longer length of stay and a trend toward higher bilirubin levels. A review of the data on rifampin in LD led to the conclusion that it should be considered only for patients with severe disease or significant comorbid conditions including immunocompromised hosts and those refractory to conventional monotherapy regimens.

Many factors should be considered when deciding on the duration of therapy. Immune status and severity of the infection are probably the two most important factors. In mild to moderate cases of LD in immunocompetent subjects with a rapid response to therapy, a duration of 7 days is sufficient. Indeed in this setting a 5-day course of azithromycin, given its long half-life, is probably sufficient. In patients with severe disease and/or immunocompromised state, a 3-week course of treatment with either fluoroquinolones or macrolides (other than azithromycin) is necessary to avoid relapse. Careful follow-up of immunocompromised patients to identify relapse of infection early is necessary. One should also remember that in some patients with legionellosis polymicrobial infection may be present.

It is likely, given the small numbers of patients with LD, that we will never get evidence from randomized trials to guide our therapeutic choices, and we will have to depend on evidence such as summarized here. There are conflicting results from systematic reviews and meta-analyses on the role for adjunctive corticosteroids in adults admitted with severe community-acquired pneumonia. One such recent study including 1,506 patients from six trials and demonstrated a 30-day mortality rate of 5.0% in the group assigned to corticosteroids, and a mortality rate of 5.9% was observed in the group assigned to placebo ($p = 0.24$). However, time to clinical stability and length of hospitalization were each reduced by approximately 1 day in the group treated with corticosteroids ($p < 0.001$) Alternatively, a separate systematic review and meta-analysis demonstrated a reduction in overall mortality among adult patients with severe community-acquired pneumonia treated with corticosteroids (relative risk [RR] 0.39; 95% CI [0.20, 0.77]) along with decreased need for mechanical ventilation (RR 0.54; 95% CI [0.50, 0.58]), decreased likelihood or acute respiratory distress syndrome development (RR 0.24; 95% CI [0.10, 0.56]), and shorter duration of hospitalization (mean difference −1.00 days (95% CI −1.79, 0.21]) Discrepancies may relate in part to definitions of severe community-acquired pneumonia used as inclusion criteria.

Suggested reading

Beaute J, Zucs P, de Jong B. Risk for travel-associated Legionnaires' Disease, Europe, 2009. *Emerg Infect Dis*. 2012;18:1811–1816.

Chediac C, Che D, Press-Cronenberger S, et al. Factors associated with mortality in community-acquired legionellosis in France. *Eur Respir J*. 2012;39:963–970.

Cristovam E, Almeida D, Calderia D et al. Accuracy of diagnostic tests for Legionnaires' disease: A systematic review. *J Med Microbiol*. 2017;66:485–489.

England AC, Fraser DW, Plikaytis BD, et al. Sporadic legionellosis in the US: The first 1000 cases. *Ann Intern Med*. 1981;94:164–170.

Fraser DW, Tsai TR, Orenstein W, et al. Legionnaires' disease: Description of an epidemic of pneumonia. *N Engl J Med*. 1977;297:1189–1197.

Gershengorn HB, Keene A, Dzierba AL, Wunsch H. The association of antibiotic treatment regimen and hospital mortality in patients hospitalized with Legionella pneumonia. *Clin Infec Dis*. 2015;60(11):66–79.

Herwaldt LA, Mana AR. Legionella: A remerging pathogen. *Curr Opin Infect Dis*. 2018;31:325–333.

Mykietiuk A, Carratalia J, Fenandez-Sabe N, et al. Clinical outcomes for hospitalized patients with Legionella pneumonia in the antigenuria era: The influence of levofloxacin therapy. *Clin Infect Dis*. 2005;40:794–799.

Pedro-Botet L, Yu VL. Legionella: Macrolide or quinolones? *Clin Microbiol Infect Dis*. 2006;12 (Suppl 3):30–35.

Soda EA, Barskey AE, Shah PP et al. Vital signs: Health care associated Legionnaires' disease: Surveillance data from 20 states and a large metropolitan area—United States, 2015. *Am J Transplant*. 2017; 17:–2215–2220.

Tablan OC, Anderson LJ, Besser R, et al., CDC, Healthcare Infection Control Practices Advisory Committee. Guidelines for preventing health-care-associated pneumonia. *MMWR Recomm Rep*. 2004;53(RR-3):1–36.

Yu VL, Plouffe JF, Pastoris MC, et al. Distribution of Legionella species and serogroups isolated by culture in patients with sporadic community-acquired legionellosis: An international collaborative survey. *J Infect Dis*. 2002; 186:127–128.

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Leprosy

Bahir H. Chamseddin and Travis Vandergriff

Epidemiology

Leprosy is an ancient disease that has been the cause of great morbidity and mortality for centuries. A 4,000-year-old skeleton with evidence of lepromatous leprosy was found in India, and DNA from the causative agent, *Mycobacterium leprae*, has been isolated from a Byzantine skeleton from Israel dated to 300–600 AD. More recent evidence has demonstrated cases of leprosy in England dating to approximately 400–500 AD. *M. leprae* is an unculturable, obligate intracellular, gram-positive, acid-fast bacillus (AFB). It multiplies very slowly in the host and grows best at 33°C/91.4°F, which accounts for its predilection for cooler parts of the body such as the skin, testis, anterior segment of the eye, mucous membranes of nasal passages, ear lobes, and extremities. A second, less common cause of leprosy, *M. lepromatosis*, is found in both the North America and Asia and has a predilection to infecting internal organs, thus implying growth at 37°C/98.6°F.

The origin of leprosy is unknown. One theory proposes that leprosy originated in a single clone in East Africa and then spread to Asia, the Middle East, Europe, and, by way of the slave trade, into West Africa. Recent evidence shows highly diverse strains of *M. leprae* in medieval Europe, suggesting a possible European origin for the disease. By all accounts, the disease is now endemic in a number of regions, mainly in Asia, Africa, South America, and the Pacific. It is especially prevalent in India and Brazil. India alone accounts for >50% of the global leprosy burden of disease. Isolated pockets of disease are found in many parts of the world, and, as a consequence of international travel, affected individuals may be encountered in any location. In the United States, infected patients may be found in any state, but most are in California, Hawaii, Florida, Texas, and Louisiana. Most cases encountered in the United States are seen in immigrants born in endemic regions; however, one-third of all patients in the United States acquire their disease without ever leaving the country.

The primary mechanism of transmission is thought to be via nasal inhalation of aerosolized organisms. *M. leprae* cannot breach intact skin. Armadillos are known to harbor *M. leprae*, and a number of cases have been traced to exposure to these animals in North and South America likely by exposure to the wild animals during hunting, consumption, or processing of armadillo meats. Polymerase chain reaction (PCR) studies indicate that nasal carriage of *M. leprae* can occur in persons without clinical evidence of infection and is transient. Serologic studies suggest that most people in endemic areas have been exposed to the organism, resulting in development of mucosal immunity that prevents progressive infection. However, transmission of the organism is likely to occur during subclinical infection. Very few exposed persons ultimately go on to develop clinical disease. The incubation period ranges from 9 months to 20 years. Risk factors for the development of clinically apparent leprosy include high bacterial load of the index case and close (household) contact with, and genetic relatedness to, the index cases. Genetic studies have identified abnormalities in innate and acquired immunity, increasing our knowledge of the genetic predisposition of some individuals to the disease. A locus within the gene *PARK2/PACRG* located on chromosome 6q25–q27 has been associated with susceptibility to leprosy, but the exact mechanism by which it exerts this influence is unclear. Global risk markers for development of the disease include increased age, poor sanitary and socioeconomic conditions, lower level of education, and food insecurity.

Pathophysiology

Much like tuberculosis, leprosy is a chronic infectious disease that develops as a consequence of both the host's immune reaction to *M. leprae* as well as from direct effects of bacillary spread and multiplication. Schwann cells infected with bacilli have been shown in mouse models to undergo reprogramming and transformation into progenitor/stem-like cells (pSLC). These reprogrammed cells promote bacterial dissemination by differentiation into other cell types, such as muscle, and later become incorporated into other body tissues. Those susceptible to infection demonstrate an impaired cell-mediated immune response to the organism. This is thought to result from a genetic predisposition because cases cluster in families, and there is a high concordance rate in identical twins.

M. leprae has a tropism for nerves that are then damaged as a consequence of immune response to intraneural bacilli as well as physical effects induced by proliferation of bacilli within the nerves. As a result, many of the clinical manifestations are due to peripheral nerve damage with loss of motor and sensory function leading to ulcers, contractures, and loss of tissue substance. Other tissues, such as the skin, may harbor innumerable organisms in some forms of the disease, and deforming cutaneous nodules may develop. Immune response to organisms in skin leads to severe forms of vasculitis with extensive cutaneous necrosis.

M. lepromatosis has been shown to heavily infect internal organs with evidence of AFB in the skin, liver, spleen, lymph nodes, bone marrow, kidneys, adrenal glands, and tracheal mucosa in patients with diffuse lepromatous leprosy. Clinical affliction by this newly discovered species is seen in nerve invasion, vasculitis, and panniculitis leading to skin ulceration and the reversal reactions related to the high AFB burden.

Classification and clinical presentation

There may be a number of different clinical presentations in patients with leprosy, depending on the level of immunity and the duration of the disease. Individuals with the early indeterminate form present with one or more scaly hypopigmented anesthetic macules of the skin appearing initially on the face, although the limbs, trunk, or buttocks may be involved. If untreated, this may progress to any form of the disease. Others present only with sensorimotor neuropathy with enlargement of the peripheral nerves without skin lesions. Nerves affected most commonly include the ulnar and median nerves, the common peroneal nerve, the posterior tibial nerve, and the facial and great auricular nerves. Other areas of the body, such as the nasopharynx, eyes, and testicles, may also be involved.

Classically, patients present with symptoms that can range from one polar form of the disease (tuberculoid) to another (lepromatous) or anywhere in between (borderline tuberculoid, borderline, or borderline lepromatous). Tuberculoid leprosy presents with a small number of asymmetric skin lesions that are hypopigmented, have well-demarcated borders, and are associated with anesthesia. Commonly, cutaneous nerves are enlarged and few bacilli are detectable on biopsy (paucibacillary form). Lepromatous leprosy presents as widely distributed symmetric skin lesions that can manifest as macules, papules, plaques, or nodules, which are red to brown (Figure 140.1). Biopsy shows dense granulomatous infiltrates and many bacilli (multibacillary form). Borderline cases may present anywhere between these two extremes.

The World Health Organization (WHO) schema is the most commonly used classification system and is based on the number of skin lesions and number of bacilli present in smears. Patients with five or fewer skin lesions without evidence of bacilli on skin smears are considered paucibacillary, whereas those with six or more skin lesions with or without bacilli on skin smears are considered to be multibacillary. Classification of patients into multibacillary and paucibacillary groups determines the duration of their treatment. Last, classification of disease can be ordered by level of disability, with grade 1 disability involving impaired peripheral sensation without visible impairments while grade 2 disability encompasses disease that has any visible impairments or physical deformities.

Leprosy in reaction refers to clinical disease produced when there is a change in the host's immune response to *M. leprae*. There are two forms of reactional leprosy. Type 1 reactions are induced by cell-mediated immunity and are referred to as *upgrading* and *downgrading* reactions. Upgrading reactions are characteristically seen in patients with borderline lepromatous disease who undergo a shift toward more tuberculoid (paucibacillary) forms. These may develop after induction of therapy. Downgrading reactions occur with transformation from a tuberculoid to a more lepromatous (multibacillary) form and often develop in the absence of treatment. Both may appear similar clinically and are manifest by erythema and edema of existing skin lesions associated with painful neuropathy and ulceration.

Type 2 reactions are immune complex–mediated and include erythema nodosum leprosum (ENL) and Lucio's phenomenon. Both of these are manifestations of immune complex–mediated vasculitis that lead to prominent inflammation and often ulceration with acute damage to nerves. Patients present with fever, multiple erythematous tender nodules, and varying degrees of neuritis, edema,

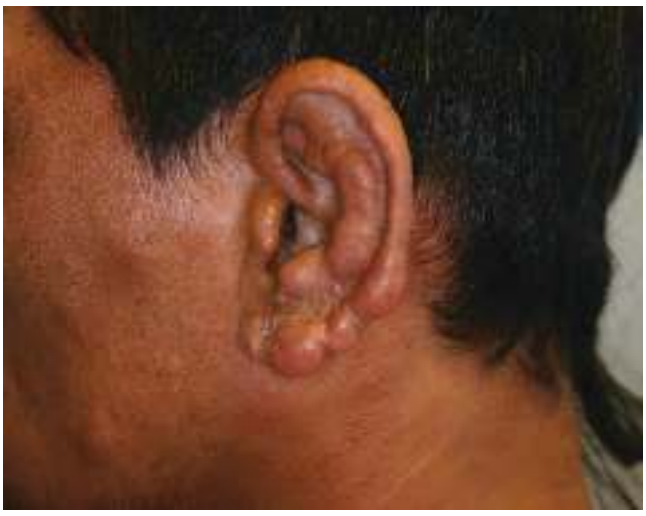

FIGURE 140.1 Lepromatous leprosy on the ear.

arthralgias, leukocytosis, iridocyclitis, pretibial periostitis, orchitis, and nephritis.

Patients infected with HIV do not have an increased incidence of leprosy, and coinfection with *M. leprae* and HIV appears to have minimal effect on the course of either disease.

Diagnosis

The diagnosis is primarily clinical and is based on the presence of one of three cardinal findings: hypopigmented or reddish patches with definitive loss of sensation, thickened peripheral nerves, and demonstration of AFB.

Definitive diagnosis of *M. leprae* is difficult because the organism cannot be cultured in vitro. The gold standard for the diagnosis of leprosy is a skin biopsy specimen obtained from the advancing edge of an active lesion and detection of bacilli in tissue sections using the Fite–Faraco staining method. The slit skin smear has a high specificity but a low sensitivity (10–50% of all leprosy patients are smear negative). Slit skin smears may be useful as an adjunctive procedure to semiquantitate acid-fast organisms in infected skin for monitoring the response of patients during and after treatment.

Serologic tests have been developed to detect IgM antibodies to phenolic glycolipid I (PGL-I), a glycolipid unique to *M. leprae*. Although individuals positive for PGL-I have approximately an eightfold risk for developing clinically apparent leprosy, it is not a useful screening test in the general population because a positive test does not necessarily predict development of the disease. A currently available enzyme-linked immunosorbent assay (ELISA) based on the LID-1 and ND-O antigens (ND-O-LID) is positive for most patients with multibacillary leprosy and has high sensitivity (95.7%) and specificity (93.2%); it has been suggested that it replace the slit skin smear test in cases of multibacillary leprosy.

Another major recent advance in the laboratory diagnosis of leprosy is the development of PCR assays that have reported specificity of 100% and a sensitivity ranging from 34% to 80% in patients with paucibacillary forms of the disease to >90% in patients with multibacillary forms of the disease.

Although the lepromin test is not used to establish diagnosis of leprosy, it can provide an indication of the immune response expected of the patient, especially in tuberculoid forms. It is accomplished by intradermal injection of 0.1 mL standardized suspension of heat-killed mycobacteria and waiting 3 to 4 weeks for a violaceous-erythematous papule to signify a cell-mediated immune response.

Treatment

Treatment depends on whether the individual has paucibacillary or multibacillary disease. Virtually all patients are treated with multidrug therapy with monthly supervision, as first implemented by the WHO in 1981 (Table 140.1); this regimen has been modified several times since then. Dapsone and clofazimine are weakly bactericidal when used alone, although they are mycobactericidal and kill >99% of bacilli when used in combination. Rifampin is highly bactericidal alone. No antileprosy drugs should be prescribed in isolation because of the likelihood of developing resistance. Administration of antibiotics renders the patient noninfectious in a matter of weeks.

TABLE 140.1 **WORLD HEALTH ORGANIZATION-RECOMMENDED DRUG THERAPY**

	Paucibacillary	Multibacillary
Monthly, supervised	600 mg rifampin	600 mg rifampin and 300 mg clofazimine
Daily, unsupervised	100 mg dapsone	100 mg dapsone and 50 mg clofazimine
Duration of therapy	6 mo	12 mo (6 mo)
Follow-up	2 yr	5 yr

Paucibacillary adult (children) patients (fewer than five lesions) receive a supervised dose of rifampin, 600 mg (450 mg) orally once per month for 3 months, and a daily unsupervised dose of dapsone, 100 mg (50 mg) orally for 6 months. At the end of 6 months, therapy is discontinued. Multibacillary patients receive a supervised dose of rifampin, 600 mg orally once monthly; a 300 mg dose of clofazimine; an unsupervised daily dose of dapsone, 100 mg orally; and a 50 mg daily oral dose of clofazimine for 12 months. A recent open label randomized controlled clinical trial featuring 600 patients with multibacillary leprosy showed no significant difference in reaction or disability outcomes after 6 months of treatment versus 12 months. Relapses may occur at a rate of 2.9 to 4.5 per 1,000 people per year but should be treated in the same manner as the initial disease, providing there is no drug resistance.

Where only a single lesion is present, the WHO recommends treatment with a single oral dose combination of rifampin, 600 mg, ofloxacin, 400 mg, and minocycline, 100 mg. The cure rate at 18 months of follow-up in patients receiving a single dose is slightly less than in those who receive 6 months of treatment (47% vs. 55%), and relapse rates appear to be slightly higher in these patients. However, the simplicity of this regimen and the fact that the overwhelming majority of these patients show clinical improvement makes this a feasible treatment option in the appropriate clinical context.

All patients are evaluated for relapse at least monthly. Most programs continue inspections for 5 to 10 years in all patients. Relapse rates vary between 1% and 3% in both paucibacillary and multibacillary patients. Patients should be instructed to recognize the signs and symptoms of recurrent disease as well as adverse reactions to medications. It may take up to 5 years for bacilli to be completely cleared in patients with multibacillary disease. Although many of the neurologic problems may be permanent, skin lesions usually disappear within 1 year of treatment, and reappearance of skin lesions is highly suggestive of relapse.

Major drug side effects are relatively uncommon with present regimens. Clofazimine may cause gastrointestinal symptoms and a purplish skin discoloration, both of which clear with discontinuation

TABLE 140.2 **RECOMMENDED TREATMENT OF REVERSAL REACTIONS**

	Type 1 reaction	Type 2 reaction (erythema nodosum leprosum, Lucio's Phenomenon)
Mild	Symptomatic	NSAIDs, symptomatic
Severe	40–60 mg prednisone	40–60 mg prednisone or 300 mg clofazimine (chronic) or 300–400 mg thalidomide
Duration	Slowly taper as tolerated	Slowly taper prednisone as tolerated Taper clofazimine to 100 mg in 12 months Taper thalidomide as tolerated to 100 mg, discontinue as soon as indicated

All patients should receive prednisone in the presence of neuritis.
Abbreviation: NSAIDs = nonsteroidal anti-inflammatory drugs.

of the drug. Dapsone often causes mild anemia, although severe anemia may result in patients with glucose-6-phosphate dehydrogenase deficiency, so all patients should be tested for this enzyme before initiation of therapy. Other side effects include agranulocytosis, cutaneous eruptions, peripheral neuropathy, gastrointestinal distress, and nephrotic syndrome. Rifampin rarely causes adverse effects but may cause orange discoloration of the urine, stool, and other body fluids. Pregnant women have safely taken dapsone and clofazimine, but experience with rifampin is limited.

Goals for the WHO Global Leprosy Strategy 2016–2020 include strengthening government ownership over healthcare surveillance and disease eradication, protection of vulnerable populations including children and underserved populations through early detection of disease, and ending social discrimination.

Treatment of reversal reactions

Reversal reactions occur in up to 25% of patients, usually during therapy. Early diagnosis and prompt treatment of reversal reactions is of great importance to prevent many of the deforming complications of leprosy (Table 140.2).

Mild reactions can be treated symptomatically; however, severe type 1 reactions with neuritis or silent neuropathy require prompt initiation of systemic glucocorticoid therapy, starting at a minimum dose of 40 to 60 mg of prednisone, tapering once the reaction is controlled. In patients with nerve damage from reactional leprosy that is present for 3 to 6 months, the response to therapy is <67%. When present for >6 months, the response to therapy is even poorer.

Mild to moderate type 2 reactions can be treated with nonsteroidal anti-inflammatory drugs and other symptomatic modalities. Severe ENL or the presence of neuritis requires prednisone (as prescribed in type 1 reactions). Clofazimine is useful for chronic reactions, and its use has been credited with the overall decrease of ENL in leprosy. Thalidomide, 300 to 400 mg orally, will suppress ENL within 48 hours and is considered the drug of choice for young men with severe ENL. Its high teratogenic potential has prevented its widespread use. Lucio's phenomenon is treated with systemic corticosteroids in addition to standardized antibacterial treatment, which should be continued during all reversal reactions. Azathioprine, methotrexate, and cyclosporine have been used to treat type 2 reactions; results have been mixed.

Suggested reading

Britton WJ, Lockwood DN. Leprosy. *Lancet*. 2004;363:1209–1219.

Fischer M. Leprosy: An overview of clinical features, diagnosis, and treatment. *J Dtsch Dermatol Ges*. 2017;15(8):801–827.

Han XY, Seo YH, Sizer KC, et al. A new Mycobacterium species causing diffuse lepromatous leprosy. *Am J Clin Pathol*. 2008;130(6):856–864.

Masaki T, Qu J, Cholewa-Waclaw J, et al. Reprogramming adult Schwann cells to stem cell-like cells by leprosy bacilli promotes dissemination of infection. *Cell*. 2013;152:51–67.

Moschella SL. An update on the diagnosis and treatment of leprosy. *J Am Acad Dermatol*. 2004;51:417–426.

Penna GO, Buhrer-Sekula S, Kerr LRS, et al. Uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): Results of an open label, randomized and controlled clinical trial, among multibacillary patients. *PLoS Negl Trop Dis*. 2017;11(7):e0005725.

Pescarini JM, Strina A, Nery JS, et al. Socioeconomic risk markers of leprosy in high-burden countries: A systematic review and meta-analysis. *PLoS Negl Trop Dis*. 2018;12(7):e0006622.

Schuenemann VJ, Avanzi C, Krause-Kyora B, et al. Ancient genomes reveal a high diversity of Mycobacterium leprae in medieval Europe. *PLoS Pathog*. 2018;14(5):e1006997.

WHO. *Global leprosy strategy 2016–2020: Accelerating towards a leprosy-free world*. Geneva: World Health Organization; 2016.

WHO Study Group. *Chemotherapy of Leprosy*. Geneva: World Health Organization; 1994.

141

Meningococcus and miscellaneous neisseriae

Chuen-Yen Lau and Edmund C. Tramont

Meningococcal infection, first recognized more than two centuries ago as epidemic cerebrospinal fever, occurs worldwide as endemic sporadic cases with the potential to spread and expand into an epidemic. Humans are the only natural host for the bacteria. Transmission of the organism occurs from person to person by direct contact with colonized respiratory secretions or airborne droplets with subsequent colonization of the nasopharynx as part of its microbiome. Nasopharyngeal carriage approximates 5% to 15% in non-epidemic periods but may approach 50% to 95% during epidemics. The carriage rate is increased when there is crowding or close personal contact, such as in military barracks, dormitories, prisons, convocations, and indoor sporting events. Spontaneous loss and acquisition of oropharyngeal and nasopharyngeal carriage typically occurs over weeks to months, though colonization may be persistent in some persons. Sexual or oral-genital transmission of meningococci may result in anogenital carriage.

Meningococcal disease (e.g., bacteremia, meningitis) rates are highest in children <1 year of age, followed by a second peak in adolescence associated primarily with exposure to persons from different locations, as is common in college dormitories (Figure 141.1). The highest case fatality rates are associated with serogroup W (21%) and serogroup C (14%), and the highest mortality occurs in patients >85 years of age (~28%). With rare exceptions, invasive meningococci have a polysaccharide capsule that forms the basis for serogrouping of strains, and, except for serogroup B, is the principal bacterial antigen to which protective immunity develops (see later discussion). Invasive disease occurs almost exclusively in persons who lack specific bactericidal anti-meningococcal antibody. However, there are four situations where antibodies may not be protective: (1) individuals with complement component or properdin deficiencies are at an increased risk for developing invasive meningococcal infections because their serum lacks the capacity for complement-antibody–mediated lysis (bactericidal activity) of the meningococcal organism; hence, complement deficiency, most often of the terminal components, or properdin deficiency should be considered in persons with recurrent episodes of invasive meningococcal infection; (2) asplenic individuals are also at increased risk for suffering invasive meningococcal disease because of decreased efficiency of clearing of the encapsulated invading microorganisms from the blood; (3) on rare occasions, persons may develop serum immunoglobulin A (IgA) antibodies that block the bactericidal action of immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies; or (4) in persons who possess genetic upper airway surfactant protein mutations that result in an impaired local first-line innate immune defense. All of these individuals should be periodically vaccinated to maintain as high a titer of anti-meningococcal antibodies as possible.

Clinical features

As with most other invasive gram-negative bacteria, the clinical consequences of meningococcal infection are primarily the result of meningococcal endotoxin (lipopolysaccharide) release and subsequent activation of the procoagulation, anticoagulation, fibrinolysis, complement, and kallikrein–kinin cascades resulting in the excessive release of various inflammatory mediators ("cytokine storm"). The clinical manifestations of meningococcal infection range from a clinically mild transient bacteremia to fulminant meningococcemia,

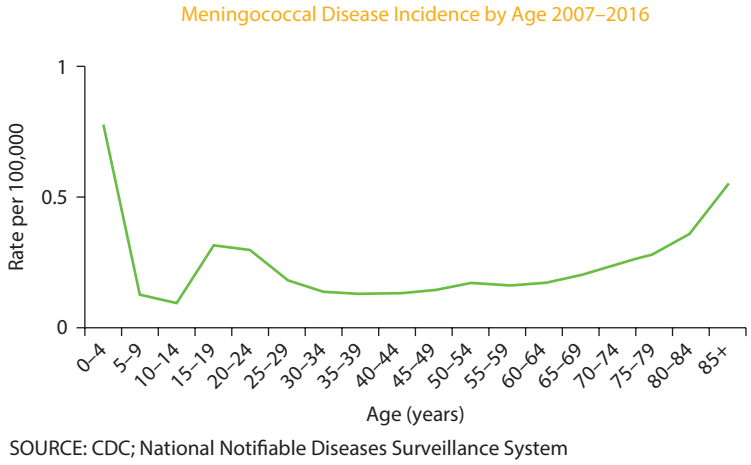

FIGURE 141.1 Rates of meningococcal disease by age group.

also referred to as *Waterhouse–Friderichsen syndrome* or *purpura fulminans* (Figure 141.2), with or without concurrent bacterial meningitis. Unless treated within hours of presentation, the mortality rate of the latter is high.

Most often, *Neisseria meningitidis* acquisition results in asymptomatic colonization of the nasopharynx and oropharynx as part of their respective microbiomes. The mildest form of invasive disease, a transient bacteremia, begins insidiously with fever, malaise, and symptoms of an upper respiratory tract infection. A few petechial skin lesions may appear, but neither signs nor symptoms of sepsis or meningitis develop. Signs and symptoms usually resolve spontaneously within 24 to 48 hours. However, the transient bacteremia may progress to acute meningococcemia heralded by fever, chills, malaise, weakness, headache, myalgias, nausea, and/or vomiting when the victim lacks functional bactericidal antibody for whatever reason.

Skin manifestations, especially a petechial rash (Figure 141.3), raise the index of suspicion for invasive meningococcal infection. The rash commonly appears in crops on the ankles, wrists, axilla, arms, legs, trunk, and mucous membranes, whereas the palms, soles, neck, and face are usually spared. The rash may also be urticarial, maculopapular, ecchymotic, or gangrenous depending on the degree of vascular pathology. In severe invasive meningococcal disease, the rash rarely fails to develop. Fulminant meningococcemia complicates acute meningococcemia in 5% to 15% of cases and is usually associated with the rash progressing into massive skin and mucosal hemorrhage, disseminated intravascular coagulopathy (DIC), and vascular collapse (Waterhouse–Friderichsen syndrome). Adrenal hemorrhage may occur despite appropriate antibiotic therapy.

Meningitis usually occurs along with the manifestations of meningococcemia but not always. Clinically, meningococcal meningitis resembles acute meningitis of any cause, presenting with fever, headache, altered sensorium/cognition, and nuchal rigidity. Painful myalgias may be a discriminating feature. *N. meningitidis* is now the most common cause of meningitis among children >6 months of age and young adults.

On rare occasions, a chronic meningococcemia develops. This is characterized by intermittent febrile episodes, lasting 2 to 10 or more days, accompanied by a variety of skin lesions (macular, maculopapular, petechial, ecchymotic, or pustular), arthralgias or arthritis, myalgias, and splenomegaly. This manifestation may last for months and is sometimes fatal, but it usually resolves spontaneously. Occasionally, *N. meningitidis* may cause oropharyngitis,

FIGURE 141.2 Purpura fulminans (Waterhouse–Friderichsen syndrome or severe ecchymotic rash).

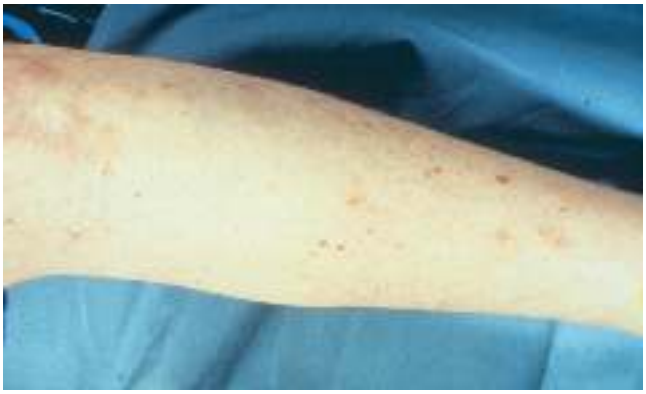

FIGURE 141.3 Petechial rash lower extremity.

sinusitis, pneumonia, conjunctivitis, endophthalmitis, proctitis, urethritis, cervicitis, immune-mediated arthritis, endocarditis, myocarditis, pericarditis, or pelvic inflammatory disease (PID). As may develop with other infections, general nonspecific helpful laboratory abnormalities include an elevated white blood cell count, C-reactive protein, and/or procalcitonin levels.

Culture and laboratory findings

N. meningitidis is an aerobic, oxidase-positive, gram-negative diplococcus (coffee bean shape) that grows best at 35°C/95°F to 37°C/98.6°F in a moist environment of 5% to 7% carbon dioxide (candle jar). The gold standard for diagnosis of systemic meningococcal infection is the isolation of *N. meningitidis* by culture from a usually sterile body fluid such as blood and/or cerebrospinal fluid (CSF) (most common), or synovial, pleural, or pericardial fluid. For culture of a normally sterile site, nonselective culture media are standard but a selective antibiotic-containing culture medium, such as Thayer–Martin, Martin–Lewis, or New York City culture medium, is necessary to reduce the overgrowth of commensals when the culture specimen is obtained from a nonsterile site such as the oropharynx, urethra, vagina, or rectum.

In meningococcal meningitis, the frequency of positive blood cultures is 50% to 60%, and the frequency of positive CSF cultures is 80% to 90%. Isolation of the organism by culture not only confirms the etiology but also allows antibiotic susceptibility testing, which has become important in light of increased antibiotic resistance, especially to the penicillins. Gram stain and culture of a skin lesion can increase the diagnostic yield, although a negative result does not exclude *N. meningitidis*. A number of rapid point-of-care diagnostic tests (RDTs) are also available, ranging from PCR to simple dipstick and agglutination tests.

Chemistry and cytologic findings suggestive of bacterial meningitis include a CSF glucose concentration of <45 mg/dL (2.5 mmol/L), a protein concentration >500 mg/dL, and a white cell count >1,000/μL. The CSF is generally cloudy with a leukocytosis consisting predominantly of polymorphonuclear neutrophils associated with hypoglycorrhachia. However, one or more of the classic findings is often absent in meningococcal meningitis. The Gram stain of the CSF is positive in about 75% of cases (Figure 141.4). Although non-specific, elevated serum white blood cell count, C-reactive protein, and procalcitonin level may inform management.

N. meningitidis is serogrouped based on the distinct chemical composition of its polysaccharide capsule. The meningococcus has been classified as serogroups A, B, C, D, 29E, H, I, J, K, L, W (W-135), X, Y, Z, and nontypeable (indicates organism is nonencapsulated). Serogroups A, B, C, W, and Y are responsible for the vast majority of cases of invasive disease. With rare exceptions, invasive meningococci are encapsulated, attesting to the virulence conveyed by the polysaccharide capsule. In contrast, meningococci colonizing mucous membranes are usually not encapsulated.

Commercial latex agglutination kits, which can also be used on body fluids such as CSF and urine, utilize latex beads coated with antibodies to meningococcal capsular antigens to detect five capsular types: A, B, C, Y, and W, but the sensitivity for serogroup B is relatively low.

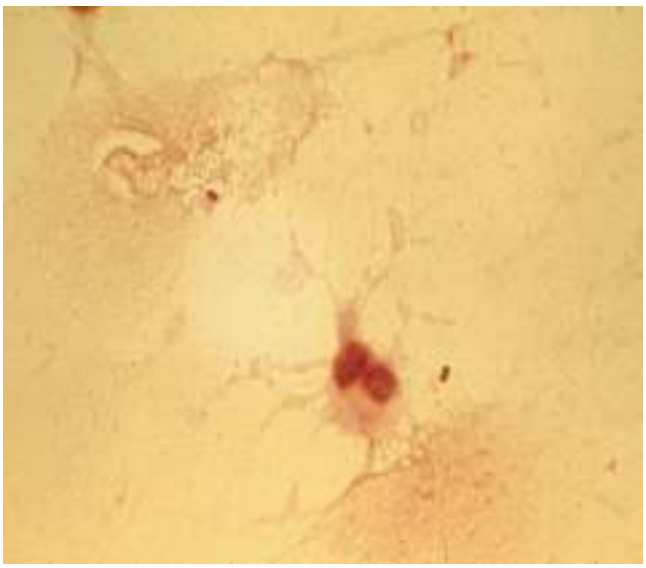

FIGURE 141.4 Gram stain of cerebrospinal fluid (CSF): note gram-negative diplococci and polymorphonuclear leukocyte.

A number of RDTs are available, ranging from PCR to simple dipstick and agglutination tests. Advantages of these tests over culture are rapidity, reliability in the setting of concomitant antibiotics, and, in the case of PCR, simultaneous testing for infection due to *N. meningitidis, Streptococcus pneumoniae, Haemophilus influenzae*, *Escherichia coli, Listeria monocytogenes, Streptococcus agalactiae*, cytomegalovirus (CMV), Enterovirus, herpes simplex (HSV-1, HSV-2), human herpesvirus (HHV-6), human parechovirus, varicella-zoster virus (VZV), or *Cryptococcus neoformans/gatii* (Biofire ME, Utah).

Therapy

Ceftriaxone is the drug of choice for meningococcal disease. Because of the potential for rapid progression, ceftriaxone therapy should be administered within 30 minutes of considering the diagnosis of meningococcal meningitis and is administered intravenously (IV), at least initially. Infected persons should receive 2 g IV every 12 hours for at least 7 days. Those who are β-lactam-allergic should receive chloramphenicol. Chloramphenicol- and ceftriaxone-resistant isolates have been encountered but are rare. Although use of penicillin G has been limited since reports of resistance in the late 1980s, meningococcal meningitis is very responsive with penicillin G once the isolate is proved to be penicillin susceptible (minimum inhibitory concentration [MIC] <0.1μg/mL). Seven days of therapy is usually sufficient but may be lengthened based on clinical judgment regarding the severity of illness, patient response, or if testing demonstrates reduced sensitivity to the selected regimen (Table 141.1).

Since exact etiology is typically unknown upon presentation, initial treatment must cover potential causes of meningitis beyond *N. meningitidis*. Empiric antimicrobial therapy is usually given for cases

TABLE 141.1 **TREATMENT OF MENINGOCOCCAL MENINGITIS**

Antibiotic	Scenario	Dosing	Comment[a]
Ceftriaxone	Preferred treatment	Adults: 2 g IV q12h Children: 100 mg/kg IV (up to 4 g) in 1–2 doses per day	Good CNS penetration
Chloramphenicol	ß-lactam allergy, preferred alternative	Adults: 12.5 mg/kg IV (up to 6 g/d) q6h Children: 75–100 mg/kg IV (up to 2–4 g/d) in 1–2 doses per day	Concentrates in CSF; potential to cause irreversible aplastic anemia; rare resistance
Meropenem[b]	Alternative	Adults: 2 g IV q8h	Limited data for use in children
Moxifloxacin[b,c]	Alternative	Adults and adolescents with skeletal maturity: 400 mg q24h	Resistant isolates have been encountered
Penicillin G	Penicillin MIC <0.1 μg/mL	Adults: 300 000 U/kg/d IV divided q4h Children: 250 000–300 000 U/kg/d IV divided q4h	Limit 24 million U/d; penicillin resistance has been reported since 1988

[a] Treatment is 7 days, but may be extended based on clinical scenario or if the organism is not fully sensitive to the selected regimen.
[b] Option for ceftriaxone-, penicillin-, and other β-lactam-allergic patients.
[c] Other quinolones have been successful.
Abbreviations: MIC = minimal inhibitory concentration; CNS = central nervous system; CSF = cerebrospinal fluid.

of presumed bacterial meningitis based on age and immune status. For immunocompetent infants <1 month of age, empiric treatment is chosen to cover group B streptococcus, *Escherichia coli* and *Listeria*. For immunocompetent patients between 1 month and 2 years of age, *Streptococcus pneumoniae, N. meningitidis, Streptococcus agalactiae, Haemophilus influenzae*, and *Escherichia coli* should be considered. From 2 to 50 years of age, *N. meningitidis* and *S. pneumoniae* are the predominant organisms. For patients older than 50 years, *S. pneumoniae*, *N. meningitidis*, *Listeria,* and aerobic gram-negative bacilli are covered. Of note, infections with *S. pneumoniae, N. meningitidis,* and *H. influenza* have significantly decreased with increased vaccine coverage.

Without a specific etiologic diagnosis, immunocompetent persons between 1 month and 50 years of age should receive initial empiric antimicrobial therapy with a broad-spectrum cephalosporin antibiotic, especially ceftriaxone or cefotaxime, plus vancomycin. Meropenem may be substituted for the cephalosporin if neither cefotaxime nor ceftriaxone can be administered. Dexamethasone may be added when neurologic deficits and sequelae of inflammation are of concern. Although dexamethasone has not been shown in prospective studies to be of benefit in meningococcal meningitis, it is often added during empiric therapy to reduce central nervous system inflammation, which is of particular concern with *S. pneumoniae*.

Supportive care is extremely important in all cases of meningitis. Potential complications such as purpura fulminans, DIC, acute respiratory distress syndrome (ARDS), neurocognitive sequelae, myocardial involvement, volume depletion, acidosis, and adrenal insufficiency should be anticipated. The mortality rate remains approximately 10% to 15%.

Long-term sequelae include hearing loss, other cranial palsies, and cognitive dysfunction. Treatment of myocardial failure can help to ameliorate pulmonary edema and poor peripheral perfusion. Adjunctive steroid therapy is indicated when acute adrenal insufficiency is a possibility, especially when the patient has progressed into the Waterhouse–Friderichsen syndrome or is obtunded. The primary treatment of DIC is aimed at the underlying cause, in this case *N. meningitidis*. Protein C concentrate has been investigated as a potential strategy to treat coagulopathy and purpura fulminans.

Prevention

Methods of prevention for meningococcal infection include respiratory droplet precautions, disease surveillance, antimicrobial chemoprophylaxis after identification of an index case, and vaccination prior to possible exposure and during outbreaks. Routine immunization is now recommended for young adults in addition to specific high-risk groups (see "Vaccine immunoprophylaxis"). Most often, *N. meningitidis* is harbored in the nasopharynx and/or oropharynx as a commensal in asymptomatic carriers. The organism is spread through direct contact, especially respiratory droplets. The risk of contracting a symptomatic *N. meningitidis* infection is approximately 4 cases per 1,000 among persons who have had "close contact" with a known carrier or patient with a virulent strain (defined as causing invasive disease). Close contacts are defined as persons living in the same household, dormitory, or barrack; attending a daycare center; handling clinical specimens or cultures; or anyone who has spent >4 hours with the index case from 10 days prior to the onset of illness through 24 hours after initiation of appropriate antibiotic therapy. This is to cover the 1- to 10-day incubation period for groups such as airline passengers, cruise shipmates, nursing home residents, and healthcare workers (Box 141.1).

Antimicrobial chemoprophylaxis

The risk of developing secondary invasive disease after exposure to a close contact is greatly diminished by chemoprophylaxis: administering prophylactic antibiotics to individuals who have had

BOX 141.1

Considered close contact of an index case

All household members
Daycare and preschool classmates, attendees, and workers
Healthcare workers with contact with oral and/or respiratory secretions from the index case
Workers and classmates in boarding schools or camps
Living in a common military barrack
Sharing an aircraft or boat cabin, especially if sitting next to the index case
Cruise shipmates with >4 hours contact with the index case
Laboratory workers handling culture from an index case

close contact to an index case (e.g., dormitory, barracks, living in the same house, prison, etc.). Antibiotics should be administered as early as possible, ideally within 24 hours of identification of the index case. Chemoprophylaxis >14 days after exposure is not necessary unless re-exposure occurs. Since pharyngeal cultures of the exposed individual are not helpful for determining the need for prophylaxis, obtaining cultures should not delay administration of prophylactic antibiotics.

Ceftriaxone, rifampin, and ciprofloxacin are used for chemoprophylaxis. Azithromycin may be used as an alternative. However, ciprofloxacin-resistant meningococcus has been reported. Furthermore, ciprofloxacin is not recommended for people <18 years or age or pregnant or lactating women due to risk of cartilage damage. Also rifampin is not recommended during pregnancy, and drug interactions must be considered (Table 141.2).

Vaccine immunoprophylaxis

Several meningococcal vaccines are now available. Menactra (MenACWY-DT) is a quadrivalent meningococcal polysaccharide vaccine conjugated to diphtheria toxoid. Another quadrivalent meningococcal polysaccharide vaccine conjugated to a mutant diphtheria toxin, Menveo (MenACWY-CRM), is also available. Nimenrix (MenACWY-TT), a quadrivalent meningococcal polysaccharide conjugated to a tetanus toxoid carrier, is available outside the United States. Two meningococcal serogroup B vaccines are now available in the United States; Trumemba (MenBFHbp) and Bexsero (MenB4C), respectively, for individuals 10 through 25 years of age. The major challenge in the development of the meningococcal serogroup B polysaccharide vaccine has been that the serogroup B polysaccharide is a poor immunogen because it is similar to human intracellular adhesion molecules. Hence, the sero-group B vaccines are based on non-capsular antigens, principally outer membrane proteins.

Meningococcal serogroup C vaccines Meningitec and NeisVacC are used in Canada, the United Kingdom, and other countries. Serogroup A vaccines MenAfriVac and PsA-TT are used in Africa. The MenHibrix/HibMenCY combination conjugate vaccine against meningococcus serogroups C and Y and *H. influenzae* type b was discontinued in 2017. The quadrivalent meningococcal polysaccharide vaccine Menomune was also discontinued in 2017.

In the United States, meningococcal vaccination against serogroups A, C, W, and Y is appropriate for persons 11 to 18 years old and 19 to 21 if starting college and living in a dormitory. Serogroup B vaccination should also be given to patients in these age groups, Vaccination against serogroups A, C, W, and Y is also indicated for patients with HIV and people traveling to or residing in endemic countries (Nepal, India [New Delhi], Mecca, and the "meningitis belt" of sub-Saharan Africa, which stretches from Senegal in the west to Ethiopia in the east). Those with prolonged increased exposure risk such as military recruits should be vaccinated against serogroups A, C, W, and Y as well as serogroup B. For patients with persistent complement component deficiencies, functional or anatomic asplenia, and individuals present during outbreaks, the following guidelines apply: children <10 should be vaccinated against serogroups A, C, W, and Y; those >10 years should be vaccinated against serogroups A, C, W, and Y as well as serogroup B. Specific schedules depend on age, host factors, geography, social circumstances, and prior history of vaccination. Select detailed recommendations are presented (Table 141.3).

TABLE 141.2 **ANTIBIOTICS USED FOR CHEMOPROPHYLAXIS OF *NEISSERIA MENINGITIDIS***

Antibiotic (route)	Age group	Dose	Duration	Comments
Ceftriaxone (IM)	Children <15 years	125 mg	Once	A regimen of choice
	Older children and adults	250 mg		
Rifampin (oral)	Children <1 month	5 mg/kg q12h	2 days	A regimen of choice
	Children ≥1 month	10 mg/kg q12h		Not recommended for pregnant women
				May reduce reliability of oral contraceptives
	Adults	600 mg q12h		Causes reddish-orange discoloration of bodily fluids
Ciprofloxacin (oral)	Adults	500 mg	Once	Not recommended for persons <18 years or pregnant/lactating women
				Can be used in children if no alternative available
Azithromycin (oral)	Children <15 years	10 mg/kg 500 mg	Once	Not routinely recommended
	Children >15 years			May be used in areas with ciprofloxacin resistance

TABLE 141.3 **VACCINATION RECOMMENDATIONS IN THE UNITED STATES FOR SELECT RISK GROUPS**

Risk group	Vaccine	Series/regimen
11–18 yo	• Menactra or Menveo (Quadrivalent ACWY vaccines) • Consider Trumemba or Bexsero (Serogroup B vaccines)	1 dose at age 11–12, booster at age 16. If 1st dose at age 13–15, booster at 16–18 years. Prefer administration from 16–18 years, but can be given up to 23 years.
19–21 yo and 1st year college in dormitory	• Menactra or Menveo (Quadrivalent ACWY vaccines) • Consider Trumemba or Bexsero (Serogroup B vaccines)	1 dose if has not yet received. Booster if prior dose given before age 16 Prefer administration from 16–18 years, but can be given up to 23 years.
HIV <2 years	• Menactra or Menveo (Quadrivalent ACWY vaccines)	4 doses of Menveo at 2, 4, 6, and 12 to 15 months 2 doses of Menactra at 9 to 23 months, 12 weeks apart Boost 3 years after primary series and then q5yrs
HIV >2 years	• Menactra or Menveo (Quadrivalent ACWY vaccines)	2 doses, 8–12 weeks apart If most recent dose before age 7, boost q3ys and then q5yrs. If ≥7, boost q5yrs
Prolonged exposure risk	• Menactra or Menveo (Quadrivalent ACWY vaccines) • Trumemba or Bexsero (Serogroup B vaccines)	1 dose, boost q5yrs 3 doses of Trumenba at 0, 1 to 2, and 6 months or 2 doses of Bexsero at least 1 month apart

Additional recommendations are available from the Advisory Committee on Immunization Practices (ACIP) for people visiting or residing in endemic regions, present during an outbreak, with persistent complement component deficiency, and functional or anatomic asplenia, including sickle cell disease.

As with the other polysaccharide-based vaccines, *H. influenzae* and *S. pneumoniae*, there is concern that vaccination could lead to an increased incidence of non-vaccine serotypes. Replacement by other serogroups has not yet materialized in the case of meningococcus.

Eculizumab

Treatment with eculizumab, a monoclonal antibody inhibitor of terminal complement used for complement-mediated hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria, is associated with a 1,000- to 2,000-fold increased risk of meningococcal disease. Patients receiving eculizumab are candidates for both vaccination and chemoprophylaxis. They should undergo vaccination against serogroups A, C, W, and Y as well as serogroup B at least 2 weeks prior to starting eculizumab if possible. Daily chemoprophylaxis with penicillin may be used during eculizumab treatment. Penicillin-allergic patients may alternatively use azithromycin.

Infections with non-pathogenic *Neisseria* species

The nonpathogenic *Neisseria* species (*N. bacilliformis, N. lactamica, N. sicca, N. flava, N. subflava, N. mucosa, N. flavescens, N. cinerea, N. macacae, N. elongata*, and *N. polysaccharea*) are usually commensals of the oropharynx and nasopharynx. Infections caused by these organisms are extremely rare, occurring primarily in immunosuppressed hosts, especially those who are hypogammaglobulinemic or have defective antibody production (i.e., chronic lymphocytic leukemia). The relative lack of virulence of these organisms is attributed to the absence of encapsulation, and hence they have no predilection to resist bacterial lysis by nonspecific components of the blood or to invade the meninges. Thus they are easily controlled by normal innate host defense mechanisms.

Because these organisms are normally part of the microbiome, local extension occurs most often as part of a mixed infection, most commonly to the ear, sinuses, and lung. Conjunctivitis, meningitis, endophthalmitis, endocarditis, and urethritis have also been reported, attesting to the common tissue tropism that these sites share with the nasopharynx. These nonpathogenic *Neisseria* are easily treated with penicillin, cephalosporins, or quinolone antibiotics.

Suggested reading

Cohn AC, MacNeil JR, Clark TA, et al.; Centers for Disease Control and Prevention (CDC). Prevention and control of meningococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62(RR-2):1–28.

Dray BM, Claus H, Hubert K, et al. Asymptomatic carriage of *Neisseria meningitis, Haemophilus influenzae, Streptococcus pneumonia,* Group A *Streptococcus and Staphylococcus aureus* among adults aged 65 years and older. *PLoS ONE*. 14:2e0212052.

Frasch CE. Vaccines for prevention of meningococcal disease. *Clin Microbiol Rev*. 1989;2(Suppl):S134–S138.

Gardner P. Prevention of meningococcal disease. *N Engl J Med*. 2006;355:1466–1473.

Gilbert D, Mollering R, Eliopoulos G, Chambers H, Saag M. *The Sanford guide to antimicrobial therapy 2018*. Sperryville, VA: Antimicrobial Therapy, Inc.; 2018.

Gossger N, Snape ND, Yu LM, et al.; European MenB Vaccine Study Group. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with and without routine infant vaccinations according to different immunization schedules: A randomized controlled study. *JAMA*. 2012;307:573–582.

Harrison LH, Pass MA, Mendelsohn AB, et al. Invasive meningococcal disease in adolescents and young adults. *JAMA*. 2001;286:694–699.

Linder KA, Malani PN. Meningococcal meningitis. *JAMA*. 2019;321:1014–2020.

Mbaeyi SA, Blain A, Whaley MJ, et al. Epidemiology of meningococcal disease outbreaks in the United States, 2009–2013. *Clin Infect Dis*. 2019 Feb 1;68(4):580–585. doi:10.1093/cid/ciy548. PMID: 29982382. Available at: https://pubmed.ncbi.nlm.nih.gov/29982382/

Sjöholm AG, Jönsson G, Braconier JH, Sturfelt G, Truedsson L. Complement deficiency and disease: An update. *Mol Immunol*. 2006;43(1–2):78–85.

Watson PS, Novy P. Bekkat-Berkarii R, Stubbe F, Banahoff A. Optimizing the timing of 4CmenB vaccination in adolescents and young adults based on immune persistence and booster response data. *Expert Rev Vaccines*. 2019;18:343–352.

Zissis CC, Sever-Chroneos Z, Shepherd VL. Pulmonary surfactant: An immunological perspective. *Cell Physiol Biochem*. 2009;25:13–26.

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Listeria

Bennett Lorber

Introduction

Listeria monocytogenes is an infrequent cause of illness in the general population, but, in certain groups, including neonates, pregnant women, elderly persons, and those with impaired cell-mediated immunity, whether due to underlying disease or immunosuppressive therapy, it is an important cause of life-threatening bacteremia and meningoencephalitis. Increasing interest in this organism has arisen from concerns about food safety following lethal foodborne epidemics.

Microbiology

Listeria monocytogenes is a small, facultatively anaerobic, nonsporulating, catalase-positive, oxidase-negative, gram-positive rod that grows readily on blood agar, producing incomplete β-hemolysis. It possesses polar flagellae and exhibits a characteristic tumbling motility at room temperature (25°C). Optimal growth occurs at 30°C to 37°C, but, unlike most bacteria, *L. monocytogenes* also grows well at refrigerator temperature (4°C to 10°C), and, by so-called cold enrichment, it can be separated from other contaminating bacteria by long incubation in this temperature range. Selective media are available to isolate the organism from specimens containing multiple species (food, stool) and are superior to cold enrichment.

In clinical specimens, the organisms may be gram variable and may look like diphtheroids, cocci, or diplococci. Routine growth media are effective for growing *L. monocytogenes* from normally sterile specimens (cerebrospinal fluid [CSF], blood, joint fluid), but media typically used to isolate diarrhea-causing bacteria from stool cultures inhibit listerial growth. Laboratory misidentification as diphtheroids, streptococci, or enterococci occurs all too often, and the isolation of a "diphtheroid" from blood or CSF should always alert one to the possibility that the organism is really *L. monocytogenes*.

Seven listerial species are recognized (*Listeria monocytogenes*, *Listeria seeligeri*, *Listeria welshimeri*, *Listeria innocua*, *Listeria ivanovii*, *Listeria grayi*, and *Listeria marthii*), but *L. monocytogenes* is almost exlusively responsible for human infection. There are at least 13 serotypes of *L. monocytogenes*, based on cellular O and flagellar H antigens, but almost all disease is due to types 4b, 1/2a, and 1/2b, limiting the utility of serotyping for epidemiologic investigations. A number of newer molecular techniques, including pulsed-field gel electrophoresis, ribotyping, and multilocus enzyme electrophoresis, have been employed to separate isolates into distinct groups and have proved useful for investigating epidemics.

Epidemiology

Listeria monocytogenes is an important cause of zoonoses, especially in herd animals. It is widespread in nature, being found commonly in soil and decaying vegetation and as part of the fecal flora of many mammals. The organism has been isolated from the stool of approximately 5% of healthy adults with higher rates of recovery reported from household contacts of patients with clinical infection. Many foods are contaminated with *L. monocytogenes*, and recovery rates of 15% to 70% or more are common from raw vegetables, raw milk, fish, poultry, and meats, including fresh or processed chicken and beef available at supermarkets or deli counters. Ingestion of *L. monocytogenes* must be a very common occurrence.

Listeriosis was made a nationally reportable disease in 2000 in the United States. Two active surveillance studies performed by the Centers for Disease Control and Prevention (CDC) in the 1980s indicated annual infection rates of 7.4 per million population, accounting for approximately 1850 cases per year in the United States, with 425 deaths. By 1993, following food industry regulations instituted to minimize the risk of foodborne listeriosis, the annual incidence had declined to 4.4 cases per million. From 1996 through 2003 the crude incidence decreased 26%; estimated cases in the United States were 2228 and 1803 in 1996 and 2003, respectively, and deaths were 462 and 378.

The highest infection rates are seen in infants ≤1 month and in adults >60 years of age. Pregnant women account for about 30% of all cases and 60% of cases in the 10- to 40-year age group. Almost 70% of nonperinatal infections occur in those with hematologic malignancy, acquired immunodeficiency syndrome (AIDS), bone marrow or solid organ transplants, or in those receiving corticosteroid therapy, but seemingly healthy persons may develop invasive disease, particularly those older than 60 years.

Nonperinatal listeriosis is almost always the result of foodborne infection. Listeriosis is a relatively rare foodborne illness (~1% of US cases) but is associated with a case-fatality rate of 16% to 20% (second only to *Vibrio vulnificus* at 35% to 39%) and causes approximately 19% to 28% of all foodborne disease-related deaths. Mortality risk factors include nonhematologic cancers, steroid medication, and renal disease.

Numerous foodborne outbreaks resulting in invasive disease (e.g., bacteremia, meningitis) have been documented, with vehicles including milk, soft cheeses, butter, smoked fish, ready-to-eat pork products, hot dogs, deli-ready turkey, sprouts, taco or nacho salads, and cantaloupes. A 2002 outbreak due to contaminated turkey deli meat resulted in the recall of more than 30 million pounds of food products, one of the largest meat recalls in US history. In 2011, *L. monocytogenes*-contaminated cantaloupes were responsible for the deadliest foodborne outbreak in US history, with 28 states reporting illness in 146 persons and death in 30 (21% mortality). The importance of food as a source of sporadic listeriosis was illuminated by two CDC studies in which 11% of all refrigerator food samples were contaminated, 64% of patients had at least one contaminated food, and, in 33% of instances, the patient and food isolates had identical strains. Delicatessen-style ready-to-eat meats, especially chicken, had the highest rates of contamination. Cases were more likely than were controls to have eaten soft cheeses or deli-counter meats, and 32% of sporadic cases could be attributed to these foods.

Human listeriosis is typically acquired through ingestion of contaminated food, but other modes of transmission occur. These include transmission from mother to child transplacentally or through an infected birth canal and cross-infection in neonatal nurseries. Contaminated mineral oil used for bathing infants was the source of one outbreak. Localized cutaneous infections have occurred in veterinarians and farmers after direct contact with aborted calves.

The CDC has established PulseNet (http://www.cdc.gov/pulsenet/), a network of public health and food regulatory laboratories that use pulsed-field gel electrophoresis to subtype food-borne pathogens to detect promptly disease clusters that may have a common source. This system has proved effective in the early detection of listeriosis outbreaks.

Pathogenesis

Except for vertical transmission from mother to fetus and rare instances of cross-contamination in the delivery suite or neonatal nursery, human-to-human infection has not been documented.

Infection most often begins after ingestion of contaminated food. The oral inoculum required to produce clinical infection is unknown; experiments in healthy mammals indicate that $\geq 10^9$ organisms are required. Alkalinization of the stomach by antacids, H_2 blockers, proton pump inhibitors, or ulcer surgery may promote infection. The incubation period for invasive infection is not well established, but evidence from a few cases related to specific ingestions points to a mean incubation period of ~30 days, with a range from 11 to 70 days. In one report, two pregnant women, whose only common exposure was attendance at a party, developed listerial bacteremia with the same uncommon enzyme type; incubation periods for illness were 19 and 23 days.

Listeria monocytogenes can cause disease without promoter organisms, but, on occasion, intercurrent gastrointestinal infection with another pathogen may enhance invasion in individuals colonized with *L. monocytogenes*. Evidence for this is found in the common history of antecedent gastrointestinal symptoms in patients and household contacts, the long incubation period from ingestion to clinical illness, and two instances in which clinical listeriosis closely followed shigellosis. Both listerial meningitis and bacteremia have occurred shortly after colonoscopy, sigmoidoscopy, and upper endoscopy.

In the intestine, *L. monocytogenes* crosses the mucosal barrier aided by active endocytosis of organisms by endothelial cells. Once in the bloodstream, hematogenous dissemination may occur to any site; *L. monocytogenes* has a particular predilection for the central nervous system (CNS) and the placenta. It is generally believed that listeriae reach the CNS by a bacteremic route, but animal experiments suggest that brainstem infection may develop by intraaxonal spread of bacteria from peripheral sites to the CNS.

Several virulence factors have been identified that enable *L. monocytogenes* to function as an intracellular organism. The bacterium possesses the cell surface protein internalin, which interacts with E-cadherin, a receptor on macrophages and intestinal lining cells, to induce its own ingestion. A membrane lipoprotein appears to promote entry into nonmacrophage cells. The major virulence factor, listeriolysin O, along with phospholipases, enables listeriae to escape from the phagosome and avoid intracellular killing. Once free in the cytoplasm, the bacterium can divide and, by inducing host cell actin polymerization, propel itself to the cell membrane. Subsequently, by means of pseudopod-like projections, it can invade adjacent macrophages. The bacterial surface protein Act A is necessary for the induction of actin filament assembly and cell-to-cell spread and, therefore, is a major virulence factor. Through this novel life cycle, *L. monocytogenes* moves from cell to cell, evading exposure to antibodies, complement, or neutrophils.

Iron, which is essential for the life of virtually all bacteria, appears to be an important virulence factor of *L. monocytogenes*. Siderophores of the organism enable it to take iron from transferrin. In vitro, iron enhances organism growth, and, in animal models of listerial infection, iron overload is associated with enhanced susceptibility to infection and iron supplementation with enhanced lethality, whereas iron depletion results in prolonged survival. Attesting to the importance of iron acquisition as a virulence factor in humans are the clinical associations of sporadic listerial infection with hemochromatosis and of outbreaks with transfusion-induced iron overload in patients receiving hemodialysis.

Immunity

Resistance to infection with the intracellular bacterium *L. monocytogenes* is chiefly dependent on T-cell lymphokine activation of macrophages but involves both innate and adaptive immune responses. The adaptive response is predominantly cell mediated as evidenced by the overwhelming clinical association between listerial infection and conditions of impaired cell-mediated immunity, including lymphoma, pregnancy, AIDS, corticosteroid immunosuppression, and tumor necrosis factor-α (TNF-α) neutralizing agents. The production of nitric oxide by activated macrophages may play a role in natural immunity to listeriosis independent of T-cell function. The role of humoral immunity is unknown, although both immunoglobulin M (absent in neonates) and classical complement activity (low in neonates) have been shown to be necessary for efficient opsonization of *L. monocytogenes*.

Although listeriosis is 100 to 1000 times more common in patients with AIDS compared with the general population, it is somewhat surprising that it is not seen more commonly, given the ubiquity of the organism. The use of trimethoprim–sulfamethoxazole (TMP–SMX) for prophylaxis against *Pneumocystis jirovecii* (*carinii*) provides protection against listeriosis. Frequency of listeriosis is not increased in those with deficiencies in neutrophil numbers or function, splenectomy, complement deficiency, or immunoglobulin disorders.

Clinical manifestations

The species name derives from the fact that an extract of the *L. monocytogenes* cell membrane has potent monocytosis-producing activity in rabbits, but monocytosis is a very rare feature of human infection.

Infection in pregnancy

Mild impairment of cell-mediated immunity occurs during gestation, and pregnant women are prone to developing listerial bacteremia with an estimated 17- to 100-fold increase in risk. Listeriae proliferate in the placenta in areas that appear to be unreachable by usual defense mechanisms, and cell-to-cell spread facilitates maternal–fetal transmission. For unexplained reasons, CNS infection is extremely rare during pregnancy in the absence of other risk factors. Bacteremia manifests clinically as an acute febrile illness, often accompanied by myalgia, arthralgia, headache, and backache. Illness may occur at any time during pregnancy but usually occurs in the third trimester, probably related to the major decline in cell-mediated immunity seen at 26 to 30 weeks of gestation. Twenty-two percent of perinatal infections result in stillbirth or neonatal death; premature labor and spontaneous abortion are common. Untreated bacteremia is generally self-limited, although if there is a complicating amnionitis, fever may persist in the mother until the fetus is aborted. Early diagnosis and antimicrobial therapy can result in the birth of a healthy infant.

There is no convincing evidence that listeriosis is a cause of habitual abortion in humans.

Neonatal infection

When in utero infection occurs, it can precipitate spontaneous abortion. The fetus may be stillborn or die within hours of a disseminated form of listerial infection known as granulomatosis infantiseptica and characterized by widespread microabscesses and granulomas that are particularly prevalent in the liver and spleen. In this entity, abundant bacteria are often visible on Gram stain of meconium.

More commonly, neonatal infection manifests similar to group B streptococcal disease in one of two forms: (1) early-onset sepsis syndrome, usually associated with prematurity and probably acquired in utero, or (2) late-onset meningitis, occurring at about 2 weeks of age in term infants, who most likely acquired organisms from the maternal vagina at parturition. Cases have occurred after cesarean delivery, however, and nosocomial transmission has been suggested.

In early-onset disease, *L. monocytogenes* can be isolated from the conjunctivae, external ear, nose, throat, meconium, amniotic fluid, placenta, blood, and, sometimes, CSF; Gram stain of meconium may show gram-positive rods and provide early diagnosis. The highest concentrations of bacteria are found in the neonatal lung and gut, which suggests that infection is acquired in utero from infected amniotic fluid rather than via a hematogenous route. Purulent conjunctivitis and a disseminated papular rash have rarely been described in neonates with early-onset disease, but clinical infection is otherwise similar to that due to other bacterial pathogens.

Bacteremia

Bacteremia without an evident focus is the most common manifestation of listeriosis after the neonatal period. Clinical manifestations typically include fever and myalgias; a prodromal illness with nausea and diarrhea may occur. Because immunocompromised patients are more likely than healthy persons to have blood cultures during febrile illnesses, transient bacteremias in healthy persons may go undetected.

Central nervous system infection

Organisms that cause bacterial meningitis most frequently (*Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae*) rarely cause parenchymal brain infections such as cerebritis and brain abscess. By contrast, *L. monocytogenes* has tropism for the brain itself (particularly the brainstem), as well as for the meninges. Many patients with listerial meningitis experience altered consciousness, seizures, or movement disorders and truly have meningoencephalitis. Ventriculoperitoneal shunt infection has been reported.

Meningitis

Active surveillance studies of bacterial meningitis conducted by the CDC indicate that *L. monocytogenes* accounts for 20% of bacterial meningitis cases in neonates as well as in those older than 60 years and carries a mortality of 22%. Worldwide, *L. monocytogenes* is one of the three major causes of neonatal meningitis, is second only to pneumococcus as a cause of bacterial meningitis in adults older than 50 years, and is the most common cause of bacterial meningitis in patients with lymphoma, patients with organ transplants, or those receiving corticosteroid immunosuppression for any reason. Twenty percent of bacterial meningitis in those older than 50 years is caused by *L. monocytogenes*; therefore, empiric therapy for bacterial meningitis in all adults older than 50 years with a negative CSF Gram stain should include an antilisterial agent (either ampicillin or TMP–SMX), especially in the absence of associated pneumonia, otitis, sinusitis, or endocarditis, which would suggest an alternative etiology.

Clinically, meningitis due to *L. monocytogenes* is usually similar to that due to more common causes; features particular to listerial meningitis are summarized in Table 142.1.

TABLE 142.1 **DISTINCTIVE FEATURES OF LISTERIAL MENINGITIS COMPARED WITH MORE COMMON BACTERIAL ETIOLOGIES**

Feature	Frequency (%)
Presentation can be subacute (>24 hours)	~60
Stiff neck is less common	15–20
Movement disorders (ataxia, tremors, myoclonus) are more common	15–20
Seizures are more common	~25
Fluctuating mental status is common	~75
Positive blood culture is more common	50–75
Cerebrospinal fluid (CSF)	
Positive Gram stain is less common	30–40
Normal CSF glucose is more common	>60
Mononuclear cell predominance is more common	~30

Brainstem encephalitis (rhombencephalitis)

An unusual form of listerial encephalitis involves the brainstem. In contrast to other listerial CNS infections, this illness usually occurs in healthy older children and adults; neonatal cases have not been reported. The typical clinical picture is one of a biphasic illness with a prodrome of fever, headache, nausea, and vomiting lasting about 4 days, followed by the abrupt onset of asymmetrical cranial nerve deficits, cerebellar signs, and hemiparesis or hemisensory deficits or both. Nuchal rigidity is present in about 50%, CSF is only mildly abnormal, and CSF culture is positive in about 40%; almost two-thirds are bacteremic. Respiratory failure develops in about 4% of cases. Magnetic resonance imaging is superior to computed tomography for demonstrating rhombencephalitis. Mortality is high, and serious sequelae are common in survivors.

Cerebritis and brain abscess

Parenchymal brain infection may occur without true abscess formation and is referred to as cerebritis; concomitant meningitis may or may not be present. Macroscopic brain abscesses account for about 10% of CNS listerial infections (Figure 142.1). Bacteremia is almost always present, and concomitant meningitis with isolation of *L. monocytogenes* from the CSF is found in 25%; both of these features are rare in other forms of bacterial brain abscess. About 50% of cases occur in known risk groups for listerial infection. Subcortical abscesses located in the thalamus, pons, and medulla are common; these sites are exceedingly rare when abscesses are due to other bacteria. Mortality is high, and survivors usually have serious sequelae.

Endocarditis

Listerial endocarditis may account for as much as 7.5% of adult listerial infections, produces both native valve and prosthetic valve disease, and has a high rate of septic complications and a mortality of 48%. Listerial endocarditis, but not bacteremia per se, may be an indicator of underlying gastrointestinal tract pathology, including cancer.

Localized infection

Focal infections from which *L. monocytogenes* has been isolated include direct inoculation resulting in conjunctivitis, skin infection, and lymphadenitis. Bacteremia can lead to hepatic infection, cholecystitis, peritonitis, splenic abscess, pleuropulmonary infection, septic arthritis, osteomyelitis, pericarditis, myocarditis, arteritis,

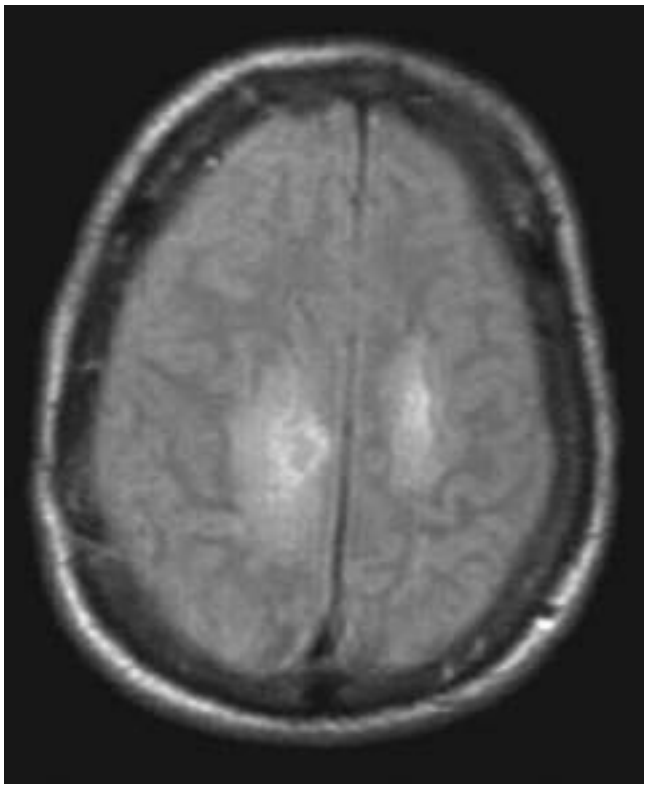

FIGURE 142.1 MRI of the brain showing bilateral frontoparietal lesions with ring enhancement (abscess) on the right. The patient was a 70-year-old man with multiple myeloma who presented with difficulty walking followed by inability to stand and progressive quadriparesis. An aspirate of the abscess grew *Listeria monocytogenes*.

necrotizing fasciitis, and endophthalmitis. Complications, including disseminated intravascular coagulation, adult respiratory distress syndrome, and rhabdomyolysis with acute renal failure, have been documented. There is nothing clinically unique about these localized infections; many, but not all, have occurred in those known to be at risk for listeriosis. Joint infection typically involves prosthetic joints in compromised hosts and requires prosthesis removal for cure.

Febrile gastroenteritis

Many patients with invasive listeriosis give a history of antecedent gastrointestinal illness, often accompanied by fever. Although isolated cases of gastrointestinal illness due to *L. monocytogenes* appear to be quite rare, at least seven outbreaks of foodborne gastroenteritis due to *L. monocytogenes* have been documented. In the largest outbreak to date 1566 individuals, most of them children between the ages of 6 and 10, became ill after eating caterer-provided cafeteria food at two schools, and 19% were hospitalized. Illness typically occurs 24 hours after ingestion of a large inoculum of bacteria (range 6 hours to 10 days) and usually lasts 1 to 3 days (range 1–7 days); attack rates have been quite high (52%–100%). Common symptoms include fever, watery diarrhea, nausea, headache, and pains in joints and muscles. Vehicles of infection have included chocolate milk, cold corn and tuna salad, cold smoked trout, and delicatessen meat. *Listeria monocytogenes* should be considered to be a possible etiology in outbreaks of febrile gastroenteritis when routine cultures fail to yield a pathogen.

Diagnosis

Listeriosis should be a major consideration as part of the differential diagnosis in any of the following clinical settings:

1. Septicemia or meningitis in infants younger than 2 months.
2. Meningitis or parenchymal brain infection in: (a) patients with hematologic cancer, AIDS, organ transplantation, corticosteroid immunosuppression, or those receiving anti-TNF agents; (b) patients with subacute presentation; (c) adults >50 years; and (d) those in whom CSF shows gram-positive bacilli.
3. Simultaneous infection of the meninges and brain parenchyma.
4. Subcortical brain abscess.
5. Fever during pregnancy.
6. Blood, CSF, or other normally sterile specimen reported to have "diphtheroids" on Gram stain or culture.
7. Foodborne outbreak of febrile gastroenteritis when routine cultures fail to identify a pathogen.

Diagnosis requires isolation of *L. monocytogenes* from clinical specimens (e.g., CSF, blood) and identification through standard microbiologic techniques. Antibodies to listeriolysin O have not proved useful in invasive disease, nor have polymerase chain reaction (PCR) probes. Antibodies to listeriolysin O may be useful during investigation of outbreaks of febrile gastroenteritis. *Listeria monocytogenes* DNA in CSF and tissue has been specifically detected by PCR assays. Real-time PCR of CSF for the *hly* gene, which encodes listeriolysin O, has been useful in diagnosing CNS listeriosis, including cases in which routine bacterial cultures were negative, but this test is not yet commercially available.

Magnetic resonance imaging is superior to computed tomography for demonstrating parenchymal brain involvement, especially in the brainstem.

Treatment

No controlled trials have established a drug of choice or duration of therapy for listerial infection. Recommendations for treatment of invasive infections are presented in Table 142.2.

Ampicillin is generally considered the preferred agent. Based on synergy in vitro and in animal models, most authorities suggest adding gentamicin to ampicillin for treatment of bacteremia in those with severely impaired cell-mediated immunity and in all cases of meningitis and endocarditis. In one uncontrolled study, the combination of TMP–SMX plus ampicillin was associated with a lower

TABLE 142.2 **INTRAVENOUS THERAPY FOR INVASIVE LISTERIOSIS**

Syndrome	Antibiotic[a]	Dosage[b]	Interval	Minimum duration
Meningitis	Ampicillin	200 mg/kg	q4h	3 wk
	plus gentamicin	5 mg/kg	q8h	
Brain abscess or rhombencephalitis	Ampicillin	200 mg/kg	q4h	6 wk
	plus gentamicin	5 mg/kg	q8h	
Endocarditis	Ampicillin	200 mg/kg	q6h	6 wk
	plus gentamicin	5 mg/kg	q8h	
Bacteremia	Ampicillin	200 mg/kg	q6h	2 wk

[a] Penicillin-allergic patients without endocarditis can be treated with trimethoprim–sulfamethoxazole alone, using 15 mg/kg of trimethoprim daily at 6- to 8-hour intervals. Patients with endocarditis should be desensitized to ampicillin and treated as above.
[b] Maximum daily dose of ampicillin should not exceed 15 g.

failure rate and fewer neurologic sequelae than ampicillin combined with an aminoglycoside.

For those intolerant of penicillins, TMP–SMX is believed to be the best alternative. Early transition to oral TMP–SMX has been used effectively and may be considered in selected patients with likely good adherence. No currently available cephalosporin should be used; none has adequate activity, and meningitis has developed in patients receiving cephalosporins. For this reason, ampicillin is always included in empirical therapy for septicemia or meningitis in infants ≤2 months of age.

Vancomycin has been used successfully in a few patients with penicillin allergy, but other patients have developed listerial meningitis while receiving the drug. Rifampin is active in vitro and is known to penetrate phagocytic cells; clinical experience is minimal, however, and in animal models the addition of rifampin to ampicillin was not more effective than ampicillin used alone. Both imipenem and meropenem have been used successfully to treat listeriosis, but caution is advised because both drugs lower the seizure threshold, treatment failures have been reported, and imipenem was less effective than ampicillin in a mouse model.

Initial dosing of antibiotics as for meningitis is prudent for all patients, even in the absence of CNS or CSF abnormalities, because of the high affinity of this organism for the CNS. Patients with meningitis should be treated for no fewer than 3 weeks; bacteremic patients without CSF abnormalities can be treated for 2 weeks.

No data exist concerning antimicrobial efficacy in listerial gastroenteritis; the illness is self-limited, and treatment is not warranted. Clinically significant antimicrobial resistance has not been encountered, but vigilance is warranted because transfer of resistance from enterococci to *L. monocytogenes* has been reported, tetracycline and quinolone resistance has emerged, and minimal inhibitory concentrations for penicillin have risen slightly. Because iron is a virulence factor for *L. monocytogenes*, it seems prudent to withhold iron replacement in patients with iron deficiency until the listerial infection is resolved.

Prevention

Food industry regulations were instituted in the United States over 20 years ago to minimize the risk of foodborne listeriosis and cut foodborne infection rates by more than one-half; rates have been relatively stable for several years. In contrast, rates of listerial infection appear to be rising in Europe.

Box 142.1 contains recommendations developed by the CDC for prevention of foodborne listeriosis.

Except from infected mother to fetus, human-to-human transmission of listeriosis does not occur; therefore, patients do not require isolation. Neonatal listerial infection complicating successive pregnancies is virtually unheard of, and intrapartum antibiotics are not recommended for mothers with a history of perinatal listeriosis.

BOX 142.1

Dietary recommendations for preventing foodborne listeriosis

For all persons

1. Cook raw food from animal sources (e.g., beef, pork, and poultry) thoroughly
2. Wash raw vegetables thoroughly before eating
3. Keep uncooked meats separate from vegetables, cooked foods, and ready-to-eat foods
4. Avoid consumption of raw (unpasteurized) milk or foods made from raw milk
5. Wash hands, knives, and cutting boards after handling uncooked foods

Additional recommendations for persons at high risk[a]

1. Avoid soft cheeses (e.g., Mexican-style, feta, Brie, Camembert) and blue-veined cheese; there is no need to avoid hard cheeses, cream cheese, cottage cheese, or yogurt
2. Leftover foods or ready-to-eat foods (e.g., hot dogs) should be reheated until steaming hot before eating
3. Consider avoidance of foods in delicatessen counters[b]

[a] Those immunocompromised by illness or medications, pregnant women, and the elderly.
[b] Although the risk for listeriosis associated with foods from delicatessen counters is relatively low, pregnant women and immunosuppressed persons may choose to avoid these foods or to thoroughly reheat cold cuts before consumption.

There is no vaccine. Listerial infections are effectively prevented by TMP–SMX given as prophylaxis against *P. jirovecii* to recipients of organ transplants or to individuals with the human immunodeficiency virus. The utility, or even the feasibility, of eradicating gastrointestinal colonization as a means to prevent invasive listeriosis is unknown. However, asymptomatic persons at high risk for listeriosis, known to have ingested a food implicated in an outbreak, could reasonably be given several days of oral ampicillin or TMP–SMX.

Suggested reading

Cartwright EJ, Jackson KA, Johnson SD, *et al*. Listeriosis outbreaks and associated food vehicles, United States, 1998–2008. *Emerg Infect Dis*. 2013;19:1–9.

Charlier C, Leclercq A, Cazenave B, *et al*. *Listeria monocytogenes*-associated joint and bone infections: a study of 43 consecutive cases. *Clin Infect Dis*. 2012;54:240–248.

Goulet V, Hebert M, Hedberg C, *et al*. Incidence of listeriosis and related mortality among groups at risk of acquiring listeriosis. *Clin Infect Dis*. 2012;54:652–660.

Hamon M, Bierne H, Cossart P. *Listeria monocytogenes*: a multifaceted model. *Nat Rev Microbiol*. 2006;4:423–434.

Le Monnier A, Abachin E, Beretti J-L, *et al*. Diagnosis of *Listeria monocytogenes* meningoencephalitis by real-time PCR for the *hly* gene. *J Clin Microbiol*. 2011;49:3917–3923.

Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with *Listeria monocytogenes*: 33 years' experience at a general hospital and review of 776 episodes from the literature. *Medicine (Baltimore)*. 1998;77:313–336.

Mylonakis E, Paliou M, Hohmann EL, *et al*. Listeriosis during pregnancy: a case series and review of 222 cases. *Medicine (Baltimore)*. 2002;81:260–269.

Ooi ST, Lorber B. Gastroenteritis due to *Listeria monocytogenes*. *Clin Infect Dis*. 2005;40:1327–1332.

United States Centers for Disease Control and Prevention. Multistate outbreak of listeriosis linked to whole cantaloupes from Jensen Farms, Colorado. December 8, 2011 (final update). http://www.cdc.gov/listeria/outbreaks/cantaloupes-jensen-farms/120811/index.html (accessed January 1, 2013).

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Nocardia

Lisa Haglund

Nocardia spp. are soilborne bacteria that are aerobic and slow-growing. In culture, they may require days to weeks before colonies appear. *Nocardia* are thin, filamentous, beaded gram-positive rods, and are variably acid-fast, 0.5 to 1.0 μm in diameter, with branching at right angles (Figure 143.1). Taxonomy of the genus has evolved considerably, and, through the use of molecular identification techniques, there are now 92 named *Nocardia* species, about half of which have been implicated in human infections. The most frequent nocardial species pathogenic for humans are *N. nova* complex, *N. brasiliensis, N. farcinica, N. cyriageorgica*, *N. abscessus* complex, and *N. transvalensis* complex. Less common human pathogens include *N. otitidiscaviarum*, *N. brevicatena-N. paucivorans* complex, and *N. pseudobrasiliensis*. *N. asteroides sensu stricto* is not currently defined in molecular terms, having been resolved into several other species. *Nocardia* are opportunistic pathogens; *N. brasiliensis* is more virulent, affecting normal hosts, and has a range geographically restricted to areas with warmer climates.

Nocardiosis is typically a suppurative infection with multiple abscesses. It is rarely granulomatous and not fibrotic. Acquisition of infection is by inhalation or by traumatic inoculation. Although nocardia are ubiquitous, they rarely colonize the human respiratory tract. Accordingly, treatment should be initiated when nocardia are isolated repeatedly from pulmonary specimens, particularly in an immunocompromised host. Antimicrobial therapy (alone or in combination with surgical drainage) is recommended, and the duration of therapy must be prolonged to prevent relapse.

Most patients with systemic nocardiosis possess underlying risk factors. Predisposing conditions are listed in Table 143.1. As the number of solid organ and hematopoietic stem cell transplantations has increased, the incidence of nocardiosis has risen. There is a correlation with the level of immunosuppression following transplantation, with most cases of nocardiosis occurring >1 but <12 months after transplantation (longer for renal transplant recipients) and at any time following intensified immunosuppression. There is also a correlation with cytomegalovirus (CMV) infection. Among HIV-infected persons, there is also a correlation with level of immunosuppression, as almost all cases of nocardiosis occur in individuals with CD4 lymphocyte counts of ≤100 cells/mm^3. In severely immunocompromised patients, co-occurrence of other opportunistic infections, including aspergillosis, mucormycosis, pneumocystosis, non-tuberculous mycobacteria, and other infections, may be found and should be sought if expected clinical improvement does not occur with appropriate therapy. Adjunctive immunotherapy with interferon-γ (IFN-γ) has been tried in cases that failed to respond to appropriate antibiotics.

Nocardiosis remains an uncommon opportunistic complication of HIV infection and transplant recipients. One possible explanation is that the prophylactic use of trimethoprim-sulfamethoxazole (TMP-SMX), pyrimethamine, or dapsone for *Pneumocystis jirovecii* (*carinii*) may also prevent nocardiosis. Nocardiosis can develop concurrently with receipt of TMP-SMZ prophylactically, especially when given at lower dosages, with preserved susceptibility to sulfa drugs in vitro.

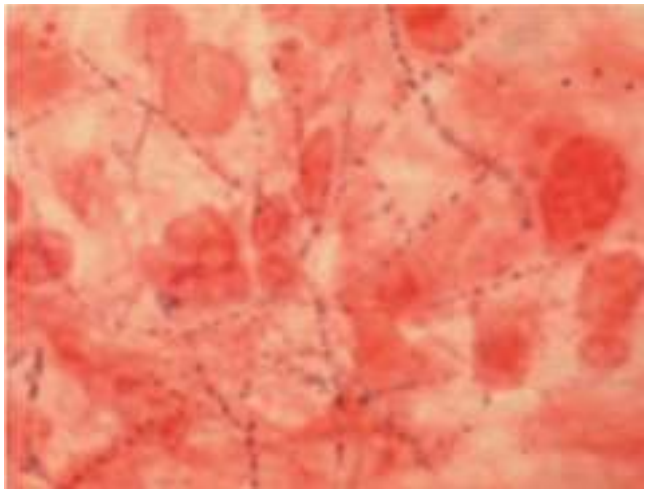

FIGURE 143.1 *Nocardia*, Gram stain.
Courtesy of David Schlossberg MD.

Pathogenesis of systemic nocardiosis

Neutrophils inhibit the growth of nocardia, but eradication of organisms requires cell-mediated immunity. If cellular immunity is impaired, *Nocardia* can cause indolent abscesses with slow spread to distant sites, such as the brain or cerebrospinal fluid. Illness is usually subacute to chronic but may be fulminant in an immunocompromised host. Weight loss, anorexia, and fatigue are common in systemic nocardiosis. Bacteremia is unusual, including central line–associated bloodstream infections (CLABSIs), which require removal of the implicated catheter for cure.

Mycetoma, cutaneous nocardiosis, traumatic nocardiosis

Nocardial species can cause mycetoma, which typically manifests as a swollen area with sinuses draining purulent material. Primary cutaneous nocardiosis manifests as nontender, red, irregularly shaped raised lesions which may form sinus tracts and drain purulent material. Regional lymphadenopathy is uncommon. *Nocardia* arthritis usually presents as a monoarthritis, commonly involving the knee. Disease is often inoculated through a puncture wound and may follow a contaminated intramuscular injection. Other inoculation nocardial infections described include postoperative wound infections, osteomyelitis, and keratitis.

Pulmonary nocardiosis

Pulmonary disease is apparent in 65% to 85% of systemic nocardial infections. The roentgenographic features include infiltrates that may cavitate, sometimes accompanied by empyema, pericarditis, or mediastinitis. There is no specific radiographic appearance, thus a high degree of suspicion must be maintained to make the diagnosis. Sputum cultures may be overgrown with other organisms before *Nocardia* colonies appear. Therefore, it may be helpful to notify the microbiology lab to use selective media and hold cultures for *Nocardia* if it is a suspected pathogen. Respiratory samples submitted for fungal culture are more likely to grow *Nocardia* than those submitted for mycobacterial (acid-fast bacillus [AFB]) culture.

TABLE 143.1 **RISK FACTORS FOR SYSTEMIC NOCARDIOSIS**

Chronic pulmonary disease	Solid organ transplantation	Systemic lupus erythematosus	Renal failure
	Hematopoietic stem cell transplantation	Systemic vasculitis	Whipple's disease
Alcoholism	Chronic corticosteroid use	Ulcerative colitis	Hypogammaglobulinemia
Cirrhosis	Other drug-induced immunosuppression	Sarcoidosis	Chronic granulomatous disease
		Bronchiectasis	
Lymphoreticular malignancy	Cushing syndrome	Cystic fibrosis	Human immunodeficiency virus infection
	Graft vs. host disease	Tumor necrosis factor (TNF-α) inhibition	Pulmonary alveolar proteinosis
Diabetes			Anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies

Nocardia meningitis and brain abscess

Central nervous system (CNS) nocardiosis is detected in 20% to 40% of systemic nocardial infections. Two-thirds have clinical findings such as fever, headache, stiff neck, or altered mental status. Hypoglycorrhachia is found in two-thirds of patients. Mildly elevated cerebrospinal fluid protein and a neutrophilic pleocytosis of approximately 1,000 white blood cells per μL are usually found. Nocardial brain abscess can be a complication of nocardial meningitis or can present in the absence of meningitis. Although meningitis without underlying brain abscess has been described, this is quite unusual, and an underlying abscess should always be suspected. Because of the high incidence of CNS infection, an imaging study of the brain should be performed if any personality or neurologic changes are found during workup of systemic nocardiosis.

Therapy of nocardiosis: Sulfonamide therapy

Sulfonamides remain the first-line agents for nocardiosis, and sulfadiazine, 6 to 8 g intravenously (IV) or orally daily, is a typical adult regimen. TMP-SMX is an alternative first-line treatment for nocardiosis. Disparity in sulfonamide susceptibility has been reported for *Nocardia*; however, several recent studies found overall 2% sulfonamide resistance in *Nocardia* spp., with less resistance to TMP-SMX, and it appears that some of the disparate observations were methodologic due to inherent difficulties in performing *Nocardia* susceptibilities for some antimicrobial agents. Table 143.2 summarizes typical dosages and durations of therapy for sulfonamide therapy of nocardiosis.

Sulfadiazine is a short-acting sulfonamide with low urinary solubility. TMP-SMX is a well-absorbed combination agent with a long plasma half-life of 11 and 9 hours for TMP and SMX, respectively. It is available orally as single- or double-strength tablets (80 mg TMP plus 400 mg SMX and 160 mg TMP plus 800 mg SMX, respectively) and as a liquid suspension containing 40 mg TMP plus 200 mg SMX per 5 mL. It is also available IV (5 mL = 80 mg TMP plus 400 mg SMX).

The most frequent side effects of TMP-SMX are upper gastrointestinal symptoms and skin rashes (3–4% each). Leukopenia, thrombocytopenia, and megaloblastic changes can develop rarely. Adverse effects of sulfonamide therapy include acute renal failure as a result of tubular damage from sulfa crystalluria. This effect may be prevented by adequate hydration and by alkalinizing the urine. Organ transplant recipients may be at increased risk of both bone marrow and renal toxicity due to overlapping toxicities with immunosuppressive medications. Hepatitis, intrahepatic cholestasis, pancreatitis, and aseptic meningitis have been reported with TMP-SMX. Serious adverse reactions are rare and include anaphylaxis, Stevens–Johnson syndrome, and hematologic effects, including thrombocytopenia, leukopenia, and hemolytic anemia.

TMP-SMX and other sulfonamides should not be given to patients with a demonstrated deficiency of folic acid or glucose-6-phosphate dehydrogenase. In HIV-infected patients, there is an increased incidence of adverse reactions to TMP-SMX, including reversible hyperkalemia and a severe hypersensitivity reaction with fever, hypotension, and multiorgan involvement on rechallenge with the drug.

Other agents with anti-nocardial activity

N. farcinica, N. pseudobrasiliensis, and other *Nocardia* spp. have been reported to have resistance to sulfonamides. The Clinical and Laboratory Standards Institute (CLSI) recommends use of the broth microdilution method for determining nocardial susceptibilities while acknowledging that consistent interpretation of sulfonamide susceptibilities, in particular, is difficult with this method. Susceptibility results are most reliable from an experienced laboratory. In vitro susceptibility does not uniformly correlate with clinical outcome in humans; therefore, clinical response should also guide selection of definitive antimicrobial therapy. The parenteral agents with greatest in vitro activity include imipenem-cilastatin (500 mg IV q6h), and amikacin (5–7.5 mg/kg IV q12h) (Table 143.3). With susceptible organisms, these agents have been as efficacious as sulfonamides in animal models; in fact, they may be more rapidly bactericidal than sulfonamides. Clinical experience

TABLE 143.2 **SULFONAMIDE DOSAGE AND DURATION OF THERAPY FOR TREATMENT OF NOCARDIA**

Type of nocardiosis	Dosage (divided BID-QID)	Duration	Comments
Cutaneous	5–10 mg/kg/d TMP-SMX[a]	2–4 mo	Longer for extensive disease or bony involvement as seen in mycetoma. Debridement helpful.
Pulmonary	10 mg/kg/d TMP-SMX	6–12 mo	12-mo minimum duration for immunocompromised host
Central nervous system	15 mg/kg/d TMP-SMX 50–100 mg/kg/d sulfadiazine	12 mo	

[a] TMP-SMX dosage based on mg/kg of the trimethoprim (TMP) component.

TABLE 143.3 **OTHER REGIMENS FOR TREATMENT OF NOCARDIA**

Drug	Dosage	Duration	Comments
Minocycline	100–200 mg PO BID	3–6 mo	Useful for pulmonary disease; poor CNS penetration
Imipenem–cilastatin	500 mg IV q6h	Until oral agent can be given	Dose must be adjusted for renal failure
Amikacin	5–7.5 mg/kg IV q12h	Until oral agent can be given	Nephrotoxic; dosage must be adjusted for renal failure
Ceftriaxone	2 g IV q12h	Until oral agent can be given	
Linezolid	600 mg PO or IV q12h		Bone marrow suppression and peripheral neuropathy

with alternative parenteral regimens is being assimilated, and treatment courses often include sulfonamide therapy. In the immunocompromised patient or in those with disseminated disease or CNS involvement, strong consideration should be given to initial empiric use of amikacin and imipenem-cilastatin while awaiting results of in vitro susceptibilities. For CNS nocardiosis, meropenem may be a useful alternative to imipenem-cilastatin, which may cause seizures; meropenem, doripenem, and ertapenem should have appropriate susceptibility testing done before being given.

Tetracyclines have good in vitro activity against some nocardial species. Minocycline has the best in vitro activity among the tetracyclines and is given 100–200 mg orally twice a day for 3 to 6 months (Table 143.3). Its drawbacks include poor cerebrospinal fluid penetration and side effects of vertigo, making it unsuitable for CNS nocardial disease.

Amoxicillin-clavulanate is an alternative to TMP-SMX or minocycline for treatment of cutaneous and lymphocutaneous disease caused by *N. brasiliensis*. Macrolides and the respiratory quinolones show some in vitro activity. Linezolid 400 to 600 mg orally twice daily has been used with success, but the long treatment course needed for nocardiosis may be complicated by drug toxicities, especially with twice-daily dosing. Tedizolid appears to be more active in vitro than linezolid, although tolerability with long-term usage has not been studied. Table 143.4 summarizes antimicrobial susceptibilities of selected *Nocardia* spp.

Suggested reading

Conville PS, Brown-Elliott BA, Smith T, Zelazny AM. The complexities of *Nocardia* taxonomy and identification. *J Clin Microbiol*. 2018;56:e01419–417.

Conville PS, Brown-Elliott BA, Wallace RJ Jr, et al. Multisite reproducibility of the broth microdilution method for susceptibility testing of *Nocardia* species. *J Clin Microbiol*. 2012;50:1270–1280.

Coussement J, Lebeaux D, van Delden C, et al. for the European Study Group for *Nocardia* in Solid Organ Transplantation. *Nocardia* infection in solid organ transplant recipients: A multicenter European case-control study. *Clin Infect Dis*. 2016;63:338–345.

Steinbrink J, Leavens J, Kauffman CA, Miceli MH. Manifestations and outcomes of nocardia infections: Comparison of immunocompromised and nonimmunocompromised adult patients. *Medicine (Baltimore)*. 2018;97:40(e12436).

Wilson JW. Nocardiosis: Updates and clinical overview. *Mayo Clin Proc*. 2012;87:403–407.

TABLE 143.4 **TYPICAL ANTIMICROBIAL SUSCEPTIBILITIES OF SELECTED *NOCARDIA* SPP.**

	N. brasilensis	*N. cyriageorgica*	*N. farcinica*	*N. nova complex*	*N. abscessus*
Sulfamethoxazole	S	S	S	S	S
Amoxicillin	R	R	R	R	R
Amoxicillin-clavulanate	S	R	S	R	S
Ceftriaxone	V	S	R	V/S	S
Imipenem	R	S	V/S	S	V
Amikacin	S	S	S	S	S
Clarithromycin	R	R	R	S	R
Minocycline	S	V	V	V	S
Ciprofloxacin	R	R	V	R	R
Linezolid	S	S	S	S	S

Abbreviations: R = resistant; V = variable susceptibility; S = sensitive.

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Pasteurella multocida

Andrew S. Webster, Paulina A. Rebolledo, Naasha J. Talati, and David S. Stephens

Pasteurella multocida ("killer of many species") is a nonmotile, gram-negative, facultative coccobacillus best known for its association with soft tissue infections after animal bites. However, *P. multocida* is also an opportunistic pathogen capable of causing invasive and life-threatening infections.

P. multocida is named in honor of Louis Pasteur, who first isolated it as the causative agent of fowl cholera in 1880. *P. multocida* is found worldwide. It commonly colonizes the upper respiratory tract of cats (70–90%), dogs (50–66%), and has been isolated from numerous other domestic pets and wild animals. Human infection is usually associated with animal exposure. Direct traumatic inoculation by a bite or scratch is the most common route of transmission; however, infection after contact with animal respiratory secretions through licks, nuzzling, or grooming is also described. Respiratory infections are uncommon but well described, and colonization of the human respiratory tract can also occur. *P. multocida* has been cultured from the respiratory tract of healthy veterinary workers and animal handlers. Antibodies against *P. multocida* are found twice as often in those who own pets or have occupational exposure to animals. Nevertheless, infections can occur in the absence of animal contact.

There are several species and subspecies of *Pasteurella* which have been shown to cause human disease, most commonly *P. multocida* subsp. *multocida, P. multocida* subsp. *septica, P. dagmatis, P. canis*, and *P. stomatis*. These organisms can resemble *Haemophilus* and *Neisseria* species when visualized on Gram stain, grow well on sheep and chocolate agar, and do not grow on MacConkey agar. Isolates from humans are typically oxidase-, catalase-, and indole-positive. Identification can be achieved by biochemical testing or molecular techniques, such as real-time polymerase chain reaction (PCR) or 16S rRNA gene sequencing. In a study of 65 clinical isolates, matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) correctly identified *Pasteurella* at the species level 89% of the time.

Pasteurella multocida has five serotypes (A, B, D, E, F) based on capsular antigens. In human studies that examined serotypes, disease is usually caused by serotypes A (respiratory) and D (bite wounds). Further classification is possible based on 16 variants of lipopolysaccharide (LPS). Most studies examining potential virulence factors have been carried out in animals, and relevance to human infection is unknown. *P. multocida* has multiple methods of iron acquisition, some of which are host-specific. Outer membrane proteins (OMP) are thought to play a role not only in iron acquisition, but also in adherence. The unique LPS may help resist actions of complement, and immune responses generated are specific to the LPS serovariant. *P. multocida* capsule can possess antiphagocytic properties and may help promote colonization. A protein toxin, *P. multocida* toxin (PMT), has been isolated from some serotype A and D strains. PMT alters cell signaling pathways with effects on host immune response, cellular differentiation, and proliferation. A summary of virulence factors is provided in Table 144.1.

TABLE 144.1 **VIRULENCE FACTORS OF *PASTEURELLA MULTOCIDA***

Virulence factor	Effect
Multiple iron acquisition methods	Ensures iron acquisition across hosts
Unique and variable lipopolysaccharide (LPS)	Resists complement, lack of universal immune response
Capsule	Antiphagocytic, may mediate colonization
Outer membrane proteins (OMP)	Adherence, iron acquisition
Pasteurella multocida toxin (PMT)	Alters host cell signaling

Clinical presentation

Infections caused by *P. multocida* can be divided into three groups: bite wound infections, infections of the respiratory tract, and invasive disease.

Bite wound infection

Infections of the skin and soft tissue most commonly follow bites or scratches but can occur after an animal licks an open wound. Bite wounds account for 60% to 86% of *P. multocida* infections. While most bite wounds are polymicrobial, *P. multocida* is found as a pathogen in 75% of infected cat bites and up to 50% of infected dog bites. Skin infection with *P. multocida* is characterized by an extremely rapid onset; local pain and inflammation often occur within 4 to 6 hours of the injury and almost always within 24 hours. Purulent drainage and lymphangitis occur in 40% of cases, but fever and systemic symptoms are often absent.

Bite wound infections with *P. multocida* can lead to serious sequelae, even with appropriate antibiotic and aggressive surgical management. Tenosynovitis, abscess formation, and osteomyelitis can result, but bacteremia is rare. Necrotizing infections have been reported. Cat bites are more commonly associated with osteomyelitis because of the deep puncture wounds that penetrate the periosteum. Poor functional outcome is common with these infections, especially when involving the extremities. In patients with risk factors for invasive infections, an apparently insignificant and uninfected wound may lead to serious sequelae weeks later.

Respiratory tract infection

Respiratory infections are the second most common infection site and tend to occur in those with underlying lung disease such as chronic obstructive pulmonary disease (COPD) or bronchiectasis. Infection can occur after inhalation of contaminated aerosols or direct inoculation of the oral cavity with animal secretions and subsequent aspiration. Acute infection can be clinically indistinguishable from other forms of bacterial pneumonia. Chronic infection has been described in a patient with bronchiectasis. *P. multocida* has been isolated as a causative agent of sinusitis, otitis, epiglottitis, supraglottitis, bronchitis, lung abscess, and empyema. Bacteremia is seen in 15% to 50% of cases of respiratory infection.

Invasive or disseminated infection

Invasive or disseminated infections generally occur in the extremes of age or in those with some form of immunocompromise: pregnancy, diabetes mellitus, cirrhosis, chronic steroid use, malignancy, HIV infection, or organ transplantation. Most cases are associated with animal bites or scratches, some are associated with animal exposure without injury, and a small percentage of cases have no history of exposure to animals. In a single-center study of 44 patients with *P. multocida* infection, immunocompromised patients were more likely to present with a non-bite, non-skin, invasive infection. These patients were more likely to require hospitalization or ICU level of care and had a higher mortality rate.

Infectious arthritis is a rare complication of *P. multocida* infection and usually occurs in patients with underlying joint disease or steroid use. Infections are usually monoarticular and primarily affect the knee. Patients with bacteremia are more likely to have polyarticular infection. Osteomyelitis is usually seen following animal bite and tends to involve the upper extremity. Prosthetic joint infection (PJI) due to *P. multocida* has been increasingly reported. In a review of 32 cases, the authors found that almost all cases had known animal contact, the knee was most commonly infected, and 42% of cases had an underlying immunosuppressing condition.

Meningitis is usually seen among infants or in adults >55 years. A 2010 review noted 36 adult cases reported in the literature; additional cases have been reported since that time. There are four mechanisms by which *P. multocida* can cause meningitis: (1) direct inoculation following animal bite, (2) contamination from colonized site after trauma or neurosurgery, (3) bacteremic seeding of meninges, and (4) local spread from an infected site, such as otitis. The clinical presentation and cerebrospinal fluid (CSF) findings are typical of bacterial meningitis. Animal contact is reported in almost all cases. Neurologic complication rates are similar to other causes of bacterial meningitis and occur in approximately 22% of adult patients. In a case series of 29 adult patients in 2002, bacteremia was reported in 60% of patients, CSF Gram stain was positive in 50%, and mortality rate approached 30%. In a 2009 review of 38 pediatric cases, bacteremia occurred in 50% of cases with seizures complicating 29% of cases. Death was observed in only 2/38 cases.

Bacteremia can occur with any primary site of *P. multocida* infection but is documented in 20% to 30% of invasive infections. The most common comorbidities observed in cases of bacteremia are cirrhosis, diabetes, and malignancy. However, up to 38% of patients have no underlying comorbidities, 17% have no animal exposure, and 13% have no localized site of infection. A review of

156 cases of *P. multocida* bacteremia found a mortality rate of 23%. Endocarditis due to multiple *Pasteurella* species has been reported, including cases of prosthetic valve disease. Left-sided endocarditis is most common, although there are reports of pulmonic valve and tricuspid valve endocarditis. Presentation is typically acute, and mortality is approximately 50%, with higher mortality rates in those with immunosuppressing conditions.

P. multocida is also known to cause intra-abdominal infections. Cases of spontaneous bacterial peritonitis have been reported, mostly in the setting of alcoholic cirrhosis. Cases of peritoneal dialysis-associated infection have also been frequently reported. A 2015 review of 37 cases revealed that 87% of patients had cat exposure, with 25 cases confirming direct contact with dialysis equipment. In 10 cases, there was visible puncture of dialysis equipment. Cases of appendicitis-associated peritonitis have also been reported.

Other serious infections caused by *P. multocida* for which there are case reports in the literature include pyelonephritis, thyroiditis, mycotic aneurysm, vascular graft infection, endophthalmitis, uvulitis, liver abscess, cholecystitis, breast expander infection, chorioamnionitis, neonatal sepsis, and chronic ulceration of the penis.

TABLE 144.2 **ANTIBIOTIC SUSCEPTIBILITIES OF *PASTEURELLA MULTOCIDA***

Usually susceptible	Variable	Usually resistant
Penicillin and derivatives	Semisynthetic penicillins	Vancomycin
Ampicillin (± sulbactam)	Oxacillin	Clindamycin
Amoxicillin (± clavulanate)	Dicloxacillin	Erythromycin (oral)
Ticarcillin (± clavulanate)	Cloxacillin	
Piperacillin (± tazobactam)	Nafcillin	
Second- and third-generation cephalosporins[a]	Cefaclor	
Cefuroxime	First-generation cephalosporins	
Cefotetan	Cephalexin	
Cefoxitin	Cefazolin	
Cefixime[b]	Cephradine	
Cefprozil[b]	Cefadroxil	
Loracarbef[b]	Erythromycin (IV)	
Cefpodoxime[b]	Aminoglycosides	
Ceftriaxone	Gentamicin	
Ceftizoxime	Tobramycin	
Cefotaxime	Amikacin	
Ceftazidime		
Advanced-generation Cephalosporins		
Ceftaroline[b]		
Ciprofloxacin[b]		
Chloramphenicol		
Trimethoprim–sulfamethoxazole[b]		
Aztreonam		
Imipenem		
Tetracycline		
Doxycycline		

[a] Cefaclor, an oral second-generation cephalosporin, is often not effective.
[b] There are few clinical data on the use of these agents but by in vitro testing they should be effective.

Therapy

Antibiotics

The antibiotic of choice for treatment of susceptible *P. multocida* infections is penicillin. Ampicillin and amoxicillin are effective, but antistaphylococcal penicillins such as oxacillin and nafcillin are not recommended. The second- and third-generation cephalosporins have good activity against *P. multocida*, but first-generation cephalosporins and cefaclor are not reliable. There are few cases of β-lactamase-producing *P. multocida* in humans reported, mostly from respiratory samples. However, rates of β-lactamase production may be increasing. A 2006 French study of 192 consecutive clinical isolates found only one β-lactamase-producing *Pasteurella* strain in a respiratory sample, but a 2015 US single-center review noted β-lactamase production in 5/32 isolates tested, including nonrespiratory sites. The authors found no difference in severity or type of infection based on β-lactamase production. Antibiotic susceptibility testing should be routinely performed.

Pasteurella is uniformly sensitive to tetracycline and chloramphenicol. Fluoroquinolones, azithromycin, clarithromycin, and trimethoprim-sulfamethoxazole (TMP-SMX) have good in vitro activity. Clinical experience with these agents is limited, but they are an option for patients allergic to penicillin and cephalosporins who cannot tolerate tetracyclines. While *Pasteurella* is universally resistant to clindamycin and vancomycin, most strains are resistant to erythromycin and only moderately sensitive to aminoglycosides. Table 144.2 shows appropriate antibiotic choices based on available data.

Prophylactic antibiotic therapy for bite wounds

Although antimicrobial therapy is indicated for infected bite wounds, its value in prophylaxis following bite injury is controversial. This is largely due to the small number of patients enrolled in such studies. The decision to prescribe antibiotics at the time of injury depends on the risk of infection, which can be assessed by the criteria in Table 144.3. In addition, specific risk factors for *P. multocida* are listed in Table 144.4. If a wound generally shows no sign of infection after 24 hours, *P. multocida* infection is unlikely to develop. However, for individuals with underlying risk factors and for bites at risk for *P. multocida* infection, prophylaxis is reasonable even if they present late. Because bite wounds usually contain multiple organisms, including anaerobes, prophylaxis is usually with amoxicillin-clavulanate for 3 to 5 days. Alternatives include

TABLE 144.3 **RISK FACTORS FOR WOUND INFECTION**

	High	Low
Type of wound	Puncture	Laceration
	Crush injury	No crushing of tissues
	Foreign material introduced	No contamination
	Extends to bone or joint	Superficial
	Requires surgical repair	No surgical repair
Site of wound	Extremity, especially hand	Trunk, buttocks, head, minor facial wounds
Species of animal	Cat, pig, bovine	Dog, rodent
Delay before presentation	>8 h	≤6 h, or >48–72 h without signs of infection
Management prior to presentation	Poor cleaning	Good cleaning
Patient characteristics	>55 yr or ≤1 yr of age	No underlying disease

TMP-SMX or quinolones, in addition to clindamycin or metronidazole to cover anaerobes. For further discussion of the management of bite wounds, see Chapter 23, "Human and animal bites."

Treatment of infected wounds

Infected wounds should be thoroughly cleaned and have deep cultures performed before the initiation of antibiotics. Surgical evaluation should be performed especially when joints or extremities are involved or when there is extensive tissue damage. If infection with intense local inflammation develops within 24 hours, *Pasteurella* should be strongly suspected. Because the rate of serious sequelae is high, the clinician should have a low threshold for admission and surgical consultation. If infection develops after 24 to 48 hours, gram-positive organisms are more likely to be the cause, and therapy should be directed toward *Staphylococcus, Streptococcus* spp., and anaerobes. However, if the patient has underlying risk factors for *P. multocida* infection, coverage for this organism should be included in the regimen. Table 144.1 shows the antibiotics of choice for *P. multocida*. Uncomplicated cellulitis should be treated for 7 to 10 days, but more complicated wound infections may require longer treatment.

TABLE 144.4 **RISK FACTORS FOR *PASTEURELLA MULTOCIDA* INFECTION**

Wound	Patient
Deep puncture	≤1 yr or >55 yr of age
Feline, porcine	Liver disease, especially cirrhosis HIV
Deep feline scratch	Solid tumors, leukemias
	Immune-modulating medications
	Chronic respiratory disease
	Collagen vascular disease
	Pregnancy
	Artificial heart valve
	History of cranial trauma or surgery

Therapy for other *P. multocida* infections

A key factor in successful treatment of *P. multocida* infections is suspicion of the organism. A history of animal contact should always be obtained, and the patient examined carefully for signs of even minor trauma. Gram stains of wounds or purulent collections are positive in up to 50% of cases. If *P. multocida* infection is a possibility, therapy should include penicillin or a second- or third-generation cephalosporin. Tetracycline, fluoroquinolones, and TMP-SMX are alternatives if β-lactam allergy is present.

In β-lactam-allergic patients presenting with meningitis, chloramphenicol can be used. Cases of successful treatment with aztreonam and meropenem have been reported. The optimal duration of treatment for meningitis and respiratory infections is unknown, but most series suggest 2 weeks and 7 to 10 days, respectively. Joint infections, osteomyelitis, and abscesses require drainage and debridement in addition to antibiotic therapy. In the review of prosthetic joint infection, prosthesis removal was required in 54% of cases. Patients with endocarditis should be treated with medical and surgical therapy, and duration of antibiotics is generally 6 weeks. Limited experience with peritoneal dialysis catheter infections shows that 2 weeks of antibiotics is typically sufficient, with 65% of cases receiving intraperitoneal antibiotics. Peritoneal dialysis catheter retention was possible in 89% of patients.

Suggested reading

Brook I. Management of human and animal bite wound infection: an overview. *Curr Infect Dis Rep*. 2009;11:389–395.

Giordano A, Dincman T, Clyburn BE, Steed LL, Rockey DC. Clinical features and outcomes of Pasteurella multocida infection. *Medicine (Baltimore)*. 2015;94(36):e1285.

Honnorat E, Seng P, Savini H, Pinelli PO, Simon F, Stein A. Prosthetic joint infection caused by Pasteurella multocida: A case series and review of literature. *BMC Infect Dis*. 2016;16(1):435.

Kawashima S, Matsukawa N, Ueki Y. *Pasteurella multocida* meningitis caused by kissing animals: A case report and review of the literature. *J Neurol*. 2010;257:653–654.

Lion C, Conroy MC, Carpentier AM, et al. Antimicrobial susceptibilities of *Pasteurella* strains isolated from humans. *Int J Antimicrob Agents*. 2006;27:290–293.

Migliore E, Serraino C, Brignone C, et al. *Pasteurella multocida* infection in a cirrhotic patient: Case report, microbiological aspects and a review of literature. *Adv Med Sci*. 2009;54(1):109–112.

Muntaner L, Surinach JM, Zuniga JM, et al. Respiratory pasteurellosis: Infections or colonization? *Scand J Infect Dis*. 2008;40:555–560.

Nseir W, Giladi M, Moroz I, et al. A retrospective six-year national survey of *P. multocida* infections in Israel. *Scand J Infect Dis*. 2009;41:445–449.

Oehler RL, Velez AP, Mizrachi M, et al. Bite-related and septic syndromes caused by cats and dogs. *Lancet Infect Dis*. 2009;9:439–447.

Poliquin PG, Lagacé-Wiens P, Verrelli M, Allen DW, Embil JM. Pasteurella species peritoneal dialysis-associated peritonitis: Household pets as a risk factor. *Can J Infect Dis Med Microbiol*. 2015;26(1):52–55.

Vondra MS, Myers JP. *Pasteurella multocida* bacteremia: Report of 12 cases in the 21st century and comprehensive review of the adult literature. *Infect Dis Clin Pract*. 2011;19(3):197–203.

Wilson BA, Ho M. Pasteurella multocida: From zoonosis to cellular microbiology. *Clin Microbiol Rev*. 2013;26(3):631–655.

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Pneumococcus

Maurice A. Mufson and Nancy B. Norton

Introduction

An enduring pathogen since its discovery in 1881, *Streptococcus pneumoniae* (pneumococcus) ranks first among all causes of community-acquired pneumonia (CAP), second as a cause of bacterial meningitis among adults, and is a frequent cause of sepsis and meningitis among children. The high case-fatality rates from invasive (bacteremic) pneumococcal disease (IPD) attest to its importance as a pervasive pathogen. Case-fatality rates in IPD approach about one in six cases of pneumonia among elderly and about one in ten among middle-aged adults, about one in three cases of meningitis among adults and one in 20 cases of meningitis in children, and nearly nil in cases of bacteremia without localization among children 4 years of age or younger. Persistent high case-fatality rates from IPD during the second half of the twentieth century, despite effective antibiotic treatment regimens, drove the development and licensure of polysaccharide vaccines for adults and children.

Diagnostic procedures

Pneumonia

The antibiotic treatment of CAP among patients admitted to hospital must be initiated without delay and should be started before the patient leaves the emergency department, based on expert empiric treatment guidelines, even before the causative organism is established by diagnostic laboratory procedures. The diagnosis of *S. pneumoniae* pneumonia initially represents a presumptive clinical judgment taking into account its common occurrence, symptoms and signs, age of the patient, and the results of rapid laboratory tests, when available. Unequivocal evidence of the specific etiologic diagnosis of *S. pneumoniae* pneumonia requires isolation of the organism from blood or another otherwise sterile site, such as pleural fluid, with results not available usually until the next day. Blood cultures should be done to assess the invasive nature of the infection and to test the isolated strain for antibiotic sensitivity, because of the increasing emergence of intermediate and high resistant strains worldwide. A single set of cultures obtained before the start of antibiotic treatment is adequate for recovery of the organism. All *S. pneumoniae* strains recovered from sputum and blood, cerebrospinal fluid (CSF), and pleural fluid must be tested for susceptibility to penicillin and other antibiotics commonly used in the treatment of pneumococcal disease. *S. pneumoniae* can be recovered also from respiratory tract secretions. The finding of pneumococci in sputum or a nasal swab should be interpreted in light of their frequent carriage in the upper respiratory tract. Their recovery from the respiratory secretions adds only modest confidence for establishing a specific etiologic diagnosis. To monitor in a community the occurrence of pneumococcal vaccine serotypes or the emergence of replacement serotypes, specific serotypes can be determined by capsular swelling procedures (quelling reaction) employing serotype-specific antisera (Statens Serum Institut, Copenhagen, Denmark).

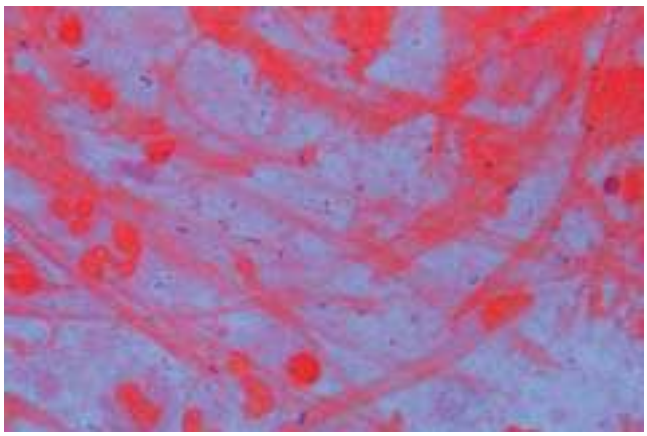

FIGURE 145.1 Gram-stained sputum specimen positive for *Streptococcus pneumoniae* demonstrates lancet-shaped gram-positive diplococci.

Although recovery of *S. pneumoniae* from blood or pleural fluid represents the "gold standard" of etiologic diagnosis in CAP, rapid laboratory procedures can provide early evidence of this infection. Such tests include recognition of the organism on a Gram-stained smear of respiratory secretions by the presence of characteristic gram-positive, lancet-shaped diplococci (Figure 145.1) and detection of pneumococcal antigen in urine. The detection of pneumococcal C-polysaccharide cell wall antigen in a urine specimen by a commercial immunochromatographic membrane assay (BinaxNOW® *Streptococcus pneumoniae* Test) provides a quick (about 15 minutes), reasonably sensitive, and highly specific test for establishing the diagnosis in adults who become blood culture positive. In IPD, the immunochromatographic membrane assay of urine is about 77% to 87% sensitive and about 97% to 100% specific. In children with IPD, it is somewhat less specific. The immunochromatographic membrane assay applied to pleural fluid also provides a sensitive and highly specific means of identifying pneumococcal antigen.

The BinaxNOW® test involves dipping a special swab into a urine specimen, or a pleural fluid specimen, at room temperature and applying the swab to an immunochromatographic membrane in a booklet-like device that is closed after the swab is set up. A positive test result, which must be read 15 minutes later, appears as a pink-to-purple colored line in a window on the cover of the booklet. Importantly, isolation of the pneumococcal organism is still necessary to assess susceptibility to penicillin and other antibiotics.

Meningitis

A specific diagnosis of pneumococcal meningitis can be confirmed quickly during the initial examination of the patient by identification of the organism on a Gram stain of CSF or by detection of pneumococcal C-polysaccharide cell wall antigen in a CSF specimen using the immunochromatographic membrane assay. The test is performed and read in the same manner as described above for testing a urine specimen. However, in patients with pneumococcal meningitis, the test shows a very high sensitivity (100% or nearly so) and very high specificity (100% or nearly so) in both children and adults. The availability of rapid diagnostic tests for the diagnosis of *S. pneumoniae* meningitis facilitates prompt initiation of appropriate antibiotic therapy while waiting for the results of the culture of CSF.

Antibiotic susceptibility testing

The spectrum of antibiotic minimum inhibitory concentrations (MICs) of *S. pneumoniae* strains is routinely determined employing automated procedures against a panel of antibiotics specified by the Clinical and Laboratory Standards Institute (CLSI, Wayne, PA). The panel of antibiotics includes penicillin, cefaclor, cefuroxime, cefotaxime, ceftriaxone, cefepime, meropenem, levofloxacin, azithromycin, erythromycin, tetracycline, chloramphenicol, clindamycin, amoxicillin-clavulanate, trimethoprim–sulfamethoxazole, and vancomycin. MIC breakpoints for non-meningitis and meningitis isolates to selected antibiotics are included in the footnotes of Tables 145.1 and 145.2, respectively.

Although automated procedures have eclipsed other means of MIC determination, the MIC of an individual isolate of *S. pneumoniae* can be determined employing the E-test (AB Biodisk, Solna, Sweden). In this test, a penicillin-impregnated plastic-coated paper strip is placed on a blood agar plate inoculated with the isolate to produce a semiconfluent growth and incubated for 24 hours in a 5% CO_2 atmosphere. The MIC represents the point of intersection of the strip by the ellipsoid zone of inhibition.

Infections due to the pneumococcus

Pneumonia

Importance

Pneumonia is the most common clinical presentation of *S. pneumoniae* infection and accounts for about 40% to 60% of CAP. *S. pneumoniae* remains the most common cause of CAP; *Mycoplasma pneumoniae* and *Haemophilus influenzae* are the second and third most common causes, respectively. Only about 20% of pneumococcal pneumonias are invasive infections. The burden of pneumococcal pneumonia represents the number of invasive and noninvasive cases. By one estimate, almost one million cases of pneumococcal pneumonia occur each year in the United States, resulting in between 100 000 and 400 000 hospitalizations. Pneumococcal pneumonia affects every age group, but it is most prevalent in children under 5 and adults greater than 65 years of age. Case-fatality rates vary widely, from about 2% in children to as high as 40% in elderly persons.

Certain underlying morbidities increase the risk of acquiring pneumococcal pneumonia. In children, these include age less than 5 years, especially less than 2 years, absence of breastfeeding, day-care attendance, exposure to cigarette smoke, and lack of immunization with PCV7 or PCV13. In adults, these include age 55 years or older, immunodeficiencies due to human immunodeficiency virus (HIV), diabetes mellitus, functional or actual asplenia, humoral immunity defects, complement deficiencies, and neutrophil dysfunction. Additional risk factors include asthma; chronic obstructive

TABLE 145.1 RECOMMENDED EMPIRIC ANTIBIOTIC TREATMENT REGIMENS FOR S. PNEUMONIAE PNEUMONIA WHEN THE DIAGNOSIS IS SUSPECTED ON CLINICAL FINDINGS OR CONFIRMED BY LABORATORY PROCEDURES OR A POSITIVE BLOOD CULTURE

Clinical assessment of pneumonia	Recommended antibiotics[a]	Recommended antibiotic dosages[a]
Ambulatory adult without any comorbidity or recent antibiotic treatment	First choice: a macrolide, either azithromycin or clarithromycin or erythromycin	Azithromycin 500 mg on d 1 and then 250 mg PO for 4 d; or clarithromycin 500 mg PO q12h for 7–14 days; or erythromycin 500 mg PO q12h for 7–14 d
	Alternate choice: doxycycline	Doxycycline 100 mg PO q12h for 7–14 d
Ambulatory adult 50 years of age and older with one or more comorbid condition and/or recent antibiotic treatment	First choice: a fluoroquinolone with antipneumococcal activity.	Levofloxacin, 750 mg PO q24h for 5 d; gatifloxacin, 400 mg PO q24h for 7–14 d; moxifloxacin, 400 mg PO q24h for 7–14 d; or gemifloxacin, 320 mg PO q24h for 7 d
	Alternate choice: amoxicillin–clavulanate or amoxicillin or cefuroxime plus a macrolide	Amoxicillin–clavulanate 875 mg/125 mg PO q12h for 7–14 d; amoxicillin 875 mg PO q12h for 7–14 d; or cefuroxime axetil 500 mg PO q12h for 7–14 d, plus azithromycin or clarithromycin as described above
Hospitalized adult with or without either comorbid conditions or recent antibiotic treatment	First choice: a fluoroquinolone with antipneumococcal activity	Levofloxacin, 750 mg PO q24h for 5 d; gatifloxacin, 400 mg PO q24h for 7–14 d; moxifloxacin, 400 mg PO q24h for 7–14 d; or gemifloxacin, 320 mg PO q24h for 7 d
	Alternate choice: ceftriaxone or cefotaxime plus a macrolide	Ceftriaxone, 1–2 g IV/IM q24h for 7–14 d; or cefotaxime, 1–2 g IV q8h for 7–14 d; plus Azithromycin, 500 mg IV, then PO, q24h for 7–10 d; or clarithromycin 500 mg PO q12h for 7–14 d

[a] *Streptococcus pneumoniae* isolated from blood or pleural fluid must be tested for antibiotic susceptibility and choice of antibiotic treatment should be based on these results. For these *S. pneumoniae* isolates (non-meningitis isolates), the MIC breakpoints in μg/mL of penicillin parenterally administered susceptible ≤2, intermediate = 4, and resistant ≥8; ceftriaxone susceptible ≤1, intermediate = 2, and resistant ≥4; cefotaxime susceptible ≤1, intermediate = 2, and resistant ≥4; azithromycin susceptible ≤0.5, intermediate = 1, and resistant ≥2; levofloxacin susceptible ≤2, intermediate = 4, and resistant ≥8. The antibiotic regimen selected should exceed these MICs.

TABLE 145.2 RECOMMENDED EMPIRIC ANTIBIOTIC TREATMENT REGIMENS FOR *S. PNEUMONIAE* MENINGITIS

Penicillin allergy	Age group	Recommendations for antibiotics	Recommendations for dosage of antibiotics[a]
No	Child	Ceftriaxone or cefotaxime	Ceftriaxone, 50 mg/kg IV q12h, or cefotaxime[a], 50 mg/kg IV q6h
		plus vancomycin	plus vancomycin, 10–15 mg/kg IV q6h (or q12h if 12–16 yr), 10–14 d
			plus dexamethasone 0.15 mg/kg IV q6h for 2–4 d, starting 10–20 minutes before first dose of antibiotics[b]
	Adult	Ceftriaxone or cefotaxime	Ceftriaxone, 2 g IV q12h, or cefotaxime, 2 g IV q4h
		plus vancomycin	plus vancomycin, 1 g IV q12h, 10–14 d
		plus dexamethasone, maybe plus rifampin	plus dexamethasone 0.15 mg/kg IV q6h for 2–4 d, 10–20 minutes before antibiotics, maybe plus rifampin, 300 mg PO q12h for 10–14 d
Yes	Child	Chloramphenicol	Chloramphenicol, 75–100 mg/kg IV q6h
		plus vancomycin	plus vancomycin 10–15 mg/kg IV q6h (or q12h if 12–16 yr), 10–14 d
		plus dexamethasone	plus dexamethasone 0.15 mg/kg IV q6h for 2–4 d, starting 10–20 minutes before first dose of antibiotics[b]
	Adult	Chloramphenicol	Chloramphenicol, 1500 mg IV q6h
		plus vancomycin	plus vancomycin, 1 g IV q12h, 10–14 d
		plus dexamethasone, maybe plus rifampin	plus dexamethasone 0.15 mg/kg IV q6h for 2–4 d, 10–20 minutes before antibiotics, maybe plus rifampin, 300 mg PO q12h for 10–14 d

[a] *Streptococcus pneumoniae* isolates recovered from cerebrospinal fluid (CSF) must be tested for antibiotic susceptibility and an antibiotic treatment regimen should be selected based on these results. For these CSF *S. pneumoniae* isolates, the MIC breakpoints in μg/mL of penicillin parenterally administered susceptible ≤0.06 and resistant ≥0.12; ceftriaxone susceptible ≤1, intermediate = 2, and resistant ≥4; cefotaxime susceptible ≤1, intermediate = 2, and resistant ≥4; vancomycin susceptible ≤1; chloramphenicol susceptible ≤4 and resistant ≥8. The antibiotic regimen selected should exceed these MICs. *S. pneumoniae* CSF isolates respond to ceftriaxone and cefotaxime because these third-generation cephalosporins achieve levels in the CSF above the MIC of most of these strains.

[b] Adjunctive dexamethasone, 0.15 mg/kg, every 6 hours for 2–4 days, in children residing in high-income countries (not low-income countries), preferably started 10–20 minutes before antibiotic therapy is begun, shows a decrease in any hearing loss and short-term neurologic sequelae, modest diminution of severity of illness, and slightly lowered case-fatality rate.

pulmonary disease; viral infections (especially influenza infection); chronic cardiac, hepatic, or renal conditions; alcoholism; and active and passive exposure to cigarette smoke.

Clinical and laboratory findings

The incubation period of pneumococcal pneumonia is 1 to 3 days. The onset of symptoms may be sudden, starting with rigors or a single shaking chill followed by high fever (102°F to 105°F), cough productive of rusty or blood-streaked sputum, dyspnea, tachypnea, hypoxia, pleuritic chest pain, and malaise. Because of pleuritic pain, patients may be observed to splint the affected lung. Other less specific symptoms include nausea, vomiting, headache, fatigue, and muscle aches. Some of the more serious complications that may develop and contribute to fatality rates are empyema, pericarditis, and respiratory failure.

Physical examination of the lungs may reveal rales over the affected lobe or segment. An increase in tactile fremitus and the presence of egophony indicates consolidation. Larger pleural effusions or empyema are demonstrated by dullness on chest percussion.

Neutrophilic leukocytosis occurs in about 80% of patients at presentation with most other patients developing leukocytosis within a few days. Some elderly and immunocompromised patients may never develop leukocytosis, so the absence of leukocytosis either at presentation or throughout the illness does not rule out pneumonia or invasive disease.

A chest radiograph should be obtained on each adult suspected of CAP. Pneumococcal pneumonia typically shows a lobar pattern of infiltration, but may demonstrate a focal segmental infiltrate. Chest radiographs may be clear early in the disease or in a dehydrated patient so a negative chest radiograph should be repeated after 24 hours. A negative chest radiograph may persist in some elderly or immunocompromised patients even in the presence of pneumonia.

Course and treatment

With appropriate antibiotic treatment the earliest response usually occurs within 12 to 36 hours, but sometimes as late as 96 hours. Fever defervesces first followed by amelioration of the respiratory rate, cough, and chest pain. Radiographic findings should not be used to assess early response to treatment because infiltrates usually clear slowly, over the next 2 to 3 weeks.

As *S. pneumoniae* is the dominant pathogen of CAP, deciding on a treatment regimen for CAP involves two key points: (1) judging the likelihood that *S. pneumoniae* is the pathogen and whether it is resistant to penicillin or other antibiotics, because as many as one-third of the *S. pneumoniae* strains exhibit intermediate or high resistance to penicillin, depending on the individual community, and (2) applying a validated quantitative severity score for assessing the severity of the pneumonia, as an adjunct to clinical judgment.

S. pneumoniae is frequently suspected as the pathogen of CAP on clinical grounds, sometimes aided by the results of rapid diagnostic procedures; however, the physician will not know whether the strain is penicillin susceptible or resistant unless cultures become positive. Consequently, appropriate antibiotic treatment must be started based on guidelines for the empiric antibiotic treatment of CAP (Table 145.1). Importantly, invasive pneumococcal pneumonia caused by intermediate resistant strains (MICs 4 μg/mL) can be successfully treated with antibiotic regimens that are employed to treat penicillin-susceptible strains.

A scoring method commonly used for stratifying risk in patients presenting with pneumonia is the CURB-65 score, which is a straightforward evaluation that divides patients into low- and high-risk categories. The patient receives one point for the presence of each of the following characteristics: *C*onfusion (acute) (≤8 on an abbreviated Mental Test), *U*rea (blood urea nitrogen > 19 mg/dL or 7 mmol/L), *R*espiratory rate > 30/minute, *B*lood pressure: diastolic < 60 or systolic < 90mm Hg, and age ≥65 years. A score of 3, 4, or 5 represents severe pneumonia with a high risk of death that must be managed in the hospital; a score of 2 represents less severe pneumonia, but one that carries an increased risk of death and should also be managed in the hospital; and a score of 0 or 1 represents mild pneumonia that can be managed on an ambulatory basis.

For an ambulatory adult without comorbid conditions or recent antibiotic treatment (within 3 months) and a CURB-65 of 0 or 1, the recommended treatment is a macrolide, either azithromycin, clarithromycin, or erythromycin, or alternatively, doxycycline (Table 145.1). For an adult older than 50 years with a score of 0 or 1, who has one or more comorbid conditions and/or recent antibiotic treatment, the recommendation is for a fluoroquinolone with antipneumococcal activity such as levofloxacin, gatifloxacin, moxifloxacin, or gemifloxacin. If *S. pneumoniae* is recovered from the patient and determined to be penicillin susceptible then amoxicillin-clavulanate or amoxicillin or cefuroxime plus either a macrolide or doxycycline is an alternative treatment.

A hospitalized (non-ICU) adult (CURB-65 score of 2 or greater) with or without comorbid conditions or recent antibiotic therapy should be treated with a fluoroquinolone with antipneumococcal activity or ceftriaxone or cefotaxime plus a macrolide (Table 145.1).

Meningitis

Importance and clinical findings

Pneumococcal meningitis, the most common bacterial meningitis, affects mainly older adults. Fatalities occur in about 20% to 30% of cases, with adults older than 50 years suffering the highest case-fatality rates. Among children, the case-fatality rate varies between 5% and 15%, substantially higher than the rate in invasive pneumococcal pneumonia. Between one-fourth and one-half of children who survive meningitis develop neurologic sequelae. The disease can develop as a complication of invasive *S. pneumoniae* pneumonia, purulent mastoiditis and sinusitis, endocarditis, asplenia, sickle cell disease, alcoholism, or a skull fracture with communication between the nasopharynx and the subarachnoid space. Patients with meningitis need to be tested for extra-meningeal sources of infection.

The clinical symptoms of meningeal inflammation include fever, headache, and stiff neck and the presence of a Kernig or Brudzinski sign or both; elevated CSF pressure; and CSF findings of frequent neutrophils, glucose level <40 mg/mL, and total protein about 100 mg/mL. Among elderly persons, the symptoms of meningitis may be confounded by changes of age, such as a stiff-feeling neck because

of arthritic changes in the cervical vertebrae or the confusion of dementia. Common neurologic complications include seizures and cranial nerve abnormalities.

Pneumococcal meningitis is a medical emergency and patients suspected of having meningitis require immediate diagnosis and treatment. A clinical diagnosis of meningitis almost always seems apparent based on clinical findings alone. A specific etiologic diagnosis of pneumococcal meningitis requires confirmatory laboratory procedures. Initially, this can be accomplished by recognition of the typical morphology of *S. pneumoniae* on a Gram smear of CSF or by testing the CSF using the rapid immunochromatographic membrane assay or both. Ultimately, the infecting strain needs to be isolated so that its MIC to the panel of antibiotics (see above, Antibiotic susceptibility testing) can be determined.

During the years 2000–2010 of routine immunization of children with PCV7, pneumococcal meningitis caused by vaccine serotypes decreased by almost two-thirds in children 2 years of age or younger and by about one-half among adults 65 years and older, but nonvaccine serotypes accounted for almost two-thirds of cases.

Treatment (Table 145.2)

Both adults and children should be treated with combination therapy, including a third-generation cephalosporin and vancomycin. Adjunctive dexamethasone, in children residing in high-income countries (not low-income countries), preferably started 10 to 20 minutes before antibiotic therapy is begun, shows a decrease in any hearing loss and short-term neurologic sequelae, modest diminution of severity of illness, and slightly lowered case-fatality rate. Adjunctive dexamethasone in adults, given 10 to 20 minutes before antibiotics, can provide some benefit, mainly by reduction of neurologic and auditory sequelae among survivors, although it does not significantly reduce case-fatality rates and questions remain of its ultimate benefit.

Otitis media

Importance and treatment

S. pneumoniae ranks among the three most common pathogens of acute otitis media (AOM) in children (*Haemophilus influenzae* and *Moraxella catarrhalis* are the other two pathogens) and penicillin-resistant *S. pneumoniae* represents a continuing problem in the treatment of this common infection. PCV7 was developed, in part, for prevention of AOM and its routine administration has substantially decreased AOM and long-term recurrent episodes due to vaccine serotypes.

Among children infected with a penicillin-susceptible strain, amoxicillin remains the preferred antibiotic (80–90 mg/kg/day PO, q12h for 5 to 7 days, limited to 1000 mg/dose) or amoxicillin–clavulanate (90 mg/kg/day PO, q12h for 10 days, preparation 600 mg/42.9 mg/5 mL suspension, given with milk or food). Treat children allergic to penicillin with erythromycin–sulfisoxazole (40–50 mg/kg/day PO, divided q6–8h, limited to 2 g/day). When penicillin-resistant strains are suspected, treat with amoxicillin–clavulanate (90 mg/kg/day PO, q12h for 10 days) or ceftriaxone (50 mg/kg IM/IV, once, limited to 1 g/dose).

AOM in adults can be treated with amoxicillin (500 mg q12h PO for 5–7 days or with more serious disease 500 mg q8h PO for 5–7 days), amoxicillin–clavulanate (500 mg/125 mg or 875 mg/125 mg PO, q12h, with food or milk), azithromycin (500 mg PO q24h × 1 day and 250 mg PO q24h × 4 days), erythromycin, clarithromycin, or trimethoprim–sulfamethoxazole. When penicillin-resistant strains are the likely pathogen, treat with azithromycin or clarithromycin.

Pneumococcal polysaccharide vaccine

Two pneumococcal vaccines of differing production are licensed (as of June 2013) for immunoprophylaxis of adults and children in the United States (see above, Introduction). The first PPSV23 received approval by the Food and Drug Administration (FDA) in 1983 and the second vaccine PCV13 received approval in February 2010.

PPSV23 is safe, cost-effective, and efficacious, with an overall efficacy rate of about 65% to 70% in immunocompetent adults for the serotypes contained in the vaccine. The 23 serotypes included in PPSV23 represent the most common serotypes that infect children and adults (namely 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F) and cover between 70% and 80% of IPD, depending upon the locality in the United States. Serotype 6A is not included in PPSV23, but is included in PCV13.

PPSV23 is recommended for adults at increased risk of serious IPD, including all adults 65 years and older and adults younger than 65 years of age who suffer certain underlying diseases including chronic heart and lung diseases, diabetes mellitus, CSF leak, cochlear implant, alcoholism, chronic liver disease and cirrhosis, functional and anatomic asplenia, lymphoma, leukemia, Hodgkin's disease, HIV infection, chronic renal failure, nephrotic syndrome, generalized malignancy, solid organ transplant, multiple myeloma, iatrogenic immunosuppression and who smoke cigarettes. However, adults 19 years of age and older who suffer immunocompromising diseases, CSF leaks, cochlear implants, and functional or anatomic asplenia, and who never previously received PPSV23 should, when these underlying diseases are recognized, receive one dose of PCV13 first and then receive one dose of PPSV23 about 8 weeks subsequently. If they previously received one or more doses of PPSV23, they should receive one dose of PCV13 one year after the last dose of PPSV23.

Routine revaccination with PPSV23 is not recommended. Adults who received their first dose of vaccine before 65 years of age should receive a second dose of PPSV23 after 65 years of age and at least 5 years after the first dose. Also a second dose of vaccine is recommended 5 years after the first dose for adults 19 years and older with immunocompromising diseases, CSF leaks, cochlear implants, and functional or anatomic asplenia. Antibodies wane over time in all adults; second doses of vaccine provide satisfactory booster responses. Injection site reactions occur somewhat more frequently after revaccination than after primary vaccination.

Recently, PCV13 was recommended for all adults age 65 years and older. If they have never received a pneumococcal vaccine the recommendation is for a single dose of PCV13 followed in 6 to 12 months by a single dose of PPSV23. However, if they have received a single dose of PPVS23 after age 65, they should receive also a single dose of PCV13 at least 1 year later. If they had received a single dose of PPVS23 before 65 years of age, then after age 65 years they should receive first a single dose of PCV13 and 6 to 12 months later a single dose of PPVS23. The two doses of PPVS23 should be given at least 5 years apart.

Routine immunization of children with PCV7 (which included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) for prevention of otitis media and IPD cases began in 2000 and ended in 2010. In assessments conducted during the ensuing 10 years, PCV7 proved highly efficacious in children, reducing substantially IPD cases due to vaccine serotypes, as much as 80% to 90%, or near elimination of some vaccine serotypes, and a reduction by at least one-half of total cases of IPD. Unexpectedly, an additional benefit of its usage in children was a substantial decrease among adults of IPD cases caused by PCV7 serotypes, likely due to diminished shedding of these serotypes by children, and consequently, less spread of these serotypes from children to adults, especially grandparents. As the number of cases of IPD due to vaccine serotypes declined both in children and adults, several other serotypes emerged worldwide to occupy this void, designated replacement serotypes, which were not included in PCV7 vaccine. The need to cover these replacement serotypes led to the development and approval of PCV13.

In 2010, PCV13 (which includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) replaced PCV7 for routine childhood immunization against pneumococcal otitis media and IPD. It is recommended for routine immunization of children 6 weeks to 5 years of age, starting at 2 months of age. The dose is 0.5 mL intramuscularly administered at 2, 4, 6, and 12 to 15 months of age. A catch-up schedule for children with an incomplete schedule of PCV13 or only PCV7 is available at the ACIP website (http://www.cdc.gov/vaccines/acip/index.html). A single dose of PCV13 is recommended for children 6 to 18 years of age. Children 2 years of age and older who are immunocompromised or have sickle cell disease or functional or anatomic asplenia should receive one dose of PPSV23 eight weeks or later after their last dose of PCV13 and a second dose of PPSV23 five years later, whereas immunocompetent children 2 years of age and older with chronic illness (chronic heart or lung diseases, cochlear implants, CSF leaks, or diabetes mellitus) should receive only a single dose of PPSV23 eight weeks or later after their last dose of PCV13.

Currently, pneumococcal vaccine coverage among at-risk adults falls short of Healthy People 2020 goals. Wider vaccine usage in children and adults can be expected to alter the prevalence of *S. pneumoniae* as an etiologic agent of AOM, pneumonia, and meningitis.

Suggested reading

Blaschke AJ. Interpreting assays for the detection of *Streptococcus pneumoniae*. *Clin Infect Dis*. 2011;52(Suppl 4):S331–S337.

Borchorst S, Møller K. The role of dexamethasone in the treatment of bacterial meningitis—a systematic review. *Acta Anaesthesiol Scand*. 2012;56:1210–1221.

Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Third Informational Supplement, M100–S23*. Wayne, Pennsylvania: CLSI; 2013.

Coco A, Vernacchio L, Horst M, *et al*. Management of acute otitis media after publication of the 2004 AAP and AAFP clinical practice guideline. *Pediatrics*. 2010;125:214–220.

Fletcher MA, Fritzell B. Pneumococcal conjugate vaccines and otitis media: an appraisal of the clinical trials. *Int J Otolaryngol*. 2012;312935: 1–15. [Erratum to "Pneumococcal Conjugate Vaccines and Otitis Media: An Appraisal of the Clinical Trials." *Int J Otolaryngol*. 2012;590206:1.

Lynch JP 3rd Zhanel GG. *Streptococcus pneumoniae*: does antimicrobial resistance matter? *Semin Respir Crit Care Med*. 2009;30:210–238.

Mandell LA, Wunderink RG, Anzueto A, *et al*. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(Suppl 2): S27–S72.

Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American city: a 20-year longitudinal study, 1978–1997. *Am J Med*. 1999;107:34S–43S.

Norton NB, Stanek RJ, Mufson MA. Routine pneumococcal vaccination of children provokes new patterns of serotypes causing invasive pneumococcal disease in adults and children. *Am J Med Sci*. 2013;345:112–120.

Thigpen MC, Whitney CG, Messonnier NE, *et al*.; Emerging Infections Programs Network. Bacterial meningitis in the United States, 1998–2007. *N Engl J Med*. 2011;26(364): 2016–2025.

146

Pseudomonas, stenotrophomonas, and burkholderia

Titus L. Daniels

Pseudomonas aeruginosa is an aerobic, gram-negative bacillus with a diversified ecologic niche. *P. aeruginosa* is highly pathogenic among immunocompromised patients and is responsible for substantial morbidity and mortality. *P. aeruginosa* is principally a healthcare-associated pathogen, although community-onset infection has been described among immunocompetent and immunocompromised patients (i.e., neutropenia, HIV, AIDS). Such patients may be encountered by primary care and subspecialty physicians alike, and diagnosis requires a high index of suspicion. Infections commonly associated with *P. aeruginosa* include pneumonias, bloodstream infections (BSI), urinary tract infections, and surgical site infections (Table 146.1). Two related species, *Stenotrophomonas maltophilia* and *Burkholderia cepacia*, are briefly discussed.

Epidemiology

The epidemiology of *P. aeruginosa* infections reflects its predilection for moist environments. In hospitals, *P. aeruginosa* has been isolated from respiratory devices, disinfectants, distilled and tap water, and sinks. *P. aeruginosa* can readily colonize the upper respiratory tract of mechanically ventilated patients, the gastrointestinal tract of patients receiving chemotherapy or broad-spectrum antibiotics, and the wounds of burn patients. Colonization usually precedes invasive infection.

Among healthcare-associated infections occurring in intensive care units, *P. aeruginosa* is among the most commonly identified pathogens. Emergence and spread of antimicrobial resistance, especially multidrug resistance (MDR), among *P. aeruginosa* is frequent. The National Healthcare Surveillance Network 2020 report revealed that 26.2% of device-associated isolates are resistant to quinolones and 20.3% are resistant to extended-spectrum cephalosporins. Furthermore, 20.7% of the isolates are resistant to carbapenems, an agent once considered universally active against *P. aeruginosa*. The emergence and spread of MDR *P. aeruginosa* challenges the clinician when selecting appropriate antimicrobial therapy and underscores the importance of obtaining cultures with susceptibility testing in patients suspected of having bacterial infections. Knowledge of local antimicrobial resistance trends is essential to ensure optimal patient outcomes.

Diagnosis

The clinical features of *P. aeruginosa* infections are indistinguishable from those of other bacterial organisms, and a definitive diagnosis requires specimen cultures from the suspected site of infection (i.e., blood, sputum, urine) to identify the organism. Other clinically important gram-negative organisms that resemble *P. aeruginosa* come from the genera *Stenotrophomonas*, *Burkholderia*, and *Ralstonia*.

TABLE 146.1 **RISK FACTORS FOR *P. AERUGINOSA* INFECTIONS**

Type of infection	Setting
Bacteremia	Neutropenia, pulmonary or urinary tract focus, burns
Pneumonia	Mechanical ventilation, neutropenia, chronic lung disease
Endocarditis	Injection drug use, prosthetic heart valve
Meningitis, brain abscess	Hematogenous or contiguous spread, neurosurgery, penetrating head trauma
Urinary tract infection	Bladder instrumentation
Osteomyelitis, septic arthritis (e.g., sternoclavicular joint)	Contiguous or hematogenous spread, injection drug use
Osteochondritis	Puncture wounds of the feet
Malignant external otitis	Diabetes, advanced age
Green nail syndrome	Water immersion, wet skin

Antimicrobial therapy

Initial selection of an agent should be guided by the site of infection, the patient's allergy history, and the institutional antibiogram. Early, aggressive antimicrobial therapy, with modification when susceptibility results become available, imparts a survival advantage and minimizes the emergence of antimicrobial resistance. Although several antipseudomonal antibiotics exist (Table 146.2), intrinsic or acquired resistance and bacterial persistence at sites of infection complicate management and eradication.

β-lactam antibiotics active against *P. aeruginosa* include the extended-spectrum penicillins, some extended-spectrum cephalosporins, the carbapenems (except ertapenem), and the monobactam aztreonam. Newer generation combination β-lactam β-lactamase inhibitors have become available for the treatment of resistant gram-negative bacteria, including *P. aeruginosa.* These agents form the basis for treatment of most *Pseudomonas* infections due to extensive clinical experience and patient tolerability. The high prevalence of reported penicillin allergy is the primary limitation.

The aminoglycosides tobramycin, amikacin, and gentamicin have excellent in vitro activity against *P. aeruginosa*. The concentration-dependent bactericidal activity and the post-antibiotic effect of aminoglycosides provide the rationale for once-daily dosing. Aminoglycoside monotherapy should be avoided due to selection of resistant mutants and increased risk of clinical failure. Renal function and serum aminoglycoside levels should be monitored closely.

The quinolones have been frequently used for the treatment of infections caused by *P. aeruginosa* and other bacteria. They possess excellent tissue penetration, good oral bioavailability, and a favorable safety profile. Ciprofloxacin is considered the more active fluoroquinolone. Increasing resistance to the quinolones, however, should temper reliance on their use as the basis for empiric therapy against *P. aeruginosa*, especially among hospitalized patients.

Use of polymyxin antibiotics has reemerged due to MDR and pandrug-resistant gram-negative infections, including *P. aeruginosa*. The polymyxins possess activity against a variety of gram-negative organisms but have been limited in use due to their adverse effects, namely nephrotoxicity and neurotoxicity. Polymyxins are currently recommended only for isolates resistant to other antibiotics. Susceptibility testing should be performed as resistance to the polymyxins has been reported.

Much controversy exists over the use of combination therapy ("double-coverage") for the treatment of infections due to *P. aeruginosa*. Data from a Cochrane review of sepsis comparing β-lactam and aminoglycoside combination therapy versus β-lactam monotherapy found no advantage to combination therapy for all-cause mortality (relative risk [RR] 1.01; 95% confidence interval [CI] [0.75, 1.35]) or clinical failure (RR 1.11; 95% CI [0.95, 1.29]). Empiric combination therapy for most serious infections may still be warranted when considering local resistance data and to ensure appropriate treatment of other possible infecting organisms. The guiding principle for selecting combination therapy should be that each agent has a unique mechanism of action; this will avoid a possible antagonistic effect and increase the likelihood that at least one administered agent is active against the offending organism; β-lactam and aminoglycoside combination therapies are the most studied and continue to be primarily recommended.

Infections caused by *P. aeruginosa*

Respiratory infections

P. aeruginosa pneumonia may follow colonization of patients in the setting of mechanical ventilation, antibiotic administration, neutropenia, AIDS, and chronic pulmonary disease, particularly in patients with cystic fibrosis (Table 146.3). Lower respiratory tract infection may be distinguished from airway colonization by an increase in quantity and purulence of respiratory secretions. Clinical manifestations may be fulminant, with fever, chills, dyspnea, productive cough, and systemic toxicity. Diffuse bronchopneumonia with nodular infiltrates is commonly seen on chest radiograph. Cavitary lesions may occasionally be seen. Pneumonia may be accompanied by bacteremia, particularly in neutropenic patients. Empiric antimicrobial treatment in the hospitalized or neutropenic patient with fever and lung infiltrate should include coverage for *P. aeruginosa*. Conventional antimicrobial therapy for *P. aeruginosa* pneumonia includes an antipseudomonal β-lactam combined with an aminoglycoside or a quinolone. Inhaled tobramycin (300 mg q12h) may be considered as adjunctive therapy.

Patients with cystic fibrosis are prone to chronic lower respiratory infections with mucoid strains of *P. aeruginosa*. These infections usually persist for a lifetime, with frequent acute exacerbations manifested by decreased exercise tolerance, increased cough and sputum, and weight loss. Therapy consists of an antipseudomonal penicillin containing ticarcillin or piperacillin plus an aminoglycoside. These patients may require large doses because of altered pharmacokinetics. Aggressive physiotherapy, nutrition, and hydration are essential.

TABLE 146.2 **ANTIMICROBIAL AGENTS FOR *P. AERUGINOSA***

Antimicrobial agent	Dose[a]/route /interval	Comment
β-Lactams		
Piperacillin–tazobactam	3.375 g IV q6h or 4.5 g IV q6h 4.5 g IV bolus, followed by 3.375 g IV q8h infused over 4 hours	Recommended interval dosing Recommended extending infusion dosing
Ceftazidime	2 g IV q8h	Preferred agent for CNS infections
Cefepime	2 g IV q12h	
Ceftazidime-avibactam	2.5 g IV q8h	
Ceftoloazone-tazobactam	1.5 g IV q8h	Recommended dose for cUTI and cIAI Recommended dose for HABP/VABP
Cefiderocol	2 g IV q8h infused over 3 hours	No gram positive or anaerobic activity
Meropenem	1 g IV q8h	
Meropenem-vaborbactam	4 g IV q8h infused over 3 hours	Addition of vaborbactam to meropenem does not increase activity against *Pseudomonas aeruginosa or Stenotrophomonas maltophilia*
Imipenem-cilastatin	0.5 g IV q6h	
Aztreonam	2 g IV q8h	Frequently reserved for penicillin-allergic patients
Quinolones		
Ciprofloxacin	400 mg IV q12h 500–750 mg PO q12h	Most active antipseudomonal quinolone in vivo
Delafloxacin	300 mg IV q12h 450 mg PO q12h	
Levofloxacin	750 mg IV/PO daily	
Prulifloxacin	600 mg PO daily	Not available in the United States
Aminoglycosides[b,c,d]		
Amikacin	15mg/kg IV once daily or 7.5 mg/kg IV q12h	
Gentamicin	5 mg/kg IV once daily or 2 mg/kg loading dose, then 1.7 mg/kg IV q8h	
Tobramycin	5 mg/kg IV once daily or 2 mg/kg loading dose, then 1.7 mg/kg IV q8h	
Polymyxins		
Polymyxin E (colistin)	1.5 mg/kg IV q8h	
Polymyxin B	0.75–1.25 mg/kg IV q12h	

[a] Suggested dosing is for adult patients with normal renal and hepatic function.
[b] Aminoglycosides are not recommended for monotherapy against *P. aeruginosa*.
[c] Once-daily aminoglycoside dosing has been shown to be effective, less nephrotoxic, and less ototoxic, and is the preferred dosing method.
[d] Aminoglycoside levels and renal function should also be closely monitored during therapy.
cIAI, complicated intra-abdominal infection; CNS, central nervous system; cUTI, complicated urinary tract infection; HABP/VABP, hospital acquired bacterial pneumonia/ventilator acquired bacterial pneumonia.

Bloodstream infections

BSI may complicate *P. aeruginosa* infections at other sites. Predisposing factors include neutropenia, hematologic malignancy, organ transplantation, vascular and urinary tract catheterization, and antibiotic use. The lower respiratory tract is the most common source of *Pseudomonas* bacteremia, followed by skin, soft tissues, and the urinary tract. Evaluation should include an aggressive search for the source of the bacteremia.

No distinct clinical characteristics differentiate *P. aeruginosa* BSI from other gram-negative bacteremias. Most patients have fever, tachycardia, and tachypnea. Many have signs of systemic toxicity with hypotension, shock, disseminated intravascular coagulopathy, and altered mental status. Skin manifestations include papules,

TABLE 146.3 **MANAGEMENT OF *P. AERUGINOSA* INFECTIONS**

Infection	Antibiotics[a]	Adjunctive
Meningitis	Ceftazidime[b] + AG	Intrathecal AG
Bacteremia	AP-BL + AG or FQ	Identify source
Endocarditis	AP-BL + AG or FQ	Valvulectomy for persistent bacteremia
Pneumonia	AP-BL + AG or FQ	Aggressive respiratory care
Malignant external otitis	AP-BL + AG or FQ	Surgical debridement may be necessary
Osteomyelitis	AP-BL + AG or FQ	Surgical debridement
Urinary tract	FQ alone or AP-BL ± AG	Remove catheter

[a] Recommended antibiotics for empiric coverage against *P. aeruginosa*. Therapy should be refined once susceptibility data are available.
[b] Aztreonam may be used for patients with penicillin or cephalosporin allergy. Other AP-BL do not achieve reliable cerebrospinal fluid concentrations.
AG, aminoglycoside; AP-BL, antipseudomonal β-lactam; FQ, fluoroquinolone (i.e., ciprofloxacin or levofloxacin).

bullae, and, rarely, ecthyma gangrenosum (Figure 146.1), a focal skin lesion characterized by hemorrhage, necrosis, and vascular invasion by bacteria. Prompt initiation of combination antimicrobial therapy is crucial because there is a high mortality. Therapy should continue for 2 to 3 weeks in seriously ill patients.

Infective endocarditis

Infective endocarditis caused by *P. aeruginosa* is rare and occurs primarily in the setting of injection drug use and occasionally with prosthetic heart valves. Injection drug users acquire this organism from nonsterile diluents such as tap water or nonsterile paraphernalia. Bacteremia with fever is invariably present. Tricuspid valve infection, which is typical, commonly presents with signs of septic pulmonary embolism. If treatment is early and aggressive with effective antibiotics, cure may be achieved without surgery. Tricuspid valvulectomy may be necessary in the event of bacteriologic failure or recurrence. Involvement of the aortic and mitral valves may manifest as a severe acute illness with sepsis and large arterial emboli necessitating early surgical valve replacement in addition to antimicrobial treatment. Combination

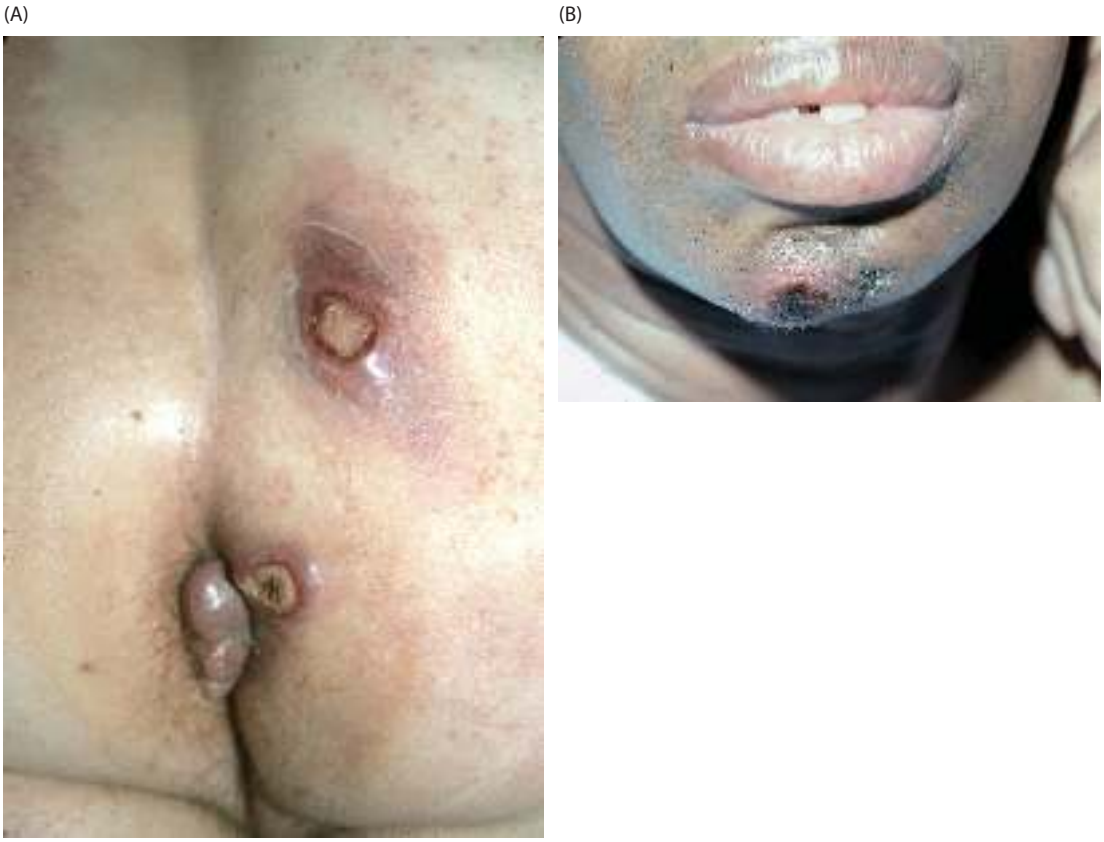

FIGURE 146.1 Ecthyma gangrenosum. (A) Lesions with ulceration and surrounding erythema. (B) A more classic lesion with necrosis and surrounding erythema.

therapy with a β-lactam agent and an aminoglycoside in high doses (e.g., tobramycin, 8 mg/kg/d) is recommended. Antibiotic therapy should be continued for at least 6 weeks.

Urinary tract infections

P. aeruginosa is a common nosocomial urinary pathogen. These infections are commonly associated with indwelling urinary catheters. Bacteremia, a common complication, may lead to metastatic infection (e.g., vertebral osteomyelitis). Symptomatic urinary tract infections should be treated by removing the catheter when possible and by administering an antibiotic. Monotherapy with an antipseudomonal β-lactam or a quinolone suffices unless there is secondary bacteremia or upper urinary tract infection. Oral quinolones may be used successfully even in complicated urinary tract infections. A 7- to 10-day course of treatment is adequate for uncomplicated cases. Longer courses of 2 to 3 weeks may be necessary for pyelonephritis, renal abscess, or complicating bacteremia. Asymptomatic bacteriuria does not typically require treatment. Eradication of the bacteriuria is often impossible if the patient has an anatomic abnormality or a foreign body, and antibiotics in this setting may select only for resistant organisms.

Meningitis

P. aeruginosa is a rare cause of meningitis and brain abscess in the general population, although it is a well-described complication of neurosurgery-related meningitis. Infection may occur by (1) extension from a contiguous structure such as mastoid or sinuses, (2) direct inoculation from penetrating trauma or neurosurgical procedures, or (3) metastatic spread from a distant site. Ceftazidime is the antimicrobial of choice because of its excellent in vitro activity and its ability to penetrate cerebrospinal fluid (CSF). Aztreonam and the carbapenems have good in vitro activity, but experience with these agents is limited. The extended-spectrum cephalosporins are not indicated for the treatment of meningitis. Addition of an aminoglycoside may be justified on the basis of possibly conferring synergy and preventing emergence of antibiotic resistance. Because of poor penetration of aminoglycosides into CSF, intrathecal or intraventricular doses may be required. There are anecdotal reports of successful therapy with parenteral ciprofloxacin, but quinolones should be used only when other antibiotics have failed or when organisms are resistant to β-lactam agents. Cure of *Pseudomonas* central nervous system infections may require surgical drainage of brain abscesses, debridement of infected tissues, and removal of prosthetic materials. A minimum of 2 weeks and as many as 6 weeks of antimicrobial therapy may be necessary.

Ear infections

Otitis externa is most commonly caused by *P. aeruginosa* and is usually associated with immersion (swimmer's ear). Patients complain of pain and pruritus. Examination reveals edema, exudate, and erythema of the pinna and external canal. This infection is treated with topical agents such as antibiotic drops (polymyxin, neomycin, or a quinolone) plus hydrocortisone or dilute acetic acid (see Chapter 6, "Otitis").

A more invasive and necrotizing process involving the bone and soft tissues of the external auditory canal and with potential to extend to the temporal bone and base of the skull is referred to as *malignant otitis externa* (Figure 146.2). This principally affects elderly persons and diabetics. Otalgia and purulent drainage from the external ear canal are present. Neurologic complications such as cranial nerve palsies may become manifest. CT or MRI is useful to delineate the extent of bone and soft tissue destruction and to monitor treatment. Because debridement may be necessary, surgical consultation is advised. Combination antimicrobial treatment is recommended for a minimum of 4 weeks. The course of treatment should be extended to 6 to 8 weeks for more extensive disease.

Bone and joint infections

P. aeruginosa causes osteomyelitis and septic arthritis as a result of hematogenous dissemination or contiguous spread. Vertebral osteomyelitis usually occurs in elderly patients with urinary tract infections associated with bladder instrumentation and in intravenous drug users. Neck or back pain with paraspinal tenderness is a

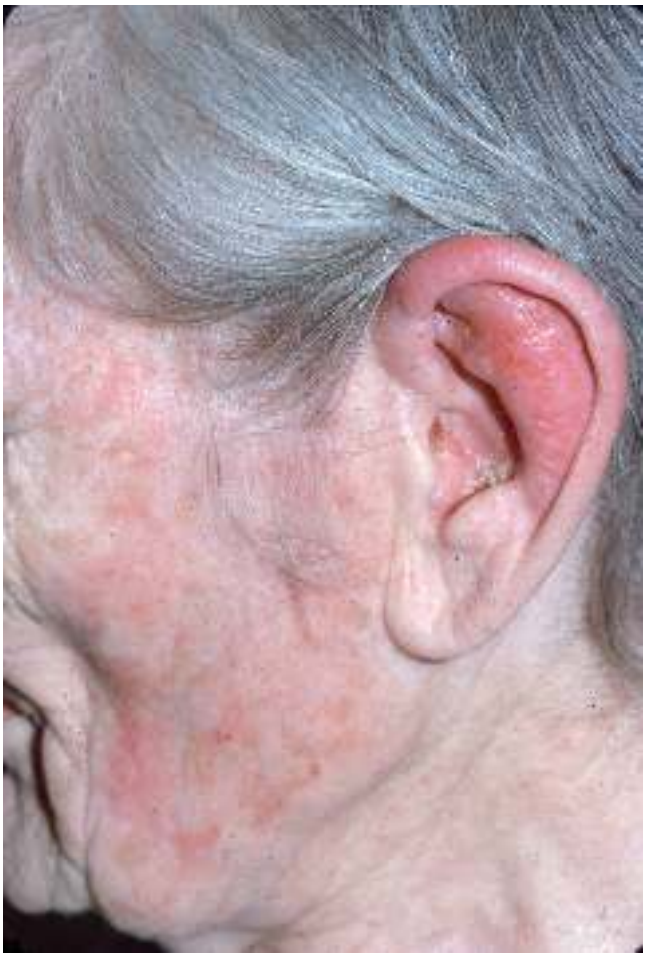

FIGURE 146.2 Malignant otitis externa. Edema and erythema of the helix, antihelix, and scapha of the ear are seen here. As infection progresses, the tragus often becomes involved. Visualization of the canal is frequently limited due to edema and pain.

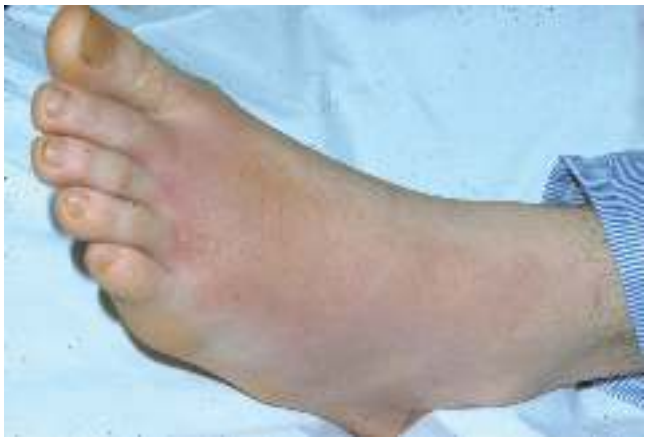

FIGURE 146.3 Osteochondritis following a nail puncture wound of the sole. Cellulitis is often a prominent feature in patients with acute osteochondritis due to *P. aeruginosa*, as evidenced in this photo. Edema is also a common finding.

common presentation. CT and MRI are sensitive diagnostic means of defining the extent of disease. The pathogen can be isolated by needle aspiration or biopsy under fluoroscopic or CT guidance. Occasionally, surgical exploration for biopsy, culture, and decompression is necessary. Removal of prosthetic material is usually necessary. Combination antibiotic therapy with an antipseudomonal β-lactam and either an aminoglycoside or quinolone should be used for a minimum of 4 to 6 weeks. Monotherapy has been used successfully, but treatment failures have occurred.

Contiguous osteomyelitis arises from direct extension of infected overlying skin and soft tissues or penetrating trauma. *P. aeruginosa* may be implicated in this setting in patients with infected diabetic foot ulcers. Vascular insufficiency and the polymicrobial nature of this infection may complicate management. The goal of therapy is to achieve effective levels of antimicrobials in bone and soft tissues. Prolonged antimicrobial treatment (up to 6 weeks), including a β-lactam antipseudomonal agent and an aminoglycoside, has been the current standard, but quinolones used either alone or in combination with a β-lactam have proved efficacious in open-label trials.

Osteochondritis of the foot involving bone and fibrocartilaginous joints is frequently seen following puncture wounds through the soles of footwear colonized by *P. aeruginosa* (Figure 146.3). Treatment consists of surgical debridement combined with an antimicrobial agent such as ceftazidime or ciprofloxacin for a minimum of 4 weeks.

Skin infections

Exposure to contaminated whirlpools, hot tubs, and swimming pools may produce *P. aeruginosa* folliculitis, a diffuse red maculopapular or vesicopustular rash (Figure 146.4). The eruption is self-limited and does not require specific antimicrobial treatment.

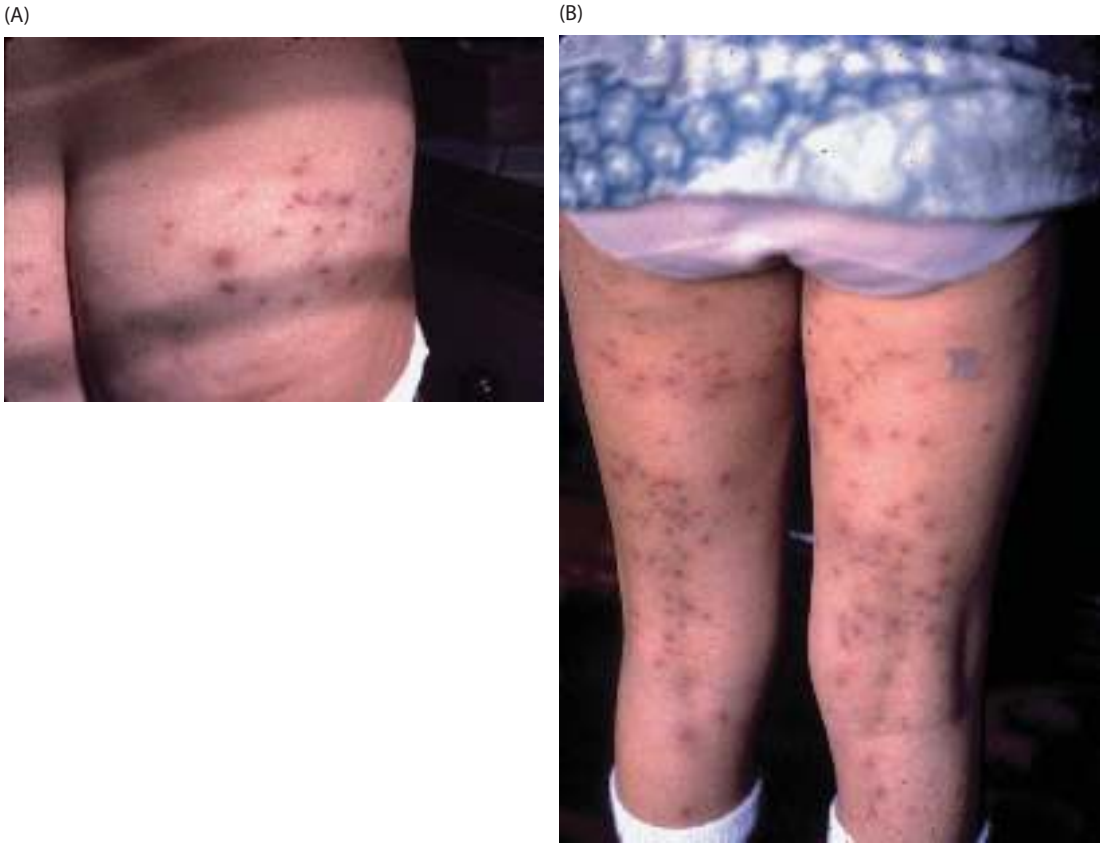

FIGURE 146.4 Folliculitis. The folliculitis of *P. aeruginosa* may appear similar to other common dermatologic conditions. The appearance of the lesions in Panel A raises the possibility of shingles. The patient in Panel B has a widespread infection that may be confused with staphylococcal infection or steroid-induced folliculitis. Culturing the contents of the lesions will aid in obtaining an accurate diagnosis.

Burn wounds may become colonized and subsequently infected with *P. aeruginosa*. Bloodstream invasion may thus occur, resulting in septicemia. Systemic antibiotic combinations should be administered. A topical agent such as mafenide acetate or silver sulfadiazine may be considered to reduce burn wound colonization. Avoidance of hydrotherapy also reduces the risk of *Pseudomonas* infections in burn patients.

Persons with a history of submersion of the hands may develop greenish discoloration of the nail plates and *Pseudomonas* nail bed infection. This condition has been called *green nail syndrome* (Figure 146.5). Treatment requires elimination of the exposure; orally administered ciprofloxacin is a useful adjunct.

The warm, moist toe webs of the feet may become infected with *P. aeruginosa*. The spaces between the third, fourth, and fifth toes are the most common sites. Toe web infections have been most commonly associated with military recruits, athletes, and laborers. Tinea pedis is a common antecedent. The infected tissue is damp, boggy, macerated, and white. Adjacent skin and subcutaneous tissue may become inflamed. More severe infection can progress to ulceration (Figure 146.6).

Pseudomonas toe web infection may resemble tinea pedis but does not improve with topical antifungal agents. *Pseudomonas* should be suspected when green pigment is visible on the patient's socks, bandages, or on dried exudate. Green toenails strongly suggest the diagnosis, and further evidence is obtained if Wood's light shows green-white fluorescence (Figure 146.7).

Treatment of toe web infections includes an antipseudomonal antimicrobial and soaking with 2% acetic acid solution. Prevention of infection is best achieved by keeping feet and toes clean and dry and by wearing work boots or athletic shoes on alternate days to allow for the lining to fully dry.

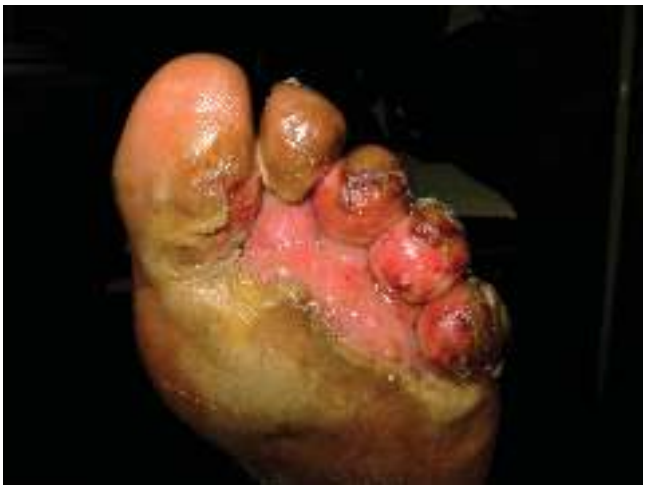

FIGURE 146.6 Toe web infection. As toe web infections progress, a characteristic macerated appearance is seen.

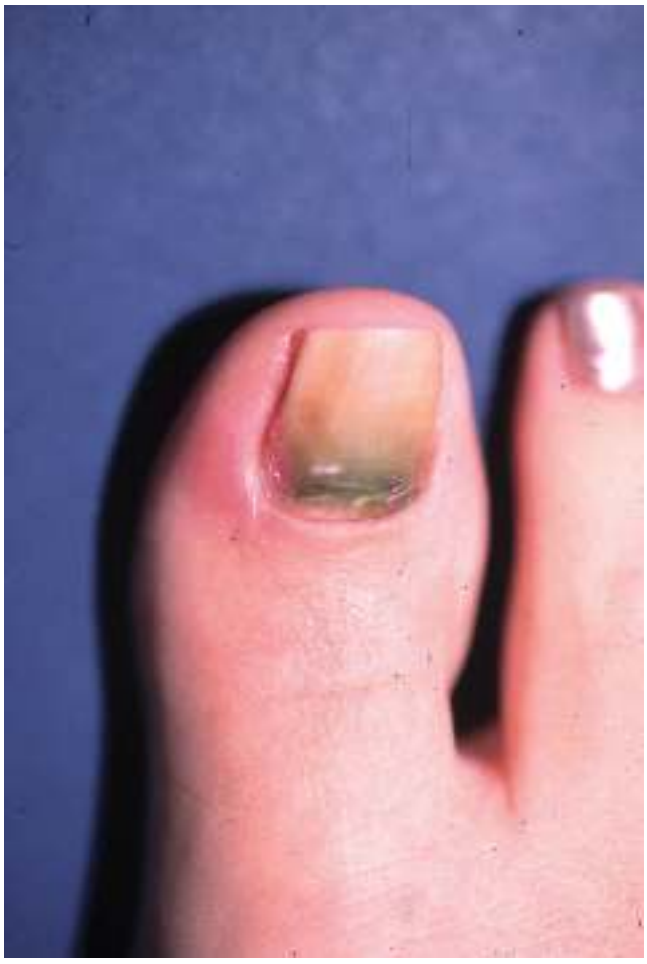

FIGURE 146.5 Green nail syndrome. Note the characteristic green appearance of the nail.

Infections caused by related species

Stenotrophomonas maltophilia is a healthcare-associated, gram-negative pathogen that may cause bacteremia, pneumonia, and wound infection. *S. maltophilia* healthcare-associated pneumonia

FIGURE 146.7 Use of a Wood's light reveals the typical luminescence classically described with *P. aeruginosa*.

is associated with mechanical ventilation, tracheostomy, use of nebulizers, and previous exposure to broad-spectrum antibiotics. Patients usually have preexisting lung conditions such as chronic obstructive pulmonary disease. Isolation of *S. maltophilia* from the respiratory tract in ventilator-associated pneumonia is an important predictor of mortality. Management of *S. maltophilia* pneumonia and other infections is often difficult because the organism is usually resistant to most antipseudomonal β-lactams, carbapenems, and aminoglycosides. Trimethoprim-sulfamethoxazole (TMP-SMX) is the antibiotic of choice for therapy. Ceftazidime, ticarcillin-clavulanate, and the quinolones have variable activity among strains. Combination therapy with TMP-SMX and a β-lactam such as ticarcillin-clavulanate or ceftazidime (if susceptibility is documented) has been proposed based on in vitro synergy and anecdotal reports of clinical efficacy. The polymyxins retain activity against selected highly resistant isolates.

Burkholderia cepacia is an opportunistic pathogen that may colonize the respiratory tract of a patient with cystic fibrosis and lead to persistent disease with progressive respiratory failure. Therapy is thwarted by antibiotic resistance to many β-lactam agents and aminoglycosides. The extended-spectrum cephalosporin agents (ceftolazone/tazobactam, ceftazidime/avibactam, cefiderocol) appear to have promise, with early in vitro data showing activity. Susceptibility testing is essential as resistance is variable to quinolones, TMP-SMX, and the carbapenems is common and variable. Chloramphenicol may retain activity, whereas the polymyxins are generally ineffective.

Suggested reading

Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(1):1–12.

Gaynes R, Edwards JR. Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis*. 2005;41:848–854.

Infectious Diseases Society of America and the American Thoracic Society. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–e111.

Kollef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: A risk factor for hospital mortality among critically ill patients. *Chest*. 1999;115:462–474.

McGowan JE. Resistance in nonfermenting gram-negative bacteria: Multidrug resistance to the maximum. *Am J Med*. 2006;119(Suppl 1):S29–S36.

Paterson DL. The epidemiological profile of infections with multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species. *Clin Infect Dis*. 2006;43:S43–S48.

Waterer GW, Wunderink RG. Increasing threat of gram-negative bacteria. *Crit Care Med*. 2001;29(Suppl 4):N75–N81.

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Rat-bite fevers

Neil S. Lipman

For 2,300 years, illness associated with rat bites has been recognized in India, which is believed to be the country of origin for the disease. The first recorded description of rat-bite fever was in lectures by a physician at Yale in the early nineteenth century. It was not until 1902 that Japanese workers describing the clinical entity in a European journal coined the term "*Rattenbisskrankheit*," or rat-bite fever. Rat-bite fever comprises two clinically similar but distinct bacterial diseases caused by unrelated agents, *Streptobacillus moniliformis, Streptobacillus notomytis*, and *Spirillum minus*. The organisms are distributed worldwide. Historically streptobacillary disease was reported to be more common in the United States and Europe, and spirillary disease more common in the Far East; however, almost all recently reported cases of rat-bite fever, which have been increasing in number, are predominantly streptobacillary. Genetic analysis of several recent disease-associated isolates has revealed that *S. notomytis*, not *S. moniliformis*, was the cause of rat-bite fever cases when exposure was to the black rat, *Rattus rattus*, and not the Norway or brown rat, *Rattus norvegicus.* The Norway rat is sold as pets, used as laboratory animal models, and is more common in many urban centers. It is likely that some of the previously reported cases of *S. moniliformis*-associated disease were cause by *S. notomytis,* as identification of the latter is challenging by conventional methods.

Rat-bite fevers are most frequently associated with the bite or, less frequently, a scratch or direct contact (e.g., kissing pet rat) with principally pet, but also wild or laboratory rats. A number of reported cases were not associated with rat bites or contact, although all patients had a history of occupational exposure to rat-infested areas or contaminated materials. Disease caused by these agents has also followed contact with a variety of other species, including mice, gerbils, guinea pigs, squirrels, dogs, cats, ferrets, turkeys, and weasels, all of which presumably had contact with rats or contaminated materials. Estimates are that 3 to 6 million animal bites occur annually in the United States of which 2% to 5% are caused by rodents. Many cases of rat-bite fever occur in individuals of low socioeconomic status in cities or, with increasing frequency, in association with pet rats, whose popularity is increasing. In 2011, it was estimated that 0.1% of US households owned one or more pet rats. Rats are also often fed to pet snakes and other reptilians with cases of rat-bite fever described in their owners. Asymptomatic rats are the principal reservoirs for the organisms that reside as commensals in the nasopharynx, middle ear, and proximal trachea.

Diagnosis is rare, likely the result of a low incidence of disease despite substantial potential exposure, a low index of suspicion of attending physicians, the routine postexposure use of effective antimicrobials, and the difficulty of isolating the organism in the laboratory. The true incidence in the United States is unknown since the disease is not reportable. Many of the reported cases in the United States are associated with children under the age of 12.

The rat is the natural reservoir and primary host of *S. moniliformis, S. notomytis*, and *S. minus*, none of which is routinely associated with natural disease in the species. Rarely, otitis media has been described with *S. moniliformis* in the Norway rat and *S. notomytis* in the black rat. The organisms are nasopharyngeal commensals and may be found in other tissues including the urine and blood. It is estimated that 10% to 100% of domestic and 50% to 100% of wild rats are colonized with *S. moniliformis*. Estimates of infection rates in laboratory rats during the first half of the previous century were similar to those reported for wild populations, but modern production techniques and maintenance, in concert with frequent monitoring of commercial suppliers, has reduced this rate dramatically. Almost all contemporary laboratory rat colonies

in developed countries are free of *S. moniliformis*. Although disease in humans has occasionally been associated with other species, these species are not believed to be commensal carriers.

Presentation

Rat-bite fevers are acute, systemic illnesses with relapsing fever. Streptobacillary rat-bite fever, streptobacillary fever, or streptobacillosis follows infection with *S. moniliformis* or *S. notomytis*. *Haverhill fever* and *epidemic arthritic erythema* are diseases caused by *S. moniliformis* acquired through ingestion of contaminated water, raw milk, or food. *Sodoku*, which derives from the Japanese word for rat (*so*) and poison (*doku*), spirillary rat-bite fever, and spirillosis are diseases resulting from *S. minus* infection. Although similar, these diseases can be differentiated clinically (Table 147.1). Streptobacillary rat-bite fever has a shorter incubation period than the spirillary form and is often accompanied by rash and arthralgia. Haverhill fever is more frequently associated with vomiting, diarrhea, and sore throat. An indurating chancre develops at the site of inoculation and accompanies clinical signs in the spirillary form. Dual infections, albeit extremely rare, may occur. Most cases of streptobacillary disease spontaneously resolve within 2 weeks. If the patient goes untreated, 13% of cases are fatal. Mortality is >50% in untreated patients with endocarditis. The clinical course of disease in infants may be particularly rapid and fatal. Mortality has been reported in adults following a short (<12 hour) presentation.

The incubation period of streptobacillary rat-bite fever is 2 to 10 days; however, onset usually occurs within 3 days of exposure. Clinical signs develop despite rapid healing of the bite wound, presumably as a result of bacteremia and septicemia. Illness of sudden onset is characterized by remittent chills, fever, headache, and myalgia and results from direct infectious as well as immune-mediated mechanisms. A morbilliform or petechial rash, which may be a result of leukocytoclastic vasculitis, develops in 75% of patients, frequently within days of onset, on either the lateral or the extensor surfaces of the extremities, sometimes involving the palms and soles. Infrequently, the rash may be generalized and/or present with pustules, desquamation, and purpura. Simultaneous with rash development, approximately 50% of patients have severe arthralgia or frank arthritis of at least one, but frequently more than one, large joint. The arthritis may be suppurative or nonsuppurative; monoarticular or migrating and polyarticular; and, rarely, occurs without other manifestations. Untreated, the course is biphasic, with fever and symptoms diminishing 2 to 5 days after onset and recurring several days later. Arthritis, endocarditis, myocarditis, pericarditis, hepatitis, pancreatitis, parotiditis, prostatitis, pneumonia, nephritis, meningitis, osteomyelitis, discitis, soft tissue abscesses, septicemia, and chorioamnionitis are reported complications. Relapsing fever with return of constitutional symptoms of 1 to 6 days' duration is not uncommon. Afebrile cases have been described.

In the United States, the spirillary form is considerably less common than streptobacillary disease. Illness follows an incubation period, usually 7 to 21 days but sometimes as short as 2 days or as long as months. There is initial healing of the bite wound. Subsequently, an indurated chancre or eschar develops at the wound site and is accompanied by a regional lymphadenitis and lymphangitis, fever, rigors, myalgia, and, in about 50% of the cases, an erythematous maculopapular rash originating from the wound. Arthritis is uncommon. Untreated, fevers and other symptoms resolve but then recur regularly, and mortality is estimated at between 7% and 13%.

Diagnosis

Diagnosis is suggested by a rat bite or rat contact, or exposure to rat-infested areas or contaminated materials, and clinical presentation. Patients may present without a history of rat bite or after a prolonged disease course. For infections caused by *S. moniliformis* or *S. notomytis*, definitive diagnosis depends on isolation of the organism by microbiologic culture and/or identification of the bacterium in culture or blood, fluid, or tissue samples by amplifying part of the 16S RNA gene using a generic primer set, followed by sequencing,

TABLE 147.1 **CLINICAL FEATURES OF RAT-BITE FEVERS**

Clinical features	Streptobacillary form	Spirillary form
Incubation period	2–10 days	7–21 days
Fever	+++	+++
Chills	+++	+++
Myalgia	+++	+++
Rash	++	++
	Morbilliform/petechial	Maculopapular
Lymphadenitis	+	++
Arthralgia, arthritis	++	–
Indurated bite wound	–	+++
Recurrent fever/constitutional signs (untreated)	Irregular periodicity	Regular periodicity

using polymerase chain reaction (PCR). A *S. moniliformis*-specific PCR, which likely also detects *S. notomytis* because of its >99.9% genetic similarity to *S. moniliformis,* has also been described using primers based on human and rodent strains. Detection by PCR in blood is more difficult than tissues because the copy number is lower, hemoglobin is inhibitory, and clearance of dead organisms is quicker after antibiotic treatment is initiated. Use of MALDI-TOF for identification has been inconsistently rewarding. There are no reliable serologic tests currently available in humans for either organism. A high index of suspicion in the laboratory is frequently necessary as these organisms are extremely difficult to isolate.

S. moniliformis and *S. notomytis* are fastidious, facultatively anaerobic, highly pleomorphic, asporogenous, gram-negative rods, measuring less than 1 × 1 to 5 μm long. Curved and looping, nonbranching filaments as long as 150 μm may be formed. Characteristic bulbous swellings have been described in older cultures or in cytologic specimens of *S. moniliformis*, resulting in dismissal of the organism as proteinaceous debris. *S. moniliformis* has two variants, the bacillary and the cell-wall–deficient, penicillin-resistant, apathogenic L-phase variant. Spontaneous conversion from one form to another, which alters the organism's sensitivity to antimicrobial agents, may be responsible for clinical relapses and resistance to therapy. *S. moniliformis* and *S. notomytis* are difficult to identify in most hospital laboratories because of their fastidious growth requirements and slow growth. The organisms may be demonstrated by Giemsa, Gram, Wright, or silver stain in blood, synovial fluid, or other body fluids; samples should be mixed with 2.5% sodium citrate to prevent clotting before examination. Blood and joint fluid should be cultured in media enriched with 15% blood; 20% horse, calf, or rabbit serum; or 10% to 30% ascitic fluid. Media employed successfully include blood agar bases, chocolate agar, Schaedler agar, thioglycollate broth, meat-infusion broth, and tryptose-based media. Nalidixic acid can be added to the media to prevent overgrowth by gram-negative bacteria. Brain–heart infusion cysteine broth supplemented with Panmede, a papain digest of ox liver, has been advocated. The medium should not contain sodium polyanethol sulfonate (SPS), an anticoagulant and bacterial growth promoter used in blood culture media, as it inhibits the growth of the organism. Inoculated media are incubated at 37°C/98.6°F in humidified 5% to 10% carbon dioxide atmosphere. Characteristic "puffballs" appear after 2 to 6 days in broth; on agar 1 to 2 mm round, gray, smooth, glistening colonies are observed. L-forms produce colonies with a typical fried-egg appearance. Identification is made by biochemical profile. The API ZYM system and fatty acid profiles may be valuable in rapid identification. In the United States the Centers for Disease Control and Prevention's Meningitis and Special Pathogens Branch or a state public health laboratory can be contacted for assistance with culture and/or diagnosis. The shell vial cell culture technique has been described to isolate *S. moniliformis* when growth in culture media was unsuccessful.

S. minus is a gram-negative aerobic, motile, rigid spiral bacterium. It is 0.2 to 0.5 × 3 to 5 μm long and has two to six wide angular windings and pointed ends with one flagellum at each pole. *S. minus* cannot be grown on any artificial medium. It may be demonstrated in dark-field microscopy in wet mounts of blood, exudate from the bite wound, cutaneous lesions, and lymph nodes or in Giemsa- or Wright-stained specimens from these sites. Isolation requires intraperitoneal inoculation of infected materials into guinea pigs or mice followed by dark-field examination of the animal's blood or peritoneal exudate 1 to 3 weeks later.

Differential diagnosis of rat-bite fevers can be broad and can include septic arthritides such as Lyme disease, gonococcal arthritis, and brucellosis and noninfectious inflammatory polyarthropathies such as rheumatoid arthritis. Presentation with fever and rash mimic systemic lupus erythematosus, viral exanthems, rickettsial infections, secondary syphilis, and drug reactions. A biologic false positive for syphilis occurs in up to 25% of patients with streptobacillary disease and in up to 50% of cases with the spirillary form.

Therapy

Both streptobacillary and spirillary forms of rat-bite fever respond well to appropriate antimicrobial therapy. *S. minus* is more sensitive to therapy. Penicillin is the drug of choice for both organisms, and a dramatic response to therapy may be expected. Dosage of 600,000 U of procaine penicillin G, administered intramuscularly, twice daily for at least 7 days, is recommended for uncomplicated forms of the disease. Intravenous penicillin therapy should be initiated until antimicrobial sensitivity is determined in cases of severe disease. Adults should receive 400,000 to 600,000 U/day, increasing dosage to 1.2 million U/d if no response is observed within 48 hours. Children are treated with 20,000 to 50,000 U/kg/d for 7 days followed by 7 days of oral penicillin V therapy. Endocarditis, if present, should be treated with high-dose penicillin G (susceptible isolates: 4.8 million U/d procaine penicillin intramuscularly; resistant isolates: 20 million U/d intravenously) in combination with gentamicin or streptomycin daily for 4 to 6 weeks. Streptomycin enhances activity against the L forms of *S. moniliformis*. Children with endocarditis should be treated with 160,000 to 240,000 U/d penicillin G up to the maximum adult dose. Tetracycline (500 mg/kg q6h by mouth) or streptomycin (7.5 mg/kg BID intramuscularly) are effective alternatives in penicillin-allergic patients. Amoxicillin-clavulanate, doxycycline, second- and third-generation cephalosporins, ciprofloxacin, chloramphenicol, clindamycin, the macrolides erythromycin and clarithromycin, and vancomycin have been successfully employed. Treatment failures have been reported with erythromycin. Prophylactic administration of penicillin may be considered following a rat bite, although the risk of nascent infection is low. However, prophylaxis should be a high consideration in infants because of the possibility of rapid progression and severe outcomes.

Suggested reading

Berger C, Altwegg M, Meyer A, Nadal D. Broad range polymerase chain reaction for diagnosis of rat-bite fever caused by *Streptobacillus moniliformis*. *Pediatr Infect Dis*. 2001;20:1181–1182.

Centers for Disease Control and prevention (CDC). Fatal rat-bite fever—Florida and Washington, 2003. *MMWR Morb Mortal Wkly Rep*. 2006;53:1198–1202.

Chean R, Stefanski DA, Wooley IJ, Francis MJ, Korman TM. Rat bite fever as a presenting illness in a patient with AIDS. *Infection*. 2012;40:319–321.

Edwards R, Fitch RG. Characterization and antibiotic susceptibilities of *Streptobacillus moniliformis*. *J Med Microbiol*. 1986;21:39–42.

Elliot SP. Rat bite fever and *Streptobacillus moniliformis*. *Clin Microbiol Rev*. 2007;37:13–22.

Eisenberg T, Ewers C, Rau J, Akimkin V, Nicklas W. Approved and novel strategies in diagnostics of rat bite fever and other Streptobacillus infections in humans and animals. *Virulence*. 2016;7:630–648.

Flannery DD, Akinboyo I, Ty JM, Averill LW, Freedman A. Septic arthritis and concern for osteomyelitis in a child with rat bite fever. *J Clin Microbiol*. 2013;51:1987–1989.

Fukushima K, Yanagisawa N, Imaoka K, Kimura M, Imamura A. Rat-bite fever due to Streptobacillus notomytis isolated from a human specimen. *J Infect Chemother*. 2018; 24:302–304.

Graves MH, Janda JM. Rat-bite fever (*Streptobacillus moniliformis*): A potential emerging disease. *Int J Infect Dis*. 2001;5: 151–154.

Khatchadourian K, Ovetchkine P, Minodier P, et al. The rise of the rats: A growing paediatric issue. *Paediatr Child Health*. 2010;15:131–134.

Loridant S, Jaffar-Bandjee MC, La Scola B. Shell vial cell culture as a tool for *Streptobacillus moniliformis* "resuscitation." *Am J Trop Med Hyg*. 2011;84:306–307.

Salmonella

Bruce S. Ribner

The salmonellae are gram-negative, non–spore-forming, facultatively anaerobic bacteria in the family Enterobacteriaceae. More than 2,500 different serotypes of *Salmonella* have been identified.

Salmonellae are widely distributed in nature. They are generally found in the gastrointestinal (GI) tracts of the hosts with which they are associated. Some salmonellae, such as *S. typhi* and *S. paratyphi*, are found to colonize only the human GI tract. Other *Salmonella* serotypes, such as *S. typhimurium*, have a wide range of hosts, including humans. Finally, some organisms, such as *S. dublin* and *S. arizona*, are rarely found in the GI tracts of humans. The specificity and range of the different serotypes helps to determine the epidemiology of infections caused by these bacteria.

Infections caused by the salmonellae are grouped into three major syndromes: gastroenteritis, typhoid or enteric fever, and localized infection outside of the GI tract. Although there is considerable overlap between these syndromes, their epidemiology and clinical presentations are distinct enough to make discussion by syndrome useful.

Gastroenteritis

Gastroenteritis accounts for most *Salmonella* infections in humans. The incidence of *Salmonella* gastroenteritis in the United States doubled during the 1980s and 1990s. Much of this increase was attributed to the widespread contamination of chickens and eggs as the industry became increasingly centralized. While the rate of *Salmonella* gastroenteritis stabilized in the late 1990s due to increased public awareness and improved sanitation during commercial processing, since then this rate has increased by 44%. It is estimated that there are 1.35 million episodes of *Salmonella* gastroenteritis annually in the United States, resulting in 26,500 hospitalizations and 420 deaths. Most cases of *Salmonella* gastroenteritis are traced to the ingestion of inadequately cooked poultry or eggs, either directly or through the consumption of such foods as Caesar salad, sauces containing raw eggs, and inadequately cooked stuffing contaminated by salmonellae from raw poultry. A recent study detected salmonellae contamination in 14% of the chickens sold in the United States: 68% of these isolates were resistant to at least one antibiotic. Beef, milk, and, rarely, fruits and vegetables have also been responsible for salmonellae infections. Pet reptiles, such as turtles, snakes, and lizards, frogs, and baby ducklings and chicks often have asymptomatic colonization of the GI tract. Young children who play with these animals may forget to wash their hands before eating, resulting in *Salmonella* gastroenteritis. Individuals at greatest risk for acquiring symptomatic disease are neonates under the age of 3 months; those with achlorhydria, either naturally or secondary to medication, or who are taking antacids; transplant recipients; individuals with lymphoma; patients with AIDS; and those aged >50 years. Children <5 years of age represent 27% of all patients with *Salmonella* gastroenteritis.

Salmonella gastroenteritis

Salmonella gastroenteritis has an incubation period of 8 to 72 hours, with shorter incubation periods being associated with higher amounts of ingested bacteria. The typical illness is accompanied by fever,

nausea, vomiting, abdominal cramping, and watery diarrhea; it lasts 4 to 7 days. The stool usually contains neutrophils, but dysentery, with gross blood and pus in the stool, is uncommon. Patients with *Salmonella* gastroenteritis occasionally have headaches and myalgias. Bacteremia, seen in approximately 8% of patients, is most common in those with impaired immunity (children <3 months and adults >65 years of age, those on corticosteroids or other immune suppressants, individuals with AIDS, those with inflammatory bowel disease, and those with hemoglobinopathies) or who are on hemodialysis. Bacteremia tends to occur early during the course of the illness. *Salmonella* gastroenteritis is typically a mild disease; it rarely leads to severe dehydration and cardiovascular collapse, although it is estimated that there are 26,500 hospitalizations and 420 fatalities a year in the United States from *Salmonella* gastroenteritis.

Approximately 50% of newborns with *Salmonella* gastroenteritis have GI carriage of the organism for >6 months. This rate decreases with age; <10% of adults remain colonized at 3 months. The administration of antibiotics during the early phase of illness is felt to increase the likelihood of carriage.

Typhoid or enteric fever

Typhoid fever is caused by salmonellae serotypes such as *S. typhi* and *S. paratyphi*, which are almost exclusively associated with humans. Transmission is by ingestion of contaminated food and water; although person-to-person transmission is possible, it is uncommon because of the large inoculum size required to cause illness in most individuals. In contrast to *Salmonella* gastroenteritis, the incidence of typhoid fever in developed countries has markedly decreased over the past few decades as sanitation and the quality of the water supply have improved. Most typhoid fever in the United States is acquired during foreign travel. A high percentage of infections acquired in the United States results from the ingestion of food prepared by chronic carriers, many of whom initially became colonized in another country.

Typhoid fever has an incubation period that is usually 7 to 21 days (range 3–60 days), depending on the size of the inoculum and the health of the host. Symptoms consist of fever, abdominal pain, hepatosplenomegaly, headache, and myalgias. Diarrhea is rare after the first few days. Although typhoid fever has classically been characterized as having a temperature–pulse dissociation with bradycardia in the face of a high fever, this phenomenon is uncommon. Rose spots, which are faint, maculopapular, salmon-colored blanching lesions found predominantly on the trunk, are seen in approximately one-third of patients. Biopsy of these lesions reveals perivascular, mononuclear cell infiltration, and culture frequently yields the organism.

Ninety percent of patients with typhoid fever have bacteremia during the first week of illness. This percentage decreases as the illness progresses. Positive stool cultures do not appear before the second week of illness, and the rate increases until, by the third week, 75% of patients have positive stool cultures. The white blood cell count is usually low in relation to the degree of illness. Occasionally an absolute leukopenia is seen.

The patient with untreated typhoid fever will have 4 to 8 weeks of sustained fever. Mortality of those with untreated disease is estimated to be 12% to 30% worldwide but only 1% in the United States. Mortality is highest in the immunocompromised, especially those with hemoglobinopathies, malaria, schistosomiasis, and infection with HIV. The major complication of untreated disease is hemorrhage from intestinal perforation secondary to ulceration and necrosis of the Peyer's patches in the ileum. Such hemorrhage may be seen during the third or fourth week of illness, often when the patient seems to be clinically improving. Other complications include pericarditis, endocarditis, splenic and hepatic abscesses, cholangitis, meningitis, and pneumonia. Ten percent of untreated patients relapse. Although one-fourth of patients with typhoid fever will have positive urine cultures, actual infection of the urinary tract with *S. typhi* and *S. paratyphi* is rare.

The differential diagnosis in a patient presenting with enteric fever may include malaria, amebiasis, and viral illnesses such as dengue or Epstein–Barr virus infection, and infection with non-*Salmonella* bacterial pathogens such as *Yersinia, Campylobacter*, and *Pseudomonas*.

Localized infections outside of the gastrointestinal tract

On rare occasions, *Salmonella* infection may present as a localized infection at a site other than the GI tract. This is most likely in patients with underlying illnesses. Sustained bacteremia with *S. choleraesuis*, *S. dublin* or *S. heidelberg* suggests an intravascular focus such as seeding of an atherosclerotic plaque or of the clot within a preexisting aneurysm, especially if the patient is elderly. If infection is localized to the abdominal aorta, surgery is generally necessary, as medical management alone is associated with a high mortality rate. Rarely, sustained bacteremia may result from endocarditis with a valve ring or septal abscess. Localized infection may also present as a hepatic or splenic abscess, especially if the patient has biliary tract stones, cirrhosis, or cholangitis.

Salmonellae are the second most common cause of gram-negative meningitis in neonates. They are also a common cause of osteomyelitis in children with hemoglobinopathies such as sickle cell disease.

Historically, *Salmonella* infection of the urinary tract was rare in the absence of nephrolithiasis, renal schistosomiasis, or renal tuberculosis. However, recent studies have documented an increase in *Salmonella* cystitis in elderly women, most of whom lacked structural abnormalities. It is felt that *Salmonella* cystitis most likely represents ascending infection of strains with greater pathogenicity for the urinary tract.

Approximately 2% of individuals who have *Salmonella* gastroenteritis will develop Reiter's syndrome. This occurs within 2 weeks of the onset of diarrhea and is associated with human leukocyte antigen (HLA) B27.

Chronic carriage

Because *Salmonella* is excreted in the stool of a high percentage of those recovering from acute infection for several months, the chronic carrier state is not considered to be present unless the

organism persists in the stool for >1 year. This occurs in approximately 1% to 4% of those with *S. typhi* infection and in fewer than 1% of those infected with other serotypes. Biliary tract carriage is most likely to occur in the elderly and those with cholelithiasis. Urinary tract carriage is most likely in those with bladder schistosomiasis and nephrolithiasis. Many chronic carriers have no clear history of a preceding acute *Salmonella* infection.

Diagnosis

Many clinical laboratories have changed to culture-independent diagnostic testing (CIDT) over the past decade. While such testing is potentially more rapid and detects pathogens that were frequently missed by culture alone in the past, they often do not identify organisms to the species level or identify the serotype of the organism. This negatively impacts the ability to detect foodborne outbreaks. They also do not provide antibiotic susceptibility information to guide treatment in those patients who require antibiotics. For these reasons, the US Centers for Disease Control and Prevention (CDC) encourages laboratories to culture specimens after a CIDT is positive (a practice called *reflex culturing*), and CIDT manufacturers have been encouraged to develop new tests to provide information that is now available only from cultured specimens.

Gastroenteritis

Although certain features may suggest *Salmonella* gastroenteritis in a patient, many other pathogens may produce an illness that is clinically indistinguishable. The diagnosis of *Salmonella* gastroenteritis depends on the isolation of the organism from a stool or blood specimen. As many clinical laboratories report that only 1% to 3% of stool specimens submitted for culture yield an enteric pathogen, and as mild gastroenteritis caused by *Salmonella* should not be treated with antibiotics (see "Therapy" section), many authorities have devised algorithms for selecting patients with gastroenteritis who should have stool cultures. Epidemiologic factors that should be sought as indicators of possible infectious diarrhea include the following: (1) travel to a developing area; (2) daycare center attendance or employment; (3) consumption of unsafe foods (e.g., raw meats, eggs, or shellfish; unpasteurized milk or juices) or swimming in or drinking untreated fresh surface water from, for example, a lake or stream; (4) visiting a farm or petting zoo or having contact with reptiles or with pets with diarrhea; (5) knowledge of other ill persons (such as in a dormitory or office or at a social function); (6) certain recent or regular medications (antibiotics, antacids, antimotility agents); (7) underlying medical conditions predisposing to infectious diarrhea (AIDS, immunosuppressive medications, prior gastrectomy, extremes of age); (8) receptive anal intercourse or oral–anal sexual contact; and (9) occupation as a food handler or caregiver. Signs and symptoms that suggest a bacterial etiology for gastroenteritis include fever, abdominal pain, and bloody stools. Some laboratories have also included a screen for the presence of fecal leukocytes or lactoferrin to select those stools that warrant further culture for enteric pathogens.

As mentioned previously, only 8% of patients with *Salmonella* gastroenteritis will have an accompanying bacteremia. This is most common in those with underlying diseases and tends to occur early during the course of the illness.

Typhoid or enteric fever

The patient with typhoid or enteric fever most commonly will present with symptoms of fever, abdominal pain, hepatosplenomegaly, headache, and myalgias. In endemic areas, the differential diagnosis is frequently between typhoid fever and malaria. Less commonly, rickettsial infection, dengue fever, plague, and tularemia may present with a similar syndrome. Systemic vasculitis may also present with a clinical picture similar to enteric fever. The definitive diagnosis of typhoid requires isolation of *S. typhi* or *S. paratyphi* or demonstration of the presence of antigens of these bacteria in body fluids. The body sites most likely to yield positive assays depend on the stage of illness. During the first week, blood cultures are most likely to be positive, whereas during the second and third week of illness stool cultures are usually positive. Cultures of rose spots, if present, and of a bone marrow aspirate are also frequently positive.

Serology for antibody to *S. typhi* antigens has been used widely in the past for the diagnosis of typhoid fever. Such assays must be used with caution as the antibodies persist for years after infection and may be elevated from vaccination. Although a fourfold rise in antibody titers in the context of an appropriate clinical illness is strong support for the diagnosis of enteric fever, a very elevated single assay can also be highly suggestive.

Localized infections outside of the gastrointestinal tract

The diagnosis of localized *Salmonella* infection outside of the GI tract depends on the isolation of the organism. This is especially true of localized infections such as visceral abscesses or endothelial infections, as there are no features that distinguish localized infection by the salmonellae as compared with the more common bacterial pathogens.

Chronic carriage

As mentioned previously, the chronic carrier state is not considered to be present unless the organism persists in the stool for >1 year. Although colonic colonization in the absence of biliary involvement has been reported, the overwhelming majority of patients with GI colonization have the gallbladder as the focus. To determine the site of colonization, a colonoscopy to detect colonic mucosal abnormalities and a culture of common bile duct drainage have been used. Imaging of the gallbladder can also be useful in determining underlying causes for colonization of the gallbladder such as cholelithiasis.

Patients with urinary tract chronic colonization can be evaluated with imaging studies to determine whether anatomic abnormalities, such as strictures or stones, are present. Such abnormalities make medical management alone less likely to be successful.

Therapy

People with diarrhea who attend or work in childcare centers, long-term care facilities, patient care, food service, or recreational water venues (e.g., pools and lakes) should follow jurisdictional recommendations for outbreak reporting and infection control.

Gastroenteritis

Salmonella gastroenteritis is usually a self-limited disease, and therapy should be primarily directed to the replacement of fluid and electrolyte losses. Antimotility agents such as loperamide are to be discouraged, especially if there is blood or mucus in the stool. Widespread resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole (TMP-SMX) now exists among the salmonellae, and multidrug-resistant salmonellae have been reported. Recent studies have shown that 5% of non-typhoidal *Salmonella* in the United States are resistant to five or more antimicrobial agents. Antimicrobial therapy for uncomplicated nontyphoidal *Salmonella* gastroenteritis, including short-course or single-dose regimens with oral fluoroquinolones, amoxicillin, or TMP-SMX, does not significantly decrease the length of illness, including duration of fever or diarrhea, and is associated with an increased risk of relapse, positive cultures after 3 weeks, antimicrobial resistance, and adverse drug reactions. However, certain patients are at increased risk for invasive infection and may benefit from preemptive antimicrobial therapy. Such patients would include neonates less than 3 months of age, those >50 years of age with cardiac, valvular, or endovascular abnormalities, or substantial joint disease, those on corticosteroids, persons with HIV infection, and persons with immunosuppression, inflammatory bowel disease, or hemoglobinopathies. Antibiotic therapy is also appropriate in those with severe disease (e.g., those with severe diarrhea, high fever, bloodstream infection, or who need hospitalization). Treatment in these patients should consist of an oral or intravenous antimicrobial administered for 7 days if immunocompetent and 14 days if immune compromised. Specific recommendations are listed in Table 148.1.

Typhoid fever

Fluoroquinolones have traditionally been the agents of choice for the treatment of typhoid fever. However, the recent emergence of nalidixic acid-resistant *S. enterica Typhi* (NARST), especially in strains acquired in southern and southeastern Asia, has led to the recommendation that other agents be preferentially used for the empiric treatment of typhoid fever. For patients who can tolerate oral therapy, azithromycin should be used for the treatment of typhoid fever. For hospitalized patients, ceftriaxone is the preferred empiric

TABLE 148.1 **THERAPY OF *SALMONELLA* INFECTIONS**

Syndrome	Suggested therapy
Gastroenteritis	
Normal host	Rehydration
Normal host with severe disease or risk factors	Levofloxacin, 500 mg (or other fluoroquinolone) once a day for 7 d; or azithromycin, 500 mg once a day for 7 d
Immunocompromised adult	Levofloxacin, 500 mg (or other fluoroquinolone) once a day for 14 days; or azithromycin, 500 mg once a day for 14 d
Neonate or immunocompromised child	None or ceftriaxone, 100 mg/kg/d in two equally divided daily doses for 7 d; or azithromycin, 20 mg/kg/d once a day for 7 d
Typhoid fever	
Adult	Ceftriaxone, 2 g IV qd for 10–14 d; or azithromycin, 500 mg PO or IV qd for 7 d
Children, pregnant women	Ceftriaxone, 100 mg/kg/d in two equally divided daily doses for 10–14 d; or azithromycin, 20 mg/kg/d IV or PO once a day for 7 d
Severe disease in those with history of travel to Pakistan, Iraq, or acquired in US	Adult: Meropenem 1 gm q8h (or other carbapenem) for 10-14 days Children: Meropenem 40mg/kg q8h (max 6000 mg/d)(or other carbapenem) for 10-14 days
All patients with severe typhoid fever (delirium, obtundation, stupor, coma, or shock)	dexamethasone, 3 mg/kg initially, followed by 1 mg/kg q6h for 48 h
Chronic carrier	
Adult	Ciprofloxacin, 500 mg PO BID for 4 wk; or amoxicillin, 1 g PO TID for 3 mo; or TMP-SMX, 160/800 mg PO BID for 3 mo
Children	Amoxicillin, 40 mg/kg PO up to 1 g TID for 3 mo; or TMP-SMX, 5 mg/kg TMP BID for 3 mo

Due to the emergence of antimicrobial resistance, therapy should be guided by resistance testing whenever possible.
Abbreviations: TMP-SMX = trimethoprim–sulfamethoxazole

agent. However, for patients with a travel history to Pakistan or Iraq, or for those who acquire disease in the United States, the CDC currently recommends that a carbapenem be used for those who cannot tolerate oral therapy. (see Table 148.1).

Most authorities recommend a short course of dexamethasone for severe disease with altered mental status or shock (see Table 148.1).

Chronic carrier

Patients with positive stool or urine cultures for salmonellae >12 months after resolving their acute infection are considered carriers. More than 80% of these patients can have the carrier state eradicated with the administration of ciprofloxacin for 1 month, oral amoxicillin for 3 months, or TMP-SMX for 3 months. The presence of anatomic abnormalities, such as biliary or kidney stones, makes eradication much more difficult and should be evaluated prior to initiating long-term therapy. In the presence of such abnormalities, surgery combined with antimicrobial therapy is often required for eradication. Patients with urinary carriage associated with *Schistosoma haematobium* should be treated with praziquantel before attempting eradication of *S. typhi*.

Prevention

The prevention of *Salmonella* infection relies on proper food handling and sanitation. In developed countries, this involves careful attention to the separation of raw and cooked foods and an awareness of the multiple ways in which cross-contamination can occur in food preparation areas. Parents should also monitor their children to ensure careful hand hygiene after contact with reptiles and fowl.

For travel to developing countries, there are currently two commercially available vaccines for the prevention of *S. typhi* infection. One is an oral live attenuated vaccine, while the second is a parenteral capsular polysaccharide vaccine. These vaccines achieve approximately 50% to 80% efficacy, starting roughly 2 weeks after vaccination, and confer protection that lasts for several years. They are recommended for travelers to parts of the world where typhoid fever is endemic. However, as none of the available vaccines is completely protective, the first line of prevention for travelers to areas where typhoid is endemic is care in consumption of food and water. Travelers should avoid tap water, ice produced from local tap water, salads, uncooked vegetables, and unpasteurized milk and milk products such as cheese, and should eat only food that has been cooked and is still hot or fruit that has been washed in clean water and then peeled by the traveler personally.

Suggested reading

Centers for Disease Control and Prevention (CDC). *Foodborne Diseases Active Surveillance Network (FoodNet):* FoodNet 2019 Preliminary Data. Atlanta, GA: US Department of Health and Human Services, CDC; 2021. https://www.cdc.gov/foodnet/reports/prelim-data-intro-2019.html

Centers for Disease Control and Prevention (CDC). *National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS):* 2018 NARMS Update: Integrated Report Summary. Atlanta, GA: US Department of Health and Human Services, CDC; 2021. https://www.fda.gov/animal-veterinary/national-antimicrobial-resistance-monitoring-system/2018-narms-update-integrated-report-summary

Centers for Disease Control and Prevention (CDC). Salmonellosis. Centers for Disease Control and Prevention website. http://www.cdc.gov/salmonella/

Centers for Disease Control and Prevention (CDC). Typhoid fever. Centers for Disease Control and Prevention website. https://www.cdc.gov/typhoid-fever/index.html

Centers for Disease Control and Prevention (CDC). Extensively Drug-Resistant Salmonella Typhi Infections Among U.S. Residents Without International Travel. Centers for Disease Control and Preventio website. 2021. https://emergency.cdc.gov/han/pdf/CDC-HAN-439-XDR-Salmonella-Typhi-Infections-in-U.S.-Without-Intl-Travel-02.12.2021.pdf

Chai SJ, White PL, Lathrop SL, et al. *Salmonella enterica* serotype Enteritidis: Increasing incidence of domestically acquired infections. *Clin Infect Dis*. 2012;54(Suppl 5):S488–S497.

Date KA, Newton AE, Medalla F et al. Changing patterns in enteric fever incidence and increasing antibiotic resistance of enteric fever isolates in the United States, 2008–2012. *Clin Infect Dis*. 2016 63:322–329.

Dolecek C. Typhoid fever and other enteric fevers. In Cohen J, Powderly WG, and Opal SM, eds. *Infectious diseases*, 4th ed. St. Louis, MO: Mosby; 2017: 1002–1007.

DuPont HL. Bacterial diarrhea. *N Engl J Med*. 2009; 361:1560–1569.

Kariuki S, Gordon MA, Feasey N, Parry CM. Antimicrobial resistance and management of invasive Salmonella disease. *Vaccine*. 2015; 33(Suppl 3):C21–C29.

Onwuezobe IA, Oshun PO, Odigwe CC. Antimicrobials for treating symptomatic non-typhoidal Salmonella infection. *Cochrane Database Syst Rev*. 2012;11:CD001167. Epub 2012 Nov.

Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. *N Engl J Med*. 2002;347(22):1770–1782.

Pegues DA, Miller SI. *Salmonella* species. In Bennett JE, Dolin R, and Blaser MJ, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 9th ed. Philadelphia. PA Elsevier; 2020:2725–2736.

Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65: 1963–1973.

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Staphylococcus

Suzanne F. Bradley

Treatment of staphylococcal infection depends on the site involved, severity of infection, and antibiotic susceptibility pattern of the organism causing the infection. Although most serious staphylococcal infections are due to coagulase-positive staphylococci (*Staphylococcus aureus*), infections due to coagulase-negative staphylococci (e.g., *S. epidermidis*) are increasing and may also be life-threatening. *S. aureus* is a highly invasive pathogen, able to spread hematogenously to many organs, thus leading to metastatic foci of infection. Coagulase-negative staphylococci are generally healthcare-associated (HA) infections that require the presence of prosthetic material to gain a foothold and cause infection.

Susceptibility to antibiotics

Staphylococci have a propensity to develop resistance to antibiotics relatively quickly. Most staphylococci are no longer susceptible to the effects of penicillins alone because the bacteria produce enzymes or beta-lactamases that inactivate many of those drugs. One approach to the problem of antibiotic resistance in staphylococci has been the use of penicillinase-resistant penicillins (e.g., nafcillin, oxacillin, and methicillin). Alternatively, penicillins have been combined with inhibitors of beta-lactamases. Examples of penicillin–beta-lactamase -inhibitor combinations include amoxicillin-clavulanate (Augmentin), ampicillin-sulbactam (Unasyn), piperacillin-tazobactam (Zosyn), and ticarcillin-clavulanate (Timentin). The penicillin and penicillin–beta-lactamase-inhibitor combinations are effective for the treatment of penicillin-resistant, but methicillin-susceptible, staphylococci.

Other β-lactam antibiotics are also useful for the treatment of methicillin-susceptible staphylococci (MSSA). First-generation cephalosporins (cefazolin, cephalexin) are the most active, followed by second-generation agents (cefuroxime, cefotetan, cefoxitin). Third-generation (ceftriaxone, cefotaxime) and fourth-generation (cefepime) cephalosporins have less activity. First-generation cephalosporins are still considered the first-line agents in this class for most serious methicillin-susceptible staphylococcal infections.

Since the 1970s, both *S. aureus* and coagulase-negative staphylococci have become increasingly resistant to β-lactam antibiotics, including penicillinase-resistant penicillins, penicillin–beta-lactamase-inhibitor combinations, cephalosporins, and carbapenems. These so-called *methicillin-resistant* strains bind most β-lactam antibiotics poorly due to the alterations in penicillin-binding proteins (PBP2a) present on their cell walls. Methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE) are common in healthcare settings worldwide. MRSA and MRSE account for more than 50% and 90% of all staphylococcal isolates causing nosocomial infection in some medical centers. These HA strains are usually resistant to many other classes of antibiotics, including macrolides, lincosamines (clindamycin), quinolones, and aminoglycosides, but some remain susceptible to sulfonamides and tetracyclines.

Newer community-associated MRSA (CA-MRSA) strains have emerged that are not related to HA-MRSA strains and are now prevalent in healthcare settings. These CA-MRSA strains are resistant to β-lactam antibiotics, but, in contrast with HA-MRSA strains, are more frequently susceptible to many classes

of antibiotics including clindamycin and sulfonamides. Strains of CA-MRSA that are resistant to erythromycin but appear to be susceptible to clindamycin on initial screening should be further tested for inducible cross-resistance to clindamycin using a double-disk diffusion test (D test). If inducible resistance is shown, the laboratory will report resistance to both erythromycin and clindamycin.

Until recently, the glycopeptide vancomycin has been the primary treatment for serious MRSA infections. However, vancomycin treatment can be slow or ineffective in clearing MRSA infection, and vancomycin-resistant *S. aureus* (VRSA) has emerged with prolonged use. Minimum inhibitory concentrations (MICs) of vancomycin appear to be increasing for MRSA. Some experts now recommend using higher dosages of vancomycin to achieve a trough serum concentration of 15 to 20 μg/mL when treating serious MRSA infections. These higher serum vancomycin concentrations may be associated with more toxicity, however. Newer semi-synthetic glycopeptides, such as telavancin, dalbavancin, and oritavancin, have been approved for treatment of skin and soft tissue infection (SSTI); their toxicity profiles are similar to vancomycin.

Other antibiotics with activity against MRSA, oxazolidinones (linezolid and tedizolid), quinupristin-dalfopristin, daptomycin, and tigecycline, have been developed. These drugs have been used primarily for serious infections when patients have side effects from vancomycin or when treatment with vancomycin fails. Currently, the greatest experience in the treatment of serious MRSA infections in patients intolerant or refractory to vancomycin has been with linezolid and daptomycin. Side effects have limited the use of quinupristin-dalfopristin. Tigecycline is bacteriostatic, and increases in all-cause mortality have been described during treatment of serious infection with this drug. The cephalosporin ceftaroline has potent activity against *S. aureus* and MRSA due to its increased ability to bind to PBP2a. The fluoroquinolone, delafloxacin, is currently approved only for the treatment of SSTI; whether it will retain its activity against MRSA or become resistant like ciprofloxacin is not known.

Although it may be tempting to treat both MSSA and MRSA infections with vancomycin or one of the newer agents, there are several reasons why this practice should be discouraged. One is that MSSA infections clear more slowly when treated with vancomycin than with a β-lactam antibiotic. The second is that the overuse of vancomycin has contributed to the increase in vancomycin resistance among enterococci (VRE) as well as *S. aureus*. Finally, resistance to newer agents has already been reported in *S. aureus*. Thus, organisms that are identified as MSSA should be treated with a penicillinase-resistant β-lactam antibiotic; only if the infecting organism is MRSA should vancomycin or newer agents be used.

The situation with coagulase-negative staphylococci is more difficult because the routine assays used by most laboratories to determine methicillin resistance are not as well established for coagulase-negative staphylococci as for *S. aureus*. Thus, some authorities recommend the use of vancomycin for serious coagulase-negative staphylococcal infections in spite of routine antimicrobial susceptibility testing that suggests methicillin susceptibility. A polymerase chain reaction test for methicillin resistance that detects the presence of the *mec*A gene that encodes for PBP2a is used in some laboratories for both *S. aureus* and coagulase-negative staphylococci; however, this test is costly, labor intensive, and not readily available at most hospitals. Detection of methicillin resistance by latex agglutination testing for the presence of PBP2a is also available.

For patients allergic to β-lactam antibiotics, other antimicrobial agents for staphylococcal infections include (depending on susceptibility results) trimethoprim-sulfamethoxazole (TMP-SMX); quinolones, such as levofloxacin or moxifloxacin; clindamycin; and erythromycin. The use of these antistaphylococcal agents should generally be restricted to the treatment of localized, uncomplicated infections. Vancomycin, daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline are alternatives for serious staphylococcal infections in allergic patients.

Infection control issues

Because of the difficulty in treating MRSA infections and the propensity for *S. aureus* to spread among patients from the hands of healthcare providers, guidelines for the control of MRSA within acute care hospitals have been issued. Patients who have MRSA should be isolated in a private room under Contact Precautions, ensuring that healthcare providers wear gloves for general care of the patient, don gowns when performing tasks likely to result in contamination of clothing by secretions, and assiduously wash their hands before and after patient care. Special care should be taken with wounds from which MRSA has been isolated and with sputum in a patient with pneumonia due to MRSA.

Routine decolonization of patients who are infected or colonized with MRSA is generally not done, in part because the effect is transient and recolonization within 90 days is common. However, for some acutely ill patients, colonization with *S. aureus* can increase the risk of infection. Recent randomized trials suggest that transient decolonization of skin with daily chlorhexidine baths and a brief course of mupirocin ointment applied to the nares can decrease the risk of MRSA infection in intensive care unit patients and *S. aureus* surgical site infections in patients undergoing cardiothoracic and orthopedic procedures. Intra-nasal povidone-iodine has been used in some settings as an alternative to mupirocin. Treatment of all patients should be discouraged as resistance to mupirocin may develop rapidly when use is chronic and widespread. Chlorhexidine resistance may also be emerging with increasing use.

Infections due to *S. aureus*

Skin and soft tissue infections

S. aureus is the most common cause of SSTI, and many SSTIs are now caused by CA-MRSA strains. Cellulitis associated with purulent drainage or exudate is most commonly due to *S. aureus*. Folliculitis, furuncles, abscesses, and wound infections are also common (Table 149.1).

Superficial infections such as impetigo may be treated with topical agents such as mupirocin. Incision and drainage alone is

TABLE 149.1 TREATMENT OF NON-CARDIAC INFECTIONS DUE TO *STAPHYLOCOCCUS AUREUS*

Infection	First-line treatment[a]	Second-line treatment[a,b]	Comments
Folliculitis Impetigo	Mupirocin		
Small abscesses	Incision & drainage		
Purulent Infections – Outpatient management			
MSSA MRSA	Incision & drainage if indicated Dicloxacillin 250 mg **OR** Cephalexin 250 mg q 6H TMP-SMX 160/800 gm q 12H	Clindamycin 300 mg q 6H Doxycycline 100 mg q 12H **OR** Clindamycin 300 mg q 6H **OR** Linezolid 600 mg q 12 H	Immunocompetent host with mild systemic illness Give oral therapy 5-10 days based on response OR If compliance not assured Dalbavancin IV 1 g followed by 0.5 g one week later OR Oritavancin IV 1.2 g x 1 dose
Purulent Infections – Inpatient management			
MSSA MRSA	Incision & drainage if indicated Nafcillin 2 g q 4H **OR** Cefazolin 2 g q 8H Vancomycin 1 g q12H	Vancomycin 1 g q12H **OR** Clindamycin 600 mg q 8H Linezolid 600 mg PO/IV q 12H **OR** Daptomycin 4 mg/kg q 24H **OR** Clindamycin 600 mg q 8H **OR** Ceftaroline 600 mg q 12H **OR** Telavancin 10 mg/kg q 24H	Presence of SIRS, hypotension Immunocompromised host Generally IV therapy or due to failure of oral treatment Treat 7-14 d based on response Maintain vancomycin trough ~ 15 μg/ml
Osteomyelitis – No hardware or devices			
MSSA MRSA	Nafcillin 2 g q 4H **OR** Cefazolin 2 g q 8H Vancomycin 1 g q12H	Vancomycin 1 g q12H Daptomycin 4 mg/kg q 24H	Treat IV 6-8 wks followed by an oral regimen Maintain vancomycin trough ~ 15 μg/ml Vertebral osteomyelitis, with or without paraspinous or epidural abscess, often requires longer duration of therapy
Septic Arthritis – Native joints			
MSSA MRSA	Nafcillin 2 g q 4H **OR** Cefazolin 2 g q 8H Vancomycin 1 g q12H	Vancomycin 1 g q12H Daptomycin 4 mg/kg q 24H **OR** Linezolid 600 mg PO/IV q 12H	Repeated needle aspiration, arthroscopic, or operative drainage essential for resolution of infection Treat 3-4 wks based on response
Pneumonia			
MSSA MRSA	Nafcillin 2 g q 4H **OR** Cefazolin 2 g q 8H Vancomycin 1 g q12H	Vancomycin 1 g q12H Linezolid 600 mg PO/IV q 12H Linezolid 600 mg PO/IV q 12H	Empyema when present must be drained Treat 7-21 d based on response Daptomycin not effective
Bacteremia			
MSSA MRSA	Nafcillin 2 gm q4H Vancomycin 1gm q12H	Vancomycin 1 gm q12H Daptomycin 6 mg/kg q12H	Length of therapy depends upon the sources of bacteremia and whether visceral foci of infection, including endocarditis are present. Careful diagnostic workup and clinical assessment of the patient is required (see text)

Abbreviations: MSSA = methicillin-susceptible *Staphylococcus aureus*; MRSA = methicillin-resistant *S. aureus*; TMP-SMX = trimethoprim-sulfamethoxazole, SIRS = systemic inflammatory response

[a] Usual adult doses. Doses of cefazolin and vancomycin dependent on renal function. For linezolid, monitor CBC weekly. Daptomycin, monitor creatine phosphokinase once or twice weekly.

[b] Second-line drugs used mostly for patients allergic or intolerant to β-lactam antibiotics.

generally reserved for small, localized abscesses in healthy patients; it is not clear that antibiotic use improves the outcome from infection. Initial empiric treatment with systemic antibiotics is recommended when the infection is more extensive, involves multiple sites, is in an area that is difficult to drain, is rapidly progressive, or systemic symptoms and signs of inflammation are present. Antibiotic therapy should be considered in older adults, diabetics, and in patients with HIV or neoplasms. In most instances where antibiotic therapy is warranted, empiric treatment should initially be directed against MRSA until culture results obtained from abscesses or purulent are known. Culture results can be particularly helpful if patients do not respond to initial therapy and in outbreak settings. For patients with less severe purulent infection who can take and tolerate oral medications, empiric therapy with TMP-SMX, doxycycline, or minocycline can be considered. In patients with systemic illness and rapidly progressive or worsening infection who warrant inpatient treatment, empiric IV vancomycin, daptomycin, telavancin, ceftaroline, and oxazolidinones can be given.

Once culture and susceptibility results are known, then antibiotic therapy can be modified appropriately. Many patients will require intravenous (IV) administration of antibiotics until the acute illness has improved, then therapy can be switched to oral agents. If MSSA is identified, nafcillin or cefazolin followed by dicloxacillin, cephalexin, or clindamycin is recommended.

Osteoarticular infections

Staphylococcus aureus is the leading cause of osteoarticular infections. These infections are difficult to treat and frequently require long-term therapy with IV antibiotics.

In general, IV therapy directed against MRSA should be used until results of culture and antibiotic susceptibilities are available from deep tissue or joint aspirates. In the case of native joint septic arthritis, drainage of infected synovial fluid is essential to preserve joint function and eradicate infection. IV therapy should continue for at least 3 to 4 weeks.

For treatment of acute osteomyelitis, IV antibiotics are generally recommended with prolonged treatment (6–8 weeks). Patients with vertebral osteomyelitis, paraspinous abscess, and/or epidural abscess often require treatment for months beyond 6 to 8 weeks of IV therapy to assure healing and prevent relapse. Prolonged treatment can usually be accomplished by giving an oral agent for MRSA (TMP-SMX, doxycycline, or clindamycin) or MSSA (cephalexin, dicloxacillin, clindamycin, or amoxicillin-clavulanate) based on antimicrobial susceptibility patterns.

Treatment of staphylococcal infections in patients with prosthetic joints or spinal hardware in place can be particularly difficult without removal of the device. For prostheses present <30 days or when symptoms have been present <3 weeks, a strategy to debride and retain the prosthesis may be tried. Two weeks of therapy consisting of oral rifampin in combination with vancomycin or daptomycin for methicillin-resistant staphylococci and rifampin plus nafcillin or cefazolin for methicillin-susceptible staphylococci is given followed by 3 months of rifampin in combination with a susceptible oral agent.

For late prosthetic infections and those with more prolonged symptoms, resection of the device is generally advised followed by 4 to 6 weeks of IV therapy with the goal of reimplantation. For patients who cannot tolerate surgical resection, IV antibiotics may be followed by chronic suppression of the infection with a susceptible and single oral agent. In no instance may rifampin be given as treatment alone due to the prompt emergence of resistance.

Pulmonary infections

In the past, *S. aureus* pneumonia was seen primarily in elderly patients with underlying illnesses. Recently, severe CA-MRSA pneumonia has been seen in children and young adults, sometimes following influenza infection or in the setting of HIV infection. Patients with severe community-acquired pneumonia requiring admission to the intensive care unit or who have necrotizing pneumonia, cavitating infiltrates, or empyema should be treated empirically for MRSA until sputum and blood culture results are known. Vancomycin or linezolid may be given empirically until culture and susceptibility results are known. Vancomycin, linezolid, or clindamycin may be given for 7 to 21 days depending on the extent of the infection and the patient response. Daptomycin should not be used because the drug does not achieve adequate lung tissue levels. Drainage of loculated fluid in the pleural space is essential for resolution of infection.

Bacteremia

S. aureus bacteremia may reflect an uncomplicated or transient event often associated with a removable focus, most often an intravascular catheter, or it may be the first indication of deep-seated visceral infection, including endocarditis. *S. aureus* bacteremia is considered uncomplicated if there is no evidence for endocarditis, there are no implanted prosthetic devices, and catheters have been removed and foci promptly drained. In addition, the patient must have resolution of fever within 72 hours of treatment, documented clearance of blood cultures drawn within 2 to 4 days of the initial positive culture, and no evidence for metastatic sites of infection.

Recent guidelines recommend that all patients with *S. aureus* bacteremia have echocardiography, and preferably a transesophageal echocardiogram (TEE). However, some studies have questioned that recommendation for uncomplicated bacteremia. Others have found that if none of the following risk factors (bacteremia >4 days' duration, presence of a permanent intracardiac device, hemodialysis dependency, spinal infection, and presence of non-vertebral osteomyelitis) is present, then the likelihood of *S. aureus* endocarditis is <1% and echocardiography is not warranted. One suggested approach is to perform a transthoracic echocardiogram (TTE) only in patients with *S. aureus* bacteremia who have one or more risk factors, complicated bacteremia, or clinical suspicion for endocarditis. If a good-quality TTE cannot exclude endocarditis, then a TEE should be performed in those patients.

For patients who have uncomplicated *S. aureus* bacteremia or complicated bacteremia without echocardiographic or deep visceral evidence of infection, 14 days of treatment with nafcillin or cefazolin for MSSA and vancomycin or daptomycin for MRSA is

recommended. For patients in whom deep-seated infections are documented and for those in whom the clinical suspicion of endocarditis remains high, longer courses of therapy (4–6 weeks) are required. Relapse of infection is common following *S. aureus* bacteremia, so patients should be carefully watched for recurrence of symptoms and signs following the discontinuation of treatment.

In contrast with *S. aureus*, metastatic complications from coagulase-negative bacteremia are uncommon. Temporary IV devices, such as central venous catheters, peripherally inserted central catheters, and midline catheters, should be removed and 7 to 10 days of antimicrobial therapy given. For semi-permanent IV devices, such as Hickman or Groshong catheters and subcutaneous ports, which are more difficult to remove, a 2-week trial of vancomycin or nafcillin with or without rifampin may be adequate to cure the infection. However, if bacteremia relapses, or if tunnel infection or septic phlebitis is present, then the catheter or port should be removed (see Chapter 105, "Intravascular catheter-related infections").

Endocarditis

S. aureus is the most common cause of native valve endocarditis; the presentation can be acute with frequent complications and high mortality. Patients with left-sided cardiac lesions may have metastatic abscesses in spleen, brain, kidney, and myocardium. Right-sided *S. aureus* endocarditis is frequently found in IV drug users. In that population, pulmonary emboli are a common presenting symptom, the mortality rate is significantly lower, and shorter courses of therapy may be indicated.

Coagulase-negative staphylococci are the most common cause of endocarditis in patients with prosthetic valves and intracardiac devices, and the presentation may be more subacute. TEE is particularly useful for detection of prosthetic valvular dehiscence and paravalvular abscesses that typically require surgical intervention. For details of specific antibiotic regimens for endocarditis, see Chapter 37, "Endocarditis."

Toxic shock syndrome

Under certain conditions, such as those brought about by the use of tampons during menstruation and by the packing of surgical wounds, *S. aureus* elaborates toxins that lead to multiorgan system disease in the absence of bacteremia. Treatment of shock and the removal of tampons or surgical packing are the primary goals of therapy. Anti-staphylococcal therapy is secondary, initiated primarily to eradicate the carriage of toxin-producing *S. aureus* strains (see Chapter 18, "Toxic shock and Kawasaki's disease").

Suggested reading

Abbas M, Paul M, Huttner A. New and improved? A review of novel antibiotics for gram-positive bacteria. *Clin Microbiol Infect*. 2017;23:697–702.

Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals From the American Heart Association. *Circulation*. 2015;132:1435–1486.

Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis*. 2015;61:e26–46.

Calfee DP, Salgado CD, Milstone AM, et al. Strategies to prevent methicillin-resistant *Staphylococcus aureus* transmission and infection in acute care hospitals: 2014 Update. *Infect Control Hosp Epidemiol*. 2014;35:772–796.

Holland, TL, Arnold C, Fowler VG. Clinical management of *Staphylococcus aureus* bacteremia: A review. *JAMA*. 2014; 312:1330–1341.

Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–111.

Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:1–38.

Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection. 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.

Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56:e1–e25.

Septimus EJ, Schweizer ML. Decolonization in prevention of health care-associated infections. *Clin Microbiol Rev*. 2016; 29:201–222.

Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59:e10–52.

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Streptococcus groups A, B, C, D, and G

Dennis L. Stevens, J. Anthony Mebane, and Karl Madaras-Kelly

Classification

In the early 1950s, Lancefield divided streptococci into groups based on carbohydrates present in the cell wall and designated the groups A through H and K through T. In addition, streptococci may be classified by their characteristics on culture on sheep blood agar. β-Hemolytic streptococci produce zones of clear hemolysis around each colony, α-hemolytic streptococci (*Streptococcus viridans*) produce a green discoloration characteristic of incomplete hemolysis, and absence of hemolysis is characteristic of γ-streptococci.

Group A

Pharyngitis

The sole member of Lancefield group A is *Streptococcus pyogenes*. Group A streptococcus is ubiquitous in the environment but with rare exceptions is exclusively found in or on the human host. About 5% to 20% of the population harbor group A streptococcus in their pharynx, and some are colonized on their skin. This organism produces a variety of suppurative infections; however, streptococcal pharyngitis, the most common, is characterized by the onset of sore throat, fever, painful swallowing, and chilliness. These symptoms combined with submandibular adenopathy, pharyngeal erythema, and exudates correlate with positive throat cultures in 85% to 90% of cases. Sore throat without fever or any of the other signs and symptoms has a low predictive value for pharyngitis caused by group A streptococcus. Rapid strep tests correlate with positive cultures in 68% to 99% of cases, but results depend greatly on the individual performing the test as well as the bacterial colony count. Colony counts >100 per plate correlated with positive rapid strep tests in 95% of patients, and counts of <100 per plate correlated with positive rapid strep tests for only 68% of patients.

Therapy

Penicillin remains the drug of choice for group A streptococcal pharyngitis and tonsillitis (Table 150.1). In the past, the purpose of treatment of streptococcal pharyngitis was largely to prevent postinfectious immunologic sequelae. However, because some patients with pharyngitis have subsequently developed streptococcal toxic shock syndrome with or without necrotizing fasciitis, it seems prudent to diagnose and treat streptococcal pharyngitis aggressively in an attempt to prevent this complication as well. Antibiotic treatment of streptococcal pharyngitis reduces pharyngeal pain and fever by approximately 24 hours in children. Penicillin treatment within 10 days of the onset of pharyngitis is extremely effective in the prevention of rheumatic fever, although it is unclear whether it prevents poststreptococcal glomerulonephritis. Penicillin fails to eradicate group A streptococcus from the pharynx in 5% to 25% of patients with pharyngitis or tonsillitis, although penicillin resistance has never been documented. The most likely explanation for such failure, particularly in patients with tonsillitis, is the inactivation of penicillin by β-lactamases produced by co-colonizing organisms such as *Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis*, and

TABLE 150.1 **STREPTOCOCCAL INFECTIONS**

Organism	Lancefield group	Type of infection	Therapy
Streptococcus pyogenes	A	Pharyngitis and impetigo	Benzathine penicillin IM, 1.2 million U for adults; 600,000 U for children ≤27 kg
			Penicillin G or V, 400,000 U PO QID for 10 d for adults; 200,000 U QID for children ≤27 kg
			Erythromycin ethyl succinate, PO 40 mg/kg/d
		Recurrent streptococcal pharyngitis, tonsillitis	Same as above or ampicillin + clavulanic acid, PO 20–40 mg/kg/d cephalosporin
			Dicloxacillin, 500 mg PO QID for 10 d for adults
			Clindamycin, 10 mg/kg/d PO in 4 doses for 10 d
		Cellulitis and erysipelas	Nafcillin, 8–12 g/d IV for 7–10 d or penicillin or ceftriaxone in appropriate doses
		Necrotizing fasciitis, myositis, and streptococcal toxic shock syndrome	Clindamycin, 900 mg IV q8h and penicillin G, 4 million U IV q4h for adults Duration until resolution of infection
		Prophylaxis of rheumatic fever	Benzathine penicillin, 1.2 million U IM q28d Penicillin G, 200,000 U PO BID for children ≤27 kg
			Sulfadiazine, 1 g/d for patients >27 kg; 500 mg/d for patients ≤27 kg Erythromycin, 250 mg PO BID
Streptococcus agalactiae	B	Neonatal sepsis	Penicillin, IV 100,000–150,000 U/kg/d in 2–3 divided doses for infants ≤7 d of age
		Postpartum sepsis Septic arthritis Soft-tissue infection Osteomyelitis Intrapartum prophylaxis	Penicillin, 200,000–250,000 U/kg/d IV in 4 divided doses for infants >7 d of age Ampicillin, 100 mg/kg/d IV in 2–3 divided doses for infants ≤7 d of age Ampicillin, 150–200 mg/kg/d IV in 4 divided doses for infants >7 d of age
			Ampicillin, 8–12 g IV in 4–6 divided doses or penicillin 12–24 million U/d for adults
			Penicillin or ampicillin as for neonatal sepsis or postpartum sepsis above
			Penicillin or ampicillin as for postpartum sepsis above
			1. Aqueous penicillin G 5 million U IV loading dose followed by 2.5 million U q4h for 4 doses
			2. Ampicillin 2 g IV loading dose followed by 1 g q4h for 4 doses
Streptococcus equi	C	Bacteremia Cellulitis	Penicillin as for streptococcal toxic shock syndrome above
Enterococcus faecalis[a]	D	Endocarditis Bacteremia	Ampicillin + gentamicin
		Urinary tract infection	
		Gastrointestinal abscess	
Streptococcus bovis	D	Bacteremia Abscesses	Penicillin as for *Streptococcus equi* above
Streptococcus canis	G	Bacteremia Cellulitis	Penicillin as for *Streptococcus equi* above
		Pharyngitis	

[a] Linezolid has activity against vancomycin-resistant enterococci (VRE). See Chapter 133, "Enterococcus," for more details.

Bacteroides fragilis. A second course of penicillin fails in >50% of patients, and treatment with dicloxacillin, a cephalosporin, amoxicillin/clavulanate, erythromycin, or clindamycin will subsequently cure 90% to 95% of patients. Recent studies demonstrate that outer membrane vesicles from *M. catarrhalis* and *H. influenzae* that are β-lactamase positive hydrolyze penicillin. Preparations containing procaine penicillin G plus benzathine penicillin are no more effective than benzathine alone but are less painful on injection. Ceftriaxone is under study for this indication. Resistance to erythromycin is about 5% in the United States, but in 1970, it reached a prevalence of 70% in Japan during a period of extensive erythromycin use in that country. In Finland and Sweden, emergence of erythromycin resistance has also paralleled erythromycin use. Recent studies from China document erythromycin and clindamycin resistance in a recent epidemic of scarlet fever following streptococcal pharyngitis. This could be a game changer if this strain spreads to other parts of the world.

Prophylactic treatment for populations at risk (e.g., schools, military) is indicated during epidemics of streptococcal pharyngitis when rheumatic fever is prevalent. The incidence of rheumatic fever has declined in developed nations but flourishes in developing countries. Antistreptococcal prophylaxis should be continuous in individuals with a history of rheumatic fever. Benzathine penicillin given intramuscularly once each month has the greatest efficacy, although oral agents such as phenoxymethyl penicillin are also effective. In recent years, the US military has demonstrated that such prophylaxis, particularly benzathine penicillin, prevents epidemics of streptococcal infections among young soldiers living in crowded conditions. Routine follow-up culture to verify eradication is not recommended except in patients with a history of rheumatic fever. Following appropriate treatment for symptomatic pharyngitis, treatment is not needed for continued positive cultures unless symptoms recur.

Scarlet fever

Severe cases of scarlet fever were prevalent in the United States, western Europe, and Scandinavia during the nineteenth century, and mortality rates of 25% to 35% were not uncommon. In contrast, scarlet fever today is rare and, when it occurs, is very mild. The primary site of infection is usually the pharynx, although surgical site infections have also been described. Classically, a diffuse, erythematous rash with sandpaper consistency appears 2 days after the onset of pharyngitis. Circumoral pallor and "strawberry" tongue are common findings, and desquamation occurs approximately 6 to 10 days later. The cause of the rash is uncertain, although most agree that extracellular toxins, likely the pyrogenic exotoxins formerly called "scarlatina toxins," are responsible. Treatment of the underlying infection with penicillin (see "Pharyngitis") and general supportive measures are indicated. Specifically, severe hyperpyrexia (fevers of 41.7°C/107°F to 43.3°C/110°F) has been described, and antipyretics may be necessary to prevent febrile seizures, particularly in children.

Pyoderma (impetigo contagiosa)

Impetigo is a superficial vesiculopustular skin infection. Although *S. aureus* is the most common organism isolated in modern times, group A streptococcus is likely the most significant pathogen. Impetigo is most common in patients with poor hygiene or malnutrition. Colonization of the unbroken skin occurs first; then minor abrasions, insect bites, and so on initiate intradermal inoculation. Single or multiple thick, crusted, golden-yellow lesions develop within 10 to 14 days. Penicillin orally or parenterally, or bacitracin or mupirocin topically, is effective treatment and will reduce transmission of streptococci to susceptible individuals. None of these treatments, including penicillin, prevents poststreptococcal glomerulonephritis. Although *S. aureus* may cause impetigo, it has never been implicated as a cause of glomerulonephritis.

Erysipelas

Erysipelas occurs most commonly in the elderly and very young. It is caused almost exclusively by group A streptococcus and is characterized by an abrupt onset of fiery red skin localized on the face or extremities (Figure 150.1). Distinctive features are well-defined margins, particularly along the nasolabial fold, scarlet or salmon red rash, rapid progression, and intense pain. Flaccid bullae may develop during the second to third day of illness, and desquamation of the involved skin occurs 5 to 10 days into the illness. In contrast, the rash of scarlet fever is generalized, has a diffuse pink or red hue that blanches on pressure, and has a sandpaper consistency. The organism is present in the lesion, although it is difficult to culture. Treatment with penicillin, a cephalosporin, or nafcillin is effective. Swelling may progress despite treatment, although fever, pain, and the intense redness usually diminish with 24 hours of treatment.

Cellulitis

S. pyogenes (group A streptococcus) is the most common cause of cellulitis, and although group A is the most common, β-hemolytic streptococci of groups B, C, and G also cause cellulitis in specific clinical settings. Patients with chronic venous stasis or lymphedema

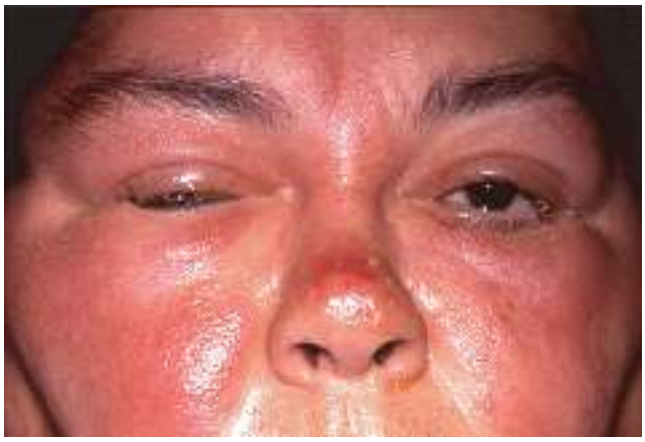

FIGURE 150.1 Erysipelas in a middle-aged woman. Note the brilliant red (salmon color) and the distinct demarcation along the nasolabial fold. The patient had a temperature of 39°C/102°F, tachycardia, normal blood pressure, and negative blood cultures. She responded well to intravenous penicillin G but developed superficial desquamation over the cheeks 10 days after admission.

are predisposed to recurrent cellulitis caused by groups A, C, and G streptococci. Cellulitis in diabetic and elderly patients, particularly those with peripheral vascular disease, may also be caused by group B streptococci. Clinical clues to the category of cellulitis such as dog bite (*Capnocytophaga*), cat bite (*Pasteurella multocida*), human bite (mouth anaerobes and *Eikenella corrodens*), freshwater injury (*Aeromonas hydrophila*), seawater (*Vibrio vulnificus*), and furuncles (*S. aureus*) are extremely important. Definitive diagnosis in the absence of such factors rests on aspiration of the leading edge of the cellulitic lesion. At best, a bacterial cause is established in only 15% of cases. Cellulitis caused by groups A, B, C, and G streptococci responds to penicillin, nafcillin, erythromycin, clindamycin, and a variety of cephalosporins. Ceftriaxone, cefpodoxime proxetil, and cefuroxime axetil have the greatest in vitro activity, and all have US Food and Drug Administration (FDA)-approved indications for the treatment of streptococcal cellulitis. Although most quinolones have efficacy in the treatment of cellulitis, older quinolones such as ciprofloxacin should be avoided because of their poor in vitro activity against streptococci. Newer quinolones may be considered as second-line therapy.

Invasive group A

In the past 20 years, there has been an increase in the number of severe group A streptococcal soft tissue infections and bacteremia associated with shock and death in 30% to 70% of cases. Shock and organ failure early in the course of infection define streptococcal toxic shock syndrome, and the inciting infection may be necrotizing fasciitis, myositis, pneumonia, peritonitis, septic arthritis, uterine infection, and others. Predisposing factors include varicella virus infections, penetrating or blunt trauma, and nonsteroidal anti-inflammatory agents.

Therapy

When large numbers of streptococci accumulate, more organisms are in the stationary phase and are less affected by β-lactam antibiotics (the Eagle phenomenon). The decreased expression of critical penicillin-binding proteins in such slow-growing bacteria presumably explains the lack of efficacy of penicillin. In vitro, clindamycin—but not penicillin—prevents synthesis of toxins. Interestingly, in experimental necrotizing fasciitis and myositis, clindamycin has markedly better efficacy than penicillin. Thus some authorities recommend treatment with both penicillin and clindamycin (and debridement when appropriate). Uncontrolled observations suggest that intravenous immunoglobulin may be helpful as well.

Group B

S. agalactiae (the only species in Lance-field group B) colonizes the vagina, gastrointestinal tract, and occasionally the upper respiratory tract of normal humans. Group B streptococci are the most common cause of neonatal pneumonia, sepsis, and meningitis in the United States and western Europe, with an incidence of 1.8 to 3.2 cases per 1,000 live births. Preterm infants born to mothers who are colonized with group B streptococci in the third trimester and have premature rupture of the membranes are at highest risk for early-onset pneumonia and sepsis. The mean time of onset is 20 hours postpartum, and symptoms are respiratory distress, apnea, and fever or hypothermia. Ascent of the streptococcus from the vagina to the amniotic cavity causes amnionitis. Infants may aspirate streptococci either from the birth canal during parturition or from amniotic fluid in utero. Radiographic evidence of pneumonia and/or hyaline membrane disease is present in 40% of cases. Type III strains account for most cases of group B streptococcal meningitis in neonates.

Late-onset neonatal sepsis occurs 7 to 90 days postpartum. Symptoms are fever, poor feeding, lethargy, and irritability. Bacteremia is common, and meningitis occurs in 80% of cases.

The standards of modern-day prenatal care include swab culture of the lower vagina and anorectum for these organisms at 35 to 37 weeks of pregnancy. Women presenting in labor without such cultures can be screened with a rapid antigen-detecting kit, although the false-negative rate may be 10% to 30%. Both passive immunization with intravenous immunoglobulin and active immunization with multivalent polysaccharide vaccine show promise and in the future may become the best approach to prevention of neonatal sepsis as well as postpartum infection in the mother. Women colonized with group B streptococcus in the third trimester should receive penicillin or ampicillin during delivery (see later discussion).

Adults with group B infections include postpartum women and patients with peripheral vascular disease, diabetes, or malignancy. Soft tissue infection, septic arthritis, and osteomyelitis are the most common presentations.

Therapy

Penicillin is the treatment of choice, although in practice many neonates are empirically treated with ampicillin, 100 to 200 mg/kg/d, plus gentamicin. Once the diagnosis is established, penicillin or ampicillin should be given (Table 150.1). Adults should receive 12 million to 24 million units of penicillin per day for bacteremia, soft tissue infection, or osteomyelitis; the dosage should be 8 to 12 g of ampicillin or 24 million units per day of penicillin for meningitis. Vancomycin or a first-generation cephalosporin is the alternative for patients allergic to penicillin. Intrapartum administration of ampicillin or aqueous penicillin G to women colonized with group B streptococcus during the third trimester, who had group B strep bacteriuria during the pregnancy, or who have premature labor or prolonged rupture of the membranes prevents group B neonatal sepsis. Infants should continue to receive ampicillin for 36 hours postpartum.

Groups C and G

Groups C and G streptococci may be isolated from the throats of both humans and dogs, produce streptolysin O, and resemble group A in colony morphology and spectrum of clinical disease. Before rapid identification tests were developed, many infections caused by groups C and G, such as pharyngitis, cellulitis, skin and wound infections, endocarditis, meningitis, osteomyelitis, and arthritis, were mistakenly attributed

to group A. Rheumatic fever following group C or G streptococcal infection has not been described. These strains also cause recurrent cellulitis at the saphenous vein donor site in patients who have undergone coronary artery bypass surgery. Both organisms are susceptible to penicillin, erythromycin, vancomycin, and clindamycin, though recent studies document clindamycin resistance in 17% of strains of group G.

Group D

Group D consists of gram-positive, facultatively anaerobic bacteria that are usually nonhemolytic but may demonstrate α- or β-hemolysis. *S. faecalis*, renamed *Enterococcus faecalis*, was previously classified as group D because it hydrolyzes bile esculin and possesses the group D antigen. *S. bovis* is also a cause of subacute bacterial endocarditis and bacteremia often in patients with underlying gastrointestinal malignancy. Enterococci are commonly isolated from stool, urine, and sites of intra-abdominal and lower extremity infection. Enterococci cause subacute bacterial endocarditis and have become an important cause of nosocomial infection, not because of increased virulence, but because of antibiotic resistance. First, person-to-person transfer of multidrug-resistant enterococci is a major concern to hospital epidemiologists. Second, superinfections and spontaneous bacteremia from endogenous sites of enterococcal colonization are described in patients receiving quinolone or moxalactam antibiotics. Last, conjugational transfer of plasmids and transposons between enterococci in the face of intense antibiotic pressure within the hospital milieu have created multidrug-resistant strains, including some with vancomycin and teicoplanin resistance.

Therapy

Serious infections with enterococci, such as endocarditis or bacteremia, require a synergistic combination of antimicrobials; that is, ampicillin or vancomycin together with an aminoglycoside (see Chapter 133, "Enterococcus"). Unlike enterococci, *S. bovis* remains highly sensitive to penicillin. Vancomycin-resistant enterococci (VRE) are being described with increasing frequency. Linezolid, an oxazolidinone antibiotic, has excellent activity against VRE, although antibiotic resistance can develop during therapy.

Suggested reading

American Academy of Pediatrics. *Report of the Committee on Infectious Diseases 1991*. Elk Grove Village, IL: American Academy of Pediatrics; 1991.

Bisno AL. Group A streptococcal infections and acute rheumatic fever. *N Engl J Med*. 1991;325:783–793.

Chen M, Yao W, Yang X, et al. Outbreak of scarlet fever associated with emm12 type group A Streptococcus in 2011 in Shanghai, China. *Pediatr Infect Dis J*. 2012;31:e158–e162.

Church D, Carson J, Gregson D. Point prevalence study of antibiotic susceptibility of genital group B streptococcus isolated from near-term pregnant women in Calgary, Alberta. *Can J Infect Dis Med Microbiol*. 2012;23:121–124.

Pfaller MA, Jones RN, Marshall SA, et al. Nosocomial streptococcal bloodstream infections in the SCOPE program: species and occurrence of resistance. The SCOPE hospital study group. *Diagn Microbiol Infect Dis*. 1997;29:259–263.

Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59:e10–e52.

Stevens DL, Tanner MH, Winship J, et al. Severe group A streptococcal infections associated with a toxic shock like syndrome and scarlet fever toxin A. *N Engl J Med*. 1989;321:1–7.

Wong CJ, Stevens DL. Serious group A streptococcal infections. *Med Clin North Am*. 2013;97(4):721–736.

151

Viridans streptococci

John L. Brusch

Viridans streptococci are a heterogeneous group of non-motile, catalase negative, gram-positive cocci. The initially identified isolates produced green hemolysis (α-hemolysis) when grown on sheep blood agar, hence the name *viridans* (green). They are subdivided on the basis of hemolysis types, Lancefield type, growth properties, and physiologic biochemical reactions into five major groups: *Streptococcus mutans*, *S. salivarius*, *S. anginosus*, *S. sanguinis,* and *S. mitis.* Various species can be distinguished on the basis of their physiologic and biochemical profiles Clinical laboratories often do not speciate isolates even if they are recovered from blood or other usually sterile sites. Isolates recovered in mixed culture or from mucosal surfaces are normally reported only as nonhemolytic or α-hemolytic streptococci. Box 151.1 lists the most common species of viridans streptococci isolated from blood cultures.

Viridans streptococci are an important part of the normal microbial flora in humans. They are indigenous to the oral cavity, upper respiratory tract, female genital tract, and gastrointestinal tract. These lack traditional virulence factors, such as endo- and exotoxins, and they are considered to be of low virulence. The sole pathogenic factor of members of the non-*S. anginosus* groups is production of an extracellular dextran, glucan, that facilitates their adherence to a preformed fibrin/platelet thrombus as well as to dental enamel. The *S. anginosus* group (*S. intermedius, S. constellatus*, and *S. anginosus*) are variably hemolytic. Their colonies are quite small on blood agar. Growth may be enhanced in the presence of carbon dioxide (CO_2). Many isolates are facultative anaerobes. Unlike other groups, *S. anginosus* possesses many pathogenic components. Surface adhesions facilitate binding the group to fibronectin, platelets and fibrin thrombi. A polysaccharide capsule can inhibit phagocytosis. Some strains possess the same genes as does *S. pyogenes* for productions of superantigens and DNAse. Many actually invade myocardial cells, valvular structures, pericardium, and extra-cardiac sites, which results in abscess formation. They do so by producing superantigens that are able to quickly trigger a massive outpouring of inflammatory cytokines. The resulting clinical picture appears much more like that of *S. aureus* than that of streptococci.

Infections

Viridans streptococci are important causes of infective endocarditis (IE). In addition, they are increasingly identified as causes of septicemia in immunocompromised individuals. Among immunocompetent individuals, these bacteria may lead to brain abscesses and a wide range of infections of the lower respiratory tract. Viridans streptococci may occur as a sole pathogen but are more typically found as part of a mixed aerobic-anaerobic infection.

Infective endocarditis

Viridans streptococci account for approximately 25% of cases of IE. Essentially, all of them represent subacute disease. The incidence of viridans streptococcal endocarditis has not changed appreciably since the American Heart Association recommended, in 2007, the cessation of routine antibiotic prophylaxis of

BOX 151.1

Most common species of viridans streptococci isolated from blood cultures

Streptococcus sanguis
Streptococcus mitis
Streptococcus salivarius
Streptococcus mutans
Streptococcus anginosus

dental procedures for all but those at greatest risk of developing IE. Those who develop *S. viridans* IE have underlying cardiac valve abnormalities, such as degenerative valve disease or rheumatic heart disease. Such valvular configurations lead to turbulence in blood flow with resultant deposition of non-infected platelets/fibrin thrombi (NBTE). (Refer to Chapter 37 for a more in-depth discussion of this process.) Viridans streptococcal IE follows an indolent course. Low-grade fever, fatigue, and malaise are characteristic early clinical manifestations. Almost inevitably there is a preexisting murmur which usually does not change in nature until far later in the clinical course. Initial presentations may be renal failure, the various cutaneous manifestations of subacute bacterial endocarditis (SBE), and back pain; all of these represent immune complex disease or embolization from the valvular vegetation. Congestive heart failure occurs far later into the illness.

The critical element for diagnosis of IE is demonstration of continuous bacteremia. In the absence of recent antimicrobial therapy, two blood cultures will retrieve this type of streptococci in 95% of cases. Echocardiography, either transthoracic or transesophageal, may provide additional diagnostic and prognostic information in those cases.

Bacteremia and septicemia

Transient bacteremia due to viridans streptococci may occur in association with dental procedures but also with routine daily activities. It is rarely of clinical significance. In contrast, prolonged bacteremia has emerged as a genuine problem among patients undergoing cancer chemotherapy, especially among children. Viridans streptococci are now a leading cause of bacteremia in febrile, neutropenic patients. Infection occurs in association with aggressive cytoreductive therapy for acute leukemia or bone marrow transplantation. These agents damage the normal mucosal barriers of the mouth and intestinal tract. Other predisposing factors include prophylactic administration of trimethoprim-sulfamethoxazole (TMP-SMX) or quinolone, presence of an indwelling central venous catheter, and use of antacids or histamine type 2 (H_2) antagonists. Physical findings are mainly cutaneous, including erythema multiforme, petechiae, desquamation of palms and soles, and maculopapular rashes A fulminant shock syndrome characterized by hypotension, rash with palmar desquamation, acute renal failure, adult respiratory distress syndrome, and death has also been described. The viridans streptococcal shock syndrome occurs in up to 25% of pediatric patients with bacteremia, with mortality rates of 40% to 100%.

Meningitis and brain abscess

Viridans streptococci are an uncommon cause of meningitis, accounting for fewer than 5% of culture-proven cases. Infections occur in patients of all ages, including neonates. The source of infection usually is underlying ear, nose, or throat pathology; endocarditis; extracranial infection; or head trauma. Clinical manifestations are typical of acute pyogenic meningitis with signs of meningeal irritation, neurologic deficits, seizures, and altered sensorium. Although cerebrospinal fluid (CSF) pleocytosis is characteristically present with viridans streptococcal meningitis, the Gram stain of CSF is positive less than half of the time.

S. angiosus and *S. aureus* are the primary causes of brain abscess, often in association with anaerobic bacteria. Predisposing conditions include head and neck infection, lung abscess, and endocarditis. Clinical manifestations of brain abscess are primarily related to the size and location of the intracranial lesion, with headache being the most common presenting complaint. Fever is present in less than half of cases. CT or MRI is useful both for diagnosis and to follow the course of antimicrobial therapy. Definitive microbiologic diagnosis can be established from culture of brain abscess material obtained by excision or through stereotactic aspiration.

Pneumonia

Viridans streptococci are frequently identified in cultures of respiratory tract secretions. When recovered from expectorated sputum, viridans streptococci should rarely be considered significant because of their presence as normal oral flora. However, they may also be found in lower respiratory tract specimens obtained from patients with pneumonia by transtracheal aspiration or protected bronchial brush. *S. viridans* may cause lower respiratory tract infection in association with other oral organisms, especially anaerobes, following aspiration of oropharyngeal material. Predisposing conditions include periodontal disease, gingivitis, depressed cough and gag reflexes, dysphagia from esophageal disease, depressed consciousness, seizures, and ethanol abuse. Pneumonia usually develops in dependent lung segments and may lead to necrosis with abscess formation and/or empyema. The diagnosis of aspiration pneumonia should be suspected by the presence of purulent sputum and an abnormal radiograph in a patient at high risk of aspiration. Viridans streptococci are also occasionally identified as sole pathogens in patients with lower respiratory tract infection.

Odontogenic infections

S. viridans, especially *S. angiosus*, may produce a wide variety of oral and endodontic infections ranging from dental caries to peritonsillar abscesses. These can spread to the sinuses, lung (empyema and lung abscess), brain, and deep space infections of the head and neck (jugular vein septic thrombophlebitis, necrotizing fasciitis of the neck).

There is also growing evidence linking chronic dental disease with coronary artery and cerebrovascular disease. Promotion of

TABLE 151.1 **ANTIBIOTIC TREATMENT OF SPECIFIED INFECTION DUE TO *STREPTOCOCCUS VIRIDANS***

Infection type	Antibiotic regimen[a]	Duration
Septicemia	Penicillin G, 12–18 million units IV qd, in divided doses, or vancomycin,[b] 15 mg/kg (not to exceed 1 g) IV q12h	2 wk
Meningitis	Ceftriaxone, 2 g IV qd, or vancomycin,[b] 15 mg/kg (not to exceed 1 g) IV q12h	2 wk
Brain abscess	Ceftriaxone, 2 g IV qd, or vancomycin,[b] 15 mg/kg (not to exceed 1 g) IV q12h, plus metronidazole, 500 mg IV or PO q6h	≥6 wk
Pneumonia[c] (aspiration)	Penicillin G, 8–12 million units IV qd, in divided doses, plus metronidazole, 500 mg P0 IV or PO q6h or β-lactam/β-lactamase inhibitor combination	2–3 wk
Endocarditis	See Chapter 37, "Endocarditis."	

[a] Doses should be adjusted according to age, weight, and renal function.
[b] For suspected or confirmed infections due to β-lactam–resistant viridans streptococci. Selection of empiric treatment for viridans streptococcal infections should take into account local patterns of antimicrobial susceptibility.
[c] Presence of enteric gram-negative bacilli might require additional antimicrobial agents.

good oral health needs to be part of an effective approach to prevention and treatment of cardiovascular disease.

Other bacteremic infections

Among other bacteremic infections are liver, spleen, or kidney abscesses and osteomyelitis. Successful therapy requires antibiotics along with appropriate drainage procedures.

Therapy

The β-lactam antibiotics have long been considered the drugs of choice for therapy for *S. viridans* infections because of previously uniform susceptibility to these agents. Resistance is now emerging as a significant problem in immunocompromised patients. Using a minimum inhibitory concentration (MIC) breakpoint criterion of ≤0.125 μg/mL for determining susceptibility, penicillin resistance has been reported in 25% to 50% of isolates recovered in some centers, with 5% to 10% of isolates resistant to high concentrations of penicillin (MIC ≥4 μg/mL). In contrast, most community isolates of viridans group streptococci, including those associated with infective endocarditis, remain susceptible to penicillin. Other β-lactam antibiotics have in vitro activity similar to that of penicillin. Vancomycin, daptomycin, and linezolid have consistently excellent activity against viridans streptococci, whereas tetracycline, clindamycin, and erythromycin have variable activity, often with 25% to 50% of isolates reported resistant. Most strains of *S. viridans* are resistant to TMP-SMX.

Because of the unpredictable antibiotic susceptibility of viridans streptococci, in vitro testing should be performed on all clinically significant isolates recovered from normally sterile body sites, such as blood or CSF. Often these cannot be performed in local clinical labs. In that case, the prescriber should consider regarding the isolate to be resistant.

Antibiotic regimens that are currently recommended for treatment of IE are summarized in Chapter 37, For streptococcal isolates that are moderately or highly resistant to β-lactam agents, penicillin should be given in combination with low doses of aminoglycoside. Table 151.1 lists recommended antibiotic regimens for the treatment of septicemia, central nervous system infections, and lower respiratory tract infections due to viridans streptococci.

In cases complicated by abscesses secondary to *S. anginosus* infection, surgical drainage is often required for cure.

Suggested reading

Bruckner L, Gigliotti F. Viridans group streptococcal infections among children with cancer and the importance of emerging antibiotic resistance. *Semin Pediatr Infect Dis*. 2006;17(3):153–160.

Brusch JL. Microbiology of infective endocarditis and clinical correlates: Gram-positive organisms. In Brusch JL, ed. *Infective endocarditis: Management in the era of intravascular devices*. New York: Informa Health Care; 2007:13–50.

Castanheira M, Jones RN, Sadar HS. Update of the *in vitro* activity of daptomycin tested against 6710 Gram-positive cocci isolated in North America. *Diagn Microbiol Infect Dis*. 2008;61:235–239.

Desimone DC, Tleyjeh IM, Correa de Sa DD, et al.; Mayo Cardiovascular Infections Study Group. Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines. *Circulation*. 2012;126:60–64.

Doern CD, Burnham CA. It's not easy being green: The viridans group streptococci, with a focus on pediatric clinical manifestations. *J Clin Microbiol*. 2010;48:3829–3835.

Fukushima K, Noda M, Saito Y, Ikeda T. *Streptococcus sanguis* meningitis: Report of a case and review of the literature. *Intern Med*. 2012;51:3073–3076.

Husain E, Whitehead S, Castell A, Thomas EE, Speert DP. Viridans streptococci bacteremia in children with malignancy: Relevance of species identification and penicillin susceptibility. *Pediatr Infect Dis J*. 2005;24:563–566.

Prasad KN, Mishra AM, Gupta D, et al. Analysis of microbial etiology and mortality in patients with brain abscess. *J Infect*. 2006;53(4):221–227.

Su TY, Lee MH, Huang CT, Liu TP,Lu JJ. The clinical impact of patients with bloodstream infection with different groups of viridans group streptococci by using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). *Medicine (Baltimore)*. 2018; 97 (50): e13607.

Suzuki J, Aoyama N, Ogawa M, et al. Periodontitis and cardiovascular diseases. *Exper Opin Ther Targets*. 2010;14:1023–1028.

152

Poststreptococcal immunologic complications

Barbara W. Stechenberg

Infections caused by group A β-hemolytic *Streptococcus (Streptococcus pyogenes)* are unusual in that they have been associated with nonsuppurative complications, acute rheumatic fever (ARF), and acute glomerulonephritis. These distinct clinical entities are not related to toxic effects of the organism and follow the infections by an interval during which immunologic mechanisms are triggered. Table 152.1 compares some features of two clinical syndromes.

Acute rheumatic fever

ARF is a multisystem collagen vascular disease that follows untreated or undetected group A streptococcal pharyngitis in <1% of persons. It is seen most commonly in children ages 5 to 15 and is associated with a genetic predisposition. It is more common in developing countries. There also appear to be strains of *S. pyogenes* more likely to be implicated in this condition (see Table 152.1).

The diagnosis of ARF is made clinically and is based on the modified Jones criteria (Table 152.2). The presence of two major or one major and at least two minor criteria suggests the diagnosis. Recent infection with *S. pyogenes* also must be suggested by either isolation of the organism from the throat or serologic evidence in the form of elevation of antistreptolysin O, antihyaluronidase, or antideoxyribonuclease B titers. The exception to this rule is chorea, which becomes manifest 2 to 6 months after infection, by which time evidence of a recent streptococcal infection may be lacking.

The most common clinical manifestations of ARF are carditis and arthritis. The former usually presents as a significant murmur, most commonly mitral insufficiency. Both myocarditis and pericarditis may accompany this valvulitis. It is the only manifestation that may result in residual disease. The arthritis is a migratory polyarthritis that generally involves the medium-size joints (elbows, wrists, ankles, and knees). Pain is often striking. Another characteristic finding is the dramatic response of the arthritis to salicylate therapy. Chorea known as Sydenham chorea or St. Vitus' dance usually occurs as an isolated, often subtle, neurologic disorder with behavioral aspects, particularly emotional lability. Erythema marginatum and subcutaneous nodules are rarely seen. The strongest diagnoses of ARF are based on carditis or chorea. The weakest is based on arthritis as a single major manifestation with two minor criteria.

The term *PANDAS* (pediatric autoimmune neuropsychiatric disorder associated with group *A Streptococcus*) has been used to refer to a group of neuropsychiatric or behavioral disorders, particularly obsessive-compulsive disorder (OCD), Tourette's syndrome, and tic disorder, with a possible relationship to group A streptococcal infections, and, perhaps, related pathologically to Sydenham chorea. Swedo and colleagues have proposed an autoimmune pathogenesis for these disorders, although this is controversial. Suggested diagnostic criteria include the presence of OCD or a tic disorder; pediatric onset; abrupt onset of symptoms or a course characterized by dramatic exacerbations of symptoms; a temporal association with group A streptococcal infection; and abnormal results of neurologic examination, such as choreiform movements, motor hyperactivity, and tics. Extensive investigation of its epidemiology, diagnosis, and treatment as well as its relationship to ARF are still underway.

TABLE 152.1 **COMPARISON OF ACUTE RHEUMATIC FEVER (ARF) AND ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS (AGN)**

Feature	ARF	AGN
Prior infection	Pharyngitis	Pharyngitis or pyoderma
M-types	3, 5, 6, 14, 18, 19, 24	Pharynx: 1, 2, 3, 4, 12, 15 Skin: 4, 9, 52, 55, 59, 60, 61
Latency	2–4 wk	Throat: 10 d Skin: 3 wk
Recurrences	Common	Rare
Antibiotic prophylaxis	Useful	Not useful
Sequelae	Common (heart)	Rare

Prevention

Primary prevention of ARF requires the proper diagnosis and treatment of *S. pyogenes* pharyngitis. The accepted standard of care is the performance of a throat culture or rapid streptococcal antigen detection test. If the latter is negative in a child, a throat culture should be done because of the variable sensitivity of that test. Treatment of streptococcal pharyngitis should be undertaken, generally with oral phenoxymethyl penicillin (penicillin V) at 250 to 500 mg two or three times a day for 10 days; if compliance is an issue, benzathine penicillin G, 1.2 million units intramuscularly (IM) (if ≥27 kg or 600 000 U if ≤27 kg), is acceptable. For patients allergic to penicillin (without anaphylaxis), a first-generation cephalosporin (e.g., cephalexin 20 mg/kg/dose twice daily, max dose = 500 mg) for 10 days is the antibiotic of choice. Alternatives are clindamycin (7 mg/kg/dose three times daily, max dose = 300 mg) or clarithromycin (7.5 mg/kg/dose twice daily, max dose = 250 mg) for 10 days or azithromycin (12 mg/kg once daily, max dose = 500 mg) for 5 days, although resistance to the latter two agents is well known. Prompt treatment should prevent most cases of ARF after symptomatic pharyngitis. Initiation of therapy up to 8 days after infection begins is probably beneficial.

TABLE 152.2 **MODIFIED JONES CRITERIA FOR ACUTE RHEUMATIC FEVER**[a]

Major criteria	Minor criteria
Carditis	Previous rheumatic fever
Arthritis	Clinical
Chorea	Fever
Erythema marginatum	Arthralgia
Subcutaneous nodules	Laboratory
	Prolonged PR interval
	Elevated acute-phase
	reactants: erythrocyte sedimentation rate, C-reactive protein, white blood cell count

[a] Requirements: (1) evidence of antecedent group A streptococcal infection and (2) two major criteria or one major and at least two minor criteria.

Therapy

Treatment of ARF involves three important areas: eradication of *S. pyogenes*, treatment of the acute manifestations, and prevention of both recurrences and infective endocarditis in those with residual carditis. The first is accomplished with the regimens for primary prevention. These regimens should be used even if the throat culture is negative at the time of diagnosis of ARF. The mainstay of treatment of ARF is salicylates, both for arthritis and mild to moderate carditis. A dosage of 70 to 80 mg/kg/day should be initiated to produce a therapeutic blood level of 20 to 25 mg/dL. This is continued for at least 2 weeks, until acute inflammation has subsided, and then decreased gradually over the next 2 to 4 weeks. Patients with arthritis should be repeatedly evaluated for carditis during the initial 2 weeks. Persons with severe carditis and/or congestive heart failure may be treated with steroids, usually prednisone, at 2 mg/kg/day acutely for at least 2 weeks, with a gradual withdrawal over 4 to 6 weeks, with the introduction of salicylates to prevent rebound. Supportive care of carditis is important; digitalization should be done slowly starting with one-quarter of the usual initial dose.

Sydenham chorea is usually self-limited over several weeks. If symptoms are debilitating, phenobarbital may be started at 15 to 30 mg every 6 to 8 hours. Haloperidol is an alternative. A short course of corticosteroids over 2 weeks with a 2- to 3-week taper may be beneficial.

Secondary prevention

Secondary prevention of infection with *S. pyogenes* is based on the fact that persons with ARF have at least 10% to 30% chance of recurrence of ARF when reinfected with this organism. Because of concerns about compliance, benzathine penicillin G, 1.2 million units IM every 4 weeks, is recommended, particularly in the first 5 years after clinical presentation and in persons with carditis. In areas of high prevalence of ARF, this regimen should be given every 3 weeks. Oral penicillin, 250 mg twice a day, is an acceptable alternative. Patients allergic to penicillin are treated with sulfadiazine, 500 mg twice a day. Erythromycin, 250 mg twice daily, should be reserved for persons allergic to both penicillin and sulfa. The duration of secondary prevention is controversial; many believe it should be lifelong, but there is evidence for discontinuing at age 21 or after 5 years (whichever is longer). Persons with residual carditis should

be educated about the importance of oral hygiene. They should receive antibiotics for prophylaxis against infective endocarditis (see Chapter 37, Endocarditis of natural and prosthetic valves: treatment and prophylaxis).

For patients with PANDAS, prompt recognition and treatment of group A streptococcal infections is important. The role of prophylactic antibiotics to prevent recurrences is unknown.

Acute poststreptococcal glomerulonephritis

Poststreptococcal acute glomerulonephritis (AGN) is an inflammatory disorder of the glomeruli. It occurs when soluble immunoglobulin G immune complexes are deposited at the glomerular basement membrane, causing complement activation and release of cytokines. This leads to infiltration of inflammatory cells. The streptococcal antigen involved has not been completely elucidated. It can follow either throat or skin infection with *S. pyogenes*. Table 152.1 lists the major strains associated with AGN and designated nephritogenic; since the early 1980s, the incidence of AGN has decreased remarkably, perhaps with a decrease in these M-types. AGN has rarely been associated with infection with group C streptococci.

The epidemiology of AGN reflects that of streptococcal pharyngitis (age 5 to 15 years; winter to spring) and pyoderma (younger age; summer months). Prompt therapy does not prevent AGN. The incubation period is about 10 days with pharyngeal strains and about 3 weeks following pyoderma.

Clinical manifestations include edema (85%), gross hematuria (25%), and hypertension (60% to 80%). A consequence of volume overload, the hypertension may lead to encephalopathic changes in a small number of patients. Symptoms referable to the cardiovascular system (cardiomegaly, congestive heart failure, pulmonary edema) are sometimes present. Fever is uncommon. Some patients have a mixed acute nephritis/nephrotic syndrome with ascites and anasarca. AGN is typically self-limited, with spontaneous diuresis and improvement in hypertension within 1 week. In fact, up to 50% have been asymptomatic during outbreaks. In children, fewer than 2% of cases are complicated by acute renal failure. This number may be higher in adults. Progression to chronic renal failure is also very unlikely.

Freshly voided urine typically demonstrates mild proteinuria, red and white blood cells, and red and white blood cell casts. Gross hematuria (usually brown) disappears rapidly, although microscopic hematuria persists for months as does the proteinuria. Striking hypocomplementemia is seen in 90% of patients, primarily C3 and CH50 with a normal C4. Diagnosis is supported by the latter finding in association with evidence of preceding *S. pyogenes* infection. Following pharyngeal infection, antistreptolysin O elevations are common. However, it is less useful following skin infections, after which anti-DNAase B or antihyaluronidase are more likely to be high. Attempts to culture the organism also should be undertaken.

Therapy

Therapy is supportive. Antibiotics should be given to eradicate any streptococcal carriage, using the same agents as described for ARF. Oral therapy should be continued for 10 days However, no data have demonstrated that this therapy either prevents AGN or alters its natural history. Patients with obvious edema, hypertension, or azotemia may require hospitalization, although most patients respond to careful restriction of fluid and salt intake. Diuretic therapy is usually successful in controlling hypertension. Prognosis is generally excellent. Relapses are rare.

There is no need for antibiotic prophylaxis to prevent future attacks because repeated episodes are rare.

Suggested reading

Berrios X, del Campo E, Guzman B, *et al*. Discontinuing rheumatic fever prophylaxis in selected adolescents and young adults. *Ann Intern Med*. 1993;118:401–406.

Ferrieri P. Proceedings of the Jones Criteria Workshop: Jones Criteria Workshop. *Circulation*. 2002;106:2521–2523.

Gerber M, Baltimore R, Eaton C, *et al*. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. A scientific statement from the American Heart Association, Rheumatic Fever, Endocarditis and Kawasaki Disease Committee. *Circulation*. 2009;119:1541–1551.

Kurlan R, Kaplan EL. The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) etiology for tics and obsessive-compulsive symptoms: hypothesis or entity? Practical considerations for the clinician. *Pediatrics*. 2004;113:883–886.

Popovic-Polovic M, Kostic M, Antic-Peco A, *et al*. Medium and long-term prognosis of patients with acute post-streptococcal glomerulonephritis. *Nephron*. 1991;58:393–399.

Shulman S, Bisno A, Clegg H, *et al*. Clinical practice guidelines for the diagnosis and management of Group A streptococcal pharyngitis; 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55:1279–1282.

Special Writing Group of the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease. Guidelines for the diagnosis of acute rheumatic fever. *JAMA*. 1992;268: 2069–2073.

Swedo SE, Leonard HL, Rapoport JL. The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) subgroup: separating fact from fiction. *Pediatrics*. 2004;113:907–911.

Tejani A, Ingulli E. Post-streptococcal glomerulonephritis. *Nephron*. 1990;55:1–5.

Veasy GL, Hill HR. Immunologic and clinical correlations in rheumatic fever and rheumatic heart disease. *Pediatr Infect Dis J*. 1997;16:400–407.

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Shigella

Eduardo Rodríguez-Noriega

Introduction

Shigellosis is an inflammatory, infectious diarrheal disease that is endemic in children living in high-risk countries. The disease can be acquired by travelers to those regions, and the risk of the disease is generally higher among men who have sex with men (MSM).

Microbiology

Shigella spp. is a gram-negative rod that belongs to the Enterobacteriaceae family of bacteria. There are four species of *Shigella*: 15 types of *S. dysenteriae*, including *S. dysenteriae* serotype 1; 15 types of *S. flexneri*, 19 types of *S. boydii*, and one serotype of *S. sonnei*. Humans are the only known natural host of *Shigella*, and the infection of shigellosis is transmitted via the fecal-oral route from person to person.

Pathogenesis

Intestinal infections of *Shigella* produce damage to the terminal ileum, colon, and rectum. The pathogen possesses multiple virulence factors, including enterotoxins, siderophores, effectors, proteases, and lipopolysaccharides. After the oral ingestion of small amounts of the bacteria, the production of enterotoxins is responsible for the initial onset of watery diarrhea.

During translocation, *Shigella* is ingested by macrophages once it invades the mucous intestinal layer. In this site, the replication and dissemination of *Shigella* spp. occurs, together with the activation of neutrophils, the production of inflammatory cytokines, epithelial abscesses and ulcerations, and the destruction of tissue, which leads to further disruption of the epithelial barrier. During this stage of infection, patients develop dysentery that is accompanied by the symptoms of bloody stool, fever, and abdominal cramps.

The further development of *Shigella*'s invasion of the intestinal layer causes the downregulation of the inflammatory response and innate immune response, the latter of which leads to diminished immune response and reinfections.

Epidemiology

In 2015, infectious diarrhea was responsible for >1,310,00 deaths worldwide in children <5 years of age. In that same age group, infectious diarrhea caused >499,000 deaths. *Shigella* and rotavirus were the two

leading causes of diarrhea-related death, contributing to the death of 164,300 and 199,000 children, respectively.

However, in a recent reassessment of the causes of diarrhea conducted within the Global Enteric Multicenter Study (GEMS), it was revealed that among 11,400 specimens collected from 5,700 cases, *Shigella* spp. was the pathogen most often encountered out of the six that were found, surpassing rotavirus, adenovirus, Shiga toxin enterotoxigenic *Escherichia coli*, *Cryptosporidium* spp., and *Campylobacter* spp. *Shigella* spp. and rotavirus, meanwhile, were found to be the most frequently found pathogens in mixed infections.

Shigellosis is known to occur regularly among travelers to regions that are considered at high risk for shigellosis. Shigellosis can be sexually transmitted by MSM who engage in oro-anal contact, have multiple sexual partners, and engage in unprotected sex. Among this group of at-risk individuals, *S. flexneri* serotype 3a in particular can cause shigellosis outbreaks in middle-aged men with no travel history to high-risk regions. A relatively new strain of *Shigella*, *S. flexneri* type 3a, has spread around the world and acquired multiple antimicrobial resistant determinants, including resistance to azithromycin.

Outbreaks can occur, particularly in cases involving MSM, through *Shigella* clusters, where resistance to more than one antibiotic can be detected, including resistance to ciprofloxacin and azithromycin. Meanwhile, *S. flexneri* may cause annual epidemics in the months of June to September in some countries; these outbreaks are usually waterborne and are frequently associated with recreational water activities involving untreated water. These epidemics are cyclic in some areas that are characterized by overcrowding and the presence of children >5 years old in families.

When outbreaks occur involving school-aged children, decisions regarding children's exclusion from school activities are another problem that must be dealt with. Exclusion policies should specify the type of treatment child patients should receive before reintegration is considered.

Clinical manifestations

The incubation period of the disease is calculated to be 1 to 4 days from the ingestion of the bacteria, although it sometimes lasts up to 8 days. Risk groups include children between the ages of 1 and 4 years, travelers to endemic areas, MSM, children in daycare, and those children's household contacts.

Asymptomatic infections can occur; most patients with the disease become symptomatic, however, with the presence of fever, headache, anorexia, vomiting, and, initially, watery diarrhea. After this initial stage, patients can develop dysentery accompanied by blood in their stool, abdominal cramps, and tenesmus.

In children, manifestations of the disease are more severe when they are infected with *S. dysenteriae* type 1. More often than other infected groups, this group of patients often exhibits leukemoid reactions, develops systemic complications associated with hemolytic uremic syndrome (HUS), experiences more frequent and more severe hyponatremia, and develops neurologic abnormalities.

In the controlled human infection model for *Shigella*, abdominal pain or cramps are found to develop in 81% of cases, followed by diarrhea in 76%, fever in 50%, nausea in 46%, dysentery in 27%, and vomiting in 24%. The presence of significant blood in stools, fevers of >38°C/101.1°F, and vomiting are important risk factors, as are subjective observations of loose stool output for a period of 24 hours.

Laboratory manifestations

Patients suffering from diarrhea caused by *Shigella*, especially in the severe dysenteric form, will have polymorphonuclear leukocytes in their stool. The presence of inflammatory cells in a patient's stool indicates the presence of an inflammatory etiology. Other diarrheal infections, such as those resulting from vibrios or viruses, do not cause inflammatory cells to appear in the feces of patients.

In >85% of patients with shigellosis, >50 fecal leukocytes can be found per high-power field. The testing of stool culture for *Shigella* requires particular selective media, is difficult to process, and requires >48 hours for a preliminary diagnosis; nevertheless, it is an essential recourse for epidemiological studies and for detecting antibiotic resistance.

Shigella dysentery is one cause of leukemoid reactions in which peripheral leukocytes counts are often >40,000. In patients with *Shigella* bacteremia, other laboratory abnormalities may occur, including elevated creatinine levels and thrombocytopenia.

In the presence of acute kidney injury, hemolytic anemia, thrombocytopenia, and proteinuria during or after an episode of infection, inflammatory diarrhea is an indication of HUS.

Recently, the use of a multiples molecular assay has been compared to conventional methods of detecting Shigella. In 1,716 stool samples, the molecular test detected 59% of the etiological agents present, compared with 39% detected using a traditional methodology. Of the episodes the molecular assay detected, 67.5% were caused by a single agent and 32.5% by multiple agents.

Intestinal complications

In patients with severe *Shigella* dysentery, critical intestinal complications can develop, including rectal prolapse, toxic megacolon, intestinal perforation, intestinal obstruction, appendicitis, and persistent diarrhea.

Systemic complications

Systemic complications, also referred to as extraintestinal complications, may include dehydration, hyponatremia, hypoglycemia, leukemoid reactions, bacteremia, metastatic infections

such as meningitis, osteomyelitis, arthritis, splenic abscess, and seizures. During or after acute infections, other complications can develop, including HUS, reactive arthritis, and irritable bowel syndrome.

The association between shigellosis and HUS is one of multiple etiologies of severe complications involving shigellosis, including *Shigella* infection with Shiga toxin *E. coli*, with a pneumococcus-induced syndrome and differential diagnoses with other causes, including atypical HUS, which develops in the presence of cobalamin C defects, and diseases that coexist with shigellosis, such as malignancy and immunosuppression.

Incidences of HUS secondary to infection with Shiga-toxin producing bacteria account for 85% to 90% of all cases of HUS as a complication of shigellosis; 5% to 10% are due to mechanisms related to the atypical HUS, and 5% are secondary to pneumococcal infections.

The development of bacteremia in cases of shigellosis occurs in children <1 year old in more than 4% of cases. Risk factors for the development of bacteremia include severe dehydration, abdominal tenderness or ileus, agitation, lethargy, and leukocytosis. Children who develop bacteremia are at elevated risk of experiencing leukemoid reactions and developing renal failure, thrombocytopenia, and HUS.

Bacteremia can also develop in adults >65 years of age who are immunocompromised or in HIV-infected women who are at risk for shigellosis while tending to sick children in their home.

Antimicrobial resistance

In a manner similar to that of other Enterobacteriaceae, *Shigella* are able to develop antimicrobial-resistant determinants that include extended-spectrum β-lactamases such as those of the CTX-M groups, TEM, and SHV. The resistance can be disseminated through plasmids and integrins, and the organism can then develop mutations and quinolone-resistant genes.

Shigella can thus develop resistance to three or more first- and second-line recommended antimicrobials. Some *S. sonnei* are occasionally found carrying the polymyxin-resistant gene MCR-1. Meanwhile, resistance to azithromycin is frequently found in isolates from older HIV-infected males, with 90% of such cases occurring in MSM. The resistance to azithromycin has recently been increasing in Southeast Asia, and has been noted especially in *S. sonnei* isolates from patients in Vietnam and Laos.

The continuing evolution of *Shigella* and its increasing resistance to antimicrobials has prompted calls for modifications to current treatment guidelines and the establishment of species-specific breakpoints for resistance and susceptibility in the future.

Treatment

Taking into consideration current local trends of resistance in *Shigella*, the recommended treatment for patients <10 years old includes the use of a quinolone as first-line therapy and the use of a β-lactam or cephalosporin as second-line therapy. In areas where resistance to quinolones is elevated, azithromycin is an alternative choice, and, in the absence of extended-spectrum β-lactamases production, cefixime can also be used.

Prevention

There is currently no vaccine available, though multiple efforts are currently under way to find the most suitable candidate.

Suggested reading

Baker KS, Dallman TJ, Ashton PM, et al. Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: A cross-sectional study. *Lancet Infect Dis*. 2015;15:913–921.

Calderaro A, Martinelli M, Buttrini M, et al. Contribution of the FilmArray((R)) Gastrointestinal Panel in the laboratory diagnosis of gastroenteritis in a cohort of children: A two-year prospective study. *Int J Med Microbiol*. 2018;308:514–521.

Collaborators GBDDD. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis*. 2017;17:909–948.

Fakhouri F, Zuber J, Fremeaux-Bacchi V, Loirat C. Haemolytic uraemic syndrome. *Lancet*. 2017;390:681–696.

Khan WA, Griffiths JK, Bennish ML. Gastrointestinal and extra-intestinal manifestations of childhood shigellosis in a region where all four species of Shigella are endemic. *PLoS One*. 2013;8:e64097.

Kotloff KL, Riddle MS, Platts-Mills JA, Pavlinac P, Zaidi AKM. Shigellosis. *Lancet*. 2018;391:801–812.

Liu J, Platts-Mills JA, Juma J, et al. Use of quantitative molecular diagnostic methods to identify causes of diarrhoea in children: A reanalysis of the GEMS case-control study. *Lancet*. 2016;388:1291–301.

Mattock E, Blocker AJ. How do the virulence factors of shigella work together to cause disease? *Front Cell Infect Microbiol*. 2017;7:64.

Porter CK, Lynen A, Riddle MS, et al. Clinical endpoints in the controlled human challenge model for Shigella: A call for standardization and the development of a disease severity score. *PLoS One*. 2018;13:e0194325.

Struelens MJ, Patte D, Kabir I, Salam A, Nath SK, Butler T. Shigella septicemia: Prevalence, presentation, risk factors, and outcome. *J Infect Dis*. 1985;152:784–790.

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Tularemia

Kari Neeman and Jessica N. Snowden

Microbiology

Francisella are small, aerobic, catalase-positive, pleomorphic, gram-negative intra- and extracellular coccobacilli. There are four recognized subspecies of *F. tularensis* (*tularensis* [type A], *F. holarctica* [type B], *F. mediasiatica*, and *F. novicida*).

Epidemiology

F. tularensis type A, which has been described as the more virulent of the subspecies, is found predominantly in North America. *F. tularensis* type B exists throughout the northern hemisphere. Tularemia is a zoonotic infection that can infect a wide variety of invertebrates such as the dog tick (*Dermacentor variabilis*), the wood tick (*Dermacentor andersoni*), the lone star tick (*Amblyomma americanum*), and deer flies (*Chrysops* spp.), and vertebrates (rabbits, muskrats, prairie dogs, other rodents, and occasionally cats). Transmission to humans is accomplished by bites of the arthropod vectors or contact with tissues or fluids from infectious animals. In addition, *F. tularensis* can be acquired by contact with or ingestion of contaminated material, including food and water, and by inhalation of infectious particles.[2] Water-associated outbreaks are predominantly associated with *F. tularensis* type B.[3] The infectious inoculum is estimated to be from 1 to 10 organisms.[4]

Tularemia occurs in all age groups, with the incidence in children the highest. Males have a higher incidence in all age categories, thought to be secondary to their occupational and leisure activities.[5] In areas where tularemia is endemic, the disease is seasonal, with the highest incidence in late spring extending throughout the summer months into early autumn.[6] In the United States, approximately 100 to 300 cases of tularemia are reported to the Centers for Disease Control and Prevention (CDC) annually, with most cases being reported from Missouri, Kansas, Arkansas, and Oklahoma over the past decade.[7]

Clinical manifestations

The clinical presentation, with severity ranging from mild to fatal disease, depends on patient characteristics, bacterial subspecies, inoculum dose, and route of transmission. The mean incubation period of tularemia is 3 to 5 days but may range from 1 to 21 days.[8] Six classical clinical presentations of tularemia have described based on the route of acquisition of the organism.(Table 154.1) Despite the route of acquisition though, generally symptom onset is abrupt with fever, chills, myalgia, vomiting, fatigue, and headache. Fever may be continuous or biphasic, with an intermittent period of defervescence. Pulse–temperature dissociation is also a classic finding.[9,10] Ulceroglandular and

TABLE 154.1 **CLINICAL FORMS OF TULAREMIA**

Form	Route of acquisition
Ulceroglandular or glandular	Vector-borne and direct contact (touching infected animals or material contaminated with *F. tularensis*)
Oculoglandular	Touching the eye with contaminated fingers or possibly from infective dust
Oropharyngeal	Ingesting contaminated food or water
Pneumonic	Inhaling contaminated dust or laboratory-acquired infection
Typhoidal	Unknown (probably oral or respiratory)

glandular tularemia are by far the most frequent forms of the disease, usually acquired by vector-borne transmission, direct or indirect contact with an infected animal. Ulceroglandular tularemia, the most common form (75% of cases), presents as a skin ulceration at the inoculation site with associated regional lymphadenopathy. The site of inoculation may become evident within the first 24 hours, with a swollen papule that progresses to rupturing, leaving a punched-out ulcer with raised edges. The skin overlying the regional lymph nodes may be inflamed, and, if untreated, approximately 50% of the lymph nodes suppurate and drain. The glandular form, the second most common form (15% of cases), lacks the more peripheral ulceration but otherwise presents similarly.[11] The oculoglandular form (1% of cases) presents with irritation and inflammation of eye and preauricular lymphadenopathy.[11] Typhoidal tularemia presents as fever of unknown origin and lacks the classic skin and lymph node involvement. The hallmark clinical findings are high fever, splenomegaly, and hepatomegaly.[12] Pneumonic tularemia occurs either after exposure to aerosolized particles of *F. tularensis* or from hematogenous spread from a distal site that can occur secondary to any other untreated form of tularemia but is more commonly seen with the typhoidal form.[13] Pulmonary infection remains the most lethal form of tularemia with a case fatality rate of 30% to 60% of those untreated.[11] In pneumonic tularemia, the course of disease differs markedly between type A and type B, with type A resulting in a more fulminant presentation.[14]

Diagnosis

Diagnosis of tularemia is based on recovery of an isolate, antigen or molecular detection, and serology. Growth of *F. tularensis* in culture is the definitive means of confirming the diagnosis of tularemia. Because *F. tularensis* has been associated with laboratory-acquired infections, laboratory personnel should be notified of the diagnostic possibility to enhance the diagnostic yield and to ensure that safety procedures are followed.[15] Culture of the organism should only be attempted in a biosafety level 2 laboratories. Since the organism grows poorly on standard media, it must be grown on media enriched with cysteine (e.g., modified Thayer-Martin media, chocolate agar) and may take upward of 10 days of incubation for growth.[16]

The diagnosis of tularemia is usually established by serologic testing; a fourfold or greater change in *F. tularensis* agglutinin titer between acute and convalescent sera confirms the diagnosis, whereas a single convalescent titer of ≥1:160 by tube agglutination or 1:128 by microagglutination is consistent with recent or past infection.[8,10] In patients with tularemia, antibodies appear approximately 2 to 3 weeks after infection and may be detected several years after recovery.

Treatment

Because tularemia is overall a fairly rare entity there have been no randomized controlled trials to determine the efficacy of antimicrobial therapy (Table 154.2). In the past, streptomycin has been the drug of choice in treating this infection. In one meta-analysis the use of streptomycin was associated with a 97% clinical cure rate compared to only 86% with gentamicin.[17] In one series involving only children, gentamicin was associated with a 93% success rate.[6] Given streptomycin's known vestibular toxicity and reports of hypersensitivity reactions among personnel involved in its administration, gentamicin has now primarily replaced streptomycin. Of note, in tularemic meningitis, streptomycin or chloramphenicol still may be the drug of choice.[18,19] Chloramphenicol and tetracyclines have been second-line therapy in the past but with their bacteriostatic activity are associated with higher relapse rates, especially with *F. tularensis* type A.[17,20] Fluoroquinolones, which have intracellular bactericidal activity, have had good in vitro activity

TABLE 154.2 **TREATMENT**

	Adults	Children
First-Line Therapy	Gentamicin 5 mg/kg IM or IV once daily × 10 days *Drug of choice in pregnancy*	Gentamicin 2.5 mg/kg IM or IV TID × 10 days
Second-Line Therapy	Doxycycline 100 mg PO/IV BID × 14 days *Not in pregnancy* Chloramphenicol 15 mg/kg IV q6h × 14 days *Not in pregnancy* Ciprofloxacin 500 mg PO BID × 10 days	Doxycycline (*Children ≥8 years old*) Weight <45 kg: 2.2 mg/kg PO/IV BID × 14 days Weight ≥45 kg: 100 mg PO/IV BID × 14 days Chloramphenicol 15 mg/kg IV q6h × 14 days Ciprofloxacin 15 mg/kg PO/IV BID × 10 days

against *F. tularensis*.[21,22] The use of ciprofloxacin for the treatment of *F. tularensis* type B has shown low relapse rates in both adult and pediatric series.[23,24] Observational studies in the United States, where *F. tularensis* type A is more prevalent, have shown greater success when fluoroquinolones (ciprofloxacin, levofloxacin) were started earlier in the disease course and given for at least 10 days or in combination with aminoglycoside initially.[7,12,25] The use of fluoroquinolones in juvenile animals has been associated with arthropathy, but a recent meta-analysis has shown that while musculoskeletal complaints are more common on therapy, they resolve with completion of therapy and therefore can be used with reassurance in pediatric patients.[26,27] In cases of *F. tularensis* as a biological weapon, post-exposure prophylaxis is recommended for all individuals within 24 hours of known exposure. Doxycycline and ciprofloxacin given orally are the preferred agents for a total of 14 days.[28]

Prevention

Prevention of human tularemia relies on avoidance of known vectors and careful handling of potentially contaminated animal tissue. Children in endemic areas should have hair and skin checked regularly for ticks. Hunters handling animal carcasses, especially rabbits, should utilize gloves and cook meat thoroughly. Previously in the United States, a live attenuated vaccine *F. tularensis* LVS was used to vaccinate at-risk laboratory workers, but currently this is under review by the US Food and Drug Administration (FDA) and is not available.

References

1. Keim P, Johansson A, Wagner DM. Molecular epidemiology, evolution, and ecology of Francisella. *Ann N Y Acad Sci*. 2007;1105:30–66.
2. Morner T. The ecology of tularaemia. *Rev Sci Tech*. 1992;11(4):1123–1130.
3. Kaya A, Deveci K, Uysal IO, et al. Tularemia in children: evaluation of clinical, laboratory and therapeutic features of 27 tularemia cases. *Turk J Pediatr*. 2012 Mar-Apr;54(2):105–112.
4. Jones RM, Nicas M, Hubbard A, et al. The infectious dose of Francisella tularensis (tularemia). *Appl Biosaf*. 2005;10(4):227–239.
5. Eliasson H et al. The 2000 tularemia outbreak: A case-control study of risk factors in disease-endemic and emergent areas, Sweden. *Emerg Infect Dis*. 2002;8:956–960.
6. Snowden J, Stovall S. Tularemia: Retrospective review of 10 years' experience in Arkansas. *Clin Pediatr (Phila)*. 2011 Jan;50(1):64–68.
7. Centers for Disease Control and Prevention (CDC). Tularemia. https://www.cdc.gov/tularemia/statistics/index.html
8. Evans ME, Gregory DW, Schaffner W, et al. Tularemia: A 30-year experience with 88 cases. *Medicine (Baltimore)*.1985;64(4):251–269.
9. Fredricks D, Remington J. Tularemia presenting as community-acquired pneumonia. *Arch Intern Med*. 1996;156:2137–2140.
10. American Academy of Pediatrics. Tularemia. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018* Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018: 861–864.
11. Levy PD, Chiang WK. Update on emerging infections: News from the Centers for disease control and prevention. *Ann Emerg Med*. 2002;40:356–360.
12. Weber IB, Turabelidze G, Patrick S, et al. Clinical recognition and management of tularemia in Missouri: A retrospective records review of 121 cases. *Clin Infect Dis*. 2012 Nov 15;55(10):1283–1290.
13. Thomas LD, Schaffner W. Tularemia pneumonia. *Infect Dis Clin North Am*. 2010 Mar;24(1):43–55.
14. Tärnvik A, Berglund L. Tularaemia. *Eur Respir J*. 2003 Feb;21(2):361–373.
15. Overholt EL, Tigertt WD, Kadull PJ, et al. An analysis of forty-two cases of laboratory acquired tularemia. Treatment with broad spectrum antibiotics. *Am J Med*. 1961;30:785–806.
16. Nigrovic LE, Wingerter SL. Tularemia. *Infect Dis Clin North Am*. 2008 Sep;22(3):489–504.
17. Enderlin G, Morales L, Jacobs RF, et al. Streptomycin and alternative agents for the treatment of tularemia: review of the literature. *Clin Infect Dis*. 1994 Jul;19(1):42–47.
18. Hofinger DM, Cardona L, Mertz GJ, Davis LE. Tularemic meningitis in the United States. *Arch Neurol*. 2009 Apr;66(4):523–527.
19. Narayanan N, Lacy CR, Cruz JE et al. Disaster preparedness: Biological threats and treatment options. *Pharmacotherapy*. 2018 Feb;38(2):217–234.
20. Dennis DT, Inglesby TV, Henderson DA, et al. Tularemia as a biological weapon: Medical and public health management. *JAMA*. 2001 Jun 6;285(21):2763–2773.
21. Johansson A, Urich SK, Chu MC, Sjöstedt A, Tärnvik A. In vitro susceptibility to quinolones of Francisella tularensis subspecies tularensis. *Scand J Infect Dis*. 2002;34(5):327–330.
22. Kiliç S, Celebi B, Acar B, Ataş M. In vitro susceptibility of isolates of Francisella tularensis from Turkey. *Scand J Infect Dis*. 2012 Dec 18:1–5.
23. Johansson A, Berglund L, Gothefors L, et al. Ciprofloxacin for treatment of tularemia in children. *Pediatr Infect Dis J*. 2000 May;19(5):449–453.
24. Johansson A, Berglund L, Sjöstedt A, Tärnvik A. Ciprofloxacin for treatment of tularemia. *Clin Infect Dis*. 2001 Jul 15;33(2):267–268.
25. Staples JE, Kubota KA, Chalcraft LG, et al. Epidemiologic and molecular analysis of human tularemia, United States, 1964–2004. *Emerg Infect Dis*. 2006 Jul;12(7):1113–1118.
26. Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. Ciprofloxacin safety in paediatrics: A systematic review. *Arch Dis Child*. 2011 Sep;96(9):874–880.
27. Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. *Clin Infect Dis*. 1997 Nov;25(5):1196–1204.
28. USAMIIRD. *Medical management of biological casualties handbook*, 8th ed. Fort Detrick: US Army Medical Research Institute of Infectious Diseases, 2014.

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Tuberculosis

Jay B. Mehta and Asim K. Dutt

In the United States, the epidemiology of tuberculosis (TB) has changed in recent years and since 1992 the incidence of TB has resumed a downward trend; from 10.4 in 1992 to 3.0 in 2013. However, infection by human immunodeficiency virus (HIV) and the increase in homelessness, poverty, and drug abuse continue to remain the major risk factors for active TB. Tuberculosis occurs most commonly among ethnic minorities, African Americans, and Hispanics 25 to 44 years of age. Immigrants from developing countries with a high prevalence of TB and drug resistance and other foreign born have contributed more than one-half of the total new cases in last few years. Drug-resistant disease is a major concern.

Diagnosis

After history and physical examination, the chest x-ray is required to support the diagnosis of TB (Figure 155.1). Whenever there is a suspicion of pulmonary TB, three spontaneously produced sputum specimens should be examined by microscopy and culture. If necessary, sputum production may be induced by inhalation of aerosol of warm saline (Figure 155.2). When suspicion of TB is high and microscopy is negative, a bronchial washing, transbronchial biopsy, or postbronchoscopy sputum may be productive. On rare occasions diagnosis must be made by open lung biopsy. Positive sputum microscopy suggests TB, but the only positive identification of *Mycobacterium tuberculosis* is by culture or DNA probe to distinguish it from less virulent nontuberculous mycobacteria (NTB). Drug susceptibility testing should be performed. For early detection of drug resistance DNA analysis might be very useful but this technology is still under investigation.

Latent TB infection

The goal of testing for latent TB infection is to identify the individuals who are at a higher risk for developing TB, and hence who would benefit from preventive therapy. Tuberculosis skin test (TST) has been in use for many decades, but the results are flawed and unreliable in detecting TB infection. With advancement in immunology and genomics, T-cell–based in vitro assays of interferon (IFN) released by T cells after stimulation with *M. tuberculosis* antigens are developed to identify TB infection. Two interferon-gamma release assays (IGRAs) are available as commercial kits: the Quanti FERON-TB gold assay (QFT-GIT) and the T-SPOT.TB (Oxford Immunotec).

Studies indicate that IFN-γ detection has higher specificity for *M. tuberculosis* and less cross-reactivity with bacille Calmette–Guérin (BCG) vaccination than TST. The sensitivity of T-SPOT.TB appears to be higher than for QFT-GIT or TST, likely because the testing platform ensures that an adequate number of mononuclear cells are available even if the lymphocyte count is low. The Centers for Disease Control and Prevention (CDC) recommends the QFT-GIT test for detection of latent infection, which has the advantage of a single test for patients. IGRAs should not be used for diagnosis of active TB. The guidelines suggest that this test can be used in place of, but not in addition to TST in situations in which CDC recommends

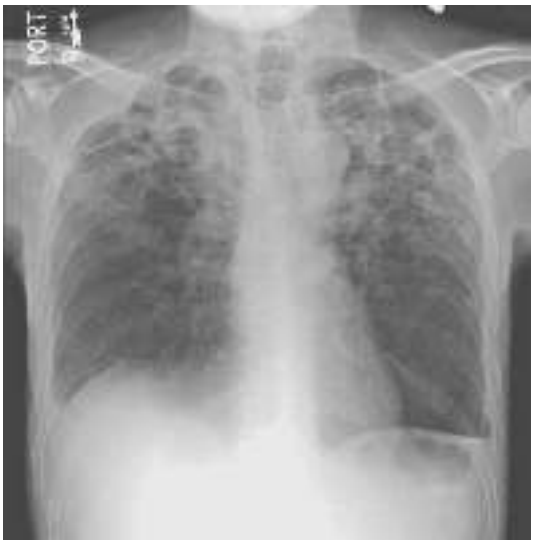

FIGURE 155.1 Pulmonary tuberculosis. Characteristic findings on chest x-ray (CXR) include upper lobe infiltrates, involvement of apical or posterior segments, and cavities with thick walls, smooth inner contours, and no air–fluid levels. Pleural reaction and distal infiltrates from endobronchial spread may be seen. Disease activity cannot be determined from the CXR alone and must be proved or excluded by sputum smear and culture.
Courtesy of Dr. David Schlossberg.

use of TST. Although the evidence is limited, IGRAs appear to be unaffected by NTB infection. *Mycobacterium marinum* and *Mycobacterium kansasii* infection are exceptions.

Diagnosis of tuberculosis

Nucleic acid amplification (NAA) tests amplify nucleic acid regions and identify the *M. tuberculosis* complex. The NAA test can be directly used in clinical specimens (such as sputum) as "direct amplification tests." The Amplicor MTB test (Roche Diagnostic System), the Amplified Mycobacterium Direct test (MTD) (Gene-Probe, Inc.), and the BD Probe-Tec ET assay (Becton Dickinson Biosciences) are commercially available. However, NAA tests cannot replace conventional tests (microscopy and culture) and should be interpreted along with conventional tests and clinical data.

Rapid detection drug resistance

Line probe assays are novel DNA strip tests that use the polymerase chain reaction (PCR). Commercially available kits include the INNO-LiPA RIF TB kit (Immunogenetics) and Geno Type MTBDR assays (Hain Lifescience). These kits are not US Food and Drug Administration (FDA) approved. Although sensitivity

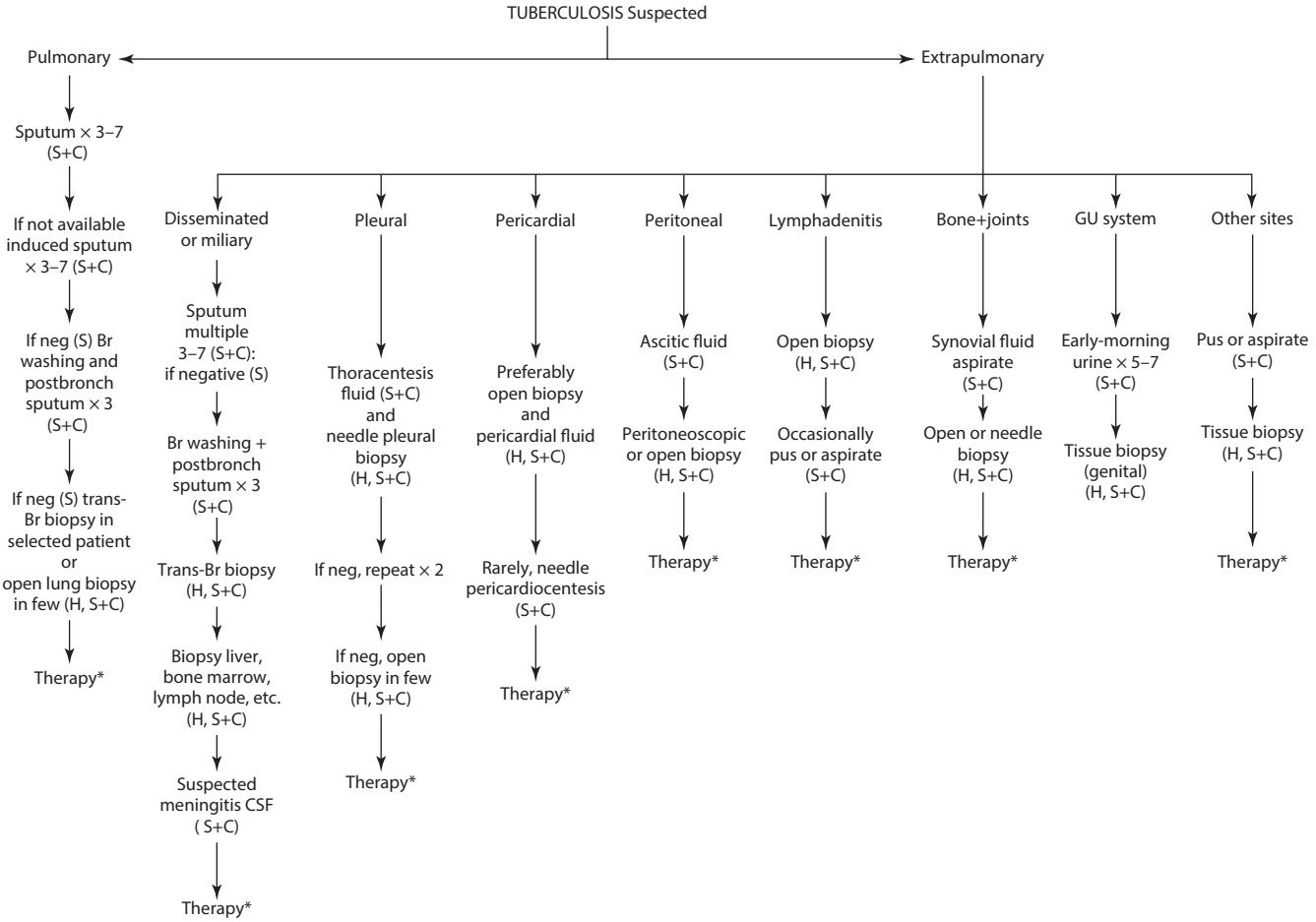

FIGURE 155.2 Diagnosis of suspected tuberculosis. S, smear; C, culture for mycobacteria; H, histology; Br, bronchial; Bronch, bronchoscopy; CSF, cerebrospinal fluid; neg, negative; GU, genitourinary. *Therapy started in suspected cases, awaiting culture results and/or clinical response.

on culture isolates may be over 95% in detecting rifampin resistance, the tests are expensive and require sophisticated laboratory support.

Also, phage-based assays are available as commercial kits but are not approved by the FDA. The test is performed in culture isolates and has high sensitivity but low specificity. This may be used for rifampin resistance in culture isolates, which increases turnaround time. The tests show promise but are not routinely used.

Extrapulmonary tuberculosis

Extrapulmonary TB cases represent 15% to 20% of the total cases but this percentage could be higher in those with HIV coinfection. TB can involve any organ of the body but the lymphatic system and bone are common sites. Miliary and central nervous system TB are rare but carry high morbidity and mortality. In most extrapulmonary TB cases plain radiograph is frequently not adequate to prove the diagnosis. CT scan or MRI is required.

Signs and symptoms of extrapulmonary TB depend upon the site involved. Atypical presentation such as chronic pain, fatigue, and failure to thrive are not uncommon in elderly patients. Clinical presentation of miliary TB can be acute or subacute. Multiorgan failure including acute respiratory distress syndrome can be life threatening. Tissue diagnosis by microscopy and culture or DNA probe confirmation is required if secretions are negative for acid-fast bacilli smear and culture. Frequently treatment has to be started while the final bacteriologic confirmation is pending.

Patients with lymphatic TB generally present with pain and swelling in the area of involvement. In children cervical lymph nodes are frequently involved.

Bone and joint disease may present with joint pain or back ache (Pott's disease). With chronic disease, destruction of bone with local sclerosis and spinal deformity is noted. Disease is most common in the lower thoracic and lumbar vertebrae. Involvement of the surrounding soft tissue may lead to cold abscess.

For the diagnosis of extrapulmonary TB, secretions and/or biopsy material must be obtained from the site (Figure 155.2). In the case of tuberculous meningitis it may be necessary to initiate therapy empirically because the disease may become irreversible before the diagnosis can be made. Low glucose, high protein, and lymphocytosis is frequently noted in cerebrospinal examination.

Therapy

Principles of chemotherapy

Initial treatment of TB should include four drugs: generally isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA). Directly observed therapy (DOT) is the preferred strategy. After daily treatment for the first 4 to 6 weeks, a twice or three time weekly regimen can be selected. Table 155.1 lists drugs, dosages, and major side effects. Several first-line bactericidal drugs are commonly combined initially because they reduce the bacterial population rapidly without the risk of resistance. Second-line drugs are most useful when resistance to two or more first-line drugs is found or they cannot be used because of life-threatening side effects or intolerance (Figure 155.3). Currently 11 drugs are approved by the FDA. Of the approved drugs, INH, RIF, EMB, and PZA are considered first-line drugs. While fluoroquinolones are not FDA approved for TB, they are commonly used for drug-resistant TB cases. Rifabutin (RBT) and rifapentine (RPT) can be considered as important drugs in certain circumstances. Streptomycin (SM) is no longer included in the list of first-line drugs.

The bactericidal drugs in suitable combinations actually kill actively multiplying extracellular bacilli in TB lesions. Rapid elimination of these bacilli renders the sputum bacteriologically negative, leading to cure. No bactericidal drug should be used alone to treat active TB because this inevitably leads to resistance to that drug. When initial therapy fails at this stage, the sputum bacteriology does not become negative, as shown by persistence of positive sputum smears beyond 2 months. Failure of therapy is usually due to emergence of drug-resistant organisms, most often due to poor compliance, prescription of an inadequate regimen, or inadequate dosage of individual drugs.

In the continuation phase of therapy, the drugs slowly eliminate small populations of intermittently metabolizing bacteria in the closed caseous lesion or within macrophages. Incomplete therapy may lead to relapse after discontinuation of treatment, often with drug-sensitive organisms.

Drug-resistant organisms

The inclusion of a number of drugs in a regimen should be based on the awareness of the circumstances under which drug-resistant bacilli are likely to be present (Box 155.1).

At the minimum, a four-drug regimen should be initiated when drug resistance is likely, until susceptibility results are available. The number of drugs in the initial regimen may have to be increased to five to seven if the organisms are resistant to three or more drugs and HIV infection is present, as often occurs in large cities in the United States and in many developing countries.

Management of tuberculosis

Newer approaches are advocated for a better outcome. For the care of patients with TB, responsibility for completion and success now lies with the healthcare providers and not the patients. The duration of treatment in the continuation phase should be extended in specific situations. New anti-TB medications show promise; these are used when necessary. DOT is strongly recommended; the patient is observed ingesting each dose of medication, for improving completion of therapy with a good outcome.

Drug regimens

There are four basic regimens recommended by the CDC for treatment of adult TB disease caused by susceptible organisms

TABLE 155.1 **ANTITUBERCULOSIS DRUGS**

Drug	Daily dosage	Twice-weekly dosage	Side effects	Mode of action
FIRST-LINE DRUGS				
Isoniazid (INH)	5 mg/kg (usually 300 mg) PO or IM	15 mg/kg (usually 900 mg) PO	Peripheral neuritis, hepatotoxicity, allergic fever and rash, lupus erythematosus phenomenon	Acts strongly on rapidly dividing extracellular bacilli; acts weakly on slowly multiplying intracellular bacilli
Rifampin (RIF)	10 mg/kg (usually 450–600 mg) PO	10 mg/kg (usually 450–600 mg) PO	Hepatotoxicity, nausea, vomiting, allergic fever and rash, flu-like syndrome, petechiae with thrombocytopenia or acute renal failure during intermittent therapy	Acts on both rapidly and slowly multiplying extracellular and intracellular bacilli, particularly on slowly multiplying persisters
Rifabutin (Ansamycin)	300 mg PO daily, twice or thrice weekly	Used as RIF substitute	Same as rifampin; uveitis, arthralgia, leukopenia	Same as above
Rifapentine	300–600 mg PO once weekly in continuation phase	Seronegative HIV, noncavitary TB	Same as rifampin; not used in HIV	
Rifamate (INH 150 mg plus RIF 300 mg)	2 capsules PO qd	2 capsules plus 2 tablets of INH (300 mg)	Same as INH/RIF	Same as INH/RIF
Rifater (INH 50 mg plus RIF 120 mg plus PZA 300 mg)	5–6 capsules PO qd		Same as INH/RIF/PZA	Same as INH/RIF/PZA
Pyrazinamide (PZA)	25–30 mg/kg PO (usually 1.5–2 g)	45–50 mg/kg PO (usually 3–3.5 mg)	Hyperuricemia, hepatotoxicity, allergic fever and rash	Active in acid pH (2.5 g) on intracellular bacilli
Ethambutol (EMB)	15–25 mg/kg/d initially, followed after 2 months with 15 mg/kg/d	50 mg/kg PO	Optic neuritis, skin rash, hyperuricemia	Weakly active against both extracellular and intracellular bacilli to inhibit the development of resistance
SECOND-LINE DRUGS				
Streptomycin	10–15 mg/kg (usually 0.5–1 g) 5 days/week; IM or IV	20–25 mg/kg (usually 1–1.5 g)	Cranial nerve VIII damage (vestibular and auditory), nephrotoxicity, allergic fever, rash	Active against rapidly multiplying bacilli in neutral or slightly alkaline extracellular medium
Kanamycin	15–30 mg/kg qd IM or IV	15–30 mg/kg	Same as streptomycin	Same as streptomycin

(*continued*)

TABLE 155.1 CONTINUED

Drug		Daily dosage	Twice-weekly dosage	Side effects	Mode of action
Amikacin		15–30 mg/kg qd IM or IV	15–30 mg/kg	Same as streptomycin	Same as streptomycin
Capreomycin		15–30 mg/kg/d IM or IV	15–30 mg/kg	Same as streptomycin	Same as streptomycin
Ethionamide		10–15 mg/kg (usually 500–750 mg) in divided doses PO with 100 mg pyridoxine	Not used	Nausea, vomiting, anorexia, allergic fever and rash, hepatotoxicity, neurotoxicity, hypothyroidism	Same as streptomycin
Cycloserine		15–20 mg/kg (usually 0.75–1 g) in divided doses with 200 mg pyridoxine PO	Not used	Personality changes, psychosis, convulsions, rash	Same as ethambutol
Para-aminosalicylic acid Thiocetazone[a]		150 mg/kg (usually 12 g) in divided doses PO 150 mg PO	Not used Used rarely	Nausea, vomiting, diarrhea, hepatotoxicity, allergic rash and fever, hypothyroidism Allergic rash and fever, Stevens–Johnson syndrome, blood disorders, nausea, vomiting	Weak action on extracellular bacilli; inhibits development of drug-resistant organisms Same as para-aminosalicylic acid
Clofazimine		200–300 mg PO qd	Not used	Pigmentation of skin, abdominal pain	Not fully known
NEWER AGENTS					
Ofloxacin	400 mg q12h	Not used	Gastrointestinal: diarrhea, nausea, abdominal pain, anorexia; central nervous system: dizziness, restlessness, nightmares, ataxia, seizures	Rapidly multiplying bacilli at neutral or alkaline pH	
Gatifloxacin	400 mg PO qd	Not used	Same as ofloxacin	Same as ofloxacin	
Levofloxacin	500 mg PO qd	Not used	Same as ofloxacin	Same as ofloxacin	
Moxifloxacin	400 mg PO qd	Not used	Same as ofloxacin	Same as ofloxacin	
Azithromycin	500 mg/d	Not used	Diarrhea, nausea, abdominal pain, elevation of liver enzymes	Rapidly multiplying bacilli in macrophages	
Clarithromycin	1 g q12h	Not used	Same as azithromycin	Same as azithromycin	

[a] Not available in the United States.

(Table 155.2). Each treatment regimen consists of an initial 2-month therapy of INH, RIF, EMB, and PZA followed by a continuation phase of 4 to 7 months.

It is recommended that the duration of treatment of any of the regimens should be extended in drug-susceptible pulmonary TB patients who show cavitations in the initial chest x-ray or whose sputum culture had not converted to negative during the intensive phase of therapy (2 months). These clinical indicators may predict adverse outcome with regard to failure and relapse. The continuation phase of therapy should be extended for another 3 months.

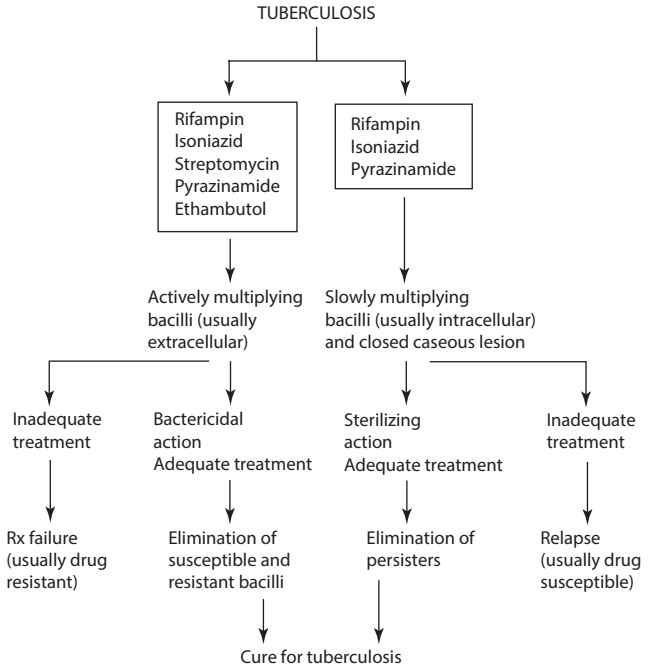

FIGURE 155.3 Principles of chemotherapy of tuberculosis.

Sputum smears and cultures must be obtained at the end of the intensive phase of treatment.

Six-month regimen

The addition of PZA to INH, RIF, and EMB daily for the initial 2 months, followed by INH and RIF daily or twice weekly for another 4 months (a total of 6 months), has proved to be highly successful. Addition of PZA accelerates reduction of the bacterial population and shortens the regimen to 6 months, although its cost is greater.

BOX 155.1

Conditions and patients with increased risk of drug-resistant TB

- History of treatment with anti-TB drugs, including preventive therapy
- Patients from areas with high prevalence of initial or primary drug resistance (>4%), e.g., urban population in the northeastern United States, Florida, California, US–Mexican border
- Foreign-born persons from areas with high prevalence of drug-resistant TB, e.g., Southeast Asia, Mexico, South America, Africa
- Contacts of persons with drug-resistant disease
- Disease in persons who are homeless, drug abusers, and HIV infected
- Persons with positive sputum smears and cultures after 2 months of chemotherapy

After drug susceptibility results are available, usually in 2 months, the regimen is modified accordingly. If the organisms are found to be susceptible to both drugs, therapy is completed with INH–RIF daily or twice weekly for another 4 months. In cases of INH resistance, therapy may consist of RIF, PZA, and EMB for a total of 6 or 9 months; INH may be included in the regimen because of its action on persisters, which generally remain INH sensitive. In RIF-resistant cases other bactericidal drugs should be continued for at least 10 to 12 months to prevent relapse. If the isolate is resistant to PZA, INH and RIF should be continued for a total of 9 months.

Treatment of multidrug-resistant disease

Where the prevalence of multidrug resistance (MDR) and HIV infection is very high, it is necessary to initiate a five- to seven-drug regimen, including second-line drugs. This is applicable to large urban populations such as in New York City, Miami, parts of New Jersey, and San Francisco, as well as for persons from developing countries.

In the treatment of MDR disease, i.e., resistance to INH and RIF, some basic principles must be followed: (1) a single drug must not be added to a failing regimen, (2) at least three new drugs that the patient has not yet taken should replace the existing drug regimen until the susceptibility results are available, (3) the total duration of therapy must be prolonged to 24 months or more, (4) the regimen should include an injectable drug for at least 4 months after the culture is converted to negative, and (5) DOT should be used to ensure compliance, because it is the patient's last chance at a cure.

Extensively drug-resistant TB (XDR-TB) has been reported recently from different parts of the world, first from South Africa. XDR-TB is defined as resistance to at least RIF and INH among the first line of anti-TB drugs (MDR-TB), in addition to resistance to any fluoroquinolone and to at least one of three injectable second-line anti-TB drugs used in TB treatment (capreomycin, kanamycin, amikacin). This development is a serious concern globally.

Most drugs used for MDR disease are second-line drugs (see Table 155.1): ethionamide, cycloserine, para-aminosalicylic acid (PAS), capreomycin, and kanamycin. Newer drugs, fluoroquinolones (gatifloxacin and moxifloxacin) and amikacin, are available but unproven. Finally, clofazimine and thiocetazone (not available in the United States) may be used but also are unproven. FDA has recently approved bedaquiline for MDR-TB but cardiac toxicity remains a concern. These second-line drugs are often rather toxic, and close monitoring is necessary. Monthly bacteriologic studies are necessary to monitor response to treatment.

Because of high failure and relapse rates in MDR-TB, surgical resection of the major diseased area of the lung is again becoming necessary after reasonable medical treatment has been given to reduce the bacterial load.

Preventive therapy for recent contacts with MDR-TB is controversial. However, possible regimens are PZA plus EMB, and PZA plus a fluoroquinolone, or EMB plus a fluoroquinolone for 12 to 24 months, during which periodic clinical, bacteriologic, and radiologic monitoring must be maintained.

The combination of RIF and PZA or rifabutin and PZA were suggested for shorter periods of time, but the regimens are highly toxic. Experts should be consulted prior to the use of the regimen.

TABLE 155.2 **DRUG REGIMENS FOR PULMONARY TB IN ADULTS CAUSED BY DRUG-SUSCEPTIBLE ORGANISMS**

Initial phase			Continuation phase			
Regimen	**Drugs**	**Interval and doses±§**	**Regimen**	**Drugs**	**Interval and doses±§**	**Range of total doses**
1	**INH**	7 days/week for 56 doses (8 weeks)	**1a**	**INH**	7 days/week for 126	182–130
	RIF	**or**		**RIF**	doses (18 weeks)	(26 weeks)
	PZA	5 days/week for 40 doses (8 weeks)			**or**	
	EMB				5 days/week for 90 doses (18 weeks)	
			1b#	**INH**	2 days/week for 36	92–76
				RIF	doses (18 weeks)	(26 weeks)
			1c	**INH**	1 day/week for	74–58
				RPT	18 doses (18 weeks)	(26 weeks)
2	**INH**	7 days/week for 14 doses	**2a**	**INH**	2 days/week for 36	62–58
	RIF	(2 weeks), then 2 days/week for 12 doses	**2b**	**RIF**	doses (18 weeks)	(26 weeks)
	PZA	(6 weeks)		**INH**	1 day/week for	44–40
	EMB	**or**		**RPT**	18 doses	(26 weeks)
		5 days/week for 10 doses			(18 weeks)	
		(2 weeks), then 2 days/week for 12 doses (6 weeks)				
3	**INH**	3 times weekly for 24	**3a**	**INH**	3 times weekly for 54	78
	RIF	doses (8 weeks)		**RIF**	doses (18 weeks)	(26 weeks)
	PZA					
	EMB					
4	**INH**	7 days/week for 56 doses	**4a**	**INH**	7 days/week for 217	273–195
	RIF	(8 weeks)	**4b**	**RPT**	doses (31 weeks)	(39 weeks)
	EMB	**or**		**INH**	**or**	118–102
		5 days/week for 40 doses (8 weeks)		**RIF**	5 days/week for 155 doses (31 weeks)	(39 weeks)
					Twice weekly for 62 doses (31 weeks)	

Abbreviations: INH = isoniazid; RIF = rifampin; PZA = pyrazinamide; EMB = ethambutol; RPT = rifapentine.
± When DOT is used, drugs may be given 5 days/week and the necessary doses adjusted accordingly.
§ Patients with cavitation in initial chest x-ray and positive cultures at completion of 2 months of therapy should receive a 7-month continuation phase.
Adapted from CDC: Core Curriculum for Tuberculosis Fifth Edition 2011.

Treatment regimens for HIV-infected persons

In the United States the current 6-month treatment consisting of INH, RIF, PZA, and EMB or SM daily for 2 months, followed by INH and RIF daily or twice weekly for another 4 months, is not adequate in HIV-infected patients. However treatment of TB in HIV-infected patients is complex and requires due attention to the patient's need for antiretroviral therapy (ART), potential drug reactions, and complication secondary to the immune reconstitution inflammatory syndrome (IRIS). Rifamycins are known to induce liver CYP3A4 enzymes that can increase metabolism of protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Rifampin is more potent an inducer than rifabutin hence rifabutin is preferred over rifampin if certain antiviral drugs are used to treat HIV infection; however, adjustment of the rifabutin dosage is still necessary with some of the antiretroviral medications. Clinically significant interactions between rifampin and nucleoside analogs are rare. Therefore, nucleoside analogs can be used within ART regimens along with a third antiretroviral agent (e.g., efavirenz).

The CDC recommends that therapy for patients with HIV infection be prolonged to 9 months or for at least 6 months following conversion of sputum cultures to negative (Table 155.2).

Treatment-limiting side effects are frequent in HIV-infected patients, and they require innovative measures. Rifabutin has fewer drug–drug interactions due to its decreased induction of the cytochrome P450 system. It works better with those HIV-positive patients who are on certain PI and NNRTI antiviral drugs. Therefore, rifabutin may be used in place of RIF. The current recommendation is that HIV-infected patients with CD4 cell counts $<100/mm^3$ should receive therapy daily during the intensive phase and daily or thrice weekly during the continuation phase. If adverse affects such as uveitis and cytopenia occur, medication must be discontinued at once and appropriate consultation should be obtained.

Smear-negative tuberculosis

Positive sputum smears indicate a large bacterial population and advanced disease, whereas negative smears generally suggest less advanced disease. Occasionally a patient who is smear negative is also culture negative but is treated for TB on the basis of clinical and x-ray findings and response to therapy. A suggested regimen for such patients is INH, RIF, PZA, and EMB for 2 months, followed by INH and RIF for an additional 2 months (4 months total). However, HIV-infected patients should be treated for a minimum of 6 months.

Extrapulmonary tuberculosis

The bacterial load in extrapulmonary TB usually is much smaller than in cavitary pulmonary TB. Thus, 6- to 9-month regimens (see Table 155.2) are adequate for treatment of extrapulmonary TB. Figure 155.2 indicates the steps in the diagnosis of pulmonary and extrapulmonary TB. It is generally recommended that the duration of therapy be prolonged in TB spondylitis (Pott's disease) and meningitis to 9 to 12 months, respectively. Corticosteroids may be added for patients with tuberculous pericarditis and tuberculous meningitis.

Directly observed therapy

The fact that most of the 6-month regimens may be given intermittently two or three times per week has led to the development of some innovative regimens. The Denver regimen consists of DOT administration of daily INH, RIF, PZA, and SM or EMB for 2 weeks, followed by twice-weekly doses for 6 weeks and then twice-weekly administration of INH or RIF for another 16 weeks. Another DOT regimen is INH, RIF, PZA, and EMB or SM three times a week for 6 months (Table 155.2, options 2 and 3).

To ensure completion of therapy, DOT is the preferred initial strategy and deserves special emphasis. DOT can be provided daily or intermittently in the office, clinic, or in the field by trained personnel. Using DOT can only improve the outcome. Aggressive interventions may be initiated when the patient misses doses.

Therapy in special situations

Pregnancy

Treatment with INH, RIF, and EMB is safe in pregnancy. SM should not be used because of toxicity to the eighth nerve of the fetus. Experience with PZA is limited in pregnancy, and at present it should be avoided if possible. If PZA is not included in the treatment regimen, the minimum duration of therapy is 9 months. Pregnancy alters the distribution and metabolism of several drugs, particularly the serum concentration of PIs are decreased. Therefore, treatment of TB in an HIV-infected pregnant woman requires special attention.

Renal failure

INH and RIF dosages need not be altered in renal failure because these drugs are excreted by the liver. Renal dialysis patients should receive the drugs after dialysis. EMB dosage must be reduced to 8 to 10 mg/kg in advanced renal failure, and the serum level should be assayed. Aminoglycoside dosage must also be adjusted, and the level should be monitored if they must be used in very unusual circumstances. PZA dosage should be reduced to 15 to 20 mg/kg.

Liver disease

Alcoholic liver disease does not preclude use of anti-TB drugs. However, monitoring for side effects must be careful and regular. In overt liver failure, one suggested regimen is amikacin plus EMB plus a fluoroquinolone.

Combined preparations

In the United States, two commercial preparations of combination drugs are available. It is advantageous to use combination preparations because they preclude the taking of only one bactericidal drug, which encourages drug resistance. Rifamate is a combination capsule of INH, 150 mg, and RIF, 300 mg, and two capsules are the recommended daily dose. Another preparation, Rifater, contains INH, 50 mg, RIF, 120 mg, and PZA, 300 mg, in each tablet; the recommended dose is five tablets daily. We strongly recommend the use of combination preparations for therapy as a safeguard against development of drug resistance and medication errors, particularly for patients not on DOT.

Corticosteroid therapy

Corticosteroids are not routinely used in the treatment of TB. Prednisone, 20 to 30 mg/day, may improve the general sense of well-being, reduce fever, increase appetite, and improve nutrition of markedly toxic or severely debilitated patients. The drug should be tapered off gradually after 4 to 8 weeks. In disseminated TB associated with hypoxemia and respiratory failure, prednisone, 40 to 60 mg/day, may improve oxygenation. Steroids have been successfully used in AIDS patients with TB, but they may promote opportunistic infections. Most authorities believe that complicated tuberculous meningitis should be treated with prednisone, 60 to 80 mg/day, slowly tapered after 8 to 12 weeks. Some advise corticosteroid therapy for all cases of tuberculous pericarditis to prevent constrictive pericarditis.

Monitoring and follow-up of patients

Intense bacteriologic monitoring is necessary during therapy of pulmonary TB. We recommend that three to five specimens of bronchial secretions (sputum) be examined initially by smear and culture, followed by drug susceptibility testing. During therapy, at least one specimen of sputum should be examined every 2 weeks until conversion to negative occurs. This permits early detection of noncompliance and impending failure. After completion of treatment, to detect early relapse, one specimen every 3 months three times should be examined before discharging the patient from the clinic.

Monitoring for side effects should be done monthly after explaining to the patient the symptoms of side effects for which to be alert (e.g., nausea, vomiting, anorexia, dark urine, jaundice). Blood should be collected for baseline complete blood count and renal and hepatic function tests. We do not recommend routine monthly blood studies. Rather, the patients are advised to discontinue medication when symptomatic and to report for repeat hepatic function studies at that time. The drugs are then adjusted to the laboratory findings. Some clinicians, however, do recommend routine blood studies, either of all patients or only of those at risk for hepatotoxicity due to underlying liver disease or with other risks for hepatotoxicity. For EMB, vision and color studies are performed monthly, and for SM or other aminoglycosides or capreomycin monthly examination for balance and hearing loss are performed.

Prophylaxis

For prophylaxis, see Chapter 113, Nonsurgical antimicrobial prophylaxis.

Suggested reading

American Thoracic Society, CDC, and Infectious Disease Society of America. Treatment of tuberculosis. *Am J Respir Crit Care Med*. 2003;167:603–662.

Dutt AK, Moers D, Stead WW. Short course chemotherapy for extrapulmonary tuberculosis. Nine years' experience. *Ann Intern Med*. 1986;104:7–12.

Furin J, Nardell EA. Multidrug-resistant tuberculosis: an update on the best regimens. *Infect Med*. 2006;23:493–504.

Goble M, Iseman MD, Madsen LA, *et al*. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med*. 1993;328:527–532.

Iseman MD. Treatment of multidrug-resistant tuberculosis. *N Engl J Med*. 1993;329:784–791.

Nahid P, Pai M, Hopewell PC. Advances in the diagnosis and treatment of tuberculosis. *Proc Am Thorac Soc*. 2006;3:103–110.

Sharme SK, Mohan A. Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control. *Chest*. 2006;130:261–272.

Weiss SE, Slocum PC, Blais FX, *et al*. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *N Engl J Med*. 1994;330:1179–1184.

Yew DD, Leung CC. Update in tuberculosis 2006. *Am J Respir Crit Care Med*. 2007;175:541–546.

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Nontuberculous mycobacteria

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Introduction

The nontuberculous mycobacteria (NTM) are ubiquitous in the environment; so much so that some experts feel they should be referred to as "environmental mycobacteria." While there are almost 150 identified NTM species, the most common NTM associated with human disease in the United States are *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, *Mycobacterium fortuitum* and *Mycobacterium abscessus*. Many other NTM species can cause human disease but are generally rarely encountered clinically, while a few NTM species, most notably *Mycobacterium gordonae*, are frequently isolated as specimen contaminants and almost never cause disease.

Infection is thought to occur from environmental exposure to the NTM with three potential portals of entry; the respiratory tract, the gastrointestinal tract, and direct inoculation of the skin and soft tissues. There had been no documented occurrences of either human-to-human or animal-to-human transmission until recent reports of the transmissibility between patients in several cystic fibrosis (CF) clinics.

The most common clinical manifestation of NTM infection in the immunocompetent host is chronic pulmonary disease. Symptoms are usually insidious in onset and variably include cough, sputum production, fatigue, weight loss, weakness, hemoptysis, and night sweats. MAC is the most common respiratory pathogen. Patients with MAC lung disease are divided between two groups. The first are primarily female patients without a history of smoking or pre-existing lung disease who have noncavitary disease characterized by nodular densities and bronchiectasis, usually in the right middle lobe and lingula. The second group are primarily male patients with pre-existing lung disease, most often chronic obstructive lung disease, and cavitary abnormalities radiographically, similar to tuberculosis.

Lymphadenitis is the most common NTM disease manifestation in children and is usually due to MAC or less commonly *Mycobacterium scrofulaceum*. The most important differential diagnosis is tuberculosis lymphadenitis, although NTM account for approximately 90% of mycobacterial lymphadenitis in children (but only 10% in adults). Symptoms are usually minimal with unilateral involvement of submandibular, submaxillary, preauricular, or cervical lymph nodes most common. Skin and soft-tissue infections are usually due to *Mycobacterium marinum* or the "rapidly growing mycobacteria" (RGM), *M. abscessus*, *M. fortuitum*, *Mycobacterium chelonae*, and are the result of direct inoculation either after trauma or surgery. Dissemination of NTM pathogens is most often associated with the severe immunosuppression of advanced acquired immunodeficiency syndrome (AIDS) and caused by MAC. Disseminated NTM infections can also occur in other immunocompromised states, sometimes associated with indwelling foreign bodies such as venous catheters, dialysis catheters, or other prosthetic devices.

Diagnostic criteria of nontuberculous mycobacterial (NTM) lung disease

The diagnostic criteria for NTM lung disease include a compilation of clinical, radiographic, and microbiologic criteria. Although a diagnosis of NTM lung disease may be suspected by one or more of these three

criteria, all must be present to establish a diagnosis. Clinical, radiographic, and microbiologic criteria are equally important. The minimum evaluation of a patient suspected of NTM lung disease should include (1) chest radiograph or, in the absence of cavitation, chest high-resolution computed tomography (HRCT) scan, (2) three or more sputum specimens for acid-fast bacilli (AFB) analysis, and (3) exclusion of other disorders such as tuberculosis and lung malignancy.

The following criteria apply to symptomatic patients with radiographic infiltrates, nodular or cavitary, or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules. These criteria fit best with MAC, *M. kansasii*, and *M. abscessus*. There is not enough known about most other NTM to be certain that these diagnostic criteria are universally applicable for all NTM respiratory pathogens. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination. Substantial variation in the epidemiology of NTM lung disease has been recognized between countries such that mindfulness of the epidemiologic data is imperative in making assessments of clinical likelihood of disease versus colonization dependent on specific NTM species.

Clinical criteria include respiratory or systemic symptoms attributed to NTM lung disease not attributable to other established diagnoses. Radiographic findings as noted above may vary, especially in the context of whether there is or is not pre-existing lung disease. In the absence of radiographic changes related to pre-existing lung disease or of cavitary change, the most common findings include nodular infiltrates, cylindrical bronchiectasis, and consolidation. Pleural disease, prominent mediastinal/hilar adenopathy, air–fluid levels, and ground-glass opacities on high-resolution chest computed tomography are not commonly seen in non-human immunodeficiency virus (HIV) patients with NTM lung disease. Microbiologic criteria also may vary. If three sputum results are available at least two AFB cultures should be positive, regardless of AFB smear results. In the absence of at least two positive cultures, consideration should be given to repeating three sputum specimens for AFB smear and culture or obtaining bronchoscopy with wash or lavage. If only one bronchial wash or lavage is available, one positive culture regardless of smear is necessary. If the sputum or bronchial wash results are nondiagnostic or another disease cannot be excluded, transbronchial or lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and yielding an NTM on culture, or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washing that is culture positive for an NTM are required.

The preferred staining procedure is the fluorochrome method. Specimens should be cultured on both liquid and solid media. Species that require special growth conditions and/or lower incubation temperatures include *Mycobacterium haemophilum*, *Mycobacterium genavense*, and *Mycobacterium conspicuum*. These species can cause cutaneous and lymph node disease. In general, NTM should be identified to the species level. Methods of rapid species identification include commercial DNA probes (MAC, *M. kansasii*, and *M. gordonae*) and high performance liquid chromatography (HPLC). Routine susceptibility testing of MAC isolates is recommended for clarithromycin only. Routine susceptibility testing of *M. kansasii* isolates is recommended for rifampin only. Routine susceptibility testing, for both taxonomic identification and treatment of RGM (*M. fortuitum*, *M. abscessus*, and *M. chelonae*) should be for amikacin, imipenem (*M. fortuitum* only), doxycycline, the fluorinated quinolones, a sulfonamide or trimethoprim–sulfamethoxazole, cefoxitin, clarithromycin, linezolid, and tobramycin (*M. chelonae* only).

Substantial changes have recently occurred in NTM taxonomy including for *M. abscessus* which underwent a taxonomic change with the identification of two new species, *Mycobacterium massiliense* and *Mycobacterium bolletii*, previously identified as *M. abscessus*. They had otherwise been identical based on the widely adopted mycobacterial speciating technique utilizing sequencing of the 16S ribosomal RNA gene. This gene is highly conserved in the mycobacterial genome such that very small sequence differences can define a new mycobacterial species. It has subsequently come to light that elsewhere in the mycobacterial genome, the organism identified as *M. massiliense* has a smaller, inactive erythromycin methylase or *erm* gene (an inducible gene that causes macrolide resistance and is discussed further below) than *M. abscessus* subsp. *abscessus*, but because the name *M. bolletii* had been applied to this species with the inactive *erm* gene first, the new "official" nomenclature for this organism is currently *M. abscessus* subsp. *bolletii* even though it is widely still referred to as *M. massiliense* in the medical literature. Molecular techniques for organism identification are becoming an increasingly necessary component for informed decision making by the clinician.

Diagnostic criteria of nontuberculous mycobacterial (NTM) extrapulmonary disease

The diagnosis of extrapulmonary NTM disease also requires a compilation of clinical, microbiologic, and histopathologic test results in the context of lack of other diagnoses to explain symptoms and findings. Microbiology and histopathology results are generally of most value. Specifically, AFB smear and culture of fluid or tissue is required. Specimens can be obtained by needle aspirate, core biopsy, or excisional biopsy. Tissue biopsy is generally the most sensitive means of obtaining a specimen for culture to establish extrapulmonary NTM disease. In some instances, histopathologic findings of granulomatous inflammation with or without AFB organisms present may be suggestive of NTM disease. However, prior to treatment for extrapulmonary NTM disease definitive identification by culture is recommended.

General principles of therapy for nontuberculous mycobacteria (Table 156.1)

The greatest misunderstanding about treatment regimens for NTM pathogens is the result of the expectation that all NTM infections should respond in a predictable manner to antimicrobial therapy, in a manner similar to *Mycobacterium tuberculosis*. That is, treatment

TABLE 156.1 **TREATMENT OF NONTUBERCULOUS MYCOBACTERIAL INFECTIONS (SEE TEXT FOR DETAILS)**

NTM species	Disease	Treatment	Comment
MAC	Pulmonary[a]	Clarithromycin 500 mg BID or azithromycin 250 mg/d plus ethambutol 15 mg/kg/d plus rifampin 600 mg/ d Consider streptomycin or amikacin 10–15 mg/kg IM or IV for severe disease	Treat for 1 year of negative AFB cultures Rifabutin 150–300 mg daily may be substituted for rifampin
MAC	Disseminated	Clarithromycin 500 mg BID or azithromycin 500 mg/d with ethambutol 15 mg/kg/d ± rifabutin 300 mg/d	Treatment lifetime or may be stopped with CD4+ T-cell count over 100 cells/mm^3 for 12 months
MAC	Lymph node Involvement	Complete surgical excision of involved nodes usually curative	If adjunctive chemo-therapy necessary, see drugs for pulmonary disease
M. kansasii	Pulmonary	Rifampin 600 mg/d Isoniazid 300 mg/d Ethambutol 15 mg/kg/d	Treat for 1 year of negative AFB cultures Clarithromycin and moxifloxacin also with excellent activity against *M. kansasii*
M. kansasii	Disseminated	Substitute rifabutin 150–300 mg/d for rifampin in HIV +	Treatment duration as for disseminated MAC
M. abscessus subsp. *bolletii*	Pulmonary	Clarithromycin 500 mg BID plus amikacin 10–15 mg/kg 3–5 times per week	Consider second parenteral drug such as cefoxitin or imipenem. Activity of linezolid, tigecycline, and clofazimine is variable
M. abscessus subsp. *bolletii*	Soft tissue	Clarithromycin 500mg BID plus amikacin 10–15 mg/kg 3–5 times per week for a minimum of 2 weeks, 4–6 months for severe infection	Consider second parenteral drug for severe disease. Removal of foreign body and surgical debridement also important. Other agent activity variable including linezolid, tigecycline, or clofazimine
M. abscessus subsp. *abscessus*	Pulmonary	Amikacin 10–15 mg/kg 3–5 times per week plus second parenteral drug such as cefoxitin or imipenem	Other agents with variable activity: linezolid, tigecycline, and clofazimine Role of azithromycin in presence of active *erm* gene is uncertain
M. abscessus subsp. abscessus	Soft tissue	Amikacin 10–15 mg/kg 3–5 times per week plus second parenteral drug such as cefoxitin or imipenem for a minimum of 2 weeks, 4–6 months for severe infection	Other agents with variable activity: linezolid, tigecycline, and clofazimine. Role of azithromycin in presence of active *erm* gene is uncertain. Removal of foreign body and surgical debridement also important
M. chelonae	Pulmonary	Clarithromycin 500 mg BID plus tobramycin 3–5 mg/kg 3–5 times per week	Consider third agent such as imipenem or linezolid. Clofazimine, doxycycline, and quinolone susceptibility varies
M. chelonae	Soft tissue	Clarithromycin 500 mg BID plus tobramycin 3–5 mg/kg 3–5 times per week for a minimum of 2 weeks, 4–6 months for severe infection	Consider third agent for severe disease. Susceptibility to imipenem, linezolid, clofazimine, doxycycline, and quinolone varies. Removal of foreign body and surgical debridement may be important
M. marinum	Soft tissue	Clarithromycin 500 mg BID plus ethambutol 15 mg/kg/d. Treat 1–2 months after resolution of symptoms (usually 3–4 months total)	Susceptible to multiple agents. Surgical debridement may also be important
M. fortuitum	Pulmonary	2 agents to which the organism is susceptible for 6 months. Consider parenteral medication for severe disease	Susceptible to multiple medications including quinolones, doxycycline, trimethoprim/sulfa, macrolides, amikacin
M. fortuitum	Soft tissue	As above. Treatment 3–6 months	
M. simiae, *M. xenopi* *M.malmoense* *M. szulgai*		Too little information to make standard or routine recommendation	Usually a macrolide-based regimen

[a] Consider three times weekly therapy (TIW) with clarithromycin 1000 mg, ethambutol 25 mg/kg/dose, and rifampin 600 mg for mild nodular/bronchiectatic (noncavitary) disease.

regimens should be based on in vitro susceptibility testing and the NTM pathogen should respond to antimicrobial agents based on in vitro susceptibility results. The most difficult and frustrating aspect of NTM therapy for most clinicians is the lack of a clear association between in vitro susceptibility results and clinical (in vivo) response for many NTM pathogens including the most common one, MAC. For many NTM, including MAC, laboratory cutoffs for "susceptible" and "resistant" do not have a demonstrable clinical correlate and have not been confirmed to be clinically meaningful. The situation is complicated further because there is a spectrum of response by NTM pathogens based on in vitro susceptibilities. For instance, diseases caused by *M. kansasii*, *M. fortuitum*, and *M. marinum* respond predictably to treatment regimens based on in vitro susceptibilities. Response of disease caused by MAC correlates with in vitro susceptibility to macrolides (clarithromycin and azithromycin), but not other agents. Lastly, there are a number of NTM species (*M. abscessus, Mycobacterium simiae, Mycobacterium malmoense*, *Mycobacterium xenopi*, etc.) for which there is no established correlation between in vitro susceptibilities and in vivo response for any antimicrobial agents. The explanation(s) for the dichotomy between in vitro susceptibility results and in vivo response (clinical outcome) for many NTM is (are) currently not known.

The presence of the *erm* gene noted above has recently provided a potential explanation for the discordance between in vitro testing and phenotypic response: erythromycin methylase (*erm*) genes encode a diverse collection of methylases that impair binding of macrolides to ribosomes, reducing the inhibitory activity of these agents. The primary mechanism of acquired clinically significant macrolide resistance for some mycobacteria, especially RGM, is the presence of an inducible *erm* gene. All isolates of *M. abscessus* subsp. *abscessus*, *M. fortuitum*, and several other RGM, but not *M. chelonae*, contain an inducible *erm* gene. The most interesting aspect of this inducible gene is that if an *M. fortuitum* or *M. abscessus* subsp. *abscessus* isolate is exposed to macrolide, the *erm* gene activity is induced with subsequent in vivo macrolide resistance which may not be reflected by the initial in vitro minimum inhibitory concentration (MIC) of the organism for the macrolide. It is only with incubation of NTM in the presence of a macrolide that the *erm* gene and the associated macrolide resistance will be identified.

The clinician must use in vitro susceptibility data for many NTM with the awareness that, unlike tuberculosis, NTM disease may not be eradicated in a given patient with therapy based on in vitro susceptibility results.

Lastly, the clinician may not uncommonly encounter different NTM isolates synchronously or metachronously, and should monitor microbiologic response during and microbiologic status after a treatment course.

Recommended drug treatment for MAC lung disease

As discussed in the general principles of NTM therapy, the macrolides (clarithromycin and azithromycin) are the only antimicrobial agents for which there is a demonstrated correlation between in vitro susceptibility and in vivo response for MAC lung disease. The cornerstones of MAC therapy, therefore, are the macrolides, clarithromycin and azithromycin, with the addition of ethambutol. These agents are then combined with companion drugs, usually a rifamycin and, possibly, an injectable aminoglycoside. It is necessary to include companion drugs with the macrolide to prevent the emergence of macrolide-resistant MAC isolates. The macrolides should *never* be used as monotherapy for treatment of MAC disease (pulmonary or disseminated). Likewise, the use of macrolide and fluoroquinolone may be associated with cardiac toxicity and puts the patient at risk for development of macrolide-resistant MAC disease.

An important illustration of how the dichotomy between in vitro susceptibility results and in vivo response in MAC disease can be detrimental is provided by the example of ethambutol. There has not been a demonstrated correlation between ethambutol in vitro susceptibility and clinical response in any previous study; however, the duration of ethambutol use is associated with improved microbiologic response for patients receiving an intermittent clarithromycin-containing regimen and the exclusion of ethambutol from treatment regimens is a major risk factor for the development of macrolide-resistant MAC. It would be potentially risky to the patient for a physician to exclude ethambutol from a multidrug MAC treatment regimen based on in vitro susceptibility results.

There is another difficult-to-explain phenomenon associated with MAC drug therapy. Patients who have failed prior MAC therapy, with or without a macrolide, have lower sputum conversion rates with macrolide-containing treatment regimens, even with macrolide-susceptible MAC isolates, than do patients with no prior therapy. Although the explanation for this observation is also not clear, it is evident that the best chance for treatment success in MAC lung disease is the first treatment effort.

The recommended treatment length for MAC pulmonary disease is a duration of therapy that includes 12 months of sputum culture negativity. This treatment goal dictates that patients should have sputum collected for AFB analysis on a regular basis throughout the course of treatment.

The intensity of MAC treatment should be proportionate to the disease burden; other considerations should be individualized patient factors including tolerance to medications, medication cost, and acceptance of necessary monitoring and risks for the multidrug regimens.

For most patients with nodular/bronchiectatic disease, or those with fibrocavitary disease who cannot tolerate daily therapy, or those patients for whom disease suppression is an appropriate goal, intermittent, three times weekly, therapy is recommended. Recommended intermittent drug dosages include: (1) clarithromycin, 1000 mg, or azithromycin, 500 to 600 mg, (2) ethambutol, 25 mg/kg, and (3) rifampin, 600 mg, given three times weekly. Intermittent therapy is not recommended for patients with cavitary disease or patients who have received previous therapy for MAC.

The recommended regimen for patients with fibrocavitary disease or severe nodular/bronchiectatic disease, includes (1) clarithromycin, 1000 mg/day (or 500 mg twice daily) or azithromycin, 250 mg/day, (2) ethambutol, 15 mg/kg/day, and (3) rifampin, 10 mg/kg/day (maximum 600 mg/day). For some

patients, the doses of clarithromycin may need to be split (e.g., 500 mg twice daily) because of gastrointestinal intolerance and for patients of small body mass (less than 50 kg) or age over 70 years, the clarithromycin dose may need to be reduced to 500 mg/day or 250 mg twice a day because of gastrointestinal intolerance.

A more aggressive and less well-tolerated treatment regimen for patients with severe and extensive (multilobar), especially fibrocavitary, disease consists of clarithromycin, 1000 mg/day (or 500 mg twice a day), or azithromycin, 250 mg/day, rifabutin, 150 to 300 mg/day, or rifampin, 10 mg/kg/day (maximum 600 mg/day), ethambutol (15 mg/kg/day), and consideration of inclusion of a parenteral agent, either amikacin or streptomycin, for the first 2 or 3 months of therapy (see dosage discussion below). Patients receiving clarithromycin and rifabutin should be carefully monitored for rifabutin-related toxicity, especially hematologic (leukopenia) and ocular (uveitis) toxicity. Active investigations are ongoing attempting to define the role of inhaled amikacin in the treatment of NTM lung disease. To date, although inhaled amikacin is often used there is very little published data supporting the indication, dose, and duration of the best use as a companion drug.

Macrolide-resistant MAC lung disease is associated with a very poor prognosis. The two major risk factors for macrolide-resistant MAC disease are macrolide monotherapy or treatment with macrolide and inadequate companion medications. The treatment strategy associated with the most success includes both the use of a multidrug regimen including a parenteral aminoglycoside (streptomycin or amikacin) and surgical resection ("debulking") of disease. The optimal drug regimen for treating macrolide-resistant strains is unknown but some experts recommend ethambutol, rifabutin, and an injectable agent. The role of other drugs, such as moxifloxacin or clofazimine, is still not known. Likewise, the future role of newer antimicrobials being developed and in early clinical usage trails for tuberculosis is equally unclear at this time.

Patients whose disease is predominantly localized to one lung and who can tolerate resectional surgery might also be considered for surgery if there is poor response to drug therapy, the development of macrolide-resistant MAC disease or the presence of significant disease-related complications such as hemoptysis. Whenever possible, this surgery should be performed at centers with thoracic surgeons who have considerable experience with lung resectional surgery for mycobacterial disease, which is potentially associated with significant morbidity and mortality.

Disseminated MAC disease

Successful treatment of disseminated MAC in persons with AIDS is based on treatment of both the mycobacterial infection and the HIV infection. Clinicians must, therefore, be aware of the drug–drug interactions between the antimycobacterial and antiretroviral medications. Current guidelines for the use of antimycobacterial drugs with HIV therapies can be found at www.cdc.gov/nchstp/tb/TB_HIV_DRUGS/TOC.htm.

All patients should be treated with clarithromycin, 1000 mg/day or 500 mg twice a day, or as an alternative, azithromycin at a dose of 500 mg daily, and ethambutol at the dose of 15 mg/kg daily. Rifabutin, if added, should be used at a dose of 300 mg daily, with adjustments for interactions with antiretroviral drugs. As with macrolide-resistant MAC lung disease, patients with macrolide-resistant strains are far less likely to be successfully treated. Other drugs that should be considered for inclusion are amikacin and moxifloxacin. Clofazimine has been associated with excess mortality in the treatment of disseminated MAC disease and should not be used. Treatment of MAC in patients with AIDS should be considered lifelong, unless immune restoration is achieved by antiretroviral therapy. MAC treatment may be stopped for patients who are asymptomatic, and have achieved a CD4+ T-cell count of over 100 cells/mm^3 for at least 12 months.

Preventive therapy for disseminated MAC is recommended for all HIV-infected patients with less than 50 CD4+ T-cells/mm^3. Based on efficacy and ease of use, azithromycin—given as 1200 mg once weekly—is the preferred agent. Clarithromycin is also effective; however, it is considered an alternative agent because it must be given twice daily and the risk of breakthrough with macrolide-resistant strains is higher with daily clarithromycin than with weekly azithromycin. Rifabutin is also effective but should only be used when a macrolide cannot be tolerated. Primary MAC prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ T-lymphocyte counts to more than 100 cells/mm^3 for more than 3 months. Primary prophylaxis should be reintroduced if the CD4+ T-lymphocyte count decreases to less than 50 to 100 cells/mm^3.

MAC lymphadenopathy

The treatment of choice for MAC lymphadenopathy, as well as localized lymphadenopathy due to most NTM pathogens, is complete surgical resection of the involved lymph nodes. When complete surgical resection is not possible, due for instance to nerve impingement or encasement by the infected nodes, then chemotherapy with MAC treatment regimens similar to those for lung and disseminated disease would be necessary.

M. kansasii pulmonary disease

The recommended regimen for treating pulmonary *M. kansasii* disease includes daily rifampin (600 mg/day), isoniazid (300 mg/day), and ethambutol (15 mg/kg/day) for a duration that includes 12 months of negative sputum cultures. Limited data suggests that intermittent therapy with rifampin, ethambutol, and clarithromycin for *M. kansasii* disease can also be successful. The recommended treatment duration, as with MAC lung disease, is a duration that includes 12 months of sputum AFB culture negativity.

Patients whose *M. kansasii* isolates have become resistant to rifampin as a result of previous therapy have been treated successfully with a regimen that consists of high-dose daily isoniazid (900 mg), high-dose ethambutol (25 mg/kg/day), sulfamethoxazole (1 g three times per

day) combined with several months of streptomycin or amikacin. The excellent in vitro activity of clarithromycin and moxifloxacin against *M. kansasii* suggests that multidrug regimens containing these agents and at least one other agent based on in vitro susceptibilities, such as ethambutol or sulfamethoxazole, are likely to be even more effective for treatment of a patient with rifampin-resistant *M. kansasii* disease.

Disseminated *M. kansasii*

The treatment regimen for disseminated disease should be the same as for pulmonary disease. Because of the critically important role of rifamycins in the treatment of *M. kansasii* disease, it is important to construct *M. kansasii* and antiretroviral treatment regimens that are compatible (see website in disseminated MAC disease discussion above). An option for treating HIV-infected patients who receive an antiretroviral regimen not compatible with rifamycins is to substitute a macrolide or moxifloxacin for the rifamycin. There is no recommended prophylaxis regimen for disseminated *M. kansasii* disease.

M. abscessus disease

M. abscessus isolates are uniformly resistant to the standard antituberculous agents. *M. abscessus* isolates generally have low or intermediate MICs, compared to achievable drug levels, to clarithromycin, amikacin, and cefoxitin. Some isolates have low or intermediate MICs to linezolid, tigecycline, and imipenem.

For serious skin, soft-tissue, and bone infections caused by *M. abscessus*, clarithromycin 1000 mg/day or azithromycin 250 mg/day should be combined with one or more of the parenteral medications (amikacin, cefoxitin, or imipenem). Macrolide, especially clarithromycin, offers little additional benefit in the presence of an active *erm* gene, e.g., *M. abscessus* subsp. *abscessus*. Intravenous amikacin is given at a dose of 10 to 15 mg/kg daily to adult patients with normal renal function to provide peak serum levels in the low 20 μg/mL range. The lower dose (10 mg/kg) should be used in patients over the age of 50 and/or in patients in whom long-term therapy (greater than 3 weeks) is anticipated. The amikacin combined with high-dose cefoxitin (up to 12 g/day given intravenously in divided doses) is recommended for initial therapy (minimum 2 weeks) until clinical improvement is evident. Cefoxitin availability or intolerance may necessitate the choice of an alternative agent such as imipenem (500 mg two to four times daily), which is a reasonable alternative to cefoxitin. For serious disease, a minimum of 4 months of therapy is necessary to provide a high likelihood of cure. For bone infections, 6 months of therapy is recommended. Surgery is generally indicated with extensive disease, abscess formation, or where drug therapy is difficult. Removal of foreign bodies such as breast implants or percutaneous catheters is important and likely essential to recovery.

In contrast to the efficacy of medication regimens for nonpulmonary disease, no antibiotic regimens based on in vitro susceptibilities have been shown to produce long-term sputum conversion for patients with *M. abscessus* lung disease. The goal of 12 months of negative sputum cultures while on therapy may be optimal, but there is no medication strategy to reliably achieve this goal. Alternative goals of therapy such as symptomatic improvement, radiographic regression of infiltrates, or improvement in sputum culture positivity, short of conversion to negative cultures, are more realistic for *M. abscessus* lung disease. Combination therapy (as outlined above) with or without macrolide plus one or more parenteral agent (amikacin, cefoxitin, or imipenem for 2–4 months) usually produces clinical and microbiologic improvement, but the cost and morbidity are significant impediments to a curative course of therapy. Several recently published series of *M. abscessus* lung disease patients treated with a combination of parenteral and oral agents suggest improved clinical response rates in contrast to historical controls. Linezolid and tigecycline may also have variable activity but also carry costs that are high and tolerance which is limited. For some patients, symptoms can be controlled with intermittent periods of therapy with clarithromycin or azithromycin alone or in combination with one or more parenteral drugs. Curative therapy for *M. abscessus* lung disease is more likely to be obtained with limited disease and a combination of surgical resection of involved lung and chemotherapy (not dissimilar to the approach to macrolide-resistant MAC lung disease). Unfortunately, with current antibiotic options, *M. abscessus* is a chronic incurable infection for most patients and, if disease is present, represents a contraindication for lung transplantation in those with advanced lung disease.

M. chelonae pulmonary and extrapulmonary disease presents in a similar fashion to *M. abscessus* but should be differentiated from *M. abscessus*/*M. chelonae* in the laboratory given the better response to antibiotics for *M. chelonae* than *M. abscessus*. This improved response to antibiotics is, in part, related to the lack of an active *erm* gene in *M. chelonae*.

M. marinum disease

M. marinum isolates are susceptible to rifampin, rifabutin, ethambutol, clarithromycin, sulfonamides, and trimethoprim sulfamethoxazole, intermediately susceptible to streptomycin, doxycycline and minocycline, and resistant to isoniazid and pyrazinamide.

For skin and soft-tissue infections due to *M. marinum* a reasonable approach is to treat with two active agents for 1 to 2 months after resolution of symptoms, typically 3 to 4 months in total. Some experts believe that minimal disease can be treated with a single agent. Excellent outcomes have also been reported for the combinations of clarithromycin and rifampin, clarithromycin and ethambutol, and the combination of ethambutol and rifampin. Clarithromycin and ethambutol are likely to provide the optimal balance of efficacy and tolerability for most patients, with the addition of rifampin in cases of osteomyelitis or other deep structure infection. Surgical debridement may also be indicated, especially for disease involving the closed spaces of the hand and for disease that has failed to respond to standard therapy.

Emerging areas of NTM infections

Increased numbers of published reports have highlighted several emerging areas of NTM infections over the past decade. These

newer and somewhat less common infections are worth noting and have linked growing numbers of individuals developing NTM infections to specific underlying disease conditions or specific home, work, or nosocomial environmental exposures, including CF, hypersensitivity pneumonitis-like lung disease (hot tub lung), and healthcare-associated NTM infections, respectively.

Cystic fibrosis-associated NTM disease

A recent cross-sectional assessment from multiple CF centers across the United States found that approximately 13% of all surveyed CF patients, and 40% over the age of 40, had NTM isolated from sputum. Similar to non-CF NTM pulmonary disease most NTM isolated were MAC (76%) or *M. abscessus* (18%). The explanation for this high prevalence of NTM in CF patients remains uncertain. Ambient exposure to NTM organisms from ubiquitous environmental water and soil sources coupled with abnormal host pulmonary factors such as altered mucociliary clearance and structural abnormalities accompanying advancing bronchiectasis may contribute to the development and phenotypic expression of NTM pulmonary disease commonly encountered in this group of patients. The diagnosis of NTM pulmonary disease in CF patients is similar to that of patients with non-CF NTM disease with the recognition that underlying bronchiectasis and other pathogens are present and may account for respiratory symptoms and radiographic abnormalities. The decision to treat NTM pulmonary infection in CF patients is complicated by a paucity of information about the effect of NTM infection on the natural history of CF, although CF patients with heavy *M. abscessus* growth from sputum appear to be at particular risk for more rapidly progressive disease and, in some instances, respiratory failure. Overall, treatment decisions require consideration of benefits weighed against risks and medication side effects for individual patients. Treatment regimens for CF patients with NTM lung disease are also similar to those for non-CF NTM pulmonary disease. CF patients on azithromycin for noninfective purposes should have surveillance for NTM in sputum prior to and during treatment with macrolides to avoid macrolide monotherapy in a patient with occult or undiagnosed NTM disease. The presence of active or untreated *M. abscessus* lung disease is a contraindication to listing for lung transplantation at many transplant centers in the United States. Recent reports of the transmissibility of *M. abscessus* species in two outpatient CF clinics is worth noting given the previous lack of human-to-human transmissibility of NTM lung disease.

Hypersensitivity pneumonitis-like NTM pulmonary disease

Several series of patients developing hypersensitivity pneumonitis-like lung disease following NTM exposure have been reported over the past decade. Most reports describe development of a typical pattern of hypersensitivity pneumonitis-like lung disease in association with hot tub exposure. Some investigators have used the term "hot tub lung" to describe this presentation. In the cases of exposure to hot tubs, MAC has been the mycobacterial organism isolated from sputum, bronchoalveolar lavage, tissue, and hot tub water. Furthermore, comparison of MAC isolates from the hot tub water and lung specimens when assessed by genotyping methods has demonstrated identical matches. Controversy still exists, however, as to whether hot tub lung is an infectious process, inflammatory process, or a combination of processes.

Hypersensitivity pneumonitis-like lung disease patients tend to be young and without preexisting lung disease. The clinical presentation varies widely from mild respiratory symptoms to respiratory failure requiring mechanical ventilatory support. Key elements to the diagnosis of MAC hypersensitivity-like lung include a compatible clinical history (subacute onset of respiratory symptoms, hot tub exposure), characteristic radiographic findings, and MAC isolates in sputum, bronchoalveolar lavage, tissue, and hot tub water (and compatible histopathology when available).

Patient prognosis is generally excellent independent of severity on presentation. The most benefit is gained by simply removing the patient from antigen exposure. In the case of hot tub lung, removal from antigen exposure generally involves drainage of hot tub water and complete avoidance of hot tub use. Whether continued exposure to ambient environmental MAC organisms can propagate the hypersensitivity pulmonary reaction is uncertain. For select patients with hypersensitivity pneumonitis-like lung disease, use of systemic corticosteroids may be of benefit and hasten recovery of pulmonary symptoms, gas exchange abnormalities, and radiographic abnormalities. Likewise, antimycobacterial therapy with the same medications as standard pulmonary MAC lung disease may be required in some patients but with shorter durations of therapy, usually 3 to 6 months. Most patients can be expected to have complete or near complete resolution of respiratory symptoms as well as pulmonary function and radiographic abnormalities.

Healthcare-associated NTM disease

Transmission of NTM disease in the healthcare setting has most frequently been linked to tap (municipal) water exposure. While various NTM species (including MAC, *M. kansasii*, *M. xenopi*, and *M. simiae*) have been isolated from municipal water supplies, *M. fortuitum* and *M. abscessus* have most often been implicated in healthcare-associated NTM disease. Even with use of potent disinfectants, including organomercurials, chlorine, bromine, 2% formaldehyde, and glutaraldehyde, after tap water exposure, NTM organisms may persist on equipment or devices. The inability to eliminate these organisms underscores the importance of avoidance of tap water for preventing healthcare-associated NTM disease. Examples of healthcare-associated NTM infections include infections involving median sternotomy, plastic surgery procedures, liposuction, laser-assisted in situ keratomileusis (LASIK), dialysis-related outbreaks, long-term central intravenous catheters, tympanostomy tubes, and prosthetic devices such as heart valves, knee and hip joints, lens implants, and metal rod bone stabilizers. Pseudo-outbreaks have involved bronchoscopes contaminated with *M. abscessus* and *Mycobacterium immunogenum*. Documented outbreaks of hygiene-associated *M. fortuitum* and *Mycobacterium mageritense* furunculosis in association with use of contaminated whirlpool footbaths have been described in nail salons.

As a result of the increased understanding of environmental NTM reservoirs and reports linking the use of tap water to healthcare-associated NTM infections it is recommended that tap water not be used in preparation of surgical procedures, prosthetics, and intravascular catheters; not used in cleaning of fiberoptic endoscopes; and not be used to rinse the mouth out prior to collecting expectorated sputum samples. Moreover, recognition that alternative medicines or unapproved substances for injection may also be at risk of contamination by NTM warrants caution against use of these products as well. Reports of transmissibility of *M. abscessus* in CF clinics as referenced above underscores the need for respiratory isolation and adherence to standard infection control principles.

Suggested reading

Aksamit TR, Philley JV, Griffith DE, Nontuberculous mycobacterial (NTM) lung disease: the top ten essentials. *Respir Med*. 2013;108(3):417–425. doi: 10.1016/j.rmed.2013.09.014.

Griffith DE. The talking *Mycobacterium abscessus* blues. *Clin Infect Dis*. 2011;52(5):572–574.

Griffith DE, Aksamit T, Brown-Elliot BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175:367–416.

Griffith DE, Brown-Elliott BA, Langsjoen B, et al. Clinical and molecular analysis of macrolide resistance in *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med*. 2006;174(8):928–934.

Hanak V, Kalra S, Aksamit TR, et al. Hot tub lung: presenting features and clinical course of 21 patients. *Respir Med*. 2006;100:610–615.

Hoefsloot W, van Ingen J, Andrejak C, et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. *Eur Respir J*. 2013;42(6):1604–1613.

Kim RD, Greenberg DE, Ehrmantraut ME, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. *Am J Respir Crit Care Med*. 2008;178(10):1066–1074.

Olivier KN, Weber DJ, Wallace RJ Jr., et al.; Nontuberculous Mycobacteria in Cystic Fibrosis Study Group. Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. *Am J Respir Crit Care Med*. 2003;167 (6):828–834

van Ingen J, Griffith DE, Aksamit TR, Wagner D. Pulmonary diseases caused by nontuberculous mycobacteria. *Eur Respir Monogr*. 2012;58:25–37.

157

Vibrios

Duc J. Vugia

Vibrios are motile, rod-shaped, facultative-anaerobic, gram-negative bacteria that can cause gastroenteritis, wound infection, and septicemia in humans. They are naturally found in marine, estuarine, and brackish waters in the United States and in other parts of the world. In the United States, they are recovered from the environment most commonly in summer and fall, when the water is warmer. *Vibrio* has also been isolated from a variety of fish and shellfish, including oysters, clams, mussels, crabs, and shrimp. Human cases of illness associated with *Vibrio* infection occur mostly in summer and fall and usually follow ingestion of raw or undercooked shellfish, particularly oysters, or exposure of a wound to fish, shellfish, or seawater. In countries with endemic or epidemic cholera, infection may occur after ingestion of any contaminated food or water; in the United States, cholera is endemic along the Gulf Coast.

Of more than 100 *Vibrio* species identified, about a dozen have caused human illnesses or been isolated from clinical specimens. The major clinical presentations associated with more commonly reported species are shown in Table 157.1. *Vibrio* spp. have been isolated more frequently from stool, wound, or blood, and less frequently from bone, cerebrospinal fluid, gallbladder, sputum, and urine.

Gastroenteritis and cholera

Clinical presentation

Gastroenteritis is the most common clinical presentation of infection with most pathogenic vibrios. The disease ranges in severity from mild, self-limited diarrhea to frank, life-threatening cholera.

Cholera is a profuse, watery diarrhea mediated via an enterotoxin produced by epidemic strains of *V. cholerae* O1 and O139. After attachment of toxigenic vibrios to intestinal epithelial cells, the cholera toxin, consisting of one A (activation) subunit and five B (binding) subunits, is generated. It stimulates intracellular cyclic adenosine monophosphate (AMP), resulting in a secretory diarrhea. Other symptoms include nausea, vomiting, abdominal cramps, and muscle cramps of extremities; fever is typically not seen because the disease is toxin-mediated and there is no invasion of the intestinal epithelium. Illness develops 4 hours to 5 days after ingestion of the bacteria and can rapidly lead to severe dehydration, electrolyte imbalance, metabolic acidosis, and death. Cholera usually lasts <7 days even without antibiotic therapy.

Gastroenteritis due to *V. cholerae* non-O1, non-O139 and other *Vibrio* species may also be mediated via an enterotoxin, but the diarrhea is usually not so severe. However, bloody stool, low-grade fever, and elevated white blood cell count may be noted along with nausea, vomiting, and abdominal cramps. The median incubation period is 1 day, ranging from 4 hours to 5 days, and the duration of illness is typically less than 7 days, ranging from 1 to 15 days.

TABLE 157.1 **COMMONLY REPORTED *VIBRIO* SPECIES AND ASSOCIATED MAJOR CLINICAL PRESENTATIONS**

	Clinical presentations		
Species	**Gastroenteritis**	**Wound infection**	**Septicemia**
V. cholerae[a]			
O1	++	+	+
O139	++		+
non-O1, non-O139	++	+	+
V. parahaemolyticus	++	++	+
V. vulnificus	+	++	++
V. alginolyticus[b]	+	++	+
V. fluvialis	++	+	+
V. furnissii	+		+
V. mimicus	++	+	+

++, Common; +, rare.
[a] Only toxigenic *V. cholerae* O1 or O139 causes cholera.
[b] Ear infection is common with *V. alginolyticus*.

Therapy

For cholera, prompt replacement of fluid volume and electrolytes with an appropriate intravenous (IV) or oral solution is critical. If the patient has severe dehydration (loss of at least 10% of body weight) or cannot drink, IV fluid replacement with Ringer's lactate is recommended. Normal saline does not contain appropriate electrolytes to correct metabolic acidosis and is therefore not recommended. If the patient can drink, a solution containing glucose and adequate electrolyte replacement is recommended, such as those prepared with the oral rehydration salts (ORS) endorsed by the World Health Organization or commercially available ORS/electrolyte replacement solutions.

Treatment of cholera with antimicrobials is secondary to fluid and electrolyte replacement and recommended for patients with moderate to severe cholera. Appropriate antibiotics can decrease volume and duration of diarrhea and shedding of vibrios. Multidrug-resistant strains of *V. cholerae* O1 have been documented in Asia and Africa, and antibiotic susceptibility testing should be performed on isolates from cholera patients to inform drug choices. For most settings, a single dose of doxycycline, 300 mg orally for adults, including pregnant women, and children 12 years and older, or 2–4 mg/kg orally for children <12 years old, is the drug of choice. Alternatively, a single dose of azithromycin or ciprofloxacin, 1 g orally for adults, including pregnant women, or 20 mg/kg up to a maximum of 1 g orally for children can also be used. Of note, quinolone-resistant strains of *V. cholerae* have been reported in South Asia. As quinolones and macrolides are used more commonly, resistance to these classes of antibiotic may increase, and, therefore, cholera patients treated with any antibiotic should have their isolates tested for susceptibility and the patients should be closely followed for appropriate clinical response.

For severe or prolonged gastroenteritis due to other vibrios, fluid and electrolyte replacement along with quinolone or doxycycline treatment is in order. However, mild or moderate gastroenteritis is usually self-limited and may not need therapy other than oral rehydration.

Extraintestinal infections

Clinical presentations

For extraintestinal sites, wound infection and septicemia are the most common clinical presentations. Wound infection with vibrios occurs after exposure of a break in skin to seawater or after a skin injury from handling fish or shellfish. Wound infection may be mild and self-limited or severe and invasive. Septicemia, which may be primary following ingestion of raw shellfish or secondary following wound infection, indicates severe disease.

Among vibrios causing extraintestinal infections, *V. vulnificus* frequently causes two important clinical syndromes: primary septicemia and wound infections. Primary septicemia occurs predominantly in adults with liver disease, including cirrhosis and hemochromatosis; alcoholism; other chronic underlying diseases, including renal failure and diabetes; or with immune suppression, including cancer and HIV infection. In these susceptible persons, septicemia usually follows ingestion of raw shellfish, typically raw oysters. Between 7 and 48 hours after eating shellfish containing *V. vulnificus*, infected patients present with fever, chills, nausea, vomiting, abdominal pain, diarrhea, mental status changes, suggestive skin lesions (including bullae, cellulitis, and ecchymoses), and often hypotension or shock. Mortality for patients with *V. vulnificus* primary septicemia is >50%, and it increases with hypotension within 12 hours of hospitalization or when appropriate antibiotic therapy is delayed.

V. vulnificus wound infection, however, results from injury to the skin from handling fish or shellfish or exposure of a fresh wound to seawater. Any healthy person may acquire this infection, but persons with the underlying diseases listed previously are at higher risk for severe skin and soft tissue infection, secondary septicemia, and death. Infected persons develop inflammation of the wound, fever, and chills 4 hours to 4 days after exposure. Wound infections range from mild cellulitis to severe necrotizing fasciitis and myositis requiring extensive debridement or amputation. Secondary disseminated skin lesions such as bullae may be due to secondary septicemia (Figure 157.1). The case fatality rate for *V. vulnificus* necrotizing fasciitis increases when surgical intervention is later than 24 hours after admission or when effective antibiotics are not used.

Therapy

For invasive *Vibrio* diseases, prompt treatment with early antibiotic administration, aggressive wound management, and supportive care are crucial. For invasive *V. vulnificus*, doxycycline (100 mg IV q12h) combined with a third-generation cephalosporin (e.g., ceftazidime 2 g IV q8h) should be given without delay. Alternatively, a fluoroquinolone (e.g., ciprofloxacin) can also be used in combination with a third-generation cephalosporin. The duration of treatment should be individualized to the presentation and clinical course but should

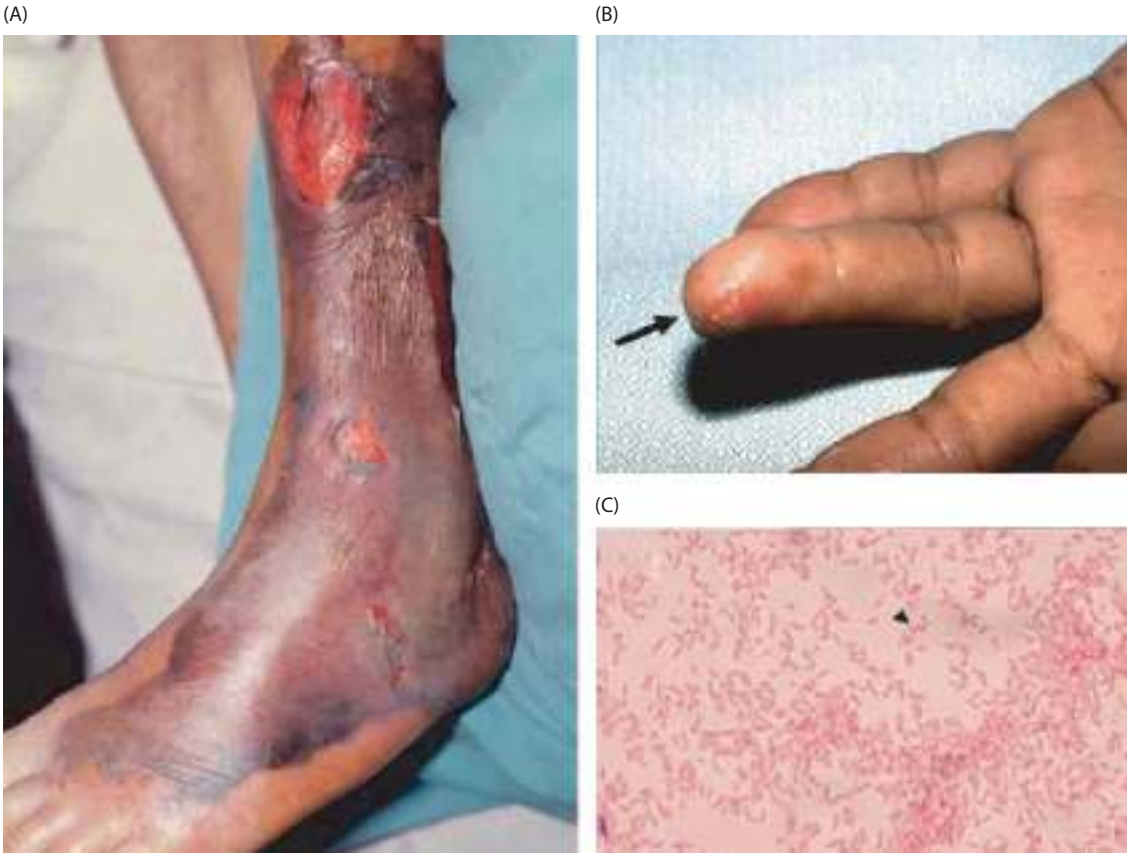

FIGURE 157.1 (A) Characteristic skin lesions associated with *Vibrio vulnificus* infection on the leg of a 75-year-old patient with liver cirrhosis in whom septic shock and bacteremia developed. (B) *Vibrio vulnificus* bacteremia developed 1 day after a fish bone injury on the fourth finger of the left hand (*arrow*) in a 45-year-old patient with uremia. (C) Gram-negative curved bacilli isolated from a blood sample of the 45-year-old patient with uremia.
From Hsueh et al. *Vibrio vulnificus* in Taiwan. *Emerg Infect Dis*. 2004;10(8):1363–1368.

be considered for at least 7 to 14 days. Necrotic tissue should be surgically debrided within 24 hours of admission and, occasionally, amputation of an affected limb may be necessary.

Laboratory diagnosis

For a patient with a gastrointestinal or cholera-like illness thought to be caused by *Vibrio*, testing of stool specimens with a culture-independent diagnostic test (CIDT, e.g., polymerase chain reaction) or culture using thiosulfate-citrate-bile salts-sucrose agar should detect the causative pathogen. Ideally, stool specimens for culture should be collected before treatment with antimicrobials.

Selective culture media are not necessary for extra-intestinal infections because common media used to culture blood and wounds contain at least 0.5% sodium chloride, which is adequate to grow halophilic (salt-loving) *Vibrio* spp.

For cholera patients already treated with antimicrobials and whose stool culture was either negative or not processed for vibrios, *V. cholerae* vibriocidal or antitoxin antibodies can be detected by serologic assays.

Prevention

Most *Vibrio* gastroenteritis, cholera, and primary *V. vulnificus* septicemia can be prevented. For prevention of cholera, travelers should be informed on whether cholera is endemic in the country or region being visited and should take appropriate precautions with all foods and drinks. In general, well-cooked foods and hot or carbonated drinks are safe. Additionally, lyophilized CVD 103-HgR, a live attenuated oral cholera vaccine (Vaxchora, PaxVax, Redwood City, California), is recommended for adults aged 18 to 64 years who travel to an area with active cholera transmission. In the United States, *Vibrio* gastroenteritis can be prevented by avoiding consumption of raw or undercooked shellfish. Patients with underlying liver and other chronic diseases or with immunosuppression, which puts them at increased risk of *V. vulnificus* septicemia, should avoid raw unprocessed oysters and other raw shellfish.

Wound infections may be difficult to prevent because vibrios exist naturally in the marine water environment. Persons with underlying conditions predisposing them to severe vibriosis should limit their exposure to seawater. For clinicians, a history of exposure to seawater, fish, or shellfish in a patient with an infected wound should raise clinical suspicion and prompt consideration of treatment for possible infection with a *Vibrio*.

Suggested reading

Baker-Austin C, Oliver JD, Alam M, et al. *Vibrio* spp. infections. *Nat Rev Dis Primers*. 2018 Jul 12;4(1):8. doi:10.1038/s41572-018-0005-8. PMID: 30002421.

Crowe SF, Newton AE, Gould LH, et al. Vibriosis, not cholera: Toxigenic *Vibrio cholerae* non-O1, non-O139 infections in the United States, 1984–2014. *Epidemiol Infect*. 2016 Nov;144(15):3335–3341. doi:10.1017/S0950268816001783.

Jacobs Slifka KM, Newton AE, Mahon BE. *Vibrio alginolyticus* infections in the USA, 1988–2012. *Epidemiol Infect*. 2017 May;145(7):1491–1499. doi:10.1017/S0950268817000140.

Kim SE, Shin SU, Oh TH, et al. Outcomes of third-generation cephalosporin plus ciprofloxacin or doxycycline therapy in patients with *Vibrio vulnificus* septicemia: A propensity score-matched analysis. *Plos Negl Trop Dis*. 2019 Jun 12;13(6):e0007478.

Trinh SA, Gavin HE, Satchell KJF. Efficacy of ceftriaxone, cefepime, doxycycline, ciprofloxacin, and combination therapy for *Vibrio vulnificus* foodborne septicemia. *Antimicrob Agents Chemother*. 2017 Nov 22;61(12):e01106–17. doi:10.1128/AAC.01106-17.

Wong KK, Burdette E, Mahon BE, Mintz ED, Ryan ET, Reingold AL. Recommendations of the Advisory Committee on the Immunization Practices for use of cholera vaccine. *MMWR*. 2017 May 12;66(18):482–485. doi:10.15585/mmwr.mm6618a6.

Centers for Disease Control and Prevention. Cholera—*Vibrio cholerae* infection. https://www.cdc.gov/cholera/index.html (accessed April 1, 2021).

Centers for Disease Control and Prevention. *Vibrio* species causing vibriosis. https://www.cdc.gov/vibrio/index.html (accessed April 7, 2021).

158

Yersinia

Royce H. Johnson and Arash Heidari

Introduction

The genus *Yersinia* consists of 17 species, only 3 of which are consistently pathogenic for humans. These are *Y. pestis*, the agent of plague and *Y. enterocolitica* and *Y. pseudotuberculosis*, which are usually, but not entirely, gastrointestinal pathogens.

Yersinia pestis

An ongoing result of the unfortunate events of September 11, 2001, has been an increase in research on *Yersinia*, particularly, *Y. pestis*. This is an ancient organism, and, since its divergence from *Y. pseudotuberculosis* 1,500 to 20,000 years ago, it has largely existed as a rodent pathogen with only occasional human transmission. Three well-described pandemics of plague have occurred. The last of these began in the nineteenth century. Alexandre Yersin first isolated *Y. pestis* in 1894. The twentieth century saw major outbreaks in Vietnam and India. Between 2010 and 2015, 3,248 cases were reported with 584 deaths. The majority of cases currently are seen in sub-Saharan Africa, particularly Madagascar.

The majority of cases seen in the United States are from New Mexico, Arizona, Colorado, California, and Oregon. Climate change may well affect the bacteria, the vector, and the hosts, resulting in potential changes in the frequency and distribution of disease. In 2015, 16 cases were reported.

There has been remarkable progress in understanding the pathogenesis of *Yersinia* infections, particularly those caused by *Y. pestis*. A partial list of these advances include the effects of *Y. pestis* on flea behavior and its avoidance of both innate and adaptive (both humeral and cellular) immune response.

Natural infection occurs most commonly through the bite of an infected flea. The majority of these patients present with febrile lymphadenitis or bubonic plague. The incubation period is typically 2 to 6 days. Inguinal and femoral nodes are most frequently involved. Axillary and cervical presentations are less common. Inhalation of respiratory droplets from infected humans or animals, especially cats, may result in primary pneumonic plague. Pneumonic plague may also result from aerosols of bioterrorism agents. The ingestion of infected meat may result in pharyngitis and disseminated infection. Systemic disease without lymphadenitis may present as gram-negative sepsis, often with gastrointestinal symptoms. This usually results from an infected flea bite that does not produce a discernible bubo. A careful epidemiologic history is essential in the evaluation of patients with lymphadenitis, sepsis, or pneumonia.

All suspected *Y. pestis* infections must be reported to public health authorities. Specimens and cultures from suspected *Y. pestis* must be handled with *extreme caution* and in accordance with state and federal law. In the United States *Y. pestis* is a federal select category A agent.

Smear and culture of lymph node aspirate, sputum, cerebrospinal fluid, buffy coat, and blood should be undertaken expeditiously as dictated by clinical presentation. Gram stain and Wright Giemsa or the preferred Wayson stain should be prepared. The latter, if positive, will reveal the classic safety pin morphology that in the appropriate clinical setting is virtually diagnostic.

Y. pestis is easily propagated on normal laboratory media aerobically or anaerobically. Identification can be undertaken by the technology available in most modern hospital microbiology laboratories. Difficulty with identification has occurred. If cultures are negative, a passive hemagglutination serology performed at the US Centers for Disease Control and Prevention (CDC) can be utilized. All suspected specimens and isolates should be referred to an appropriate public health laboratory. The Insitut Pasteur developed a rapid diagnostic test using immunochromatography of specific F1 antigen in Madagascar.

Most isolates of *Y. pestis* have predictable sensitivity, and there is not a trend to increasing antimicrobial resistance. Naturally resistant isolates have been identified. There is also the likelihood that bioterrorism constructs of *Y. pestis* would be resistant to many antimicrobials. According to a recent publication by the CDC, Etest is equivalent to the reference broth dilution, and disk diffusion testing is not recommended. Rapid susceptibility methods are on the horizon.

Therapy

Streptomycin has been used as therapy since the 1940s. Its availability may be an issue. Gentamicin has been used successfully as an alternative (see Table 158.1).

TABLE 158.1 **THERAPY OF *YERSINIA PESTIS***

Preferred antibiotic	Classification for use
Streptomycin 1g q12h IM, may be given IV if necessary (some authorities would double the dose on the first day)	Availability an issue Call Pfizer Monitor renal, vestibular, and otic toxicity
Gentamicin 5–7 mg/kg/d Given as 2–3 doses IV	Monitor renal, vestibular, and otic toxicity Monitor blood levels and adjust for renal function
Ciprofloxacin 400 mg q8h IV 500 mg q12h PO	Not approved for pediatric use <16 yr
Levofloxacin 750 mg daily IV or PO	Not approved for pediatric use <16 yr
Moxifloxacin 400 mg daily IV or PO	Not approved for pediatric use <16 yr May be preferred in renal failure over other fluoroquinolones
Doxycycline 100 mg q12h IV or PO Some authorities would double the dose on the first day	Not approved for pediatrics ≤8 yr or in pregnancy
Chloramphenicol 25–30 mg/kg loading dose; reduction to 15 mg/kg q6h as patient improves	Predominantly for patients with meningitis and children. Meropenem may be an alternative in meningitis

There has been significant success with the use of tetracyclines in therapy of *Y. pestis*. In recent years doxycycline has been the tetracycline of choice. A randomized trial comparing gentamicin and doxycycline was conducted in Tanzania. The results were equivalent with <5% deaths.

A murine bubonic plague model demonstrated that ciprofloxacin was as effective as ciprofloxacin plus gentamicin and possibly more effective than gentamicin monotherapy. A recent in vitro pharmacodynamic model evaluated ciprofloxacin, moxifloxacin, gentamicin, ampicillin, and meropenem against streptomycin. All of the drugs out performed streptomycin. There are countervailing in vitro data that streptomycin and ciprofloxacin may be more active against both extracellular and intracellular organisms than either gentamicin or doxycycline. There are mouse data suggesting that levofloxacin-resistant organisms are significantly less fit than streptomycin-resistant organisms. Typical antibiotic courses are 7 to 10 days. Meningitis may require longer therapy.

Yersinia enterocolitica and *Y. pseudotuberculosis*

Y. enterocolitica and *Y. pseudotuberculosis* are most frequently associated with enterocolitis. Infection with *Y. enterocolitica* occurs much more often than with *Y. pseudotuberculosis*.

Y. enterocolitica is an important cause of enterocolitis worldwide, especially in colder climates and winter months. This is distinctly different from most enteropathogenic organisms. Most current data from the CDC estimate that *Y. enterocolitica* causes >117,000 illnesses with 35 deaths in the United States annually. Food, particularly pork, contaminated milk, and untreated water. have long been recognized as sources of infection. Serogroup O:3 is responsible for the majority of disease in the United States. The incubation period is 1 to 14 days, typically at the shorter end of this spectrum. Immunocompromised individuals, those with iron overload or treated with iron-chelating agents, and those with alkalinization of the stomach are at increased risk. Children have a greater risk when compared to adults.

The most common presentation is enteritis or enterocolitis, not unlike shigellosis. Typical symptoms include diarrhea, occasionally bloody, fever, abdominal pain, and vomiting. *Y. pseudotuberculosis* and *Y. enterocolitica* can present with abdominal pain that mimics appendicitis. Careful abdominal imaging with ultrasound or CT can usually distinguish *Yersinia*-induced mesenteric lymphadenitis from appendicitis. *Y. enterocolitica* can cause suppurative infection, including pharyngitis, pneumonia, empyema, hepatic abscess, lymphadenitis, and genitourinary and musculoskeletal infections. Sepsis, endocarditis, pericarditis, and myocarditis have all been reported. Rare cutaneous infections have also been reported.

Y. enterocolitica and *Y. pseudotuberculosis* have both been implicated in immunopathologic disease, including erythema nodosum, uveitis, and reactive arthritis. There may be a link to

TABLE 158.2 **THERAPY FOR *YERSINIA ENTEROCOLITICA***

Preferred antibiotic for serious infections	Classification of use
Ceftriaxone	
2 g in adults or 100 mg/kg/d for children	
Or	
Ciprofloxacin	Not approved for pediatrics ≤16 yr
400 mg q8h if susceptibility is shown	
Plus	
Gentamicin 5–7 mg/kg	
Given in 2–3 IV doses	
Other agents likely to be effective:	
Trimethoprim–sulfamethoxazole	
10 mg/50 mg/kg/d IV as 2 doses	
Doxycycline 100 mg q12h IV	Not approved for pediatrics ≤8 yr

inflammatory bowel disease. A role for *Y. pseudotuberculosis* in Kawasaki disease has been suggested.

Diagnosis of active infection is primarily by culture. Isolation from blood and sterile sites should not prove challenging in untreated patients. Culture of stool and other contaminated sites is more difficult. Cold enrichment and selective media may be helpful, but this usually requires specific discussion with the microbiology laboratory.

Therapy

Therapy is usually not required for *Y. enterocolitica* and *Y. pseudotuberculosis* gastroenteritis or mesenteric lymphadenitis in immunocompetent hosts (see Tables 158.2 and 158.3). Extraintestinal disease, particularly sepsis, requires antimicrobial therapy. Sepsis with either of the two species has a high mortality.

Y. enterocolitica often produce β-lactamases, thus precluding the use of penicillin and many cephalosporins. Most *Yersinia* strains are resistant to macrolides. Resistance to fluoroquinolones has been reported in Spain.

TABLE 158.3 **THERAPY FOR *YERSINIA PSEUDOTUBERCULOSIS***

Preferred antibiotic for serious infections (sepsis)	Classification of use
Ampicillin	
2 g q4h IV (200 mg/kg)	
Plus gentamicin	
5–7 mg/kg/d in 2–3 doses	
Alternative agent Doxycycline 100 mg q12h IV	Not approved for pediatric use ≤8 yr

Suggested reading

Bertherat E. Plague around the world 2010–2015. *Wkly Epidemiol Rec*. 2016 Feb 26;91(8):89–93.

Butler T. Plague into the 21st century. *Clini Infect Dis*. 2009;49: 736–742.

Kwit N, Nelson C, Kugeler K, et al. Human plague-United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2015 Aug 28;64(33):918–919.

Lemaitre N, Ricard I, Pradel E, et al. Efficacy of ciprofloxacin-gentamicin combination therapy in murine bubonic plague. *PLoS One*. 2012;7(12):e52503.

Li B, Yang R. Interaction between *Yersinia pestis* and the host immune system. *Infect Immun*. 2008;76(5):1804–1811.

Louie A, VanScoy B, Liu W, et al. Comparative efficacies of candidate antibiotics against *Yersinia pestis* in an *in vitro* pharmacodynamic model. *Antimicrob Agents Chemother*. 2011;55(6):2623–2628.

Mwengee W, Butler T, Mgema S, et al. Treatment of plague with gentamicin or doxycycline in a randomized clinical trial in Tanzania. *Clin Infect Dis*. 2006;42:614–621.

Rosner BM, Stark K, Werber D. Epidemiology of reported *Yersinia enterocolitica* infections in Germany, 2001–2008. *BMC Public Health*. 2010;10:337. doi:10.1186/1471–2458–10–337.

Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clini Infect Dis*. 2017 Nov 29;65(12):1963–1973.

Stenseth NC, Atshabar BB, Begon M, et al. Plague: Past, present, and future. *PLoS Med*. 2008;5(1):e3.

Tarr GAM, Chui L, Lee BE, et al. Performance of stool-testing recommendations for acute gastroenteritis when used to identify children with 9 potential bacterial enteropathogens. *Clini Infect Dis*.2018 Dec. doi:10.1093/cid/ciy1021.

Tsang TM, Felek S, Krukonis ES. Ail binding to fibronectin facilitates *Yersinia pestis* binding to host cells and Yop delivery. *Infect Immun*. 2010;78(8):3358–3368.

Urich SK, Chalcraft L, Schriefer ME, et al. Lack of antimicrobial resistance in *Yersinia pestis* isolates from 17 countries in the Americas, Africa, and Asia. *Antimicrob Agents Chemother*. 2012;56(1):555–558.

Wendte JM, Ponnusamy D, Reiber D, et al. *In vitro* efficacy of antibiotics commonly used to treat human plague against intracellular *Yersinia pestis*. *Antimicrob Agents Chemother*. 2011;55(8):3752–3757.

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Miscellaneous gram-positive organisms

Iqra Choudary, Steven K. Schmitt, and Roberto Baun Corales

Pediococcus species

Pediococci are gram-positive cocci that grow in pairs and tetrads and belong to the lactic acid bacteria group. Normal inhabitants of the gastrointestinal tract, they are used extensively in industry to ferment cheese and other dairy products, soy products, and alcoholic beverages. Thirteen species of pediococci are recognized today, but only *Pediococcus acidilactici* and *Pediococcus pentosaceus*, typically found in sugar-rich foods, have been identified as human pathogens. In recent years, these organisms have been increasingly recognized as a cause of bacteremia, endocarditis, and pneumonitis in the immunocompromised host. These organisms have also been isolated from intra-abdominal infections such as peritonitis and hepatic abscesses. Risk factors for *Pediococcus* infections include prior antibiotic therapy, abdominal surgery, and gastric feeding.

Diagnosis is made by isolation and identification of the organism from cultures of blood or other body fluids. *Pediococcus* species may be difficult to distinguish from enterococci and *Leuconostoc* species given its association with food. Approximately 95% of clinical isolates will cross-react with group D streptococcal antisera. Tests that aid in distinguishing pediococci from other organisms include a negative pyrrolidonyl arylamidase (PYRase) test and the absence of gas production from glucose. With newer application of molecular genetic techniques to determine relatedness of food-associated lactic acid bacteria, reorganization of the genus with novel morphologic or phenotypic differentiation of *Leuconostoc* species from *Pediococcus* species is being studied.

Pediococci are intrinsically highly resistant to vancomycin and other glycopeptides. Most strains are moderately susceptible to penicillin and ampicillin. Minimum inhibitory concentrations (MICs) are variable for cephalosporins. Imipenem appears active against all isolates, as does gentamicin. In vitro susceptibility to linezolid and daptomycin has been demonstrated. There have also been case reports of daptomycin being successfully used to treat pediococcocal endocarditis. Resistance to quinupristin–dalfopristin, erythromycin, clindamycin, tetracycline, tobramycin, and amikacin has been described. If a serious *Pediococcus* infection is suspected (e.g., on the basis of the characteristic tetrad morphology on Gram stain), intravenous penicillin at a dosage of 12 million or more units daily or imipenem may be used as empiric therapy. Susceptibility testing, preferably by MIC rather than disk diffusion, should be performed to determine appropriate therapy (Table 159.1).

Leuconostoc species

Leuconostoc species are catalase-negative, gram-positive coccobacilli that have been increasingly recognized as human pathogens over the last decade. These organisms are normally found in dairy products and vegetable matter and are used in the production of wine, dairy products, and dextrans. *Leuconostoc* species are not considered part of the normal human flora, but they have been isolated from the feces, vagina, and gastric fluid, primarily in hospitalized patients. Immunocompromised patients and those treated with vancomycin, to which leuconostocs are intrinsically resistant, may have gastrointestinal colonization with these organisms.

TABLE 159.1 **RECOMMENDED DRUG OF CHOICE FOR THE MISCELLANEOUS GRAM-POSITIVE ORGANISMS**

Organism	Antibiotic (Ab) (alternative Ab)	Route	Dosage	Duration
Pediococcus	Penicillin G Imipenem (Cephalosporins) (Linezolid)	IV	12 million U	(10–14 d)[a]
Leuconostoc	Penicillin G Ampicillin (Clindamycin) (Erythromycin) (Daptomycin)	IV	≥12 million U	(10–14 d)[a] 4 to 6 wk for endocarditis
Lactobacillus	Penicillin G Penicillin G and gentamicin (Clindamycin) (Erythromycin) (Linezolid)	IV IV IV	12million U daily 20–24 million U daily for endocarditis 1.0 mg/kg q8h	(10–14 d)[a] 6 wk
Oerskovia	Penicillin G, TMP–SMX (Vancomycin)	IV	(Moderate to high dosage)[a]	4–6 wk for endocarditis
Rothia	Penicillin G, (Vancomycin) (Cephalosporins) (Fluoroquinolones)	IV	20 million U daily for endocarditis	6 wk
Arcanobacterium	Erythromycin Penicillin V Penicillin G ± aminoglycosides (Clindamycin) (Tetracycline) (Linezolid)	PO/IV PO IV	40mg/kg (4 divided doses) 250–500 mg QID 2 million U q4h (for endocarditis)	10d Until clinical response 4–6 wk
Rhodococcus	Vancomycin (V) or imipenem plus rifampin (AIDS) or erythromycin (Sulfonamides) (Chloramphenicol) (Linezolid)	IV IV PO IV/PO	1 g q12h 500 mg q6h 600 mg/d 500 mg–1 g QID	2 wk 2–4 wk
Abiotrophia *Granulicatella* *Gemella*	Ampicillin or penicillin + gentamicin			

[a] Suggested by some authorities.
Abbreviations: TMP–SMX = trimethoprim–sulfamethoxazole; AIDS = acquired immunodeficiency syndrome.

Leuconostoc species may cause bacteremia in otherwise healthy neonates. At least four *Leuconostoc* species (including *Leuconostoc mesenteroides, Leuconostoc paramesenteroides, Leuconostoc cremoris*, and *Leuconostoc citreum*) may cause human infections. Risk factors for *Leuconostoc* infection include lengthy hospitalization requiring tracheostomy or parenteral nutrition, intravascular catheters, prior antibiotic therapy, prematurity, short gut syndrome, and serious underlying disease. *Leuconostoc* infections have been associated with pancreatitis, necrotizing enterocolitis, meningitis, and chylothorax to name a few.

Diagnosis is based on identification of the organism from cultures of blood or other sterile body fluids. On Gram stain the organisms appear as pairs or chains of slightly elongated gram-positive cocci that may appear rod-like. They may be difficult to distinguish from viridans streptococci, enterococci, lactobacilli, or pediococci. Helpful tests include the production of gas from glucose; a negative catalase, oxidase, and PYRase test; and the absence of arginine hydrolysis.

Leuconostoc isolates, like pediococci, are uniformly resistant to vancomycin and other glycopeptides. Most strains are susceptible

to penicillin, clindamycin, and gentamicin. Susceptibility to the cephalosporins, quinolones, and trimethoprim–sulfamethoxazole (TMP–SMX) is variable. Daptomycin and linezolid show activity against *Leuconostoc* spp. Resistance to quinupristin/dalfopristin has been demonstrated. Penicillin, the drug of choice, should be given at relatively high dosages (≥12 million units daily). In the case of penicillin allergy or resistance, therapy should be based on results of susceptibility testing. Appropriate therapy may also include removal of potentially infected devices such as indwelling intravascular catheters.

Lactobacillus species

Lactobacillus species are gram-positive rods that normally inhabit the human mouth, vagina, and gastrointestinal tract. More than 50 species of lactobacilli are recognized, many of which are used in the production of cheese, yogurt, pickles, and fermented beverages. Lactobacilli are widely considered to have low pathogenicity, and over the last decade have been used as probiotic factors (e.g., immunomodulation, microbe–microbe interactions, epithelial barrier protection), as part of prevention and treatment protocols for post-antibiotic enteric infections, vehicles for oral immunization, and as part of treatment policies called *ecoimmunonutrition*. Nevertheless, they have been reported to cause infections, including bacteremia, endocarditis, intra-abdominal and hepatic abscesses, meningitis, and pneumonia. Risk factors for serious infections caused by *Lactobacillus* species include underlying immunocompromised state (including human immunodeficiency virus [HIV] disease) and gastrointestinal surgery. Prior antibiotic therapy, particularly with vancomycin (to which most lactobacilli are resistant), has also been identified as a clinical risk factor. In patients with *Lactobacillus* bacteremia and endocarditis, cancer, recent surgery, and diabetes mellitus were identified as underlying risk factors. Additional history of dental infection or manipulation is common.

Diagnosis is based on identification of the organism from sterile body fluids. Lactobacilli are gram-positive rods, but they may appear coccoid if grown on solid media. Cultures grown in broth are more reliable for assessing morphology. Some *Lactobacillus* isolates may be difficult to distinguish from *Leuconostoc* species and streptococci. The combination of tests for gas production from glucose, arginine hydrolysis, PYRase, and carbohydrate fermentations should allow proper identification.

Intravenous penicillin (≥12 million units daily) is generally the drug of choice for serious infections. Endocarditis should be treated with penicillin 20 million to 24 million units daily plus gentamicin for 6 weeks. Lactobacilli are usually resistant to glycopeptides such as vancomycin. Susceptibility to cephalosporins and quinolones is variable, and most isolates are resistant to tetracycline and TMP–SMX. Most strains are susceptible in vitro to clindamycin, a possible alternative therapy in penicillin-allergic patients, but few clinical data are available. Lactobacilli are usually susceptible in vitro to linezolid but may be resistant to daptomycin and quinupristin–dalfopristin. Because of variable activity, susceptibility testing is critical in developing a treatment regimen. In the patient allergic to β-lactams who has endocarditis, penicillin desensitization should be considered.

Oerskovia and *cellulosimicrobium* species

Oerskovia species are yellow, gram-positive, non-acid-fast organisms with extensively branched filaments. They were first described by Orskov in 1938 as "motile *Nocardia*." Their usual habitat is soil, although they have also been isolated from decaying plant materials and grass cuttings. Two species of *Oerskovia* were originally recognized: *Oerskovia turbata* and *Oerskovia xanthineolytica*. Recently, *O. xanthineolytica* has been reclassified as *Cellulosimicrobium cellulans*, and *O. turbata* has been proposed for reclassification as a novel *Cellulosimicrobium* species. Both are rare causes of opportunistic infection in humans but should be considered as potential pathogens of low virulence, especially in the setting of indwelling devices. Reported infections caused by *Oerskovia* and *Cellulosimicrobium* species include native and prosthetic valve endocarditis, peritonitis, central venous catheter infections, bacteremia in immunocompromised hosts (including patients with acquired immunodeficiency syndrome [AIDS]), acalculus cholecystitis, prosthetic joint infection, keratitis, and endophthalmitis due to a penetrating eye injury. Several reported cases have been associated with exposure to soil, marine sediment, and bacterial contamination of hydrophilic contact lens solutions.

The diagnosis of *Oerskovia* and *Cellulosimicrobium* infections rests on laboratory identification from clinical specimens. Gram stain may reveal pleomorphic gram-positive nonmotile rods that can be mistaken for *Corynebacterium* spp. Culture reveals yellow colonies that are catalase positive when grown aerobically. They may be distinguished from other *Nocardia*-like organisms in that they are facultatively anaerobic and do not produce aerial mycelia. Identification is based on carbohydrate fermentation testing.

Successful treatment of *Oerskovia* infections requires removal of the contaminated foreign body in addition to appropriate antibiotic therapy, although some published cases report treatment without removal of infected vascular or peritoneal catheters. Antibiotics to which clinical isolates of *Oerskovia* and *Cellulosimicrobium* have been reported to be susceptible include penicillin (including extended-spectrum penicillins), vancomycin, TMP–SMX, cephalothin, and amikacin. Intermediate susceptibility or resistance has been described for ampicillin, ciprofloxacin, doxycycline, erythromycin, gentamicin, clindamycin, and the third-generation cephalosporins. Therapy should be based on susceptibility testing of the isolate. However, if culture results suggest *Oerskovia* infection, empiric parenteral penicillin or TMP–SMX therapy seems prudent while awaiting results of susceptibility testing.

Rothia species

Rothia dentocariosa is a small gram-positive pleomorphic rod belonging to the family Micrococcaceae. These organisms, common components of the normal oral microflora, were first isolated from carious dentine. The first description of human disease due to *Rothia* species was not reported until 1975, when the organism was recovered from a periappendiceal abscess. Over the last decade,

a number of case reports have described *Rothia* species as causing native and prosthetic valve endocarditis, aortic root abscess, neck abscess, peritonitis, septic arthritis, osteomyelitis, and pneumonia. The patient often has a history of recent dental infection or dental manipulation or is immunocompromised; however, a recent report includes identification in throat cultures of healthy individuals. *Rothia dentocariosa* has been isolated in lymph nodes of patients with cat scratch disease (CSD), suggesting a possible role, together with *Bartonella henselae*, in the pathogenesis of CSD. Another species of this genus (*Rothia mucilaginosa*, formerly known as *Stomatococcus mucilaginosus*) was found to be a member of the normal oral flora. This species has been described as opportunistic agents of infection in cases of endocarditis, meningitis, peritonitis, and other infections.

Diagnosis of *Rothia* infections depends on identification of the organism from the cultures of blood or other body fluids. *Rothia* species are catalase positive, nonmotile, urease negative, and indole negative. On Columbia chocolate horse blood agar, they appear to be gray and have a mucoid tendency after 48 hours of incubation. The organisms may appear branched, resembling *Actinomyces* or *Nocardia* species. They are distinguished from these genera by carbohydrate fermentation testing. *Rothia mucilaginosa* forms cocci in clusters and displays variable catalase reactions ranging from negative to weakly positive to strongly positive. The inability to grow in 5% NaCl distinguishes *R. mucilaginosa* from members of *Staphylococcus* and *Micrococcus* genera.

Penicillin is the drug of choice for treatment of infections due to *Rothia* spp. Because rare isolates may be resistant to penicillin, susceptibility testing should be performed. For endocarditis due to penicillin-susceptible strains, intravenous penicillin at dosages of 20 million units per day for 6 weeks is recommended. In the case of penicillin resistance or drug allergy, vancomycin, netilmicin, or teicoplanin therapy may be effective. *Rothia* species may also be susceptible in vitro to ciprofloxacin, rifampin, third-generation cephalosporins, vancomycin, chloramphenicol, and gentamicin. Resistance to amikacin, kanamycin, ciprofloxacin, and TMP–SMX has been described. In endocarditis cases due to *Rothia* spp., cardiac surgery may be beneficial when antimicrobial therapy alone is unsuccessful. Dental evaluation should also be considered in patients with infections due to *Rothia* species because carious or infected teeth may be a source of recurrent infection.

Arcanobacterium species

Arcanobacterium haemolyticum (formerly known as *Corynebacterium haemolyticum*) are facultatively anaerobic gram-positive to gram-variable pleomorphic rods (slender at first, sometimes clubbed, or in angular arrangements) that are nonmotile and nonsporulating. They are considered commensals of human nasopharynx and skin and are transmitted person to person by the droplet route. *Arcanobacterium* species have been recognized as causes of pharyngitis and cervical lymphadenopathy (indistinguishable from the pharyngitis caused by *Streptococcus pyogenes*) with additional symptoms of fever, pruritus, nonproductive cough, scarlatiniform skin rash with mild desquamation, and occasional formation of peritonsillar abscesses. Cutaneous infections, including ulcers, wound infection, cellulitis, and paronychia, are marked in some cases by the elaboration of lipid-hydrolyzing enzyme (sphingomyelinase D), producing dermonecrosis. Sepsis has been seen in immunocompromised states. Central nervous system (CNS) infections (brain abscess, cerebritis, meningitis), endocarditis, osteomyelitis, otitis media, sphenoidal sinusitis, empyema, and cavitary pneumonia have also been described.

Diagnosis is made by isolation and identification of the organism from cultures of blood, pharynx, skin lesions, or other clinical specimens (e.g., CNS abscess, cerebrospinal fluid [CSF], aortic valve, bone). Isolates of *Arcanobacterium* spp. are weakly acid fast, but this characteristic is typically not used for identification. On Loeffler's medium, the morphology closely resembles *Corynebacterium diphtheriae*. Tests that aid in diagnosis include fermentation of dextrose, lactose, and maltose but not mannitol or xylose. Colonies appear circular, discoid, opaque, and whitish, with a rough surface and friable consistency, a uniform feature at 48 hours of a black opaque dot at the center of each colony, and hemolysis at 24 to 48 hours incubation. Because *Arcanobacterium* species may present as part of polymicrobic infections with typical respiratory pathogens, they are often overlooked. Diagnosis often occurs only after repeated isolation. Increased awareness in microbiology laboratories of this organism may allow further elucidation of its pathogenicity in soft-tissue infections.

Most isolates of *A. haemolyticum* are susceptible to erythromycin, gentamicin, clindamycin, and third-generation cephalosporins. Newer studies report susceptibility to linezolid as well. They are resistant to sulfonamides and nalidixic acid in vitro. The drug of choice is erythromycin, 40 mg/kg orally or intravenously in four divided doses per day (2 g maximum). Although there have been reports of treatment failure with penicillin attributed to tolerance and failure to penetrate the intracellular location of the pathogen, penicillins with or without aminoglycosides are also widely used antibiotics, in most cases with success. In cases of abscess or tissue necrosis, surgical drainage or debridement may be a necesssary adjunct to antibiotic therapy.

Rhodococcus species

Rhodococcus equi (formerly known as *Corynebacterium equi*), zoonotic organisms readily found in soil contaminated with stool of grazing animals, particularly young horses, are nonfastidious, strict aerobic gram-positive bacteria displaying rod-to-coccus pleomorphism, with fragmenting and occasionally palisading forms. *Rhodococcus* are well-documented veterinary pathogens, causing granulomatous pneumonia in foals. They are opportunistic pathogens found in immunocompromised patients, including transplant patients and HIV-infected persons. Documented clinical presentations include slowly progressive granulomatous pneumonia with lobar infiltrates progressing to cavitating lesions on chest radiograph; abscesses of the central nervous system, pelvis, and subcutaneous tissue; and lymphadenitis. Vertebral osteomyelitis and pulmonary malakoplakia have also been reported. Recently, two cases of nosocomial *R. equi* infection have been associated with

ventriculoperitoneal shunts. Mortality exceeds 50% among AIDS patients with documented *R. equi* pneumonia, which is associated with a high rate of relapse despite adequate treatment. A newly described species of *Rhodococcus, Rhodococcus tsukamurella*, may cause multiple lung cavitary lesions in immunosuppressed patients and patients with indwelling foreign bodies.

Rhodococcus equi forms salmon pink colonies on blood agar from clinical specimens after 2 to 3 days of incubation. Colonies can be mucoid and coalescing; growth on Lowenstein–Jensen medium allows earlier detection of pigment. Synergistic hemolysis (resembling the CAMP test), displayed by cross-streaking on sheep blood agar with any of a number of other bacteria, including *A. haemolyticum, Staphylococcus aureus*, and *Corynebacterium pseudotuberculosis*, has been helpful in the diagnosis. In addition, *Rhodococcus* isolates are nonreactive to catalase, urease, and phosphatase and exhibit acid-fast staining. Some diagnostic laboratories use a commercial kit (API CORYNE strip; bioMerieux-Vitek, Hazelwood, MO) for identification. Prompt identification is necessary for optimal patient management.

Most strains are susceptible to inhibition by glycopeptide antibiotics, rifampin, and macrolides. Susceptibility to linezolid has been documented. Resistance to β-lactam antibiotics (except carbapenems) has been reported. The high relapse rate and attributable mortality rate, especially among AIDS patients, makes it difficult to recommend a standard treatment protocol. Repeat cultures are warranted during treatment to discover acquired resistance. A combination of at least two antibiotics parenterally (including a glycopeptide and rifampin) followed by oral maintenance therapy is recommended. Surgical wound resection has been performed in some cases, sometimes in combination with antimicrobial therapy. Antimicrobial prophylaxis may prove of benefit in AIDS patients. Recent data suggest treatment for *R. tsukamurella* infections to be a combination of β-lactam and aminoglycoside, along with removal of affected medical devices.

Abiotrophia and *granulicatella* species

First described in 1961 by Frenkel and Hirsch these were initially thought to be nutritionally variant streptococci (NVS). They are members of normal oral cavity flora and have been documented as agents of bacteremia and endocarditis in immunocompromised patients. They form gram-positive cocci in pairs and chains under optimal nutritional conditions (pyridoxal-supplemented media) but may display pleomorphic cellular morphology when growth conditions are suboptimal. Strains of these genera usually grow as small α-hemolytic colonies on chocolate agar but not on sheep blood agar unless the medium is supplemented or other bacteria are present to provide compounds needed for growth. Most strains exhibit positive PYR and LAP tests. They are susceptible to β-lactam agents, although elevated MICs for β-lactams have been observed for some strains. A combination of ampicillin and gentamicin is recommended for endovascular infections with these organisms.

Gemella species

This genus has recently grown to include a total of six species (*Gemella haemolysans, Gemella morbillorum, Gemella bergeriae*, *Gemella sanguinis, Gemella cuniculi*, and *Gemella palaticanis*). Most strains are PYR and LAP positive. They produce colonies on blood agar that resemble viridans streptococci. Although the cellular morphology of *G. morbillorum* resembles that of streptococci, *G. haemolysans* forms *Neisseria*-like diplococci that may also be arranged in tetrads and clusters and may appear to be gram variable. *Gemella haemolysans* is part of the normal flora of the oral cavity, *G. morbillorum* is part of the normal flora of the gastrointestinal tract, *G. cuniculi* has been reportedly isolated from rabbits, and *G. palaticanis* has been identified only in dogs but recently associated with a case of endocarditis in a child. *Gemella* strains have been isolated from cases of meningitis. It has been shown that these organisms are susceptible to vancomycin, penicillin G, and ampicillin. Synergy is seen between penicillin or vancomycin and gentamicin or streptomycin. Hence, penicillin and gentamicin are recommended for the treatment of *Gemella* endocarditis.

Helcococcus species

Helcococcus kunzii is currently the only species in this genus of PYR-positive, LAP-negative cluster-forming cocci that has been isolated from human clinical specimens. It forms small, nonhemolytic, slowly growing colonies on blood agar. This species has been described in recent reports as an agent of wound infection, bacteremia, and endocarditis. They are susceptible to vancomycin and β-lactam agents.

Lactococcus species

The genus *Lactococcus* was created to accommodate non-β-hemolytic Lancefield group N streptococci normally isolated from dairy products. Seven species have been currently recognized, with four subspecies. Members of this genus are homofermentators of lactic acid and resemble either streptococci or enterococci in terms of phenotypic traits and are infrequently isolated opportunistic pathogens. Though lactococci are commonly considered food-grade bacteria, they have been isolated from cases of endocarditis and a variety of other infections. They are susceptible to vancomycin and other β-lactam agents.

Globicatella species

The description of the species *Globicatella sanguinis* is α-hemolytic, PYR positive, LAP negative, and salt tolerant. They form cocci in chains. *Globicatella* spp. have been identified as a rare cause of shunt-associated meningitis and bacteremia. They are susceptible to vancomycin and β-lactam agents.

Aerococcus genus

This genus contains seven species. The most well-known species of this genus, *Aerococcus viridans*, forms clusters and though mostly associated with disease in lobsters, it has been noted as an infrequent cause of infection in compromised hosts. Another species, *Aerococcus urinae*, has been well documented as an agent of urinary tract infections and endocarditis in immunocompromised patients. Aerococci form α-hemolytic colonies on blood agar. *Aerococcus viridans* colonies are larger than those of *A. urinae*. These two species also differ in other phenotypic traits (*A. viridans* is PYR positive and LAP negative, whereas *A. urinae* is PYR negative and LAP positive). *Aerococcus urinae* is susceptible in vitro to a number of β-lactam agents and vancomycin; time-kill studies suggest a need for combination therapy, including an aminoglycoside for bactericidal therapy in endovascular infection.

Suggested reading

Alcaide ML, Espinoza L, Abbo L. Cavitary pneumonia secondary to Tsukamerella in AIDS patient: first case and review of literature. *J Infect*. 2004;49:17–19.

Bou G, Saleta JL, Tomas M, et al. Nosocomial outbreaks caused by *Leuconostoc mesenteroides* subsp *mesenteroides*. *Emerg Inf Dis*. 2008;14:968–971.

Cho EJ, Sung H, Park S, Kim MN, Lee SO. *Rothia mucilaginosa* pneumonia diagnosed by quantitative cultures and intracellular organisms of bronchoalveolar lavage in a lymphoma patient. *Ann Lab Med*. 2013;33:145–149.

Goyal R, Singh NP, Mathur M. Septic arthritis due to *Arcanobacterium haemolyticum*. *Ind J Med Microbiol*. 2005;23:63–65.

Haakensen M, Dobdon MC, Haakensen M, Dobs Hill J, Ziola B. Reclassification of *Pediococcus dextrinicus* as *Lactobacillus dextrinicus* comb. *Int J Syst Evol Microbiol*. 2009;59:615–621.

Husni RN, Gordon SM, Washington JA, et al. Lactobacillus bacteremia and endocarditis: review of 45 cases. *Clin Infect Dis*. 1997;25:1048–1055.

Ruoff KL. Miscellaneous catalase-negative, gram-positive cocci: emerging opportunists. *J Clin Microbiol*. 2002;40:1129–1133.

Tan TY, Ng SY, Thomas H, Chan BK. *Arcanobacterium haemolyticum* bacteraemia and soft-tissue infections: case report and review of literature. *J Infect*. 2006;53:69–74.

Urbina BY, Gohh R, Fischer SA. *Oerskovia xanthineolytica* endocarditis in a renal transplant patient: case report and review of literature. *Transplant Infect Dis*. 2003;5:195–198.

Yamshchikov A, Schuetz A, Lyon M. *Rhodococcus equi* infection. *Lancet Infect Dis*. 2010;10:350–359.

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Miscellaneous gram-negative organisms

Sampath Kumar and Kamaljit Singh

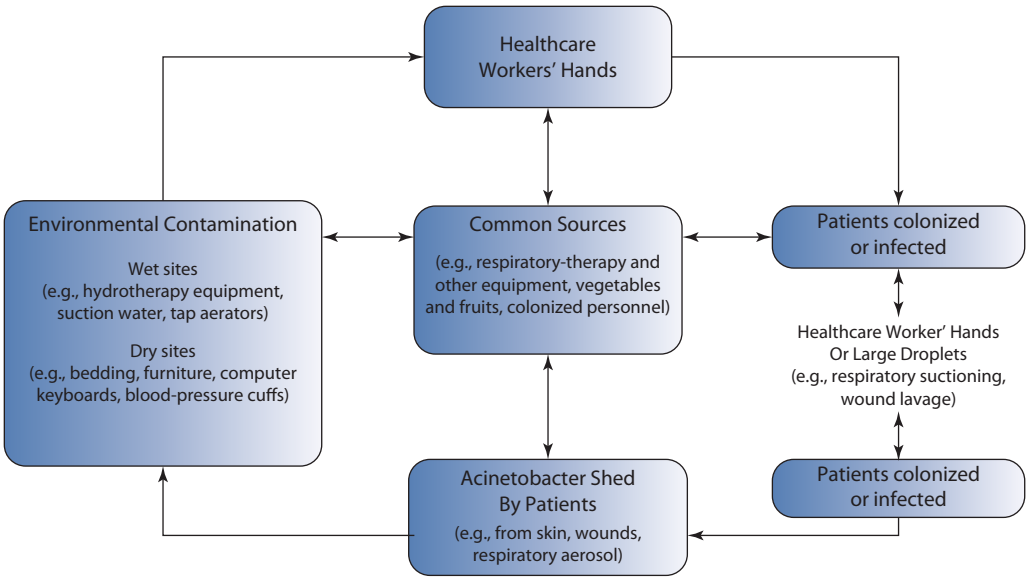
Most gram-negative infections are caused by organisms in the Enterobacteriaceae family or the *Pseudomonas* genus; however, a few are caused by a heterogeneous group of miscellaneous gram-negative organisms. These organisms do not fit conveniently into a single genera and have undergone frequent taxonomic changes, making understanding them even more difficult for clinicians. The clinical presentation varies widely, affecting different types of hosts and requiring a variety of antibiotics for therapy (Table 160.1). Varied predisposing environmental and host factors are outlined in Table 160.2.

Acinetobacter

Acinetobacter is a member of the family *Moraxellaceae*, with at least 25 genospecies. *A. calcoaceticus, A. lwoffii*, and *A. baumannii* are the species most commonly reported in the clinical literature. Because of problems with conventional methods for separating the *Acinetobacter* spp., the term "*A. calcoaceticus-baumannii* complex" is sometimes used. However, the use of matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDR-TOF MS) has allowed for rapid and accurate species identification that is superior to conventional methods. *Acinetobacter* spp. are nonmotile, oxidase-negative, gram-negative coccobacilli often appearing as diplococci and thus are easily confused with *Neisseria* or *Haemophilus* spp. They differ from the Enterobacteriaceae in that they do not grow anaerobically or reduce nitrates. They are distinguished from *Neisseria* and *Moraxella* by their negative oxidase reaction. Virulence factors include a polysaccharide capsule that may prevent phagocytosis and fimbriae that potentiate adherence to epithelial cells. Multidrug resistance among *Acinetobacter* spp has increased substantially over the past decade due in part to the organism's ability to accumulate multiple resistance genes carried on integrons or mobile genetic elements.

Epidemiology

Acinetobacter spp. are widely distributed in the environment, found in food, soil, water, and sewage. *Acinetobacter* spp. may be found on inanimate surfaces, including hospital equipment such as ventilator tubing, resuscitation bags, humidifiers, sinks, mist tents, dialysis baths, angiography catheters, pressure transducers, and plasma protein solutions. They are found on the skin of many animal species and humans, usually as commensal organisms. They are found as part of the normal oral flora and in the genitourinary and gastrointestinal tracts. The reservoirs, sources, and transmission patterns for *Acinetobacter* in healthcare facilities is outlined here.



Reservoirs, Sources, and Transmission Patterns for Acinetobacter in Healthcare Facilities

Weinstein RA, Silvia Munoz-Price, L Acinetobacter infection *N Eng J Med.* 2008;358:1271–81

Pathogenesis and clinical syndromes

A. baumannii is the most commonly found species in human clinical specimens followed by *A. lwoffii*. *Acinetobacter baumannii* is increasingly recognized as one of the most important causes of nosocomial infections and is of particular concern because of its propensity for multidrug resistance. Most infections due to *A. baumannii* are nosocomial, occurring in severely debilitated patients who have been exposed to broad-spectrum antibiotics in the intensive care unit, mechanical ventilators, and invasive devices (e.g., central venous catheters). In addition, *A. baumannii* is a cause of serious infections among military personnel returning from the Middle East, often with carbapenem-resistant strains of *A. baumannii,* and in victims of natural disasters. A wide variety of human infections due to *A. baumannii* have been reported, including ventilator-associated pneumonia, septicemia, endocarditis, meningitis, urinary tract infections, wound infections including necrotizing fasciitis, abscesses, peritonitis, osteomyelitis, and eye infections. Purulent pericarditis has been reported in

TABLE 160.1 **ANTIMICROBIAL THERAPY OF MISCELLANEOUS GRAM-NEGATIVE BACILLI**

Organism	First-line therapy	Alternative therapy
Acinetobacter	Ampicillin–sulbactam, piperacillin–tazobactam, imipenem–cilastatin, meropenem, ceftazidime, amikacin Minocycline Eravacycline	Fluoroquinolones, trimethoprim–sulfamethoxazole (TMP-SMX), tigecycline, colistin Phage therapy
Achromobacter	Imipenem-cilastatin, meropenem, tigecycline	Piperacillin–tazobactam, ceftazidime, TMP-SMX
Alcaligenes	Imipenem-cilastatin, meropenem, TMP-SMX	Amoxicillin–clavulanate, ceftazidime, piperacillin–tazobactam
Capnocytophaga canimorsus	Penicillin	Clindamycin, imipenem–cilastatin, ampicillin–sulbactam, amoxicillin–clavulanate
Pseudomonas oryzihabitans/luteola	Fluoroquinolones, ceftazidime, piperacillin-tazobactam	Imipenem–cilastin, meropenem, aztreonam, aminoglycosides, TMP-SMX
Chromobacterium	Imipenem-cilastin, ciprofloxacin, tigecycline	Tetracycline, TMP-SMX, gentamicin
Elizabethkingia meningoseptica	Vancomycin, rifampin, levofloxacin	Tigecycline, TMP-SMX
Ochrobactrum anthropi	Imipenem-cilastin	TMP-SMX, tetracyclines, aminoglycosides, fluoroquinolones

TABLE 160.2 **ENVIRONMENTAL AND HOST FACTORS PREDISPOSING TO INFECTIONS WITH MISCELLANEOUS GRAM-NEGATIVE BACILLI**

Organism	Environmental factors	Host factors	Infection
Acinetobacter	Ventilator tubing, resuscitation bags, humidifiers, sinks, mist tents, dialysis bags, angiography and IV catheters, pressure transducers, plasma protein solutions	Severely debilitated, recent surgery, instrumentation prior colonization prior β-lactam use prior fluoroquinolone use prior ICU stay ESRD on hemodialysis	Septicemia, endocarditis, meningitis, pneumonia, UTI, wound infections, abscesses, peritonitis, osteomyelitis, eye infections
Achromobacter	Contaminant in disinfectants, diagnostic tracer solution, IV CT contrast, hemodialysis solutions, ventilators, humidifiers, pressure transducers	Severely debilitated, recent neurosurgery	Community-acquired bacteremia, meningitis, chronic otitis media, hospital-acquired meningitis, bacteremia, ventriculitis, endocarditis, endophthalmitis, corneal ulcers, pharyngitis, pneumonia, wound infections, peritonitis, UTI, abscesses
Alcaligenes	Dairy products, rotten eggs, hospital equipment	Severely debilitated	Septicemia, native and prosthetic valve endocarditis, meningitis, meibomianitis, chronic purulent otitis, pyelonephritis, hepatitis, appendicitis, diarrhea
Capnocytophaga	Normal oral, gastrointestinal, respiratory, and vaginal flora of humans; *C. canimorsus* in canine oral flora	Severely immunocompromised, children with malignancies, neutropenia, mucositis, asplenia, alcohol abuse	Bacteremia, septicemia, keratitis, conjunctivitis, endophthalmitis, corneal ulcer, endocarditis, pericardial abscess, mediastinitis, lung and subphrenic abscess, empyema, peritonitis, abdominal abscess, septic arthritis, lymphadenitis, juvenile periodontitis
Chromobacterium	Enters through the skin or ingestion of contaminated food or water	Neutrophil defects (e.g., chronic granulomatous disease)	Local cellulitis, lymphadenitis, septicemia, osteomyelitis, arthritis, meningitis, ocular infections, and pneumonia
Chryseobacterium	Soil, water, use of contaminated fluids in the hospital, nebulizers, flush solutions, pressure transducers, contaminated disinfectants and anesthetics, ice machines, peritoneal dialysis solutions	Neonates, premature infants, adult immunocompromised patients	Neonates: meningitis, hydrocephalus Adults: endocarditis, pneumonia, peritonitis, keratitis, wound infection, meningitis
Pseudomonas oryzihabitans/luteola	Soil, water, flushing solutions	Patients with indwelling foreign material, malignancies, immunosuppressive therapy, postsurgical state, history of IVDU, chronic renal failure, bone marrow transplant, cirrhosis	Septicemia, bacteremia, subdural empyema, pneumonia, peritonitis, biliary tract infection, abscesses, wound infection, empyema, line infections, prosthetic joint infections

Abbreviations: UTI = urinary tract infection; CT = computed tomography; IVDU = intravenous drug use.

immunosuppressed patients. The most common sites of isolation of *A. baumannii* are the respiratory and urinary tracts. The mortality can be as high as 40% to 60% in patients with septic shock and up to 30% in patients with ventilator-associated pneumonia, usually associated with underlying disease (e.g., diabetes, malignancy, and renal failure). *Acinetobacter* spp. play a significant role in the colonization of hospitalized patients, making it difficult to differentiate true infection from colonization.

A. baumannii is commonly multidrug-resistant due to expression of β-lactamases, altered porin channels, and efflux pumps. Treatment is best guided by specific antibiotic testing and sensitivity patterns within each hospital. Most *A. baumannii* strains are resistant to penicillin, ampicillin, first-generation cephalosporins, gentamicin, and chloramphenicol and show variable susceptibility to second- and third-generation cephalosporins, trimethoprim-sulfamethoxazole (TMP-SMX), and tetracyclines. Ampicillin-sulbactam and

sulbactam alone have intrinsic bactericidal activity and have been used with good success in susceptible strains. Other therapeutic options include broad-spectrum cephalosporins such as ceftazidime or cefepime, carbapenems, and minocycline. In recent years, many institutions have noted the emergence of carbapenem hydrolyzing strains of *A. baumannii* due to the production of OXA-type carbapenemases or metallo-β-lactamases including NDM (New Delhi metallo-β-lactamase). For pan-resistant strains of *A. baumannii*, colistin (or polymyxin B) and tigecycline either singly or in combination may offer reasonable therapeutic alternatives. Newer antibiotic combinations including ceftazidime-avibactam, ceftolozane-tazobactam and meropenem-varborbactam are not effective. *A. lwoffii* tends to be more susceptible than the other *Acinetobacter* spp.

Achromobacter

Epidemiology

Achromobacter spp. are widely distributed in nature, including in soil and water. They may be part of the normal flora of the lower gastrointestinal tract. *Achromobacter* spp. have been found as contaminants in disinfectants, diagnostic tracer solutions, intravenous CT contrast solutions, hemodialysis solutions, ventilators, humidifiers, and pressure transducers.

The genus *Achromobacter* consists of a number of species, of which two are of clinical relevance: *A. xylosoxidans* and *A. denitrificans*. These are gram-negative rods that are oxidase-positive and grow on MacConkey agar.

Clinical syndromes

Achromobacter spp. have been commonly reported as causative agents in a variety of nosocomial and community-acquired infections. *A. xylosoxidans* has been isolated from many types of specimens, including blood, cerebrospinal fluid (CSF), bronchial washings, urine, and wounds. It represents an opportunistic pathogen in immunosuppressed patients and has been reported to cause chronic otitis media, meningitis and ventriculitis after neurosurgical manipulation, bacteremia, endocarditis, endophthalmitis, corneal ulcers, pharyngitis, pneumonia, surgical wound infections, peritonitis and urinary tract infections, and abscesses. Mortality can approach 52% in patients with *A. xylosoxidans* bacteremia.

A. xylosoxidans colonizes the respiratory tract of cystic fibrosis patients and is associated with exacerbations of pulmonary symptoms. Antibiotic selection should be guided by susceptibility testing. Imipenem-cilastatin is the most consistently effective agent in vitro against *A. xylosoxidans*. Most strains are resistant to aminoglycosides and cephalosporins (including cefepime) except ceftazidime. Piperacillin-tazobactam, ticarcillin-clavulanate, fluoroquinolones, meropenem and TMP-SMX are generally effective. For severe infections, initial combination therapy may be necessary; synergistic activity has been established for combinations with meropenem.

A. denitrificans is reported to have been isolated from many clinical specimens, but its clinical significance remains controversial. It has been reported to cause urinary tract infections, otitis externa, and bacteremia associated with intravenous catheters.

Alcaligenes

Epidemiology

Alcaligenes consist of gram-negative rods or cocci that are oxidase-positive and obligate aerobes. *A. faecalis* is the most commonly isolated species in the clinical laboratory. Some *A. faecalis* (previously named *A. odorans*) produce a greenish color on blood agar plates and have a characteristic fruity, apple odor. These organisms are found in soil and water as well as on normal human skin and in gastrointestinal tract flora. Dairy products and rotten eggs have been sources of *Alcaligenes*. These organisms have also been isolated from hospital equipment.

Clinical syndromes

Clinically important infections are found in severely debilitated patients and patients with cystic fibrosis. Most infections are opportunistic and acquired from contaminated hospital equipment (e.g., nebulizers, respirators, and lavage fluid). *Alcaligenes* spp. are a rare cause of bacteremia (blood isolates have also been obtained from patients without clinical evidence of sepsis), native and prosthetic valve endocarditis, meningitis, chronic purulent otitis, keratitis, pyelonephritis, hepatitis, appendicitis, and urinary tract infection. *Alcaligenes* isolated from the blood of patients with septicemia is thought to be associated with contaminated hospital equipment. *A. faecalis* isolation from the urine is often considered to be a contaminant; it is also found in diabetic ulcers with mixed flora, and its clinical significance is difficult to determine.

A. faecalis is generally susceptible to the β-lactam drugs, fluoroquinolones, aminoglycosides, and TMP-SMX. On the basis of in vitro studies, third-generation cephalosporins or the addition of clavulanic acid to amoxicillin or piperacillin-tazobactam may be more consistently effective. Greater antibiotic resistance is seen in hospitals.

Capnocytophaga

Epidemiology

Capnocytophaga encompasses a group of capnophilic (CO_2 requiring), microaerophilic, gram-negative rods. The organisms are slow-growing, thin, and often fusiform bacilli that display gliding motility on agar media. The oxidase- and catalase-negative clinically relevant species include *C. ochracea, C. sputigena, C. haemolytica, C. granulosa, C. leadbetteri*, and *C. gingivalis* (formerly Centers for Disease Control and Prevention [CDC] group DF-1). These species are normal members of the human oral microbiota and can be

isolated from individuals with periodontal disease. *C. canimorsus* and *C. cynodegmi* are oxidase- and catalase-positive and found as part of the normal oral flora of domestic pets

Clinical syndromes

C. ochracea, C. sputigena, C. haemolytica, C. granulosa, C. leadbetteri, and *C. gingivalis* have been reported to cause septicemia and other infections including endocarditis, osteomyelitis, soft tissue infections, endophthalmitis, endometritis, and peritonitis. The clinical presentation includes fevers, chills, myalgia, nausea or vomiting and diarrhea, abdominal pain, mental confusion, and headache. In a Danish study, the mortality in 39 cases with septicemia was approximately 31%, with eight patients dying of fulminant sepsis complicated by disseminated intravascular coagulation (DIC) after admission. They are also causative agents of localized juvenile periodontitis (together with *Aggregatibacter* [formerly *Actinobacillus*] *actinomycetemcomitans*) and other periodontal disease. *Capnocytophaga* may cause systemic disease in both immunocompetent and immunocompromised patients, particularly with neutropenia and in the presence of oral mucositis. These patients usually present with bacteremia and septicemia. In immunocompetent patients, *Capnocytophaga* may be isolated from polymicrobial infections of the respiratory tract including pulmonary abscess and empyema or contaminated wounds (e.g., clenched fist injuries).

Human *Capnocytophaga* spp. are generally susceptible to clindamycin, erythromycin, tetracycline, chloramphenicol, quinolones, and imipenem-cilastatin. Susceptibilities are variable for penicillin, expanded-spectrum cephalosporins, and metronidazole. In general, these organisms are resistant to aztreonam, aminoglycosides, vancomycin, trimethoprim, and colistin. β-lactamase production has been reported in 2.5% to 32% of isolates (detected by the nitrocefin test). Clindamycin is thought to be the most active drug in vitro. In immunocompromised patients with bacteremia, antibiotics should be given for 10 to 14 days after documenting negative blood cultures. For immunocompetent patients, the duration of therapy should be dictated by the site and extent of infection, and therapy should be given in conjunction with adequate surgical drainage.

C. canimorsus and *C. cynodegmi* are part of the normal oral flora of dogs and cats. *C. canimorsus* is isolated more commonly and appears to be more virulent. It is generally associated with dog bites, causing a wide spectrum of illness ranging from mild to fulminant infection, including septic shock and death. The case fatality rate is approximately 25%. Predisposing factors to serious infection mainly include prior splenectomy, alcohol abuse, liver cirrhosis, and immunosuppression (steroids or hematologic malignancies). In these individuals, the infection tends to be fulminant, with shock, DIC, hemorrhagic skin lesions mimicking meningococcemia, gangrene, renal failure, and death. More than 75% of cases report exposure to a dog, either through contact or a bite. *C. canimorsus* has been reported to cause meningitis, endocarditis, pneumonia, empyema, corneal ulcer, septic arthritis, cellulitis, and wound infections after a dog bite or cat scratch.

The diagnosis is established by blood cultures although other specimens may also yield the organism (e.g., wound cultures, CSF). In most reports, cultures become positive within 3 to 7 days. Clinicians should alert the microbiology laboratory if infection due to *C. canimorsus* is suspected so that blind subculture of blood cultures on enriched media can be performed. In asplenic patients, the organism may be demonstrated on a Gram stain of the buffy coat. In one alcoholic patient, the organisms were seen on a peripheral blood smear.

Routine susceptibility tests of *C. canimorsus* are difficult to perform because of slow growth and lack of standardized methods. However, it is generally reported to be susceptible to most antibiotics, including penicillins, imipenem-cilastin, erythromycin, vancomycin, clindamycin, third-generation cephalosporins, chloramphenicol, rifampin, doxycycline, and quinolones. Susceptibility to aminoglycosides and trimethoprim is unclear and may depend on the method used. Penicillin is considered the drug of choice for *C. canimorsus* infections.

Chromobacterium

Chromobacterium violaceum is the species most commonly isolated in the clinical laboratory although it is seldom regarded as pathogenic. *C. violaceum* is a slightly curved, gram-negative rod with an almond-like smell, and it produces a distinctive water-insoluble violet pigment on blood agar. The organism grows within 24 hours on conventional media. *C violaceum* is included in the database of current MALDI-TOF MS systems. Humans with neutrophil defects (e.g., chronic granulomatous disease) may be particularly susceptible to infections with this organism.

Chromobacterium is generally found in the environment (soil, fresh water, and food). It grows optimally at 20°C/68°F to 37°C/98.6°F; hence, most infections have been documented in tropical or subtropical climates. It is a rare infection, thought to enter the body through contaminated wounds, although ingestion of contaminated food or water may play a role. The most common clinical presentation is a local cellulitis and regional or diffuse lymphadenitis. Widespread dissemination may occur, resulting in septicemia and multiorgan failure. Mortality is 60% to 70%, depending on the host and accuracy of diagnosis. Other presentations have included fever, skin lesions, abdominal pain, osteomyelitis, arthritis, meningitis, ocular infections, and pneumonia.

C. violaceum is generally resistant to most penicillins and colistin. It is susceptible to imipenem-cilastatin, fluoroquinolones, tigecycline, tetracyclines, and gentamicin. TMP-SMX has been used successfully as outpatient therapy after prolonged intravenous therapy with other agents.

Elizabethkingia

Elizabethkingia spp., formerly *Chryseobacterium* spp., are long, thin, slightly curved, oxidase-positive, indole-positive gram-negative rods. They are common inhabitants of soil and water and are found in hospital environments. *E. meningoseptica* is a

well-recognized human pathogen most commonly associated with nosocomial infections and outbreaks in intensive care units,. Two new species of *Elizabethkingia, E. miricola* and *E. anophelis* have been reported to cause human infections. *E. miricola* was initially identified from condensation water collected on the Russian Mir space station, while *E. anophelis* was recovered from the midgut of *Anopheles gambiae* mosquitoes in the Gambia. Misidentification of *Elizabethkingia* spp. is common using traditional biochemical and commercial phenotypic identification systems, but MALDI-TOF MS provides more reliable identification. In particular, *E. anophelis* is often misidentified as *E. meningoseptica* using traditional biochemical methods.

E. meningoseptica is an uncommon pathogen in adults and rarely causes infections in children beyond the newborn period. It is highly pathogenic for premature infants and has been associated with neonatal sepsis and meningitis. The development of meningitis may be insidious. The prognosis is extremely poor, with mortality >60%. Half of the survivors develop significant neurologic complications, including hydrocephalus. Although rarely encountered, it is important to diagnose the disease accurately because epidemics may occur in nurseries. Meningitis has also been reported in adults, particularly among immunocompromised patients. Other clinical presentations in adults include bacteremia, endocarditis, pneumonia, peritonitis, keratitis, and wound infections. Most of the described cases are nosocomial infections associated with the use of contaminated fluids in the hospital (nebulizers, flush solutions for arterial catheters, pressure transducers, ice machines, contaminated disinfectants, contaminated anesthetics, peritoneal dialysis). *E. anophelis* has been reported as a cause of severe sepsis particularly in Asian countries but also as a cause of large outbreaks in the Midwestern United States (Wisconsin, Illinois, and Michigan). The clinical presentation included bacteremia, pneumonia, meningitis, urinary tract infection, biliary sepsis, and skin and soft tissue infection. In the Wisconsin outbreak, 89% of cases were attributed to community-onset infection, and patients were usually elderly with comorbidities such as diabetes, cirrhosis, alcohol dependence, chronic kidney disease, and malignancy. The case fatality rate due to *E. anophelis* infection is high, ranging from 24% to 60%. *E. miricola* is a rare cause of pneumonia, bacteremia, and urinary tract infection and appears to be more prevalent in Asia.

Antimicrobial selection is difficult because *Elizabethkingia* are inherently resistant to multiple antibiotics, and susceptibilities vary with the method used. Results of testing, particularly with the disk diffusion, E-test, and agar dilution tests, are considered unreliable. The broth microdilution test is recommended for susceptibility determination for *Elizabethkingia* spp. Most isolates produce β-lactamases and are resistant to cephalosporins, carbapenems, aminoglycosides, and TMP-SMX. *E. meningoseptica* demonstrates variable susceptibility to piperacillin-tazobactam and quinolones

More recent studies have recommended use of levofloxacin for *E. miricola* strains based on in vitro results demonstrating low minimum inhibitory concentrations (MICs). *E. anophelis* isolates in the Wisconsin outbreak were highly susceptible to cefepime (90%) and minocycline (97.5–100%). Antimicrobial therapy should be continued for at least 2 weeks after sterilization of the CSF. Recovery is the rule in immunocompetent older patients infected with contaminated materials; however, the prognosis is poor in immunocompromised patients.

Pseudomonas oryzihabitans, *P. luteola*, *P. fluorescens*, *P. putida*, and *P. stutzeri*

Pseudomonas oryzihabitans and *P. luteola* are oxidase-negative, aerobic, gram-negative rods with a distinct yellow pigment. After 48 hours of incubation, colonies are typically rough or wrinkled. They are found in water, soil, and other damp environments. Eighty-four percent of the reported cases have been associated with the presence of a foreign material, including intravascular catheters, dialysis catheters, or artificial grafts. Other associated host factors include malignancy, immunosuppressive therapy, postsurgical state, chronic renal failure, previous antibiotic therapy, intravenous drug use, long-term corticosteroid use, liver cirrhosis, and bone marrow transplantation. Infections associated with these organisms include sepsis, bacteremia, line infections, pneumonia, prosthetic joint infections, subdural empyema, peritonitis, biliary tract infections, surgical wound infections, abscesses, and empyema.

In many studies, resistance has been shown to the first- and second-generation cephalosporins, and most isolates are also resistant to ampicillin and tetracycline. They are sensitive to the ureidopenicillins, third-generation cephalosporins, carbapenems, aminoglycosides, and quinolones. There is a difference in susceptibility to TMP-SMX: *P. luteola* is resistant and *P. oryzihabitans* is sensitive. Clinically, most patients have been treated with ciprofloxacin with a favorable outcome.

The increase in number of reported cases of *P. fluorescens* and *P. putida* infection is frequently related to the presence of intravascular catheters in immunocompromised patients and dialysis catheters in continuous ambulatory peritoneal dialysis. *P. fluorescens* can be isolated from the skin of blood donors and result in contaminated blood transfusions, infected flushes, pseudobacteremia, and pseudo-outbreaks. *P. putida* has been implicated in nosocomial bacteremia, pneumonia, peritonitis, and neonatal sepsis. *P. stutzeri* infections are uncommon, but this organism has been reported as a cause of bacteremia, nosocomial brain abscess, and meningitis in immunocompromised patients. Infections such as osteomyelitis, septic arthritis, and endophthalmitis after cataract surgery have also been reported. These organisms are generally susceptible to most antipseudomonal antibiotics.

Ochrobactrum

These are oxidase- and urease-positive, gram-negative coccobacilli formerly designated as CDC group Vd-1 and Vd-2 and *Achromobacter* groups A, C, and D. Two species are currently described as human pathogens, *Ochrobactrum anthropi* and *O. intermedium*, although other *Ochrobactrum* spp. have rarely been recovered from clinical samples. It may be difficult to differentiate the two pathogenic *Ochrobactrum* spp. using traditional phenotypic methods but *O.*

intermedium is colistin-resistant and grows at 41°C/105°F. Both *Ochrobactrum* species are closely related to *Brucella* species, leading to occasional misidentification by automated systems. *O. anthropi* is a low-virulence pathogen affecting immunocompromised patients and is often associated with vascular device-related infections, hemodialysis, urinary and respiratory tract infections, continuous ambulatory peritoneal dialysis peritonitis, activation-induced cell death, and pacemaker infections. Cases have been described where resolution of bacteremia has occurred without antibiotic administration or despite administration of resistant antibiotics. *O. anthropi* is usually resistant to most penicillins and cephalosporins, and is susceptible to carbapenems, aminoglycosides, fluoroquinolones, TMP-SMX, and tetracyclines.

Oligella, Ralstonia, Rhizobium, Shewenella, Sphingomonas, Roseomonas, Weeksella, and *Bergeyella*

Oligella are small coccobacilli and consist of two species, *O. urethralis* (formerly *Moraxella urethralis*) and *O. ureolytica*. Most isolates have been taken from urine, often associated with indwelling urinary catheters, and these can rarely cause bacteremia, septic arthritis, and pyelonephritis. *O. urethralis* is susceptible to most antibiotics including penicillin, while *O. ureolytica* exhibits variable susceptibility patterns.

Ralstonia pickettii is the only clinically significant member of the *Ralstonia* genus, and it has been implicated in pseudobacteremias and nosocomial outbreaks due to contaminated infusions.

Rhizobium spp. (former *Agrobacterium*) are occasionally isolated from clinical specimens but rarely linked with human infection. *R. radiobacter* is the only clinically significant species and produces pink, mucoid colonies on MacConkey agar. It has been most commonly isolated from blood followed by peritoneal dialysate or ascites fluid, and it is also associated with infections of transcutaneous devices in immunocompromised patients. Antibiotic susceptibility is variable, and treatment should be guided by individual susceptibility testing. Most isolates are susceptible to broad-spectrum cephalosporins, carbapenems, piperacillin-tazobactam, fluoroquinolones, and gentamicin (but not tobramycin).

Shewanella putrefaciens and *S. algae* are the type species most commonly isolated from human clinical specimens. The habitat for *S. algae* is saline, and *S. putrefaciens* has been isolated from fish, poultry, meats, and water samples. They are associated with skin and soft tissue infections and bacteremia, especially in immunocompromised patients. They are usually susceptible to most antibiotics except for penicillin and first-generation cephalosporins.

Sphingomonas (formerly *Pseudomonas*) *paucimobilis* and *S. paucimobilis* are yellow-pigmented, weakly oxidase-positive, gram-negative rods that classically infect immunocompromised patients. They can be isolated from a variety of clinical specimens, including blood, CSF, urine, wounds, and the hospital environment. Most strains are colistin-resistant but susceptible to vancomycin, tetracycline, TMP-SMX, aminoglycosides, and imipenem-cilastin, and have variable susceptibility to penicillins and quinolones.

Roseomonas are the most frequently isolated pink-pigmented gram-negative coccobacilli. They are an uncommon cause of human infection but are occasionally isolated from blood, usually due to device-associated bacteremia. They have also been isolated from abscesses, wounds, dialysis fluid, and genitourinary sites. Most strains are susceptible to imipenem-cilastatin, amikacin, and fluoroquinolones. *Roseomonas* spp. are usually resistant to penicillins and cephalosporins.

Weeksella virosa and *Bergeyella zoohelcum* are morphologically and biochemically similar organisms. Both species are oxidase-negative and susceptible to most antibiotics including penicillin. *W. virosa* is isolated mainly from urine and vaginal samples.

Bergeyella zoohelcum is part of the normal oral flora of dogs and cats, and human isolates frequently result from dog or cat bites.

Suggested reading

Almuzara M, Limansky A, Ballerini V, et al. In vitro susceptibility of *Achromobacter spp* isolates: comparison of disk diffusion, Etest and agar dilution methods. *Int J Antimicrob Agents*. 2010;35:68–71.

Fishbain J, Peleg AY. Treatment of *Acinetobacter* infections. *Clin Infect Dis*. 2010;51:79–84.

Hagiya H, Ohnishi K, Maki M, Watanabe N, Murase T. Clinical characteristics of *Ochrobactrum anthropi* bacteremia. *J Clin Microbiol*. 2013;51(4):1330–1333.

Han MS, Kim H, Lee Y, et al. Relative prevalence and antimicrobial susceptibility of clinical isolates of *Elizabethkingia* species based on 16S rRNA gene sequencing. *J Clin Microbiol*. 2016;55(1):274–80.

Jacquier H, Carbonnelle E, Corvec S, et al. Revisited distribution of nonfermenting gram-negative bacilli clinical isolates. *Eur J Clin Microbiol Infect Dis*. 2011;30:1579–1586.

Jacquier H, Monnier AL, Carbonnelle E, et al. In vitro antimicrobial activity of "last-resort" antibiotics against unusual nonfermenting gram-negative bacilli clinical isolates. *Microb Drug Resist*. 2012;18:396–401.

Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumanii*: Emergence of a successful pathogen. *Clin Microbiol Rev*. 2008; 21:538–582.

Philippon A. β-lactam resistance in other nonfermentative strict aerobic gram-negative bacilli. In Courvalin P, Leclercq R, Rice LB, eds. *Antibiogram*. Washington, DC: ESKA Publishing, ASM Press; 2010.

The nonfermentative gram-negative bacilli. In Winn W Jr, Allen S, Janda W, et al., eds. *Koneman's color atlas and textbook of diagnostic microbiology*, 6th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2003: 305–391.

Vaneechoutte M, Dijkshoorn L, Nemec A, Kampfer P, Wauters G. *Acinetobacter, Chryseobacterium, Moraxella* and other nonfermentative gram-negative rods. In Versalovic J, Carroll KC, Funke G, Jorgensen JH, Landry ML, Warnock DW eds. *Manual of clinical microbiology*, 10th ed. Washington, DC: ASM Press; 2011.

Warren JS, Allen SD. Clinical, pathogenetic, and laboratory features of *Capnocytophaga* infections. *Am J Clin Pathol*. 1986;86:513–518.

Weinstein RA, Silvia Munoz-Price, L Acinetobacter infection *N Eng J Med*. 2008;358:1271–1281.

Section 19

Specific organisms: Spirochetes

Syphilis and other treponematoses

Arlene C. Seña and Adaora A. Adimora

Treponemes are members of the family *Spirochaetaceae*, which also contains *Borrelia* and *Leptospira*. Although most treponemes do not cause disease in human beings, a few cause substantial morbidity. This chapter briefly reviews the clinical manifestations and treatment of syphilis in adults and the nonvenereal treponematoses: yaws, pinta, and bejel.

Syphilis

Transmission and stages of infection

Syphilis is primarily transmitted through sexual contact with infectious mucocutaneous lesions in primary and secondary syphilis. Mother-to-child transmission can occur from transfer of the spirochete through the placenta or, less commonly, from contact with infectious exudates or blood through the birth canal. Transmission of syphilis through blood products is now rare due to routine screening of donors.

Like other treponemal diseases, the clinical manifestations of syphilis are divided into early and late stages. Early syphilis is further divided into primary, secondary, and early latent stages. During the latent syphilis stage, patients have positive serologic tests for syphilis but no other signs of disease. Although clinical staging is useful for diagnosis and treatment, it is also imprecise; overlap between stages is relatively common. For reporting and surveillance purposes, the US Centers for Disease Control and Prevention (CDC) recently changed their terminology from early latent syphilis and late latent syphilis to "early non-primary non-secondary syphilis" and "unknown duration or late syphilis," respectively. These changes were made to remove the term "latent" from the case definitions in order to clarify that certain clinical manifestations (e.g., neurosyphilis, ocular syphilis) may occur during any stage of syphilis.

Primary and secondary syphilis

Treponema pallidum subsp. *pallidum*, the causative agent of syphilis, usually enters the body through breaks in the epithelium that occur during sexual contact. Some organisms persist at the site of entry, whereas others disseminate via the lymphatic system throughout the body, proliferating and stimulating an immune response. The incubation period of primary syphilis is usually about 21 days, although extremes of 10 to 90 days have been noted.

The first clinical manifestation is usually a chancre at the site of genital trauma. The chancre begins as a red macule that subsequently becomes papular and then ulcerates. The lesion is painless with a well-defined margin and thickened, rubbery base. If untreated, the chancre persists for 3 to 6 weeks and then heals. Nontender regional lymphadenopathy also develops.

In untreated individuals, *T. pallidum* disseminates throughout the body, and secondary syphilis develops about 4 to 10 weeks after the chancre's onset. Common symptoms include malaise, headaches, sore throat, fever, musculoskeletal pains, and weight loss. Physical examination of persons with secondary syphilis reveals rash in 75% to 100%, regional or generalized lymphadenopathy in 50% to 85%, and mucosal ulceration in 5%

to 30%. The appearance of the rash can vary greatly, but lesions are often maculopapular or papulosquamous and often involve the entire body, including the palms and soles (Figure 161.1). Broad, flat lesions, known as *condylomata lata*, may develop in warm, moist areas, such as the scrotum, vulva, or perianal regions. Patchy alopecia and shallow painless mucosa ulcerations, called *mucous patches*, may also be seen.

The diagnosis of primary or secondary syphilis is based on the characteristic chancres or mucocutaneous lesions, along with demonstration of *T. pallidum* by direct detection methods and/or serologic tests for syphilis. Like the chancre, these clinical manifestations of secondary syphilis resolve spontaneously with or without therapy. However, a small proportion of patients develop complications such as hepatitis, syphilitic glomerulonephritis with nephrotic syndrome, anterior uveitis, choroiditis, arthritis, bursitis, or osteitis.

Recent cases of ocular syphilis have occurred among patients with primary or secondary syphilis. Presenting symptoms vary and have included eye redness, pain, blurry vision, floaters, and vision loss—often with posterior uveitis.

Neurosyphilis

T. pallidum can invade the central nervous system during any stage of syphilis. Asymptomatic neurosyphilis can occur with laboratory abnormalities in the cerebrospinal fluid (CSF) during primary or secondary syphilis. These abnormalities may resolve spontaneously or with treatment, or result in early symptomatic neurosyphilis in 5% of patients.

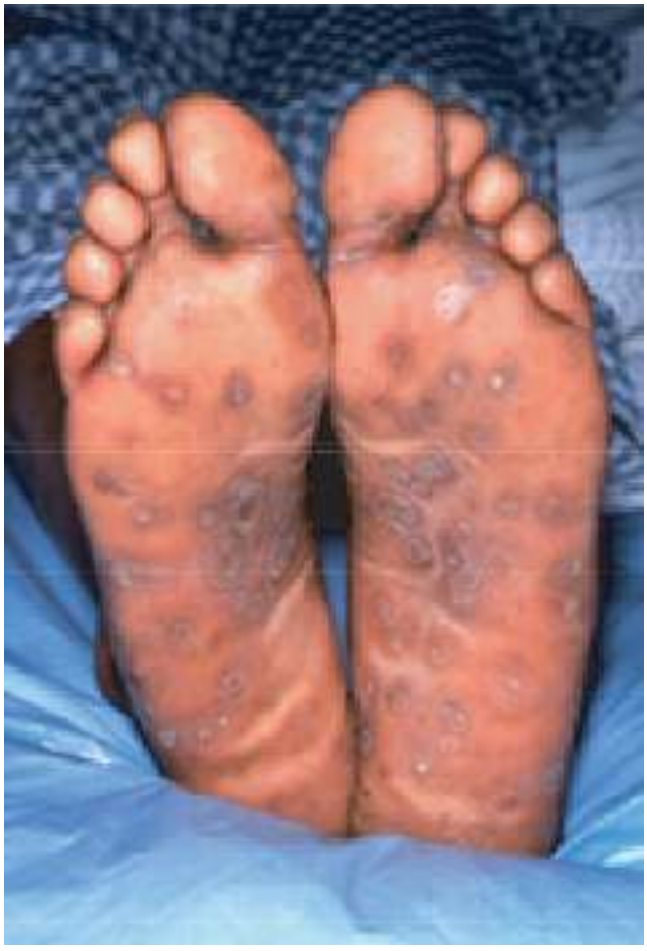


FIGURE 161.1 Secondary syphilis. Papulosquamous lesions on soles. Courtesy of David Schlossberg, MD.

Syphilitic meningitis most commonly occurs during the first year of infection. Patients may present with headache, fever, stiff neck, and photophobia. Cerebral involvement may result in seizures or hemiplegia. Cranial nerve palsies are especially common. Characteristic CSF findings that support the diagnosis in patients with reactive syphilis serologies include a lymphocytic pleocytosis, increased protein, and hypoglycorrhachia, but a reactive CSF Venereal Disease Research Laboratory (VDRL) confirms the diagnosis. Other manifestations of early neurosyphilis may include cranial neuritis or ocular involvement.

Meningovascular syphilis usually occurs about 5 to 12 years after infection in patients between the ages of 30 and 50 years and may involve the cerebrum, brainstem, or spinal cord. The pathophysiology involves chronic meningitis and infarction due to syphilitic endarteritis. In cerebrovascular syphilis, the middle cerebral artery is most commonly involved, and hemiparesis, aphasia, and seizures commonly occur. CSF usually reveals a lymphocytic pleocytosis with increased protein and a positive CSF VDRL. The major parenchymatous forms of neurosyphilis are general paresis and tabes dorsalis, which tend to occur between 2 and 30 years and 3 and 50 years, respectively, after initial infection. Both are now uncommon diseases.

General paresis is a chronic meningoencephalitis that results from direct invasion of the brain by *T. pallidum* and combines both psychiatric and neurologic manifestations. Early symptoms, such as irritability, memory loss, headache, and personality changes, may evolve into emotional lability, paranoia, and confusion. Pupillary abnormalities occur in more than half of patients with general paresis. In untreated patients, the interval between onset of symptoms and death can range from a few months to about 5 years.

Serum non-treponemal serologic tests are reactive in 95% to 100% of patients with generalized paresis. CSF VDRL is usually positive, but a negative result alone does not exclude the diagnosis. Differential diagnosis includes Alzheimer's disease, chronic alcoholism, and multiple sclerosis.

Tabes dorsalis is characterized by lightning pains and various combinations of other neurologic signs and symptoms, such as ataxia, bladder disturbances, pupillary abnormalities, absent ankle or knee reflexes, Romberg's sign, impaired vibratory and position sense, and development of extremely large, unstable, painless joints known as Charcot's joints. Although most patients have positive serum non-treponemal tests, 10% of patients with tabes will have nonreactive non-treponemal titers but positive treponemal tests. CSF may be normal or may reveal lymphocytic pleocytosis and elevated protein.

Non-neurologic manifestations of tertiary syphilis

Syphilitic heart disease, now an uncommon cause of cardiovascular disease, occurs 15 to 30 years after initial infection. During the early phases of infection, *T. pallidum* can disseminate to the heart and lodge in the aortic wall, where they may cause endarteritis of the vasa vasorum of the aorta with resultant scarring and destruction of the vessel's wall. Major cardiac manifestations include thoracic aneurysm, aortic regurgitation (without associated aortic stenosis), and coronary ostial stenosis.

Late benign syphilis is another now uncommon form of tertiary syphilis. It results from the chronic inflammatory response to *T. pallidum* and the formation of a granulomatous lesion called a

gumma, which most commonly occurs in the skin and bones but may also invade the viscera, muscles, and other structures.

Syphilis in persons with HIV infection

In the past decade, there has been a dramatic increase in early syphilis among men who have sex with men, particularly those with coexistent HIV infection. Syphilis and HIV share common means of transmission and other risk factors, and syphilis, like other genital ulcer diseases, facilitates HIV transmission. Clinical observation and case reports suggest that patients with HIV may experience a more aggressive course of syphilis, with more frequent occurrence of neurosyphilis especially in the early stages of infection. Ocular syphilis and syphilitic hepatitis may occur more often among persons with HIV. Occasional unusual serologic reactions can occur in HIV-infected patients including very high or fluctuating nontreponemal antibody titers; false-positive non-treponemal tests and false-negative treponemal tests have also been documented. Nevertheless, available data suggest that HIV infection does not significantly change the presentation, clinical course, or response to treatment of syphilis. Markers of immune function such as CD4 count and HIV viral load also do not appear to affect serological outcomes among HIV-seropositive persons with syphilis.

Syphilis in pregnancy

The clinical manifestations of syphilis are not altered in pregnancy; however, syphilis has widespread complications for both the infected mother and the fetus. Adverse pregnancy outcomes include early fetal loss, preterm delivery, low birth weight, and congenital syphilis in the neonate. Recent increases in congenital syphilis underscore the importance of maternal syphilis screening and prenatal care.

Laboratory tests

Direct examination

Direct microscopic examination can provide immediate diagnosis of primary and secondary syphilis. Dark-field microscopy must be used because *T. pallidum*'s narrow width (0.15 μm) renders the organism below the level of resolution of light microscopy. Wet preparations can be made from the skin or mucous membrane lesions of primary or secondary syphilis. Examination reveals tightly coiled organisms 6 to 14 μm long and 0.25 to 0.30 μm wide, with corkscrew motility. When examination of specimens must be delayed or oral lesions evaluated, direct fluorescent antibody testing can be useful; however, this test is not widely available due to its complexity. Polymerase chain reaction (PCR) assays are most useful for genital ulcers and other exudative lesions, but no US Food and Drug Administration (FDA)-approved test is available. A real-time PCR is offered by some commercial laboratories for use on genital lesion swabs and cerebrospinal fluid.

Serologic tests

Serologic tests for syphilis measure either nonspecific non-treponemal antibody or specific treponemal antibody. Non-treponemal antibody tests measure immunoglobulin G (IgG) and IgM to lipoidal material released from damaged host cells as well as to lipoprotein-like material and cardiolipin released by the treponemes. Non-treponemal antibody titers generally correlate with disease activity; titers fall progressively over time and are expected to decrease fourfold in response to therapy. The following non-treponemal tests are commonly used: VDRL test, rapid plasma reagin (RPR), the toluidine red unheated serum test (TRUST), and the unheated serum reagin test (USR). Biologic false-positive non-treponemal test results occur in 1% to 2% of the general population and are associated with several conditions such as viral infections (including HIV and viral hepatitis), pregnancy, malignancy, autoimmune diseases, and advanced age. False-negative results can occur from the *prozone phenomenon* in which patients with high non-treponemal titers can have weak or negative results at low dilutions due to excess antibody, although this is rare.

Specific treponemal antibody tests are needed to confirm a current or past diagnosis of syphilis. These tests detect antibodies formed in response to treponemal antigens. Treponemal tests usually remain reactive after treatment, but a small proportion of infected persons can become seronegative. Commonly used treponemal tests include the fluorescent antibody absorption (FTA-ABS), microhemagglutination assay for *T. pallidum* (MHA-TP), and the *T. pallidum* particle agglutination (TP-PA) test for syphilis.

Several new automated treponemal enzyme immunoassays (EIAs), immunoblots, chemiluminescence immunoassays, and multiplex flow immunoassays for *T. pallidum* that detect treponemal IgM and/or IgG have been FDA approved as screening and confirmatory tests for syphilis diagnosis. The majority of the newer assays use recombinant *T. pallidum* antigens to detect treponemal antibodies from patient specimens. Rapid, point-of-care tests, which can provide results within 20 minutes, have also been developed primarily for detection of treponemal antibodies; one of the rapid tests has received FDA approval and may be useful in settings with limited laboratory capabilities.

Traditionally, non-treponemal tests are used for screening followed by a treponemal test for confirmation. However, with the development of automated treponemal-based assays, some larger laboratories are using a reverse screening algorithm for syphilis testing. In the reverse algorithm, a positive treponemal test result is followed by a non-treponemal test to determine active infection. If the non-treponemal test is negative, then a second treponemal assay is recommended to confirm the results of the initial treponemal test. An individual with a positive treponemal test but negative non-treponemal titer may have early syphilis, late latent syphilis, past treated syphilis, or a false-positive treponemal test. Therefore, obtaining a thorough patient history to determine risks for recent exposures or past infections is critical to determining patient management. Treatment is usually indicated for persons with positive treponemal tests and nonreactive non-treponemal tests unless a history of treatment exists.

CSF evaluation

CSF should be examined in all syphilis patients with neurologic signs or symptoms (e.g., acute or chronic meningitis, ophthalmic or auditory symptoms, cranial nerve palsies, motor or sensory deficits, cognitive dysfunction), evidence of active tertiary syphilis, and in those with probable treatment failure, especially among persons with HIV. Performance of lumbar puncture among asymptomatic

HIV-seropositive patients is controversial but may be considered among coinfected persons with a non-treponemal titer ≥1:32 and CD4 count of ≤350 cells/mm^3.

When CSF specimens are free of blood contamination, a positive CSF VDRL test confirms the diagnosis of neurosyphilis. However, the sensitivity of the CSF VDRL is limited and a negative test does not rule out neurosyphilis, especially in the presence of CSF pleocytosis and increased CSF protein levels. The CSF FTA-ABS is more sensitive than the CSF VDRL, but false-positive results have been reported.

Treatment and follow-up

Treatment and follow-up are outlined in Boxes 161.1 and 161.2 for adults with and without HIV. Benzathine penicillin G is the drug of choice for all stages of syphilis infection. Doxycycline is

BOX 161.1

Management of syphilis in adults including pregnant women without known HIV infection

Primary, secondary, or early latent syphilis (duration ≤1 yr)

Treatment

- Benzathine penicillin G, 2.4 million U IM once
- If penicillin-allergic:[a]
- Doxycycline 100 mg PO BID for 2 wks *or* tetracycline 500 mg PO QID for 2 wks
- Ceftriaxone 1 g IM *or* IV for 10–14 d (caution: some patients with penicillin allergy are also allergic to ceftriaxone)

Treatment (for pregnant women)

- Benzathine penicillin G, 2.4 million U IM once (if penicillin allergic, patients should be desensitized and treated with penicillin); some experts follow with benzathine penicillin G, 2.4 million U IM administered 1 wk after the initial dose

Management and follow-up

- HIV testing
- If evidence of neurologic or ophthalmic disease, evaluate for neurosyphilis and do slit-lamp examination
- Repeat serology and clinical examination at 6 and 12 mo for HIV-negative persons
- Repeat serology at 28–32 weeks' gestation and at delivery for pregnant women
- If symptoms persist or recur, or there is sustained fourfold increase in RPR or VDRL titers, consider treatment failure or reinfection. Repeat HIV testing, consider LP, and retreat
- If RPR or VDRL titers do not fall fourfold within 6–12 mo of treatment, conduct additional clinical and serologic follow-up

Late latent syphilis or syphilis of unknown duration

Treatment

- Benzathine penicillin G, 2.4 million U IM every wk, for 3 wks
- If penicillin-allergic[a]:
- Doxycycline, 100 mg PO BID for 4 wks or tetracycline, 500 mg PO QID for 4 wks

Treatment (for pregnant women)

- Benzathine penicillin G, 2.4 million U IM every wk for 3 wks (if penicillin-allergic, patients should be desensitized and treated with penicillin)

Management and follow-up

- HIV testing
- Examine CSF before treatment if any of the following are present:
- Neurologic or ophthalmic signs or symptoms
- Evidence of active tertiary syphilis (e.g., aortitis or gumma)
- Treatment failure
- Repeat quantitative VDRL or RPR at 6, 12, and 24 mo. Repeat serology at 28–32 weeks' gestation and at delivery for pregnant women
- Patients with a normal CSF examination should be retreated for latent syphilis if:
- Serologic titers have a sustained (>2 weeks) fourfold increase or
- An initially high titer (≥1:32) fails to fall at least fourfold within 12–24 mo or
- Patient develops signs or symptoms consistent with syphilis

Tertiary syphilis (gumma or cardiovascular syphilis without neurosyphilis)

Treatment

- Benzathine penicillin G, 2.4 million U IM weekly for 3 wks
- If penicillin-allergic, use treatment for late latent syphilis[a]

Treatment (for pregnant women)

- Benzathine penicillin G, 2.4 million U IM every wk for 3 wks (if penicillin-allergic, patients should be desensitized and treated with penicillin)

Management
HIV testing
Examine CSF

Neurosyphilis
Treatment
Aqueous crystalline penicillin G, 18–24 million U per day, given as 3–4 million U IV q4h or continuous infusion for 10–14 d; some experts follow with benzathine penicillin G, 2.4 million U IM weekly for 3 wks
Alternative (if compliance is certain):
Procaine penicillin, 2.4 million U IM every day for 10–14 d, plus probenecid, 500 mg PO QID for 10–14 d; some experts follow with benzathine penicillin G, 2.4 million U IM weekly for 3 wks
Management
HIV testing
Repeat CSF examination every 6 mo until CSF cell count is normal
Consider retreatment if cell count has not decreased after 6 mo or if CSF is not normal after 2 yr

Abbreviations: HIV = human immunodeficiency virus; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory test; LP = lumbar puncture; CSF = cerebrospinal fluid.

[a] HIV-infected, penicillin-allergic patients who receive alternative therapies should be closely monitored. If compliance cannot be ensured, patients should be desensitized and treated with penicillin.

BOX 161.2

Treatment of HIV-positive patients with syphilis

Primary and secondary syphilis
Treatment
Benzathine penicillin G, 2.4 million U IM once
If penicillin-allergic: Manage according to recommendations for HIV-negative patients with primary and secondary syphilis (see Table 161.1)
Management
Clinical and serologic evaluation 3, 6, 9, 12, and 24 mo after therapy
Examine CSF if RPR or VDRL titers fail to show a fourfold decrease within 6–12 mo or there is other evidence of treatment failure
If CSF normal, retreat with penicillin G, 2.4 million U IM weekly × 3 wks
If CSF suggests neurosyphilis, treat for neurosyphilis as in Table 161.1
Early latent syphilis
Manage and treat according to recommendations for HIV-negative patients with primary and secondary syphilis (see Table 161.1). Patients with penicillin allergy whose compliance with alternative therapy or follow-up cannot be ensured should be desensitized and treated with penicillin
Late latent syphilis or latent syphilis of unknown duration
Treatment and management
Consider CSF examination
If CSF normal, give benzathine penicillin G, 2.4 million U IM weekly × 3 wks
If penicillin-allergic: Manage according to recommendations for HIV-negative patients with late latent syphilis or latent syphilis of unknown duration. However, patients with penicillin allergy whose compliance with alternative therapy or follow-up cannot be ensured should be desensitized and treated with penicillin
If CSF suggests neurosyphilis, treat for neurosyphilis as in Table 161.1
Management
Clinical and serologic evaluation 6, 12, 18, and 24 mo after therapy
Examine CSF and retreat accordingly if:
Clinical symptoms develop or RPR or VDRL titers rise 4-fold at any time or RPR or VDRL titer fails to fall fourfold between 12 and 24 mo
Neurosyphilis
Treatment and management as in Table 161.1

Abbreviations: CSF = cerebrospinal fluid; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory test; HIV = human immunodeficiency virus.

an effective alternative therapy for patients with penicillin allergies, but there are limited data on other alternatives such as ceftriaxone. Because there are no proven alternatives to penicillin for treatment of maternal syphilis, pregnant women who are allergic to penicillin should undergo desensitization and be treated with penicillin. HIV-positive patients with syphilis should be treated with the same recommended treatment regimens as HIV-negative patients, according to the stage of syphilis. Patients should be informed about the possibility of a Jarisch-Herxheimer reaction, an acute febrile reaction frequently accompanied by headache and myalgia, that can occur within the first 24 hours after the initiation of therapy, especially for early syphilis. Antipyretics can be used to manage symptoms as needed.

Clinical and serologic follow-up of patients after syphilis treatment is essential due to the potential for treatment failure. For HIV-negative persons, repeat evaluation should be performed at 6 and 12 months after therapy for early syphilis, and at 6, 12, and 24 months for latent syphilis. For pregnant women, serologic titers should be repeated at 28 to 32 weeks' gestation and at delivery at a minimum, and monthly among those at risk for reinfection. Although non-treponemal titers may fall more slowly among HIV-positive patients than in individuals who are HIV-negative after treatment, more frequent follow-up in HIV-seropositive patients is recommended (see Box 161.2) due to the potential for treatment failure. Vigilant follow-up for patients coinfected with HIV is important to document resolution of infection or to prompt immediate evaluation if relapse, reinfection, or other complications occur.

Serologic response to therapy is demonstrated by at least a fourfold decrease in non-treponemal titers from baseline (two dilution decrease, i.e., from 1:64 to 1:16) or seroreversion to a nonreactive non-treponemal test. However, despite appropriate treatment, approximately 12% of HIV-seropositive and HIV-seronegative patients with syphilis will have serological non-response (less than fourfold decline in non-treponemal titers). A higher proportion of patients may remain serofast after therapy, defined as persistently positive low-level nontreponemal antibody titers without seroreversion. Patients who do not exhibit an appropriate serological response to therapy may warrant subsequent clinical and serologic monitoring. However, the benefit of retreatment remains unclear for persons with persistent non-treponemal antibody titers in the absence of reinfection or treatment failure. Patients who have evidence of treatment failure based on recurrent signs or symptoms or a sustained (>2 weeks) fourfold increase in non-treponemal titers should undergo HIV testing and CSF examination, especially when there are symptoms suggestive of neurosyphilis.

For patients with neurosyphilis and evidence of CSF pleocytosis, follow-up CSF examination should be repeated every 6 months after treatment. The CSF white cell count should decrease within 6 months; this may occur more slowly in HIV-infected patients than in HIV-negative persons. Regardless of HIV status, retreatment should be considered if the CSF cell count has not decreased after 6 months or if the CSF parameters do not normalize 2 years after therapy.

Nonvenereal treponematoses

Yaws, pinta, and bejel (endemic syphilis) are caused respectively by *T. pallidum* subsp. *pertenue*, *T. carateum*, and *T. pallidum* subsp. *endemicum*. These diseases, seen mainly in tropical and subtropical regions, are transmitted by direct contact with infected skin lesions and not primarily by sexual contact. Like venereal syphilis, these diseases have self-limited primary and secondary stages, a latent stage, and a late stage with destructive lesions. The causative agents are morphologically indistinguishable from *T. pallidum* subsp. *pallidum*, and the serologic responses they elicit are identical to those of venereal syphilis. Yaws and bejel are more common among children, while pinta occurs more frequently among adults.

Yaws occurs in the tropical regions of Africa, the Pacific, and Southeast Asia. About 3 to 5 weeks after infection, papules develop, which enlarge, erode, and then spontaneously heal. A generalized secondary eruption of similar lesions occurs weeks to months later, sometimes associated with osteitis or periostitis. In the late stage, infected persons may develop hyperkeratoses on the palms and soles; plaques, nodules, and ulcers of the skin; and gummatous bone lesions.

Pinta occurs in remote parts of Mexico, Central America, and South America. About 7 to 21 days after infection, small, red, pruritic papules develop, which enlarge, become squamous, and merge with other primary lesions. These lesions eventually heal, but residual hypopigmentation persists. Three to 12 months after the appearance of the primary lesions, small scaly papules known as *pintids* appear. These may eventually become brown, gray, or blue and may recur as long as 10 years after initial infection. Depigmented lesions develop in the late stage.

Bejel occurs in Africa and western Asia. Unlike yaws and pinta, bejel is spread not only by direct contact but also by eating and drinking utensils. Primary lesions are seldom seen. Secondary manifestations include mucous patches, condylomata lata, split papules at the angles of the mouth, and lymphadenopathy. Gummatous lesions of the skin, nasopharynx, and bones are common in the late stage.

Diagnosis can be made by dark-field examination of lesions or serologic testing, or, for yaws and bejel, by PCR testing. A rapid point-of care assay for antibody detection is available for diagnosis of yaws.

Long-acting penicillin G is the treatment of choice. Azithromycin is also recommended, although resistance has been reported during treatment of yaws.

Suggested reading

Centers for Disease Control and Prevention (CDC). Syphilis testing algorithms using treponemal test for initial screening—four laboratories, New York City, 2005–2006. *MMWR Morb Mortal Week Rep*. 2008;57:872–875.

Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Morb Mortal Week Rep*. 2015;64:1–137.

Hook EW. Endemic treponematoses. In Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 8th ed. New York: Saunders, Elsevier Inc.; 2015: 2710–2713. e1

Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. *JAMA*. 2014; 12:1905–1917.

Ghanem KG. Review: Neurosyphilis: A historical perspective and review. *CNS Neurosci Ther*. 2010;16(5):e157–e168.

Ghanem KG. Management of adult syphilis: Key questions to inform the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. *Clin Infect Dis*. 2015;61:S818–S836.

Giacani L, Lukehart SA. The endemic treponematoses. *Clin Microbiol Rev*. 2014;27(1):89–115.

Mitjà O, Godornes C, Houinei W, et al. Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study. *Lancet*. 2018;391(10130):1599–1607.

Oliver SE, Cope AB, Rinsky JL, et al. Increases in ocular syphilis-North Carolina, 2014–2015. *Clin Infect Dis*. 2017;65:1676–1682.

Pillay A. Centers for Disease Control and Prevention: Syphilis summit: Diagnostics and laboratory issues. *Sex Transm Dis*. 2018;45(9S Suppl 1):S13–S16.

Radolf JD, Tramont EC, Salazar JC. Treponema pallidum (Syphilis). In Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*,8th ed. New York: Saunders, Elsevier Inc.; 2015: 2684–2709. • 015

Seña AC, White BL, Sparling PF. Novel *Treponema pallidum* serologic tests: A paradigm shift in syphilis screening for the 21st century. *Clin Infect Dis*. 2010;51(6):700–708.

Seña AC, Zhang XH, Li T, et. al. A systematic review of syphilis serological treatment outcomes in HIV-infected and HIV-uninfected persons: Rethinking the significance of serological non-responsiveness and the serofast state after therapy. *BMC Infect Dis*. 2015;15:479.

Lyme disease

Janine Evans

Lyme disease, a systemic illness caused by the spirochete *Borrelia burgdorferi*, is the most common tick-borne disease in the United States. In 2011, 48 states reported 24 364 cases of Lyme disease using the Council of State and Territorial Epidemiologists (CTSE)/Centers for Disease Control and Prevention (CDC) surveillance case definition. Since the original discovery of Lyme arthritis in the mid 1970s the clinical spectrum of Lyme disease has expanded to include a wide variety of organ systems, primarily the skin, joints, nervous system, and heart. Protean symptoms, uncertainty in diagnosis due to lack of definitive testing methods, and public fear of late sequelae of disease often lead to overdiagnosis and overtreatment. Although optimal therapy of some of the clinical features of Lyme disease is unclear, better understanding of the natural history, epidemiology, and pathogenesis of Lyme disease helps in the often confusing and difficult decisions related to diagnosis and treatment.

B. burgdorferi has been isolated from blood, skin, cerebrospinal fluid (CSF) specimens, and (rarely) other specimens from infected patients although, with the exception of skin biopsy specimens, culture of *B. burgdorferi* from sites of infection is a low-yield procedure. *B. burgdorferi* displays phenotypic and genotypic diversity and has been classified into separate genospecies, five of which are pathogenic to humans: *Borrelia burgdorferi sensu stricto*, which includes all strains studied thus far from the United States and some European and Asian strains, and *Borrelia garinii*, *Borrelia afzelii, Borrelia spielmanii*, and *Borrelia bavariensis*, which are found in Europe and Asia. *B. afzelii* seems primarily associated with a chronic skin lesion, acrodermatitis chronica atrophicans, rare in the United States, and *B. garinii* is predominant among CSF isolates.

Lyme disease occurs in three principal foci in the United States: the Northeast, the upper Midwest, and the Pacific Coast. These areas correspond to the distribution of the predominant tick vectors of Lyme disease in the United States, *Ixodes scapularis* in the East and Midwest, and *Ixodes pacificus* in northern California. Lyme disease also occurs widely in Europe, where it is transmitted by the sheep tick, *Ixodes ricinus*, and *Ixodes persulcatus*, the taiga tick. The latter is distributed throughout eastern Europe and Asia.

The largest number of reported cases of Lyme disease in Europe are from Germany, Austria, Slovenia, Sweden, the Czech Republic, and the Baltic states. *I scapularis* have a 3-stage, 2-year life cycle. Transovarial passage of *B. burgdorferi* occurs at a low rate. Ticks become infected with spirochetes by feeding upon a spirochetemic animal, typically small mammals, during larval and nymphal stages. In highly endemic areas from 20% to more than 60% of *I. scapularis* carry *B. burgdorferi*. Humans are only an incidental host of the tick; contact is typically made in areas of underbrush or high grasses, but may occur in well-mown lawns in endemic areas. Lyme disease occurs most commonly during April through July when nymphal *I. scapularis* feed. Animal models show that transmission is unlikely to occur before a minimum of 36 hours of tick attachment and feeding.

Clinical manifestations

Clinical features of Lyme disease are typically divided into three general stages termed early localized, early disseminated, and late persistent infection. These stages may overlap, and most patients do not exhibit all

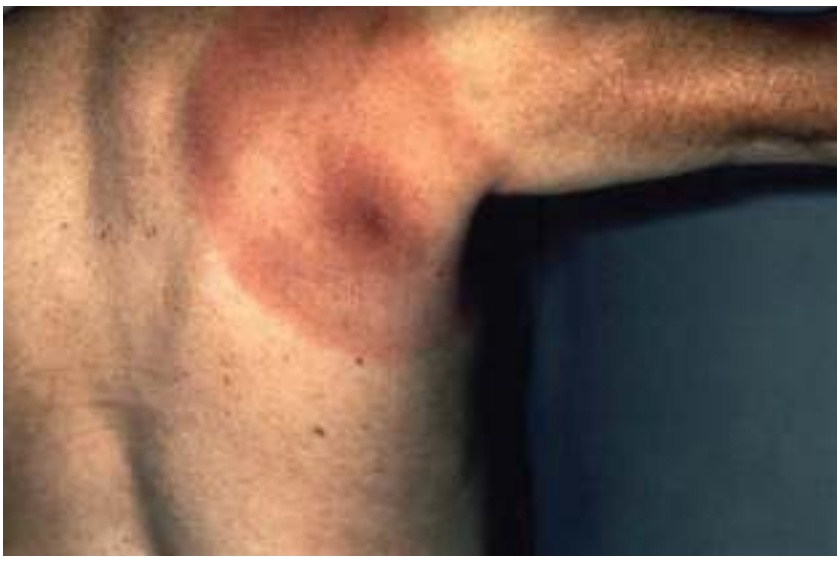


FIGURE 162.1 Classic erythema migrans lesion.

stages. Direct invasion of the organism with a resultant vigorous inflammatory reaction has been demonstrated to be responsible for many of the clinical manifestations associated with Lyme disease, so the manifestations respond to antibiotic therapy. Some features, such as late neurologic deficits and chronic arthritis, may respond poorly to treatment. It is not absolutely clear that live organisms are responsible for these later symptoms.

Early localized disease

Erythema migrans (EM), the hallmark of Lyme disease, begins at the site of a deer tick bite after 3 to 32 days (Figures 162.1 and 162.2). It is reported by 60% to 80% of patients, appearing as a centrifugally expanding erythematous macule or papule, often with central clearing. The thigh, groin, and axilla are common sites. The lesion may be warm, pruritic, and painful, but is often asymptomatic and easily missed if out of sight. Occasionally, these lesions may develop blistering or scabbing in the center, remain an even, intense red without clearing, or develop a bluish discoloration. Spirochetes are present in the EM lesion and can be readily cultured from the expanding edge. Mild musculoskeletal flu-like symptoms such as a low-grade fever, chills, malaise, headache, fatigue, arthralgias, and myalgias may accompany EM lesions. Theoretically such symptoms can occur without dissemination of the organism, via local generation of cytokines. Untreated EM resolves after several weeks and treated lesions clear within several days.

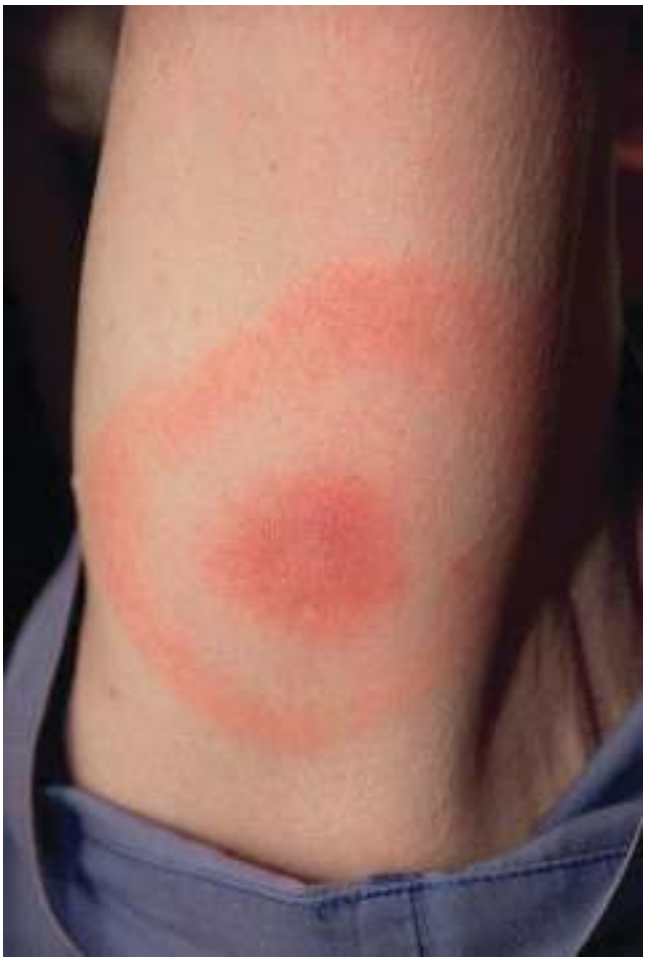


FIGURE 162.2 Erythema migrans lesion.

Early disseminated

In some patients the spirochete disseminates hematogenously to multiple sites causing characteristic clinical features. Secondary annular lesions, sites of metastatic foci of *Borrelia* in the skin, develop within days of onset of EM in about half of US patients. They are similar in appearance to EM, but are generally smaller, migrate less, and lack indurated centers. In addition to musculoskeletal flu-like

symptoms, mild hepatitis, splenomegaly, sore throat, nonproductive cough, testicular swelling, conjunctivitis, and regional and generalized lymphadenopathy may sometimes occur during early stages.

Diagnosis of early localized and early disseminated Lyme disease is based on clinical presentation, because serologic confirmation is often lacking and culture is not readily available. EM is diagnostic of Lyme disease although atypical lesions and rashes mimicking EM may be confusing. A history of a tick bite and residence or travel in an endemic area should be sought in patients presenting with rashes compatible with EM or a flu-like illness in summer. Specific immunoglobulin (Ig)M antibody responses against *B. burgdorferi* develop 2 to 6 weeks after the onset of EM. Immunoglobulin (Ig)G antibody levels appear approximately 6 weeks after disease onset but may not peak until months or even years into the illness. The highest titers occur during arthritis. Antibodies are typically detected using indirect immunofluorescence, enzyme-linked immunosorbant assay (ELISA), and immunoblotting (Western blot). Antibody responses may persist for months to years after successful eradication of infection. Two-tier testing is recommended, with ELISA screening done first and if positive an immunoblot performed.

Late disease

Late manifestations of Lyme disease typically occur months to years after the initial infection. In the United States, arthritis is the dominant feature of late Lyme disease, reported in approximately 60% of untreated individuals. Less often, individuals develop late chronic neurologic disease. Another late finding (years) associated with this infection is a chronic skin lesion, acrodermatitis chronica atrophicans, well known in Europe but rare in the United States. These late manifestations are discussed below.

Therapy

Early Lyme disease

The symptoms of early Lyme disease resolve spontaneously in most cases; therefore, the goals of therapy for early localized and mild early disseminated Lyme disease are to shorten the duration of symptoms and reduce the risk of developing serious late manifestations of infection. Treatment of these stages with oral antibiotics is adequate in the majority of patients (see Table 162.1). In patients with acute disseminated Lyme disease but without meningitis, oral doxycycline appears to be equally effective as parenteral ceftriaxone in preventing the late manifestations of disease. Initial studies of treatment for early Lyme disease reported therapy with phenoxymethyl penicillin, erythromycin, and tetracycline, in doses of 250 mg four times a day for 10 to 20 days, shortened the duration of symptoms of early Lyme disease. Phenoxymethyl penicillin and tetracycline were superior to erythromycin in preventing serious late manifestations of disease. Subsequent clinical trials have proven amoxicillin and doxycycline to be equally efficacious. Amoxicillin has largely replaced use of penicillin because of greater in vitro activity against *B. burgdorferi*. It is the preferred antibiotic choice in children under the age of 8 years. Concomitant use of probenecid has not been definitively shown to improve clinical outcome and is associated with a higher incidence of side effects. Doxycycline is usually selected over tetracycline because of its twice-daily dose schedule, increased gastrointestinal absorption and tolerability, and greater central nervous system (CNS) penetration. Doxycycline is effective in treating *Anaplasma phagocytophilum* (formerly known as *Ehrlichia phagocytophila*), an organism also transmitted by *I. scapularis* ticks; amoxicillin is not. Cefuroxime axetil, an oral second-generation cephalosporin, has been shown to be about as effective as amoxicillin and doxycycline in treating early Lyme disease; azithromycin, an azilide analog of erythromycin, somewhat less so. Macrolide antibiotics are not recommended as first-line therapy for early Lyme disease. Long-term follow-up of patients treated during early stages of Lyme disease support the current dosing regimens. Patients who received a 14- to 21-day course of a recommended antibiotic rarely developed late manifestations of illness. Recent studies have indicated that a 10-day course of doxycycline is adequate therapy for EM. Jarisch–Herxheimer-like reactions, an increased discomfort in skin lesions and temperature elevation occurring within hours after the start of antibiotic treatment, have been encountered in 14% of patients treated for early Lyme disease. They typically occur within 2 to 4 hours of starting therapy, are more common in severe disease, and are presumably due to rapid killing of a large number of spirochetes.

Minor symptoms including arthralgia, fatigue, headaches, and transient facial palsy are common following treatment and generally resolve over a 6-month period. Patients with disseminated disease are most likely to experience persistent symptoms. These symptoms may be due to retained antigen rather than due to ongoing infection with *B. burgdorferi*, since longer courses of antibiotics have not been shown to shorten their duration. Prolonged courses of antibiotics should be reserved for those patients with evidence of persistent infection with *B. burgdorferi*.

Lyme carditis

Cardiac involvement occurs in up to 10% of untreated patients. Transient and varying degrees of atrioventricular block several weeks to months after a tick bite are the most common manifestations. Other features are pericarditis, myocarditis, ventricular tachycardia, and on rare occasions, a dilated cardiomyopathy; valvular disease is not seen. Carditis is typically mild and self limited although patients may present quite dramatically in complete heart block, and some require the insertion of a temporary pacemaker. In most cases, carditis resolves completely, even without treatment with antibiotics. Studies examining endomyocardial biopsy specimens from patients with Lyme carditis have indicated that direct invasion of *B. burgdorferi* into myocardium and an associated inflammatory reaction are responsible for the clinical events. Although optimal treatment of carditis is unknown, oral therapy for mild forms of cardiac involvement is usually sufficient. Intravenous antibiotics and cardiac monitoring are recommended for patients with varying, high-degree heart block and more serious cardiac involvement. The benefit of concomitant use of aspirin or prednisone and antibiotics in treating patients with

TABLE 162.1 **TREATMENT GUIDELINES**

Antibiotic regimen	Comments
Erythema migrans	
Amoxicillin, 500 mg 3 times daily for 14–21 d	Pediatric dose is 25–50 mg/kg/d three times daily
Doxycycline (Vibramycin), 100 mg twice daily for 10–21 d	Also effective against *Anaplasma phagocytophium*; not recommended for children under 8 years of age, pregnant or lactating women
Cefuroxime axetil (Ceftin), 500 mg twice daily for 14–21 d	Pediatric dose 30 mg/kg/d twice daily
Azithromycin (Zithromax), 500 mg daily for 7–10 d	Not recommended as first-line therapy; less effective than other regimens
Early disseminated disease (without neurologic, cardiac, or joint involvement)	
Initial treatment is the same as for erythema migrans except duration of treatment may be extended to 21–28 d	
Neuroborreliosis Isolated seventh nerve palsy	
Initial treatment is the same as for erythema migrans except duration of treatment is 21–28 d. The need for cerebrospinal fluid examination remains controversial	
All other neurologic manifestations (including meningitis, radiculoneuritis, peripheral neuropathy, encephalomyelitis, chronic encephalopathy)	
Ceftriaxone (Rocephin), 2 g daily for 14–30 d	30-d regimen associated with fewer relapses in patients with chronic encephalopathy
Penicillin G, 20 million units daily for 14–28 d	Pediatric dose 200 000–400 000 units/kg/d every 4 h
Cefotaxime sodium (Claforan), 2 g every 8 h	Pediatric dose 150–200 mg/kg/d in 3–4 divided doses for 14–28 d
Doxycycline, 100 mg twice daily (oral or intravenous) for 14–28 d	No published experience in the United States
Carditis	
Doxycycline, 100 mg orally twice daily for 21 d	For first degree heart block, PR interval <0.3 s
Amoxicillin, 500 mg three times daily for 21 d	For first degree heart block, PR interval <0.3 s
Ceftriaxone, 2 g daily for 14–21 d	Optimal duration of therapy is unknown
Penicillin G, 20 million units daily for 14–30 d	Optimal duration of therapy is unknown, given in divided doses every 4 h
Arthritis Amoxicillin 500 mg four times daily for 30–60 d	Oral regimens should be limited to patients without evidence of neurologic involvement. Oral treatment may be extended for 60 d if no response to 30-d course
Doxycycline 100 mg two times daily for 30–60 d	
Cefuroxime axetil, 500 mg twice daily for 30–60 d	For patients with doxycycline and penicillin allergy
Ceftriaxone, 2 g daily for 14–30 d	
Lyme disease in pregnancy	
Amoxicillin, 500 mg three times daily for 21 d	For early localized disease only
Ceftriaxone, 2 g daily for 14–28 d	
Penicillin G, 20 million units daily for 14–28 d	Given in divided doses every 4 h
Asymptomatic tick bite	
No treatment or single dose of 200 mg doxycycline	For pregnant women, a 10-d course of amoxicillin may be considered
Asymptomatic seroconversion	No treatment necessary

Lyme carditis is uncertain. Despite the generally benign course of Lyme carditis, several cases of permanent heart block have been reported, presumably caused by a vigorous inflammatory response. Short courses of prednisone may be considered in patients with prolonged dense heart block despite adequate antibiotic therapy.

Dilated cardiomyopathy is a rare complication of Lyme disease reported in Europe but not yet in the United States. The majority of the patients were from endemic areas for Lyme disease, had other clinical features of disease, and were seropositive for anti-*B. burgdorferi* antibodies. Their myopathy was cured by antibiotic treatment.

Early neurologic disease

Early neurologic involvement occurs in 15% to 20% of untreated patients and appears within 2 to 8 weeks after the onset of disease. Manifestations include cranial nerve palsies, meningitis or meningoencephalitis, and peripheral neuritis or radiculoneuritis, often appearing in combination. Unilateral or bilateral seventh nerve palsies are the most common neurologic abnormalities. Presenting symptoms depend upon the area of the nervous system involved: patients with meningitis present with fever, headache, and a stiff neck; those with Bannwarth's syndrome (primarily in Europe) develop severe and migrating radicular pain lasting weeks to several months; and those with encephalitis have concentration deficits, emotional lability, and fatigue. In patients with early CNS involvement analysis of CSF typically reveals a lymphocytic pleocytosis. Specific antibodies against *B. burgdorferi* may also be present and concentrated in the CSF relative to the serum concentration; they are useful to confirm disease.

Intravenous antibiotics are recommended for all cases of neuroborreliosis except isolated seventh nerve palsy. Patients presenting with a Bell's-like palsy who have features that suggest possible CNS involvement, such as high fever, headache, or stiff neck, should undergo a lumbar puncture looking for evidence of more extensive disease. The most experience in the treatment of CNS Lyme disease has been with aqueous penicillin and third-generation cephalosporins. Although optimal duration of therapy is unknown, it is recommended that patients be treated for two to four weeks. Ceftriaxone, in doses of 1 to 2 g/day, is the agent of choice because of better CNS penetration and ease of administration. Patients with persistent symptoms after recommended antibiotic therapy pose a particular management problem. It is often unclear whether these symptoms are due to resolving inflammation or ongoing infection. Meningitis and sensory symptoms usually resolve within days to weeks; other features may take months to improve. In most cases it is not necessary to continue antibiotic therapy until complete recovery.

Late manifestations

Arthritis

Arthritis is the dominant feature of late Lyme disease, occurring in up to 60% of untreated patients days to years after initial infection (mean of 6 months). The initial pattern of involvement may be migratory arthralgias (early) followed in 60% of patients by intermittent attacks of arthritis lasting from days to months. Large joints, particularly the knee, are most commonly involved. Swelling is often prominent, with large effusions and Baker's cysts. Serologic testing in patients presenting with arthritis is positive in almost all cases.

Lyme arthritis has been treated successfully with oral and intravenous antibiotics. In early studies examining response to intravenous benzathine penicillin, 2.4 million units intramuscularly weekly for 3 weeks, 7 of 20 patients responded compared with 0 out of 20 in the control group. Intravenous ceftriaxone 2 to 4 g daily for 2 to 4 weeks has been thought to be superior to benzathine penicillin. Oral regimens using doxycycline, 100 mg twice a day for 4 weeks, and amoxicillin plus probenecid, 500 mg of each orally four times a day for 4 weeks, have reported success in 18 of 20 patients and 16 of 18 patients, respectively. Response to antibiotics is typically excellent but effusions may take months to resolve completely. An additional 4 weeks of oral antibiotic therapy has been recommended for patients with persistent arthritis following initial 4-week treatment.

A small subgroup of Lyme arthritis patients develop a chronic, potentially erosive arthritis unresponsive to antibiotics. These patients often have major histocompatability class II gene products, HLA DR4, accompanied by strong serum IgG responses to *Borrelia* outer surface proteins A or B (OspA or OspB). Repeated courses of antibiotics have not been shown to improve clinical outcome. Treatment with anti-inflammatory medications and intra-articular steroid injections can be helpful in reducing joint swelling. Surgical synovectomy has cured a number of such patients. Resolution of the arthritis eventually occurs; in some patients it may take up to 3 to 5 years.

Late neurologic lyme disease

Chronic neurologic syndromes, which are relatively uncommon, may occur months to years after initial infection. Cognitive dysfunction, affective changes, seizures, ataxia, peripheral neuropathies, and chronic fatigue have all been reported. The most common late-stage neurologic syndrome reported in the United States, called Lyme encephalopathy, is characterized by subtle cognitive impairment. Because these complaints are often nonspecific and may be associated with post-Lyme syndromes, it is important to look for and document evidence of ongoing *B. burgdorferi* infection. Lymphocytic pleocytosis is uncommon in late neurologic disease, but increased intrathecal *B. burgdorferi*-specific antibodies may well be present. Careful evaluation with neuropsychological testing can help to distinguish cognitive abnormalities in Lyme disease from those associated with chronic fatigue states and depression. Chronic neurologic dysfunction usually improves with antibiotics but may not completely reverse. Late neurologic manifestations of Lyme disease are treated with intravenous antibiotics. Agents with demonstrated efficacy are aqueous penicillin and third-generation cephalosporins. Doxycyline, both oral and intravenous forms, have been reported to be successful in treating late CNS Lyme disease in Europe.

Ocular disease

Ocular lesions in Lyme disease are rare, but have involved every portion of the eye and vary depending on the stage of the disease. The most common ophthalmic presentations in early disease

include conjunctivitis, photophobia, and neuro-ophthalmologic manifestations due to cranial nerve palsies. The incidence of seventh nerve palsies is similar in Europe and the United States. The most severe ocular manifestations occur in late stages; they include episcleritis, symblepharon, keratitis, iritis, choroiditis, panuveitis, and retinal vasculitis. Serologic testing in these patients is typically positive.

Experience treating late ocular lesions in Lyme disease is scanty. The most success has been with the use of intravenous ceftriaxone in doses of 2 to 4 g daily for 10 to 14 days.

Pregnancy

Intrauterine transmission of *B. burgdorferi* is uncommon, usually occurring in cases of obvious disseminated infection during pregnancy. No uniform pattern of congenital anomaly has been reported. Prenatal exposure to Lyme disease has not been found to be associated with an increased risk of adverse pregnancy outcome. Optimal treatment of the pregnant patient with Lyme disease is unknown, but the recommended regimens have not been associated with adverse outcomes. Oral antibiotics for early localized disease is sufficient, and intravenous antibiotics are recommended for patients with symptoms suggesting disseminated disease.

Tick bites

The risk of infection from a deer tick bite in a Lyme disease endemic area is low. In mice, infected ticks have been attached for over a 36-hour period before significant risk of developing Lyme disease occurred. In a controlled double-blind study in patients with tick bites, no patient asymptomatically seroconverted, no treated patient developed EM, and the 2 of 182 untreated patients who did develop EM were successfully treated with oral antibiotics. These results support marking and watching a tick bite, and should EM develop, treating it early, when antibiotics are most effective. A single dose of doxycycline has been shown to be effective in reducing the development of Lyme disease. The Infectious Diseases Society of America (IDSA) guidelines recommend offering the single-dose doxycycline if the attached tick can be reliably identified as an adult or nymphal *I. scapularis* tick, it is estimated to have been attached for >36 hours, prophylaxis can be started within 72 hours after tick detachment, and the local rate of infection of these ticks with *B. burgdorferi* is greater than 20%. Doxycycline prophylaxis for children under 8 years is not recommended.

Seropositive patient with nonspecific symptoms

Patients with nonspecific symptoms such as myalgias, arthralgias, concentration difficulties, and fatigue are frequently tested for Lyme disease. Some patients, especially those from endemic areas, test positively and are treated for presumed Lyme disease, often without improvement in their symptoms. In several studies over 50% of patients reporting to Lyme disease clinics did not have evidence of Lyme disease, and the reason for a lack of response to antibiotics was an incorrect diagnosis. Objective clinical evidence in support of the diagnosis of Lyme disease should be sought prior to initiating antibiotics, treatment should be given for the recommended duration and then discontinued, and the patient observed for resolution of symptoms.

Post-lyme disease syndrome

Some patients continue to have subjective symptoms after completion of recommended courses of antibiotics for Lyme disease. Symptoms typically include arthalgias, myalgias, fatigue, and neurocognitive difficulties. A study of patients treated for EM reported that approximately 5% to 15% of patients experienced subjective symptoms when evaluated 6 to 12 months after treatment. Such symptoms may persist for 5 or more years after treatment. This postinfectious syndrome does not appear to be related to persistent infection with *B. burgdorferi*. In a study of patients with post-Lyme disease syndrome there were no significant outcome differences between the groups who received either intravenous ceftriaxone for 30 days followed by oral doxycycline for 60 days and those that received placebo. The IDSA guidelines do not recommend antibiotic therapy for patients with chronic (>6 months) subjective symptoms after recommended treatment regimens for Lyme disease.

Prevention of lyme disease

Recommended personal protective measures against tick bites include wearing light-colored clothing, long-sleeve shirts, and long pants; tucking pant legs into socks; using a tick repellent on clothing and exposed skin; and performing regular body checks for ticks, strategies that require significant self-motivation. Environmental strategies include the application of acaricides onto vegetation where the ticks live, acaricides delivered directly to tick hosts to kill ticks on the animals, and excluding deer from areas. The last is not practical in most environments.

Public interest in human and veterinary vaccines prompted researchers to develop a safe and effective vaccine for the prevention of Lyme disease. The results of two large safety and efficacy trials using recombinant OspA preparations reported the vaccine to be safe and effective in preventing Lyme disease in most people. LYMErix™ was approved by the US Food and Drug Administration (FDA) for use in individuals aged 15 and older in 1999. The vaccine manufacturer discontinued production in 2002, citing insufficient consumer demand. Protection provided by this vaccine diminishes over time. Individuals that received the Lyme disease vaccine prior to 2002 are probably no longer protected against Lyme disease.

Summary

Antibiotic regimens are recommended according to results of clinical trials and evolving clinical judgments, and depend upon the stage of infection and the organ system involved. Successful eradication of the infecting organism, *B. burgdorferi*, appears to occur in the majority of patients with Lyme disease using these treatment guidelines. Patients with persistent symptoms following antibiotic therapy, particularly those with previous evidence of disseminated disease, pose a difficult management problem. Most persistent symptoms are likely due to retained antigens and not the result of persistent infection or to noninfectious sequelae such as fibromyalgia. In the former patients, resolution of symptoms occurs over the course of weeks to months and does not require prolonged courses of antibiotics; in the latter, treatment is that of the associated syndrome. Rarely, persistent or recurrent symptoms are due to continued or recurrent infection and require additional courses of antibiotics. Such patients require careful diagnostic evaluation to determine the need for additional treatment.

Suggested reading

Hayes EB, Piesman J. How can we prevent Lyme disease. *N Engl J Med*. 2003;348:2424–2430.

Hu L. In the clinic Lyme disease. *Ann Intern Med*. 2012;157(3): ITC2-2–ITC2-16.

Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med*. 2001;345:85–92.

Rahn DW, Evans J, eds. *Lyme Disease*. Philadelphia, PA: American College of Physicians; 1998.

Stamel G, Wormser G, Gray J, Strle F. Lyme borreliosis. *Lancet*. 2012;379:461–473.

Steere AC. Lyme disease. *N Engl J Med*. 2001;345:115–125.

Steere AC, Angelis SM. Therapy for Lyme arthritis, strategies for the treatment of antibiotic-refractory arthritis. *Arthritis Rheum*. 2006;54:3079–3086.

Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43:1089–1134.

Wormser GP, Ramanathan R, Nowakowski J, et al. Duration of antibiotic therapy for early Lyme disease. *Ann Intern Med*. 2003;138:697–704.

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Borreliosis

Sally J. Cutler

Background

The relapsing fever spirochetes comprise a number of different species (Table 163.1) with many transmitted by specific tick species; classical relapsing fever species are transmitted by rapid-feeding soft tick species, whereas the more recently described *Borrelia miyamotoi* is transmitted by hard tick vectors. *B. recurrentis* is the notable exception in that it is transmitted by clothing lice.

Clinical presentation

The chief sign is that of fever, often accompanied by chills, headaches, arthralgia, myalgia, and tachycardia. Other signs may include jaundice, petechial rash, conjunctivitis, nausea, hepatosplenomegaly, and epistaxis. Infection with *B. duttonii* has been associated with significant perinatal mortality in endemic regions such as Tanzania. *B. miyamotoi*, like other relapsing fever infections, manifests with fever but does not typically produce the classical relapsing febrile episodes. Instead, infection is often accompanied by thrombocytopenia and nonspecific influenza-like symptoms, although immunocompromised individuals have presented with neurological signs.

Although eventually eliminated by the adaptive immune response, repeat infections can occur in a previously infected individual.

Treatment

Cases are usually managed with penicillin, doxycycline, or tetracycline treatment (Table 163.2). Some prefer penicillin as it is believed that this makes Jarisch–Herxheimer reactions (JHR) less likely. Less frequently, cephalosporins, erythromycin, and chloramphenicol have been used.

Jarisch–Herxheimer reactions

The JHR was first described by Adolf Jarisch in 1895 and later by Karl Herxheimer in 1902, in relation to another spirochetal infection, syphilis, but this also occurs in approximately 5% of relapsing fever patients upon treatment. Patients may show an exacerbation of symptoms or "therapeutic shock" during the initial 24 hours after commencing treatment. The JHR is mediated by a release of pyrogenic cytokines (including tumor necrosis factor-α [TNF-α], interleukin [IL]-6, and IL-8) and is treated symptomatically.

TABLE 163.1 **CHARACTERISTICS OF RELAPSING FEVER BORRELLIAE**

Organism name	Arthropod vector/reservoir	Vertebrate reservoirs	Clinical infection	Geographic region
B. recurrentis	*Pediculus humanus*	Man	LBRF–human	Africa (formerly worldwide)
B. baltazardii	Unknown	Unknown	TBRF–human	Iran
B. crocidurae	*Ornithodoros sonrai*	Rodents	TBRF–human	West Africa
B. duttonii	*Ornithodoros moubata*	Man	TBRF–human	Africa (Central, Eastern)
B. hermsii	*Ornithodoros hermsi*	Rodents	TBRF–human; canine	Canada, Western USA
B. hispanica	*Ornithodoros marocanus; Ornithodoros occidentalis; Ornithodoros kairouanensis* (formerly *Ornithodoros erraticus*[a])	Rodents	TBRF–human	Algeria, Morocco, Portugal, Spain, Tunisia
B. latyschewii	*Ornithodoros tartakovskyi*	Rodents; reptiles	TBRF–human	Central Asia, Iran, Iraq
B. mazzottii	*Ornithodoros talaje*	Armadillos; rodents	TBRF–human	Southern USA, Mexico, Guatemala
B. merionesi	*Ornithodoros costalis Ornithodoros merionesi*	Rodents	Unknown	North Africa
B. microti	*Ornithodoros erraticus*[b]	Rodents	TBRF human	Africa, Iran
B. parkeri	*Ornithodoros parkeri*	Rodents	TBRF–human	Western USA
B. persica	*Ornithodoros tholozani*	Rodents; bats	TBRF–human; cat	Asia, Middle East
B. turicatae	*Ornithodoros turicata*	Rodents	TBRF–human; canine; birds	USA, Mexico
B. venezuelensis	*Ornithodoros rudis*	Rodents	TBRF–human	Central and South America
Candidatus B. fainii	*Ornithodoros faini*	Bats	TBRF–human	Zambia
Candidatus B. kalaharica	*Ornithodoros savignyi*	Unknown	TBRF–human	Africa

[a] *Ornithodoros erraticus* represented a complex. Recent taxonomic molecular studies redressed the phylogeny suggesting that *O. erraticus sensu stricto* is not an efficient vector for *Borrelia*.
[b] Molecular confirmation of *O. erraticus* identity unavailable at time of writing.
Abbreviations: LBRF = louse-borne relapsing fever; TBRF = tick-borne relapsing fever.

TABLE 163.2 **TREATMENT OF RELAPSING FEVER BORRELIOSIS**

Antibiotic	Dosage used	Duration	Comments
Penicillin	400,000–600,000 IU/d	7–14 d	Single dose can be curative for LBRF CNS involvement
Tetracycline	200–250 mg BID to 500 mg QID	7–14 d	Single dose can be curative for LBRF
Doxycycline	200–250 mg 4 mg/kg/d	7–14 d	Can be used as prophylaxis (200 mg/d on day 1, then 100 mg daily for 4 d postexposure)
Erythromycin	500 mg QID (50 mg/kg children)	7–14 d	During pregnancy or children
Chloramphenicol	500 mg QID (12.5 mg/kg children)	7–14 d	During pregnancy or children
Ceftriaxone	2 g/d	7–14 d	CNS involvement

Abbreviation: CNS = central nervous system.
Azithromycin shows promising *in vitro* activity, but the author is unaware of its evaluation clinically for treatment of relapsing fever patients.

Transmission and pathogenesis

Transmission of tick-borne relapsing fever (TBRF) occurs during the feeding of *Ornithodoros* soft ticks (up to 20–30 minutes), generally while their host is sleeping. The relapsing fever transmitted by hard ticks, though not as rapidly transferred as that in soft ticks, can result in infection with just 1 day of tick attachment. The spirochetes may be present within the tick salivary glands, coxal fluid, and feces, facilitating transmission to their vertebrate host. Transovarial transmission occurs for some TBRF borreliae.

Unlike TBRF, in louse-borne relapsing fever (LBRF), the borreliae within the louse vector penetrate the louse's gut epithelium where they can multiply in the louse hemolymph and are also able to be excreted in louse feces, but they do not undergo transovarial transmission. Human transmission occurs through crushing lice or their feces into skin abrasions often through scratching.

Once the human is infected, spirochetes multiply in the blood, sometimes to levels of up to 100,000/mm^3. This spirochetemia evokes the typical febrile response after which this infection is named. The induced antibody response clears the bloodborne infection; however, the spirochetes soon reemerge, having undergone antigenic variation. A new wave of infection follows that again is eventually controlled through the host's antibody response. Clinically, up to 4 to 5 febrile episodes can occur in LBRF, whereas up to 13 relapses have been recorded for TBRF. Persistence within the human host is a result of a complex interplay of antigenic variation, complement evasion strategies, erythrocyte rosetting, and potentially other mechanisms.

The spirochetes show varying neurotropic potential. This can promote cerebral hemorrhage, for example with *B. recurrentis*. They cross the placenta, with associated fetal loss through abortion or congenital infection, particularly *B. duttonii*. Myocarditis and hepatic failure may complicate infection with some of the more virulent members of the relapsing fever borreliae (*B. recurrentis/B. duttonii*), where mortality can reach 10% in untreated cases.

Laboratory diagnosis

Microscopy has been the primary diagnostic approach, with demonstration of the spirochetes in blood with Wright's or Giemsa stains, silver staining, or the use of dark-field microscopy for observing motile spirochetes (Figure 163.1). Although these methods can detect the causative species, sensitivity is poor, particularly for some species such as *B. crocidurae*, where the blood burden is lower than in, for example, *B. recurrentis*. This is further complicated by the need to collect blood during febrile episodes. It is not possible to differentiate species using microscopy.

Animal inoculation can recover and identify cultivable strains. Cultivation can also be achieved from clinical samples into specialized media (such as BSKII) but this is technically demanding. This has been largely superseded by molecular identification approaches, and molecular diagnostics are currently the mainstay for both detection and typing of relapsing fever borreliae.

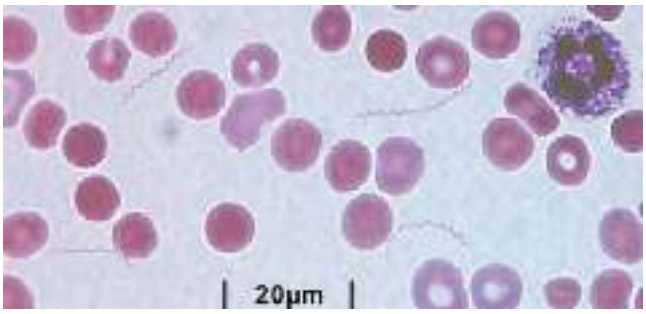

FIGURE 163.1 Giemsa-stained spirochetes in a blood film.

Current epidemiology

The relapsing fever spirochetes have been divided into Old World and New classes; however, with improving phylogenetic tools, this division now appears artificial. The prevalence of tick-borne strains correlates with specific regions, particularly African TBRF, probably resulting from climatic conditions conducive for its tick vector. This has not been the case for louse-borne *B. recurrentis*, which was formerly worldwide, but now is restricted to areas where clothing lice persist.

Figure 163.2 depicts the global location of relapsing fever.

It is increasingly apparent that the burden of relapsing fever infections in endemic regions is underdiagnosed. Recent reports from Senegal have suggested that this is the cause of some 13% of fevers presenting at local dispensaries, representing an alarming 11 to 25 cases per 100 person-years. Studies of febrile patients in Morocco have suggested that 20.5% were TBRF cases. Although not at these levels, cases are more frequently being detected in the United States.

Epidemiology of LBRF has changed drastically with the reduced level of infestation with clothing lice. The infection remains in areas of extreme poverty such as Ethiopia, sometimes spilling into adjacent regions, such as an outbreak in the Darfur region of Sudan. During this outbreak between 1999 and 2000, some 20,000 cases occurred with a 10% mortality rate.

Reservoirs of infection

The majority of relapsing fever spirochetes are zoonoses with vertebrate reservoir species (Table 163.1). In the majority of cases, these reservoir species are rodents; however, bats, birds, and reptiles may also play a reservoir role. The notable exceptions are *B. recurrentis* and *B. duttonii*, both of which have an exclusive human reservoir. Many also consider the tick vector a reservoir of infection for TBRF, facilitated by transovarial transmission of infecting

FIGURE 163.2 Global location of relapsing fever.

Borrelia to the next generation and the impressive longevity of these ticks, which can survive for many years with their infecting spirochetes.

Risk groups

Both LBRF and TBRF have their greatest burden among those living in extreme poverty. Occupational contact with tick-infested environments has resulted in clusters of infection, particularly among military personnel who have used caves during training activities, with a resulting clinical burden of up to 6.4 cases/100,000 in Israel. Similarly, conservation workers are at risk. Imported cases have been encountered through migration and tourism, typically in rural regions where intermittently used holiday accommodation has provided refuge for reservoir hosts and their associated tick vectors.

Control and prevention

Relapsing fever spirochetes remain susceptible to penicillin, tetracycline/doxycycline, chloramphenicol, ceftriaxone, and erythromycin (Table 163.2). Wide use of antimicrobials coupled with improvements in living conditions have reduced the incidence of infection. This is not so apparent for the tick-borne forms of disease that persist in their longer lived tick vector/reservoirs and through zoonotic vertebrate reservoir species. The burden of TBRF among subsistence agro-pastoralist communities in developing nations remains substantial. Use of acaricides has met with some success, but costs are prohibitive. If contact is unavoidable, doxycycline prophylaxis has been used for short-term prevention.

Suggested reading

Antinori S, Mediannikov O, Corbellino M, Raoult D. Louse-borne relapsing fever among East African refugees in Europe. *Travel Med Infect Dis*. 2016;14:110–114.

Cutler SJ. Relapsing fever borreliae: A global review. *Tickborne Borrelia Infect*. 2015;35:847–865.

Cutler S, Vayssier-Taussat M, Estrada-Peña A, Potkonjak A, Mihalca AD, Zeller H. A new *Borrelia* on the block: *Borrelia miyamotoi*—a human health risk? *Eurosurveillance*. 2019;24. https://doi.org/10.2807/1560-7917.ES.2019.24.18.1800170

Cutler SJ, Ruzic-Sabljic E, Potkonjak A. Emerging borreliae: Expanding beyond Lyme borreliosis. *SI Vectors Vector-Borne Dis*. 2017;31:22–27.

Cutler SJ, Idris JM, Ahmed AO, Elelu N. *Ornithodoros savignyi*, the tick vector of "*Candidatus* Borrelia kalaharica" in Nigeria. *J Clin Microbiol*. 2018;56.

Guerrier G, Doherty T. Comparison of antibiotic regimens for treating louse-borne relapsing fever: a meta-analysis. *Trans R Soc Trop Med Hyg*. 2011;105:483–490.

Krause PJ, Fish D, Narasimhan S, Barbour AG. *Borrelia miyamotoi* infection in nature and in humans. *Clin Microbiol Infect*. 2015;21:631–639.

Malincarne L, Schiaroli E, Ciervo A, et al. Meningitis with cranial polyneuritis and cavernous sinus thrombosis by *Borrelia crocidurae*: First autochthonous case in Europe. *Int J Infect Dis*. 2019;82:30–32.

Stete K, Rieg S, Margos G, Häcker G, Wagner D, Kern WV, Fingerle V. Case report and genetic sequence analysis of *Candidatus* Borrelia kalaharica, Southern Africa. *Emerg Infect Dis*. 2018;24:1659–1664.

Wagemakers A, Staarink PJ, Sprong H, Hovius JWR. *Borrelia miyamotoi*: A widespread tick-borne relapsing fever spirochete. *Trends Parasitol*. 2015;31:260–269.

Warrell DA. Louse-borne relapsing fever (*Borrelia recurrentis* infection). *Epidemiol Infect*. 2019;147:e106.

164

Leptospirosis

Daniela E. DiMarco

Overview

Leptospirosis is a zoonotic disease caused by spirochetes from the genus *Leptospira*, of which >200 serovars infect humans. Infections are most commonly caused by *L. interrogans,* one of at least 10 pathogenic species. Infection in humans typically occurs after exposure to a contaminated environmental source (e.g., water or soil contaminated by rodent urine) or an infected animal. *Leptospira* penetrate intact mucous membranes and abraded skin and disseminate widely via the bloodstream. Symptoms develop 5 to 14 days after exposure. Most patients have an abrupt onset of a self-limited, 5 to 7 day anicteric illness characterized by fever, headache, conjunctival suffusion, myalgias, chills, cough, neck stiffness, and/or prostration (Box 164.1), though frequency of symptomatology reported is highly variable across studies and regions.[1–3] An estimated 10% of patients will present with severe disease, having jaundice, hemorrhage, renal failure, and/or neurologic dysfunction (Weil's disease).[4] The major clinical manifestations of severe disease may result from secondary vasculitis (Box 164.2).

Classically, leptospirosis has been considered a biphasic illness. However, many patients with mild disease will not have symptoms of the secondary "immune" phase of illness, and patients with very severe disease may have progression from onset of illness to jaundice, renal failure, hemorrhage, hypotension, and coma. The incubation period from initial exposure ranges from days up to 4 weeks after exposure (mean 10–12 days). The illness is biphasic in about half of patients, with relapse occurring approximately 1 week after resolution of the initial febrile illness. A late complication is anterior uveitis, seen in up to 12% of patients months to years after convalescence.[5] Leptospirosis in pregnancy is associated with spontaneous abortion, but it is not known to increase the rate of congenital anomalies.[4]

Case fatality rates for leptospirosis are estimated at 5–15% in severe disease, while mild infection is usually self-limited.[4] Death often results from complications of renal failure, gastrointestinal and/or pulmonary hemorrhage, and acute respiratory distress syndrome (ARDS). Highest morbidity and mortality from leptospirosis is seen in more rural and resource-limited regions where the disease is thought to be underrecognized and underreported.[6]

Epidemiology

Leptospirosis is endemic to tropical environments, though infection also occurs in seasonally in temperate climates. According to the US Centers for Disease Control and Prevention (CDC), it is estimated that there are >1 million cases annually worldwide, with <200 of those occurring in the United States (primarily in Puerto Rico and Hawaii).[4] Globally, the majority of cases are among men (80%) and younger adults (aged 20–49).[7] Several outbreaks internationally and in the United States highlight the significance of recreational water activities and risks associated with exposure to floodwaters and travel, especially to Southeast Asia or for adventure tourism.[3,8,9] Occupational exposures remain a concern internationally, particularly related to

BOX 164.1

Symptoms and signs of leptospirosis

Fever (84–100%)
Headache (9–99%)
Myalgias, muscle tenderness (20–100%)
Vomiting and/or diarrhea (5–78%)
Conjunctival suffusion (4–99%)
Jaundice (5–93%)
Hepatomegaly (15–83%)
Splenomegaly (2–49%)
Meningeal signs (5–27%)
Oliguria (26%)
Cough (20–57%)
Skin rash (7–8%)

BOX 164.3

Epidemiology and exposure considerations for leptospirosis

Leptospira are excreted in animal urine and survive in the environment for up to 6 months
Common in the tropics, especially in urban slums
Recreational exposures: Windsurfing, kayaking, swimming, camping, and adventure tourism
Occupational exposures: Farmers, sewer workers, military personnel working in the tropics, veterinarians, abattoir workers, and others with exposure to rodent urine or bites (homeless population, rodent control workers)
Outbreaks seen after floods

farming.[1] Knowledge of epidemiologic risk factors is key to making the diagnosis (Box 164.3).

Diagnosis

An epidemiologic risk assessment is key to making a timely and accurate diagnosis of leptospirosis, particularly in the setting of fever in a traveler. Since the clinical presentation is often indistinguishable from influenza, acute viral hepatitis, malaria, and other viral and rickettsial vector-borne infections, these too should be included in the differential. The prominent myalgias, conjunctival suffusion, elevated serum creatine phosphokinase, and the relatively mild (two- to threefold) elevations in transaminases seen in leptospirosis may help to distinguish icteric leptospirosis from an acute viral infection (Box 164.4).

There are several different diagnostic assays for *Leptospira*, yet the diagnosis remains challenging due to test-specific technical limitations and availability. Serologic and culture-based testing methods remain the standard. Both are limited by low sensitivity in very early infection, and neither are species or serovar specific. Traditionally, the diagnosis is made retrospectively by a four-fold rise in titer from the acute to convalescent phase, as measured by the microscopic agglutination test (MAT).[10,11] Though the MAT is the gold standard, limitations include cross-reactivity with other spirochetes, technical performance challenges, lab requirements to maintain a culture supply, and overall limited availability; primarily found at reference labs like the CDC. Enzyme-linked immunosorbent assay (ELISA) kits are commercially available and detect immunoglobulin M (IgM) antibodies, thus enabling diagnosis during the first week of illness.[10] Culture of blood and cerebrospinal fluid is best if collected early in the acute phase and requires prolonged incubation for growth. Urine cultures may also be intermittently positive for several months.[10,11] Polymerase chain reaction (PCR) testing is available for more rapid diagnosis and has been demonstrated to be most sensitive in the early phase of illness in a selected populations with high pre-test probability of disease.[12] Due to limited availability of the MAT, commercial IgM assays have become first-line testing, with the MAT or PCR as the confirmatory assay. Immunohistochemical staining for pathology specimens and dark-field microscopy are also available. Within the World Health Organization Leptospirosis Guideline, it is noted that rapid screening tests are commercially available, which employ

BOX 164.2

Pathogenesis of leptospirosis

Vasculitis with damage to capillary endothelial cells contributes to the following:
Renal tubular dysfunction
Hepatocellular dysfunction
Pulmonary hemorrhage
Muscle focal necrosis
Coronary arteritis

BOX 164.4

Prominent diagnostic test abnormalities in severe leptospirosis

Renal failure, with or without acute interstitial nephritis
Liver injury: Two- to threefold elevations in transaminases and alkaline phosphatases, conjugated hyperbilirubinemia
Elevated creatine phosphokinase with myositis
Thrombocytopenia, elevated sedimentation rate
Cerebrospinal fluid lymphocyte predominant pleiocytosis, elevated protein, and normal glucose with aseptic meningitis
Abnormal chest radiographs: Patchy alveolar pattern in lower lobes with or without interstitial/alveolar hemorrhage
Electrocardiogram abnormalities: Sinus tachycardia, myocarditis, first-degree atrioventricular block

BOX 164.5

Treatment of leptospirosis

Outpatient treatment: Doxycycline, 100 mg PO BID for 7 days in adults

Severe infection: Penicillin G, 1.5 million units IV q6h, ampicillin 0.5–1g IV q6h, or ceftriaxone 1 g IV or IM daily

Chemoprophylaxis: 200 mg doxycycline PO once weekly while at high risk (e.g., travellers, military personnel)

various antibody detection technologies, though confirmatory testing for any result is advised using MAT.[13]

Treatment

Although the illness is self-limited and often mild, treatment is recommended. Doxycycline, 100 mg orally twice daily for 7 days is recommended for mild illness.[14] Alternative regimens for mild disease include azithromycin or amoxicillin.[11] Penicillin G at a dosage of 6 million units per day in divided doses has been successful for early treatment of severe disease, and ceftriaxone (1 g/d) appears to be equally efficacious and has the benefits of simpler dosing schedules and potential intramuscular administration (Box 164.5).[15,16] Jarisch–Herxheimer reactions (fever, rigors, hypotension, and tachycardia) may occur on initiation of antibiotic therapy. In cases of severe disease, supportive care and management of hypotension, renal failure, and hemorrhage are crucial for reducing morbidity and mortality from infection. There is insufficient evidence to support the use of steroids in severe disease.[17] Immunization of animals, chemoprophylaxis, and personal protective measures in high risk areas are keys to preventing infection.

References

1. Bharti AR, Nally JE, Ricaldi JN, et al. Leptospirosis: A zoonotic disease of global importance. *Lancet Infect Dis*. 2003;3(12):757–771.
2. Katz AR, Ansdell VE, Effler PV, Middleton CR, Saski DM. Assessment of the clinical presentation and treatment of 353 cases of laboratory-confirmed leptospirosis in Hawaii, 1974–1998. *Clin Infect Dis*. 2011 1 Dec;33(11):1834–1841. https://doi.org/10.1086/324084
3. Plank R, Dean D. Overview of the epidemiology, microbiology, and pathogenesis of Leptospira spp. in humans. *Microbes Infect*. 2000;2(10):1265–1276.
4. Centers for Disease Control and Prevention (CDC). Leptospirosis fact sheet for clinicians. January 30, 2018. https://www.cdc.gov/leptospirosis/pdf/fs-leptospirosis-clinicians-eng-508.pdf
5. Pappachan JM, Mathew S, Thomas B, Renjini K, Scaria CK, Shukla J. The incidence and clinical characteristics of the immune phase eye disease in treated cases of human leptospirosis. *Indian J Med Sci*. 2007 Aug;61(8):441–447.
6. Costa F, Hagan JE, Calcagno J, et al. Global morbidity and mortality of leptospirosis: A systematic review. *PLoS Negl Trop Dis*. 2015;9(9):e0003898. https://doi.org/10.1371/journal.pntd.0003898
7. Torgerson PR, Hagan JE, Costa F, et al. Global burden of leptospirosis: Estimated in terms of disability adjusted life years. *PLoS Negl Trop Dis*. 2015;9(10):e0004122. https://doi.org/10.1371/journal.pntd.0004122
8. Centers for Disease Control and Prevention (CDC). Update: Leptospirosis and unexplained acute febrile illness among athletes participating in triathlons: Illinois and Wisconsin, 1998. *MMWR*. 1998 21 Aug;47(32):673–676.
9. Centers for Disease Control and Prevention (CDC). Outbreak of acute febrile illness among participants in EcoChallenge Sabah 2000: Malaysia, 2000. *JAMA*. 2000;4 Oct;284(13):1646.
10. Schreier S, Doungchawee G, Chadsuthi S, Triampo D, Triampo W. Leptospirosis: Current situation and trends of specific laboratory tests. *Exp Rev Clin Immunol*. 2013 Mar;9(3):263–280. https://doi.org/10.1586/eci.12.110
11. Haake DA, Levett PN. Leptospirosis in humans. *Curr Topics Microbiol Immunol*. 2015;387:65–97. https://doi.org/10.1007/978-3-662-45059-8_5
12. Agampodi SB, Niroshan JD, Nockler K, Mayer-Scholl A, Vinetz JM. Redefining gold standard testing for diagnosing leptospirosis: Further evidence from a well-characterized, flood-related outbreak in Sri Lanka. *Am J Trop Med Hyg*. 2016 7 Sep:95(3):531–536. https://doi.org/10.4269/ajtmh.16-0033
13. Human Leptospirosis: Guidance for Diagnosis, Surveillance, and Control. World Health Organization, 2003. Available here: https://apps.who.int/iris/bitstream/handle/10665/42667/WHO_CDS_CSR_EPH_2002.23.pdf;jsessionid=2371A39FB5BDDCBE6462AABD78659E5B?sequence=1
14. McClain JB, Ballou WR, Harrison SM, Steinweg DL. Doxycycline therapy for leptospirosis. *Ann Intern Med*. 1984 May;100(5):696–698.
15. Watt G, Padre LP, Tuazon ML, Calubaquib C, Santiago E, Ranoa CP, Laughlin LW. Placebo-controlled trial of intravenous penicillin for severe and late leptospirosis. *Lancet (London)*. 1988 27 Feb;1(8583):433–435.
16. Panaphut T, Domrongkitchaiporn S, Vibhagool A, Thinkamrop B, Susaengrat W. Ceftriaxone compared with sodium penicillin g for treatment of severe leptospirosis. *Clin Infect Dis*. 2003 15 Jun;36(12):1507–1513. https://doi.org/10.1086/375226
17. Rodrigo C, de Silva NP, Goonaratne R, et al. High dose corticosteroids in severe leptospirosis: A systematic review. *Trans R Soc Trop Med Hyg*. 2014 Dec;108(12):743–750. https://doi.org/10.1093/trstmh/tru148

Section 20

Specific organisms: Mycoplasma and Chlamydia

165

Mycoplasma

Ken B. Waites and Sixto M. Leal, Jr.

Mycoplasmas are the smallest free-living organisms and are unique among prokaryotes in that they lack a cell wall, a feature that is largely responsible for their biologic properties and lack of susceptibility to many commonly prescribed antimicrobial agents. Mycoplasmas are usually mucosally associated, residing primarily in the respiratory and urogenital tracts and rarely penetrating the submucosa except in the case of immunosuppression or instrumentation, when they may invade the bloodstream and disseminate to many different organs and tissues throughout the body. Intracellular localization occurs in some species, such as *M. genitalium* and *M. pneumoniae* and may contribute to the chronicity that characterizes many mycoplasmal infections.

There are at least 17 species of mycoplasmas and ureaplasmas for which humans are believed to be the primary host and numerous others of animal origin that have been detected occasionally, most often in the setting of immunosuppression. Several human mycoplasmal species are commensals in the upper respiratory or lower urogenital tracts. Five species are responsible for the majority of clinically significant infections that may come to the attention of the practicing physician. These species are *M. pneumoniae*, *M. hominis, M. genitalium*, *Ureaplasma urealyticum*, and *U. parvum*. *M. fermentans* is another mycoplasma of human origin that may behave as an opportunist. *M. fermentans* has been detected in throat cultures of children with pneumonia, in some cases when no other etiologic agent was identified, but the frequency of its occurrence in healthy children is not known. This mycoplasma has also been detected in adults with an acute influenza-like illness and in bronchoalveolar lavage specimens from patients with the AIDS and pneumonia. *M. amphoriforme* is the newest human mycoplasma to be described. It has been detected in persons with antibody deficiencies suffering from recurrent bronchitis as well as immunocompetent hosts with lower respiratory tract symptoms. However, its true role as a human pathogen has not yet been firmly established. Oral commensal species such as *M. salivarium* are known to cause arthritis in immunocompromised persons with antibody deficiencies. Other mycoplasmas of animal origin occasionally cause zoonotic infections.

Mycoplasma pneumoniae respiratory disease

M. pneumoniae occurs endemically and occasionally epidemically in persons of all age groups, most commonly in school-aged children, adolescents, and young adults. The common misconception that *M. pneumoniae* disease is rare among very young children and older adults has sometimes led to failure of physicians to consider this organism in differential diagnoses of respiratory infections in these age groups. Failure to consider *M. pneumoniae* as an etiologic agent in cases of severe pneumonia may also lead to misdiagnosis since this organism can cause severe respiratory disease that has caused death in some cases, usually in otherwise healthy persons. It is likely that serious disease occurs more often than is currently appreciated but goes undetected when specific tests to detect *M. pneumoniae* are not performed. *M. pneumoniae* is perhaps best known as the primary cause of "walking or atypical pneumonia," but the most frequent clinical syndrome is tracheobronchitis or bronchiolitis, often accompanied by upper respiratory tract manifestations. Typical complaints can persist for weeks to months and include hoarseness, fever, cough which is initially

nonproductive but later may yield small to moderate amounts of non-bloody sputum, sore throat, headache, chills, coryza, and general malaise. The throat may be inflamed but cervical adenopathy is uncommon. Bronchopneumonia, involving one or more lobes, often develops in infected persons, accounting for 20% or more of community-acquired pneumonias overall and an even greater percentage in closed populations such as college dormitories, military barracks, and prisons. The incubation period is generally 1 to 3 weeks and household spread is common. Epidemiologic studies have shown *M. pneumoniae* was second only to *Streptococcus pneumoniae* as an etiologic agent of pneumonia in adults requiring hospitalization. Hospital admission may be necessary in about 10% of children and adults with *M. pneumoniae* infection, but recovery is usually complete without sequelae. Coinfection and secondary infections can occur, increasing patient morbidity and mortality. Some people may experience extrapulmonary complications at variable time periods after onset or even in the absence of respiratory illness. Such complications most commonly include skin rashes, pericarditis, hemolytic anemia, arthritis, meningoencephalitis, peripheral neuropathy, and pericarditis. Other nonspecific manifestations include nausea, vomiting, and diarrhea. Mycoplasmal infection may also be associated with exacerbations of asthma. Whether the organism can act independently in the pathogenesis of asthma has not been firmly established, but the fact that it can induce a number of inflammatory mediators such as IgE and that administration of macrolide antibiotics improves lung function of asthmatic persons with evidence of mycoplasmas in their airways suggests this possibility is worthy of further study.

Following inhalation, *M. pneumoniae* moves by gliding motility to the ciliated respiratory epithelium where its polar organelle mediates cytadherence through a complex system of protein adhesins. The community-acquired respiratory distress syndrome (CARDS) exotoxin of *M. pneumoniae* is an adenosine diphosphate (ADP)-ribosyltransferase located over the entire surface of the cell that contributes to host cell damage by inducing ciliostasis, airway vacuolization, elicitation of a lymphocytic and eosinophilic airway exudate, and upregulation of various cytokines and chemokines. Clinical manifestations and host cell damage are also mediated by other virulence factors including nucleases, hydrogen peroxide, and production of autoantibodies that react with a variety of host tissues. Autoimmune reaction is thought to be responsible for many of the extrapulmonary complications associated with mycoplasmal infection. However, *M. pneumoniae* has been isolated from extrapulmonary sites such as synovial fluid, cerebrospinal fluid (CSF), pericardial fluid, and skin lesions, and it has also been detected by polymerase chain reaction (PCR) assays at additional extrapulmonary sites.

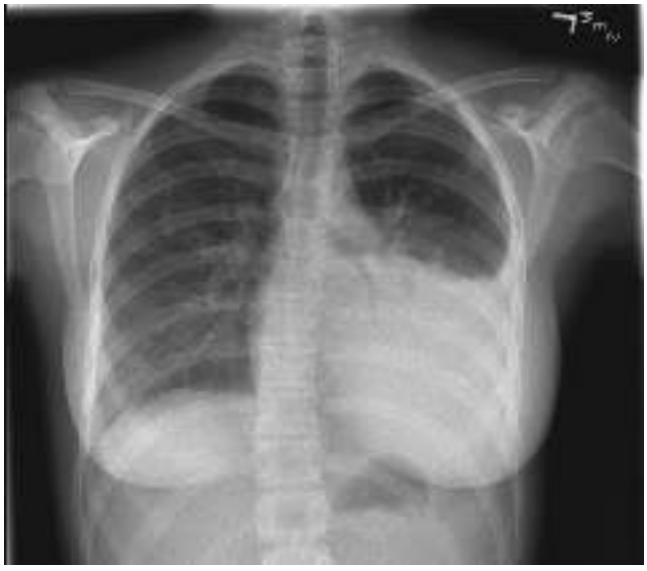

FIGURE 165.1 Chest radiograph of a female adolescent with polymerase chain reaction (PCR)-proven mycoplasmal pneumonia, demonstrating bilateral infiltrates.
Radiograph courtesy of T. Prescott Atkinson, MD, PhD.

The hemogram is often normal, but about one-fourth of patients may develop leukocytosis and one-third may demonstrate an elevated erythrocyte sedimentation rate. The cellular response of the sputum is mononuclear, with no bacteria visible by Gram stain (due to lack of a cell wall). In about 50% of patients, a cold agglutinin titer of ≥1:32 may develop by the second week of illness, disappearing by 6 to 8 weeks. Production of cold agglutinins is due to IgM autoantibodies directed against the I antigen on host erythrocytes. However, it is not a specific test for *M. pneumoniae*, since other microorganisms may induce similar reactions. Several viruses, *Chlamydia pneumoniae*, *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Legionella* spp., and even some mycobacteria or fungi can produce infections which are clinically indistinguishable and may coexist with mycoplasmal infection.

Lung involvement tends to be unilateral, but can be bilateral. Diffuse reticulonodular or interstitial infiltrates involving the lower lobes and appearing as streaks radiating from the hilus to the base of the lung are the most common radiographic abnormalities. True lobar consolidation is uncommon, but pleural effusion may develop in about 25% of cases. Abnormalities on chest radiographs often appear more severe than the clinical condition of the patient would predict. A typical radiographic presentation of mycoplasmal pneumonia is shown in Figure 165.1.

Due to widespread lack of diagnostic services, length of time until results can be obtained, impracticality of obtaining diagnostic specimens, and similarity of clinical syndromes due to different microorganisms, clinicians often do not attempt to obtain a microbiologic diagnosis in mild to moderately ill outpatients suspected of having *M. pneumoniae* infection and elect to treat empirically. Rapid point-of-care diagnostics would enable same-visit diagnosis of *M. pneumoniae* infection in the outpatient setting and prompt appropriate antibiotic treatment and mitigation of disease progression. Unfortunately, such testing is not currently available. Progression of the illness to sufficient severity requiring hospitalization justifies the search for a specific microbiologic etiology. This testing is often performed with large molecular-based respiratory pathogen syndromic panels, by culture, and/or serologic tests for *M. pneumoniae*. Clinical laboratories may offer culture through a reference laboratory familiar with the complex cultivation requirements of mycoplasmas. Respiratory tract specimens suitable for culture include throat swabs, sputum, tracheal aspirates, bronchial lavage

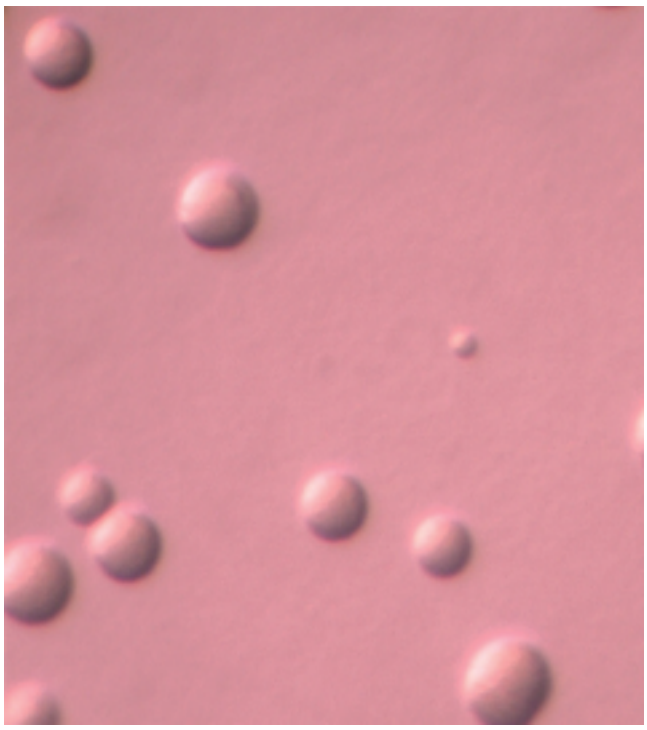

FIGURE 165.2 Spherical colonies of *Mycoplasma pneumoniae* approximately 100 μm in diameter growing on SP4 agar (126×).

fluid, pleural fluid, or lung biopsy tissue according to the patient's clinical condition. Care should be taken in specimen collection, inoculation into a suitable transport medium (such as SP4 broth) at bedside whenever possible, and not allowing desiccation. Freezing at −70°C/−94°F is advised if specimens cannot be transported to the diagnostic laboratory immediately after collection. Growth in culture is slow, requiring 3 to 6 weeks in some cases. Growth of a glucose-fermenting mycoplasma in SP4 broth and development of microscopic spherical colonies approximately 100 μm in diameter on SP4 agar, as shown in Figure 165.2, are presumptive evidence of *M. pneumoniae*. Since some of the upper respiratory commensal mycoplasmal species may also grow on this medium, it is necessary to confirm the identity of the organisms using PCR assay. Due to the turnaround time, expense, and limited availability, culture is rarely used for routine diagnosis of *M. pneumoniae* infection and is more useful for epidemiological purposes.

Serology has been used historically to confirm *M. pneumoniae* infection. Enzyme-linked immunosorbent assays are preferred over complement fixation assays or cold agglutinin titers. Since primary infection does not guarantee protective immunity against future infections and residual antibody may remain from earlier encounters with the organism, there has been a great impetus to develop sensitive and specific tests that can differentiate between acute or remote infection. Definitive diagnosis requires seroconversion documented by paired serum specimens obtained 2 to 4 weeks apart and assayed at the same time. Although single-titer qualitative and quantitative IgM or IgA assays purported to detect current infection are available, IgM can persist for many weeks after acute infection and as many as 50% of adults may not mount a detectable IgM response. Conversely, some children may not mount a measurable IgG response. Therefore, reliance on a single serologic test can be clinically misleading, and paired assays for both IgM and IgG are recommended. Even then, the interpretation of serologic results can often be confusing and inconclusive.

Molecular-based systems for rapid detection of *M. pneumoniae* alone or in combination with other respiratory pathogens are now available within institutions or through reference laboratories. The US Food and Drug Administration (FDA) has cleared assays targeting *M. pneumoniae* as part of a large panel of pathogens that include the BioFire (bio Mérieux), ePlex (GenMark), and MagPix (Luminex), and the QIAstat-Dx (Qiagen) platforms. Singleplex assays targeting *M. pneumoniae* include the FDA-cleared *Mycoplasma* Direct (Meridian) and laboratory-developed assays at reference labs such as the UAB Diagnostic Mycoplasma Laboratory and the Centers for Disease Control and Prevention (CDC). There are many other commercial molecular-based detection systems available in Europe and other locations. Given the limitations of culture and serology, molecular-based detection is the method of choice for detection of acute *M. pneumoniae* infection.

Treatment of *Mycoplasma pneumoniae* infections

Formerly it was believed that mycoplasmal respiratory infections were entirely self-limited and that no antimicrobial treatment was indicated. More recently it has been shown that appropriate antimicrobial therapy will shorten the symptomatic period and hasten radiologic resolution of pneumonia and recovery, even though organisms may be shed for several weeks. In general, the clinical efficacy of antimicrobial therapy is correlated with severity of pneumonia and elapsed time of illness before treatment is begun. A summary of treatment alternatives for *M. pneumoniae* respiratory infections is provided in Table 165.1.

M. pneumoniae is generally susceptible to macrolides, ketolides, tetracyclines, and fluoroquinolones such that in vitro susceptibility testing to guide therapy is not indicated at present. Susceptibility testing would also be impractical most of the time because clinical isolates are generally not available and because of the prolonged time that would be necessary to obtain the results. Macrolide resistance in *M. pneumoniae* has been known to occur for many years, but it was believed to be quite rare and of minimal clinical significance. Over the past two decades, the emergence of macrolide-resistant *M. pneumoniae* infections due to mutations in domain V of 23S ribosomal RNA that result in diminished clinical response to macrolide therapy is worrisome. This resistance now affects more than 90% of *M. pneumoniae* isolates in China and Japan and also occurs in the United States and Europe. Surveillance data from the United States from 2015 to 2018 found 7.6% macrolide-resistant infections overall, with resistance rates generally higher in the northeastern and southern regions than in the western states. Laboratory-developed PCR assays at the UAB Diagnostic Mycoplasma Laboratory and the CDC include high-resolution melt curve analyses to identify

TABLE 165.1 **TREATMENT OPTIONS FOR RESPIRATORY TRACT INFECTIONS CAUSED BY *MYCOPLASMA PNEUMONIAE*[a]**

Drug	Route	Dosage/24 h		Comments
		Pediatric	Adult	
Doxycycline	PO	4 mg/kg loading dose d 1, then 2–4 mg/kg/d in 1–2 doses × 10–14 d	200 mg loading dose d 1, then 100 mg q12h × 9–13 d	All tetracyclines have a detrimental effect on the skeletal development and bone growth of the fetus and should not be used in the second half of pregnancy or in children <8 yrs of age unless there is no other alternative
	IV	Same as PO	Same as PO	
Tetracycline	PO	25–50 mg/kg/d in 4 doses × 10–14 d	250–500 mg q6h × 10–14 d	
	IV	10–20 mg/kg/d in 2–4 doses × 10–14 d	500 mg–1 g q6–12h × 10–14 d	
Tigecycline	IV	Not recommended	100 mg loading dose, then 50 mg q 12h x7-14d	
Erythromycin	PO	20–50 mg/kg/d in 3–4 doses × 10–14 d	250–500 mg base/stearate q6h or 400–800 mg ethylsuccinate q6h × 10–14 d	Erythromycin is rarely used because newer macrolides are better tolerated and have longer half lives enabling once daily dosage.
	IV	25–40 mg/kg/d in 4 doses × 10–14 d	Same as PO	
Azithromycin	PO	10mg/kg/d on d 1, then 5 mg/kg/d × 4 d; not to exceed 250 mg/d	500 mg d 1, then 250 mg qd × 4 d or 2 g given as a single dose	IV formulation is not approved for use in persons <16 yrs of age
	IV	Not recommended	500 mg qd IV × 2 d, then 500 mg PO qd × 7–10 d	
Clarithromycin	PO	15 mg/kg/d in 2 doses × 7–14 d	250–500 mg q12h × 7–14 d (immediate release) or 1 g qd × 7 d (extended release)	No IV formulation is available
Levofloxacin	PO	6 mo–4 yrs: 8–10 mg/kg dose divided q12h × 10 d 5–12 yrs: 8–10 mg/kg dose divided q24h × 10d (max 750 mg per dose) Adolescents: 8–10 mg/kg divided q24h (max 750 mg per dose) × 10 d	750 mg qd × 5 d or 500 mg qd x -14d	Fluoroquinolones are not approved to treat respiratory tract infections in persons under 18 yrs of age, but levofloxacin has been used successfully to treat macrolide-resistant *M. pneumoniae* infections in children who failed treatment with macrolides.
	IV	Same as PO	Same as PO	
Moxifloxacin	PO	Not recommended	400 mg qd × 7–14 d	
	IV	Not recommended	Same as PO	
Gemifloxacin	PO	Not recommended	320 mg qd × 7 d	No IV formulation is available

[a] Treatment recommendations are primarily for management of community-acquired pneumonia with antibiotics approved for treatment of this condition although they are also appropriate for tracheobronchitis due to this organism. Choice of routes for administration depends on the severity of the clinical condition being treated. Most *M. pneumoniae* infections can be adequately treated with oral medication.

genotypes associated with macrolide resistance. Commercial PCR assays targeting macrolide resistance are in development but are not currently available.

The macrolides clarithromycin and azithromycin are broad-spectrum agents used primarily for treatment of community-acquired respiratory infections caused by a wide array of bacteria. These agents are very active in vitro against *M. pneumoniae* and inhibit its growth at comparable or lower minimum inhibitory concentrations (MICs) than those of erythromycin unless the strain has ribosomal mutations conferring

macrolide resistance. These drugs have proven clinical efficacy and approved therapeutic indications for pneumonia caused by this organism. Care must be taken because of numerous potential drug interactions with these macrolides. Clarithromycin and azithromycin are available as pediatric oral suspensions, and azithromycin is also available as an intravenous (IV) formulation. Tetracycline and its analogs are also effective in vivo and in vitro, but should not be used in children due to potential bone and tooth toxicity. Clindamycin is effective in vitro, but it may not be active in vivo and should not be considered a first-line treatment. None of the β-lactams, sulfonamides, or trimethoprim is effective in vitro or in vivo against *M. pneumoniae*.

Fluoroquinolones exhibit bactericidal anti-mycoplasmal activity but are less potent in vitro than the macrolides against *M. pneumoniae*. Development of quinolones with documented clinical efficacy and approved indications for treating *M. pneumoniae* has been driven largely by the need for therapeutic alternatives for β-lactam- and macrolide-resistant *S. pneumoniae* and the desire for agents that can be used as empiric monotherapy for respiratory infections due to other typical and atypical organisms. At present, fluoroquinolones are not approved for treatment of respiratory infections in persons <18 years of age, but these drugs are widely used for treatment of respiratory infections in adults and represent an alternative therapy for *M. pneumoniae* disease in children when there is treatment failure due to macrolide resistance.

Mycoplasmas are slow-growing organisms; thus one would logically expect respiratory infections to respond better to longer treatment courses than might be offered for other types of infections. Thus, a 14- to 21-day course of oral therapy is appropriate for some drugs, but some of the newer agents have shown clinical efficacy against mycoplasmal pneumonias with shorter durations. For example, a 5-day course of oral azithromycin is approved for treatment of community-acquired pneumonia due to *M. pneumoniae*.

In addition to the administration of antimicrobials for management of *M. pneumoniae* infections, other measures such as cough suppressants, antipyretics, and analgesics should be given as needed to relieve the headaches and other systemic symptoms. Since most extrapulmonary manifestations are diagnosed late in the course of disease, the benefit of early treatment is unknown. However, high-dose steroid therapy and/or IV immunoglobulin may help reverse neurologic symptoms, if present. If treatment of extrapulmonary mycoplasmal infections is necessary, and/or the patient is immunosuppressed, selection of an agent that exhibits bactericidal activity, such as a fluoroquinolone, is most appropriate and administration of the drugs for longer durations will be required.

Fortunately, the treatments of choice for *M. pneumoniae* are appropriate for many of the other microbial agents responsible for community-acquired respiratory infections. This is especially important in view of the fact that, in the major proportion of ambulatory patients seeking medical care, the identity of their infectious organism is never determined.

Genital *Mycoplasma* and *Ureaplasma* infections

Ureaplasma spp. and *M. hominis* can be isolated from the lower genital tract in the majority of sexually active women; their occurrence is somewhat less frequent in men. The presence of genital mycoplasmas in so many asymptomatic persons has made it difficult to prove their pathogenic potential. For some conditions in which ureaplasmas have been detected such as cystitis, male urethritis, urinary calculi *Ureaplasma* spp., and for cases of pelvic inflammatory disease (PID) in which *M. hominis* has been detected, evidence is sufficient to implicate these organisms as etiologic agents in a subset of clinical cases. For other conditions such as prostatitis and bacterial vaginosis the evidence is not as clear-cut. Only a subgroup of otherwise healthy adult men and women who are colonized will develop clinically significant genitourinary disease due to these organisms, but the risk factors are poorly understood. Table 165.2 summarizes diseases associated with or caused by genital mycoplasmas and ureaplasmas.

The ability of genital mycoplasmas to be transmitted vertically from mother to offspring in utero or at the time of delivery has led to considerable efforts to ascertain their role as perinatal pathogens. Isolation of *Ureaplasma* spp. from the chorioamnion of pregnant women has been consistently associated with histologic chorioamnionitis and is inversely related to birth weight, even when adjusting for duration of labor, rupture of fetal membranes, and presence of other bacteria. *Ureaplasma* spp. can be isolated from endometrial tissue of healthy, nonpregnant women, indicating that they may be present at the time of implantation and might therefore be involved in early pregnancy losses. Numerous studies have shown that the presence of ureaplasmas alone or with other bacteria in the chorioamnion is independently associated with birth at <37 weeks of gestation regardless of the duration of labor. The ability of ureaplasmas to invade the amniotic fluid early in gestation and initiate inflammation provides the setting through which they can also produce inflammation in the lower respiratory tract of the developing fetus and neonate. Over the past several years there has been increasing evidence that these organisms may cause congenital pneumonia and initiate events leading to chronic lung disease of prematurity or bronchopulmonary dysplasia. Superficial mucosal colonization in the newborn period tends to be transient and without sequelae, but neonates, especially those born preterm, have been shown to be susceptible to development of a variety of systemic conditions due to either *M. hominis* or ureaplasmas, including bacteremia and meningitis.

For many years *U. urealyticum* was the only species known to infect humans. However, this organism was eventually subdivided into two separate species, *U. urealyticum* and *U. parvum*, based on 16S rRNA sequences. *U. parvum* is the more common species isolated from clinical specimens, but both species may occur simultaneously. Many clinical studies have not distinguished between the two species except in recent years because nucleic acid amplification tests are necessary to discriminate between them. Evidence is

TABLE 165.2 **DISEASES ASSOCIATED WITH OR CAUSED BY GENITAL MYCOPLASMAS**

Disease	*Ureaplasma* spp.	*M. hominis*	*M. genitalium*
Male urethritis	+[a]	−	+
Chronic prostatitis	±	−	±
Epididymitis	±	−	−
Urinary calculi	+	−	−
Cystitis/pyelonephritis	+	+	−
Bacterial vaginosis	±	+	±
Cervicitis	−	−	+
Pelvic inflammatory disease	−	+	+
Infertility	±	−	+
Chorioamnionitis	+	±	−
Spontaneous abortion	±	±	−
Prematurity/low birth weight	+	±	+
Intrauterine growth retardation	+	−	−
Postpartum/postabortal fever and endometritis	+	+	−
Neonatal pneumonia	+	+	−
Neonatal chronic lung disease	+	−	−
Neonatal bacteremia/meningitis	+	+	−
Neonatal abscesses	+	+	−
Extragenital disease in adults[b]	+	+	+
Posttransplant hyperammonemia	+	+	_

− = no association or causal role demonstrated. In some conditions for *M. genitalium* this may reflect the fact that no studies using appropriate techniques to detect this organism have been performed.
+ = causal role.
± = significant association and/or strong suggestive evidence, but causal role not proven.
[a] *U. urealyticum* is more commonly involved in urethritis than *U. parvum*
[b] these include conditions such as septic arthritis, bloodstream invasion, abscesses, wound infections, lung infections, endocarditis, and osteomyelitis.

accumulating to suggest that *U. urealyticum* may be more pathogenic in some conditions such as male urethritis.

Extragenital infection with *M. hominis* and/or *Ureaplasma* spp. beyond the neonatal period is usually associated with some degree of immunocompromise, such as congenital hypogammaglobulinemia, iatrogenic immunosuppression following solid organ transplantation, or with invasive procedures such as instrumentation of the urinary tract. Ureaplasmas and other mycoplasmas are etiologic agents of septic arthritis in the setting of congenital antibody deficiencies and should be considered early when attempting to diagnose these conditions.

While the virulence factors and pathogenesis of *M. pneumoniae* infections have been studied extensively, there is considerably less known about how urogenital mycoplasmas produce disease. *M. genitalium* has a polar organelle similar to that of *M. pneumoniae* that facilitates its attachment and internalization into host cells. Other known virulence factors of *M. genitalium* include nucleases that provide a source of nucleotide precursors and antimicrobial resistance. *M. hominis* and *Ureaplasma* spp. do not possess a recognizable polar attachment organelle. However, *M. hominis* has a variable adherence-associated antigen (Vaa) that is involved with cytadherence and avoidance of host immune response through antigenic variation. Additional surface proteins such as OppA are also involved in cytadherence and induction of apoptosis in host cells. Ureaplasmas are also capable of attachment to a variety of host cell types, including urethral epithelia, spermatozoa, and erythrocytes. As with *Mycoplasma* spp., variation in ureaplasma surface antigens facilitates their persistence in invasive sites. Production of ammonia by both *M. hominis* and *Ureaplasma* spp. is responsible for their production of hyperammonemia in lung transplant recipients and for formation of urinary calculi by ureaplasmas. Ureaplasmas also produce an IgA protease.

Genitourinary or extragenital diseases suspected to be due to mycoplasmas warrant appropriate diagnostic tests when available and treatment if infection is confirmed. This is of particular importance if the organisms are recovered in the absence of other possible microbial etiologies and if the infection is present in a normally sterile site (e.g., *M. hominis* isolation from joint fluid). Practitioners will usually have

to rely on familiarity with clinical syndromes typically due to genital mycoplasmas and treat empirically if facilities for laboratory diagnosis are not readily available. Many of the conditions associated with a mycoplasmal etiology can also be due to a variety of microbial agents and some conditions such as PID can be polymicrobial. Therefore, the selection of drugs must take into account multiple causes.

Both *M. hominis* and ureaplasmas grow rapidly and can be detected in cultures of appropriate specimens within 2 to 5 days. *M. hominis* can be suspected on routine bacterial media as pinpoint colonies that do not show up on Gram stain. Preferred culture methods require proper handling and bedside inoculation of transport broth to enhance recovery of these organisms. Urethral or wound swabs, cervicovaginal or prostatic secretions, urine, respiratory specimens such as those described for *M. pneumoniae*, CSF, and blood or other body fluids or tissues are appropriate for culture depending on the clinical setting. Cultures are available mainly through larger hospital laboratories or reference laboratories. *M. hominis* hydrolyzes arginine in liquid media, produces typical fried-egg colonies on SP4 or A8 agar, and can be presumptively identified by rate of growth and colony morphology (Figure 165.3). Definitive identification requires characterization by PCR. Ureaplasmas can be identified to the genus level by typical colony morphology on A8 agar and urease activity (Figure 165.4). Species determination for ureaplasmas grown in culture requires PCR but is not usually performed for diagnostic purposes.

Currently there are no commercial serologic assays or rapid molecular detection tests available for *M. hominis* and *Ureaplasma* spp. in the United States, but several PCR-based assays are sold in Europe, and reference laboratories in the United States offer laboratory-developed singleplex and multiplex PCR assays for organism detection. Antimicrobial susceptibility testing has been standardized for human mycoplasmas and ureaplasmas with interpretive breakpoints available in the Clinical and Laboratory Standards Document M43A. However, in vitro susceptibility testing is limited to reference laboratories capable of culturing these fastidious organisms. Susceptibility testing can be accomplished by a reference laboratory in 3 to 5 days for *M. hominis* and *Ureaplasma* spp. There are no rapid molecular assays capable of identifying antibiotic resistance in *M. hominis* and *Ureaplasma* spp.

FIGURE 165.3 Fried egg-type colonies of *Mycoplasma hominis* up to 110 μm in diameter (132×).

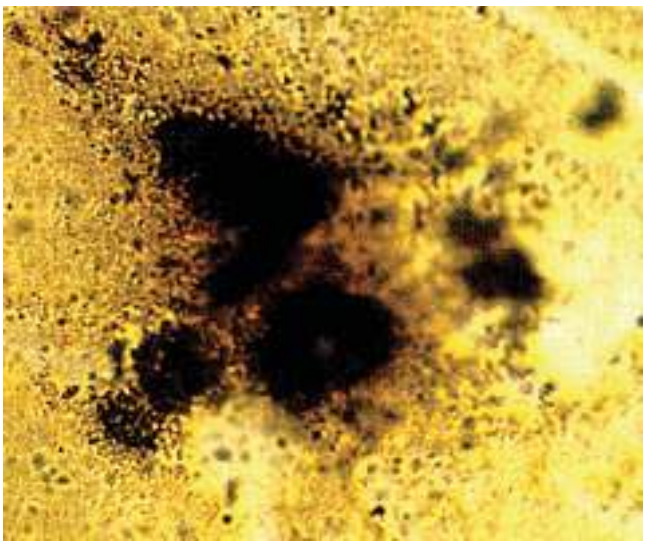

FIGURE 165.4 Granular brown urease-positive colonies of *Ureaplasma* species 15 to 60 μm in diameter from a vaginal specimen growing on A8 agar (100×).

M. genitalium was first isolated from urethral specimens in men with urethritis. It occurs much less commonly in the lower urogenital tract of asymptomatic persons than does *M. hominis* or *Ureaplasma* spp., affecting approximately 1% of young adults in the United States with a global prevalence range of 1% to 6.4%. Asymptomatic carriage is highest amongst sexually transmitted infection clinic attendees, ranging from 9% to >50%. Availability of the PCR assay has greatly enhanced the understanding of the role of *M. genitalium* in human disease. Several clinical studies support a causal role in male urethritis, indicating that it may be responsible for 15% to 25% of all cases and approximately 18% to 46% cases of non-chlamydial non-gonococcal urethritis. *M. genitalium* is also a cause of cervicitis and PID. Although it has been found in the respiratory tract and synovial fluid it has not been implicated in extragenital disease to the same extent as *M. hominis* and *Ureaplasma* spp. Younger age, black race, and non-Hispanic ethnicity have been identified as risk factors for *M. genitalium* infections.

M. genitalium culture is extremely slow, sometimes requiring several weeks to months for the organisms to form typical spherical colonies on SP4 agar. Thus, molecular identification and detection of genotypic resistance markers is essential to render a definitive diagnosis and guide antimicrobial treatment. Until recently, PCR tests to detect *M. genitalium* for clinical diagnostic purposes in the United States were available only through specialized reference laboratories. However, in January 2019, the first commercial molecular-based assay to detect *M. genitalium* (Hologic) obtained FDA clearance. Availability of *M. genitalium* detection on the widely utilized Panther platform will likely enable identification of more infected individuals and provide an accurate assessment of disease burden. Molecular assays targeting *M. genitalium* antimicrobial resistance markers are available at specialized reference laboratories, such as the UAB Diagnostic Mycoplasma Laboratory, although commercial tests for detection of macrolide resistance are under development.

Treatment of genital *Mycoplasma* and *Ureaplasma* infections

Oral tetracyclines have historically been the drugs of choice for use against urogenital infections due to *M. hominis*, but resistance may occur in up to 50% of isolates in some populations. It is important to note that although the association of treating mycoplasma infections with macrolides is imprinted in the minds of many clinical trainees, *M. hominis* is the important exception to this rule, with almost universal macrolide resistance. Clindamycin remains active against *M. hominis* in vitro and is clinically efficacious.

In contrast, *Ureaplasma* spp. are typically resistant to clindamycin and sometimes to tetracyclines but are almost always susceptible to macrolides. A survey of clinical isolates of *Ureaplasma* spp. from various states found that 45% possessed the *tetM* transposon conferring resistance to tetracyclines. The degree of resistance may vary according to geographic area, type of patient population, and previous exposure to antimicrobial agents. Occasional macrolide-resistant *Ureaplasma* spp. have been reported, and, despite in vitro susceptibility, tetracycline or macrolide treatment of vaginal ureaplasmas is not always successful.

There are reports of fluoroquinolone resistance in both *M. hominis* and *Ureaplasma* spp. caused by mutations in DNA gyrase and/or topoisomerase IV, usually after prolonged exposure to these drugs, but most isolates remain susceptible in vitro. Activity of fluoroquinolones is not affected by tetracycline or macrolide resistance. Ciprofloxacin and ofloxacin are generally less active in vitro than levofloxacin and moxifloxacin.

Occurrence of acquired resistance to tetracyclines, fluoroquinolones, and macrolides in *M. hominis* and *Ureaplasma* spp. lends support to the recommendation that in vitro susceptibility testing is indicated when these organisms are recovered from a normally sterile body site, from immunocompromised hosts, and/or from persons who have not responded to an initial treatment.

Treatment alternatives for urogenital infections in adult and neonatal infections are provided in Tables 165.3 and 165.4, respectively.

TABLE 165.3 **TREATMENT OPTIONS FOR UROGENITAL AND SYSTEMIC INFECTIONS IN ADULTS CAUSED BY *MYCOPLASMA HOMINIS*, *MYCOPLASMA GENITALIUM*, AND *UREAPLASMA* SPECIES**[a]

Drug	Route	Dosage/24 h	Comments
Doxycycline	PO	200 mg loading dose d 1, then 100 mg q12h × 7 d	All tetracyclines have a detrimental effect on the skeletal development and bone growth of the fetus and should not be used in the second half of pregnancy or in children <8 yrs of age unless there is no other alternative
	IV	Same as PO	Treatment failures have been described for *M. genitalium* urethritis.
Tetracycline	PO IV	250–500 mg q6h × 7 d 125–500 mg q6–12h × 7 d	Activity may be inhibited in some strains of *M. hominis* and *Ureaplasma* spp. possessing *tetM*
Minocycline	PO	100 mg q12h × 14d	Activity may be inhibited in some strains of *M. hominis* and *Ureaplasma* spp. possessing *tetM*. May be useful for treatment of macrolide and fluoroquinolone-resistant *M. genitalium* infections.
	IV	200 mg initially, then 100 mg q12h × 14 d	
Erythromycin	PO IV	250–500 mg q6h × 7 d Same as PO	Not active against M. *hominis*
Azithromycin	PO	500 mg × 1 d then 250 mg × 4 d or	Not active against *M. hominis*. In vitro resistance is common and treatment failures have been described for *M. genitalium* urethritis.
		1 g as a single dose	
	IV	500 mg/d × 2 d, then 500 mg PO qd	
Clindamycin	PO	150–450 mg q6h × 7 d	• Not active against *Ureaplasma* spp.
	IV	150–900 mg q6–8h × 7 d	
Ofloxacin	PO IV	200–400 mg q12h × 7 d Same as PO	• Fluoroquinolones are not approved for use in persons <18 yrs of age
Levofloxacin	PO	500 mg qd × 7–14 d	
	IV	Same as PO	
Moxifloxacin	PO IV	400 mg q12h × 10 d Same as PO	Moxifloxacin does not have approved indications for treatment of urogenital infections, but it has been effective in men with *M. genitalium* urethritis who failed treatment with azithromycin. In vitro resistance and treatment failures may also occur.

[a] Treatment options are based on accepted regimens for urogenital infections involving other microorganisms that are expected to be suitable for infections caused by genital mycoplasmas based on in vitro susceptibility data in circumstances where there are no approved microbiologic indications. Route and duration of treatment depend on the severity of the clinical condition being treated. For extragenital and/or systemic infections, particularly those involving immunocompromised persons, a longer duration of treatment may be necessary than those listed. Joint infections may require several weeks to months of antimicrobial administration. Recommendations are based primarily on published case reports due to the lack of objective data from clinical trials.

TABLE 165.4 **TREATMENT OPTIONS FOR NEONATAL INFECTIONS WITH *MYCOPLASMA HOMINIS* AND *UREAPLASMA* SPECIES**[a]

Drug	Route	Dosage/24 h	Comments
Doxycycline	PO IV	4 mg/kg loading dose d 1, then 2–4 mg/kg/d in 1–2 doses × 10–14 d Same as PO	Tetracyclines are contraindicated in children <8 yrs of age unless no other alternative is available. Activity may be inhibited in some strains of *M. hominis* and *Ureaplasma* spp. possessing *tetM*. This drug has been used to successfully treat neonatal meningitis due to *M. hominis* and *Ureaplasma* spp., but treatment failure has been reported with *Ureaplasma* spp.
Tetracycline	PO IV	25–50 mg/kg/d in 4 doses 10–20 mg/kg/d in 2–4 doses	Tetracyclines are contraindicated in children <8 yrs of age unless no other alternative is available. Activity may be inhibited in some strains of *M. hominis* and *Ureaplasma* spp. possessing *tetM*
Chloramphenicol	PO IV	Not recommended For neonates up to 2 wks of age, use 25 mg/kg/d in 1 dose, thereafter 50 mg/kg/d in 1 dose	Chloramphenicol has been used successfully to treat neonatal meningitis due to *M. hominis* and *Ureaplasma* spp., but there has also been a report of treatment failure with *M. hominis*. Frequent monitoring of hematologic parameters and blood levels of the antibiotic are necessary due to its potential toxicity.
Erythromycin	PO IV IV	20–50 mg/kg/d in 3–4 doses 25–40 mg/kg/d in 4 doses Same as PO	Not active against *M. hominis*. Despite poor CSF penetration, this drug has been used successfully to treat neonatal meningitis due to *Ureaplasma* spp., but treatment failure has also been reported. Oral erythromycin should be avoided if alternatives are available due to an association with infantile hypertrophic pyloric stenosis.
Azithromycin	IV	20 mg/kg/d in a single dose × 3 d	Azithromycin has been shown to eradicate *Ureaplasma* spp. From the respiratory tract of preterm neonates without adverse sequelae in a small number of cases.
Clindamycin	PO IV	10–25 mg/kg/d in 3–4 doses × 10–14 d 10–40 mg/kg/d in 3–4 doses. Do not exceed 15–20 mg/kg/d	Not active against *Ureaplasma* spp. This drug has been used to successfully treat neonatal infections due to *M. hominis*

[a] No treatment guidelines for neonatal infections with genital mycoplasmas are available. Treatment options have been compiled based on in vitro susceptibility data and information described in published case reports. No dosages have been approved for neonates, so amounts listed are based on data applicable to older infants and children.

Very few clinical antibiotic trials have included microbiologic data specific for genital mycoplasmas, and there have been no systematic comparative evaluations of treatment regimens for extragenital infections in adults or for neonatal infections. Thus, treatment recommendations in Tables 165.3 and 165.4, including dosages and duration, are based largely on in vitro susceptibility data, outcomes of treatment trials evaluating clinical response to syndromes such as PID and urethritis that may be due to genital mycoplasmas, and individual case reports. For infections such as urethritis that may be venereally transmitted, sexual contacts of the index case should also receive treatment.

Clinical studies have encountered frequent treatment failures with the tetracyclines for urethritis caused by *M. genitalium*, and it was initially believed azithromycin would be a better option. However, reports of treatment failures with azithromycin and detection of *M. genitalium* isolates with elevated MICs to this drug or mutations conferring macrolide resistance (42–80%) indicate it will not always be effective. Macrolide-resistant *M. genitalium* infections have been successfully treated with fluoroquinolones (e.g., moxifloxacin). However, *M. genitalium* fluoroquinolone resistance in the United States is approximately 30% in HIV-infected men who have sex with men, with 11% additionally exhibiting macrolide resistance, according to a study from Alabama. In Europe and Japan, fluoroquinolone resistance is approximately 5–8% and 47%, respectively. Treatment regimens for macrolide- and fluoroquinolone-resistant infections are limited. A 14-day course of minocycline has proved effective in some cases. Pristinamycin has also been used successfully to treat multidrug-resistant *M. genitalium,* but it is not generally available outside of France.

Experience with mycoplasmal or ureaplasmal infections in immunocompromised patients, especially those with hypogammaglobulinemia (who have been the best studied), demonstrate that even though mycoplasmas are primarily noninvasive mucosal pathogens in the normal host, they have the capacity to produce destructive and progressive disease. Infections may be caused by resistant organisms refractory to antimicrobial therapy and require prolonged administration of a combination of IV antimicrobials, IV immunoglobulin, and/or antisera prepared specifically against

the infecting species for weeks to months. Even with aggressive therapy, relapses are still likely to occur. Repeat cultures of affected sites may be necessary to monitor in vivo response to treatment and antimicrobial susceptibility testing should be obtained, if possible.

Isolation of *M. hominis* or *Ureaplasma* spp. from CSF in neonates with pleocytosis, progressive hydrocephalus, or other neurologic abnormality; pericardial fluid; pleural fluid; tracheal aspirate in association with respiratory disease; abscess material; or blood are justification for specific treatment in critically ill neonates when no other verifiable microbiologic etiologies of the clinical condition are apparent. Azithromycin has a number of advantages over erythromycin from the pharmacokinetic standpoint, but there has been very modest clinical experience with this drug in treatment of neonatal ureaplasmal infections. A recent study demonstrated that azithromycin given intravenously at a dosage of 20 mg/kg/d in a single dose for 3 days successfully eradicated ureaplasmas from the respiratory tract of a small number of preterm neonates. Parenteral tetracyclines have been used to treat neonatal meningitis due to either *M. hominis* or *Ureaplasma* spp. despite contraindications, but erythromycin or other macrolides such as azithromycin for *Ureaplasma* spp., clindamycin for *M. hominis*, or chloramphenicol for either species are alternatives. No single drug has been successful in every instance in eradication of these organisms from CSF of neonates. Duration of treatment and drug dosages for systemic neonatal mycoplasmal or ureaplasmal infections have not been critically evaluated, but a minimum of 10 to 14 days of therapy for invasive disease such as meningitis is suggested based on experience in individual cases where microbiologic follow-up has been assessed.

Other mycoplasmal species

A variety of mycoplasmal species can be isolated from the upper respiratory tract or urogenital tracts of humans. Some of them occur fairly commonly as commensals in healthy persons, whereas others are found less often. Some of these organisms have been implicated in case reports as agents of invasive disease, usually in immunosuppressed persons. No guidelines for their detection or treatment are possible due to the infrequency of isolation and lack of clinical isolates on which in vitro susceptibility tests have been performed. In the case of *M. fermentans*, its antimicrobial susceptibilities are generally similar to those of *M. hominis*, but scant information is available for other species. If a clinical isolate of one of these opportunistic mycoplasmal species is available, in vitro susceptibility tests can sometimes be performed to guide treatment providing the organism will grow well enough in vitro to perform the test. Otherwise, empiric use of drugs shown to be effective against other mycoplasmal species as shown in Tables 165.1, 165.3, and 165.4 should be considered, with the choice being based on the type of infection encountered and status of the host.

Suggested reading

Bharat A, Cunningham S, Kreisel D, et al. Disseminated Ureaplasma infection as a cause of fatal hyperammonemia in humans. *Sci Transl Med.* 2015;7(284):284re3–284re3.

Bradshaw C, Jensen JS, Waites KB. New horizons in *Mycoplasma genitalium* treatment. *J Infect Dis*. 2017;216(Suppl); S412–419.

Bradshaw CS, Jensen JS, Tabrizi SN, et al. Azithromycin failure in *Mycoplasma genitalium* urethritis. *Emerg Infect Dis*. 2006;12:1149–1152.

CDC. 2015 Sexually Transmitted Diseases Treatment Guidelines. Emerging issues. https://www.cdc.gov/std/tg2015/emerging.htm

Dionne-Odom J, Geisler WM, Aaron KJ, et al. High prevalence of multidrug-resistant *Mycoplasma genitalium* in HIV-infected men who have sex with men in Alabama. *Clin Infect Dis.* 2018;66:796–798.

Fernández J, Karau MJ, Cunningham SA, et al. Antimicrobial susceptibility and clonality of clinical *Ureaplasma* isolates in the United States. *Antimicrob Agents Chemother*. 2016;60:4793–4798.

Gatski M, Martin DH, Theall K, et al. *Mycoplasma genitalium* infection among HIV-positive women: Prevalence, risk factors and association with vaginal shedding. *Int J STD & AIDS*. 2011;22:155–159.

Getman D, Jiang A, O'Donnell M, et al. *Mycoplasma genitalium* prevalence, coinfection, and macrolide antibiotic resistance frequency in a multicenter clinical study cohort in the United States. *J Clin Microbiol.* 2016; 54:2278–2283.

Horner P, Martin D. *Mycoplasma genitalium* infection in men. *J Infect Dis*. 2017;216(Suppl 2):S396–S405.

Kannan TR, Baseman JB. ADP-ribosylating and vacuolating cytotoxin of *Mycoplasma pneumoniae* represents unique virulence determinant among bacterial pathogens. *Proc Natl Acad Sci USA*. 2006;103:6724–6729.

Kannan TR, Hardy RD, Coalson JJ, et al. Fatal outcomes in family transmission of *Mycoplasma pneumoniae*. *Clin Infect Dis*. 2012;54:225–231.

Le Roy C, Pereyre S, Henin N, et al. French prospective clinical evaluation of the Aptima *Mycoplasma genitalium* CE-IVD assay and macrolide resistance detection using three distinct assays. *J Clin Microbiol*. 2017;55:3194–3200.

Marston BJ, Plouffe JF, File TM, et al. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. The Community-Based Pneumonia Incidence Study Group. *Arch Intern Med*. 1997;156:1709–1718.

Merchan LM, Hassan HE, Terrin ML, et al. Pharmacokinetics, microbial response, and pulmonary outcomes of multidose intravenous azithromycin in preterm infants at risk for ureaplasma respiratory colonization. *Antimicrob Agents Chemother.* 2015;59:570–578.

Schelonka R, Katz B, Waites KB, et al. A critical appraisal of the role of *Ureaplasma* in development of bronchopulmonary dysplasia using meta-analytic techniques. *Pediatr Infect Dis J*. 2006;24:1033–1039.

Shimada Y, Deguchi T, Yamaguchi Y, et al. *gyr*B and *par*E mutations in urinary *Mycoplasma genitalium* DNA from men with non-gonococcal urethritis. *Int J Antimicrob Agents*. 2010;36:477–478.

Suzuki S, Yamazaki T, Narita M, et al. Clinical evaluation of macrolide-resistant *Mycoplasma pneumoniae*. *Antimicrob Agents Chemother*. 2006;50:709–712.

Taylor-Robinson, D. Mollicutes in vaginal microbiology: *Mycoplasma hominis, Ureaplasma urealyticum, Ureaplasma parvum* and *Mycoplasma genitalium*. *Research Microbiol.* 2017;168(9–10):875–881.

Tully JG, Taylor-Robinson D, Cole RM, et al. A newly discovered mycoplasma in the human urogenital tract. *Lancet*. 1981;1:1288–1291.

Unemo M, Salado-Rasmussen K, Hansen M, et al. Clinical and analytical evaluation of the new Aptima *Mycoplasma genitalium* assay, with data on *M. genitalium* prevalence and antimicrobial resistance in *M. genitalium* in Denmark, Norway and Sweden in 2016. *Clin Microbiol Infect*. 2018;24:533–539.

Waites, KB, Duffy, LB, Bébéar, CM, et al. *Methods for antimicrobial susceptibility testing for human mycoplasmas: Approved guideline M43-A*. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.

Waites KB, Katz B, Schelonka RL. Mycoplasmas and ureaplasmas as neonatal pathogens. *Clin Microbiol Rev*. 2005;18:757–789.

Waites KB, Xiao L, Paralanov V, et al. Molecular methods for the detection of *Mycoplasma* and *Ureaplasma* infections in humans: A paper from the 2011 William Beaumont Hospital Symposium on molecular pathology. *J Mol Diagn*. 2012;14:437–450.

Waites KB, Xiao L, Liu Y, et al. *Mycoplasma pneumoniae* from the respiratory tract and beyond. *Clin Microbiol Rev.* 2017;30:747–809.

Wiesenfeld H, Manhart L. *Mycoplasma genitalium* in Women: Current knowledge and research priorities for this recently emerged pathogen. *J Infect Dis.* 2017;216(Suppl 2):S389–S395.

Chlamydia pneumoniae

Margaret R. Hammerschlag

The first isolates of *Chlamydia pneumoniae* were obtained serendipitously during trachoma studies in the 1960s. After the recovery of a similar isolate from the respiratory tract of a college student with pneumonia in Seattle, Grayston and colleagues applied the designation "TWAR" after their first two isolates, TW-183 and AR-39. *C. pneumoniae* appears to be a common human respiratory pathogen. The mode of transmission remains uncertain but probably involves infected respiratory tract secretions. Spread of *C. pneumoniae* within families and enclosed populations, such as military recruits, prisons, and nursing homes, has been reported. The proportion of community-acquired pneumonia in children and adults associated with *C. pneumoniae* infection has ranged from 0% to >44%, varying with geographic location, the age group examined, and the diagnostic methods used. Early studies that relied on serology suggested that infection in children <5 years was rare; however, subsequent studies using culture and/or polymerase chain reaction (PCR) have found the prevalence of infection in children beyond early infancy to be similar to that found in adults.

Studies that have used culture have found a poor correlation with serology, especially in children. Although 7% to 13% of children 6 months to 16 years of age enrolled in two multicenter pneumonia treatment studies were culture positive, and 7% to 18% met the serologic criteria for acute infection with the microimmunofluorescence (MIF) test, they were not the same patients. Only 1% to 3% of the culture-positive children met the serologic criteria, and approximately 70% were seronegative. By age 20, approximately 50% of persons will have detectable anti-*C. pneumoniae* immunoglobulin G (IgG). Seroprevalence may exceed 80% in some populations.

Prolonged culture positivity lasting from several weeks to several years after acute infection has been reported. Asymptomatic nasopharyngeal carriage also occurs in 2% to 5% of adults and children. The role that asymptomatic carriage plays in the epidemiology of *C. pneumoniae* is not known, but possibly these persons serve as a reservoir for spread of infection.

Most *C. pneumoniae* infections are probably mild or asymptomatic. Initial reports emphasized mild, atypical pneumonia clinically resembling that associated with *Mycoplasma pneumoniae*. Generally, pneumonia associated with *C. pneumoniae* is not clinically indistinguishable from other pneumonias. Coinfection with other pathogens, especially *M. pneumoniae* and *Streptococcus pneumoniae*, are frequent. *C. pneumoniae* pneumonia has been associated with severe illness and even death, although the role of preexisting chronic conditions as contributing factors in many of these patients is difficult to assess. In some cases, however, *C. pneumoniae* clearly appears to be implicated as a serious pathogen, even in the absence of underlying disease. *C. pneumoniae* has been isolated from the empyema fluid in several patients with severe pneumonia.

The role of host factors in *C. pneumoniae* infection remains to be determined. *C. pneumoniae* appeared to be responsible for 14% to 19% of episodes of acute chest syndrome in children with sickle cell disease. *C. pneumoniae* infection in these patients appeared to be associated with more severe hypoxia than infection with *M. pneumoniae. C. pneumoniae* is also an inflammatory trigger for asthma.

The role of *C. pneumoniae* in upper respiratory infections is less well defined. *C. pneumoniae* has been isolated from the middle ear fluid of children and adults with otitis media and has also been implicated as a cause of pharyngitis. *C. pneumoniae* infection has been implicated in a wide variety of chronic diseases and conditions, including atherosclerosis, Alzheimer's disease, macular degeneration, and arthritis. However, many of these studies are hampered by the lack of standardized methods for the diagnosis of *C. pneumoniae* infection.

Laboratory diagnosis

A specific laboratory diagnosis of *C. pneumoniae* infection can be made by identification of the organism from nasopharyngeal or throat swabs, sputa, or pleural fluid, if present, by culture or nucleic acid amplification test (NAAT). The nasopharynx appears to be the optimal site for isolation of the organism. The relative yield from throat swabs and sputum is not known. Isolation of *C. pneumoniae* requires culture in tissue; the organism cannot be propagated in cell-free media. *C. pneumoniae* grows readily in cell lines derived from respiratory tract tissue, specifically, HEp-2 and HL cells. Culture with an initial inoculation and one passage should take 4 to 7 days.

Nasopharyngeal cultures can be obtained with Dacron-tipped, wire-shafted swabs. Each lot of swabs should be treated in a mock infection system to ensure that no inhibitory effects occur on either the viability of cells or recovery of chlamydiae. Specimens for culture should be placed in appropriate transport media, usually a sucrose phosphate buffer with antibiotics and fetal calf serum, and stored immediately at 4°C/39°F for no longer than 24 hours. Viability decreases if specimens are held at room temperature. If the specimen cannot be processed within 24 hours, it should be frozen at −70°C/−94°F until culture can be performed. After 72 hours of incubation, culture confirmation can be performed by staining with either a *C. pneumoniae* spp.-specific or a *Chlamydia* genus-specific (antilipopolysaccharide [anti-LPS]) fluorescein-conjugated monoclonal antibody.

There are now three multiplexed PCR respiratory panels cleared by the US Food and Drug Administration (FDA) that include *C. pneumoniae*: BioFire FilmArray, GenMark ePlex, and Luminiex NxTAG Respiratory Pathogen Panel. Each includes respiratory viruses and *M. pneumoniae*. The BioFire FilmArray also includes *Bordetella pertussis*. Studies using these panels have found the performance in adults and children with respiratory illness to be generally equivalent. Identification of *C. pneumoniae* has been low, <1%, which is consistent with epidemiologic studies done over the past 10 years. If the assays are run onsite, the turnaround time is usually 1 to 2 hours.

Because isolation of *C. pneumoniae* was initially considered to be difficult and limited, emphasis was placed on serologic diagnosis. The MIF test is not standardized or FDA-approved. Although enzyme immunoassay (EIA) serology test kits offer the promise of standardized performance and objective endpoints, none has been evaluated adequately in comparison to culture or PCR. Most have been compared only with MIF. None has FDA clearance or approval for use in the United States. One commercial assay, the Medac rELISA, uses a recombinant LPS antigen; others are based on LPS-extracted EBs or synthetic peptides. These kits can measure IgG, IgM, and IgA antibodies, but cutoffs vary from kit to kit, and the criteria for a positive result (acute infection, past infection) can be very complex. The US Centers for Disease Control and Prevention (CDC) has proposed modifications of the serologic criteria for diagnosis of *C. pneumoniae* infection. Although the MIF test was considered to be the only serologic test currently acceptable, the criteria were made significantly more stringent. Acute infection as determined by MIF was defined as a fourfold rise in IgG or an IgM titer of ≥16, and the use of a single elevated IgG titer was discouraged. However, the use of paired sera also affords only a retrospective diagnosis, which is of little help in terms of deciding how to treat a patient. An IgG titer of ≥16 was considered to indicate past exposure, but neither elevated IgA titer nor any other serologic marker was thought to be a validated indicator of persistent or chronic infection. The CDC did not recommend the use of any EIA for detection of antibody to *C. pneumoniae*.

Therapy

C. pneumoniae is susceptible to tetracyclines, macrolides, and quinolones. Most of the treatment studies of pneumonia caused by *C. pneumoniae* published thus far have relied entirely on diagnosis by serology; consequently, microbiologic efficacy could not be assessed. Anecdotal reports have suggested that prolonged courses, up to 3 weeks, of either tetracyclines or erythromycin may be needed to eradicate *C. pneumoniae* from the nasopharynx of adults. The results of two pediatric multicenter pneumonia treatment studies found that 10-day courses of erythromycin and clarithromycin and 5 days of azithromycin suspension were equally efficacious; they eradicated the organism in 79% to 86% of children. Quinolones, including levofloxacin and moxifloxacin, also have been demonstrated to have 70% to 80% efficacy in eradicating *C. pneumoniae* from adults with community-acquired pneumonia. Most patients improved clinically despite persistence of the organism. Persistence does not appear to be secondary to the development of antibiotic resistance.

Based on these limited data, regimens for respiratory tract infection caused by *C. pneumoniae* are listed in Table 166.1. Some patients may require retreatment.

TABLE 166.1 **REGIMENS FOR RESPIRATORY TRACT INFECTION CAUSED BY *CHLAMYDIA PNEUMONIAE***

Adults	Children
Doxycycline, 100 mg 2 × a day for 14–21 d	Erythromycin suspension, 50 mg/kg/d for 10–14 d
Tetracycline, 250 mg 4 × a day for 14–21 d	Clarithromycin suspension, 15 mg/kg/d for 10 d
Azithromycin, 1.5 g over a period of 5 d	Azithromycin suspension, 10 mg/kg on day 1 followed by 5 mg/kg/d once daily on days 2 to 5
Levofloxacin, 500 mg/d orally or intravenously for 7–14 d	
Moxifloxacin, 400 mg/d orally for 10 d	

Suggested reading

Fajardo KA, Zorich SC, Voss JD, et al. Pneumonia outbreak caused by *Chlamydophila* pneumoniae among US Air Force Academy cadets, Colorado, USA. *Emerg Infect Dis*. 2015;21:1049–1051.

Hammerschlag MR, Kohlhoff SA, Gaydos CA. *Chlamydia pneumoniae*. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas and Bennett's: Principles and Practice of Infectious Diseases, 9th ed. Elsevier, Inc. Philadelphia, PA; 2020:2323–2331.

Kohlhoff SA, Hammerschlag MR. Treatment of chlamydial infections: 2014 update. *Expert Opin Pharmacother*. 2015;16:205–212.

Roulis E, Polkinghorne A, Timms P. *Chlamydia pneumoniae*: Modern insights into an ancient pathogen. *Trend Microbiol*. 2013;21:120–128. doi:pii: S0966–842X(12)00197–7. 10.1016/j.tim.2012.10.009.

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Chlamydophila psittaci (psittacosis)

Thomas J. Marrie

Epidemiology and pathogenesis

The first description of a respiratory illness following exposure to a sick bird (a parrot) was by Ritter in 1879. In 1892, Morange described an outbreak of respiratory illness following exposure to sick parrots; he named this illness *psittacosis* (from *psittakos*, Greek for parrot). In 1930, investigators in the United Kingdom, the United States, and Germany isolated the causative agent which eventually was named *Chlamydia psittaci.*

Chlamydiae are gram-negative obligate intracellular bacterial pathogens. The phylum Chlamydiae has two genera—*Chlamydia* and *Chlamydophila*. *Chlamydophila* species are *C. pecorum*, *C. pneumoniae*, *C. psittaci*; *C. abortus*, *C. caviae,* and *C. felis*.

Chlamydophila psittaci spp. consists of at least 20 genotypes with isolates from a variety of mammals, reptiles, and many avian species. The genome of *C. psittaci* has 1,156,417 base pairs. There are 8 serovars (A to F, M56 and WC) and 9 genotypes of *C. psittaci*. Serovars A to F are of avian origin, and M 56 and WC are of mammalian origin. WC was isolated from Wolfsen cattle and M56 from muskrats. Genotype A is most commonly found in psittacine birds; Genotype B in feral pigeons and other bird species; it is endemic in European non-psittacine birds; Genotype C is found in ducks and dogs; Genotype D is found in poultry, especially turkeys; Genotypes E and F are uncommon but are found in various bird species. In one study of 10 human isolates of *C. psittaci* from the Netherlands genotype A accounted for 5 isolates; B for 3; C for 1, and there was 1 novel isolate that may represent a new genotype of *C. psittaci*.

C. psittaci along with other Chlamydiae has a unique development cycle with elementary (the infectious particle) and reticulate (the intracellular replicative particle) bodies. After infection elementary bodies (EBs) attach to and enter the host cell by endocytosis. Elementary bodies differentiate into reticulate bodies (RBs), and, after about 36 hours, the RBs differentiate back into EBs. About 500 to 1,000 EBs accumulate in the cell as intracytoplasmic inclusions. During this process, chlamydial antigens are released onto the host cell surface, inducing a host immune response. Release of EBs occurs by several processes including extrusion of the inclusion. The EB is metabolically inactive whereas the RB is metabolically active. In humans, following inhalation, *C. psittaci* reaches the alveoli and from there spreads to regional lymph nodes, the bloodstream, and the reticuloendothelial cells of the liver and spleen. A lymphocytic inflammatory response occurs in the alveoli and interstitium of the lungs resulting in edema of the alveolar walls and interstitial tissues. Occasionally necrosis occurs. Histologically the alveolar spaces are filled with fluid, red blood cells, and lymphocytes. The macrophages may contain Levinthal-Coles-Lille cytoplasmic inclusions (the RBs) that are characteristic of psittacosis.

In turkeys *C. psittaci* infects epithelial cells and macrophages in the respiratory tract. This is followed by spread via the bloodstream and localization of the organisms in epithelial cells and macrophages in various organs.

C. psittaci has been found worldwide in 467 species from 30 bird orders. Affected birds include members of the parrot family (macaws, cockatoos, parakeets, budgerigars), finches (canaries, bullfinches, goldfinches, sparrows), poultry (hens, ducks, geese, turkeys), pigeons, pheasants, egrets, gulls, puffins, swans, pheasants, and doves.

The organism is excreted in the feces of infected birds, and transmission to humans is via aerosolization of the organism. Transmission can occur in the absence of apparent illness in the birds. In a study conducted in a German chicken and turkey slaughterhouse, 85% of the chicken flocks were polymerase chain reaction (PCR)- and culture-positive for *C. psittaci*, as were 57% of the turkey flocks. Genotype D was isolated. Eighty-seven percent of the employees were positive for this organism by PCR and 61% by culture. Air sampling revealed viable *C. psittaci* organisms.

Person-to-person transmission can occur but is so uncommon that respiratory precautions for patients with psittacosis are not recommended. However, the case of a 73-year-old man who was admitted with severe pneumonia due to *C. psittaci* may change that. Subsequently, there were 10 cases of psittacosis due to exposure to this patient, 7 of whom were healthcare workers.

Pet store workers, veterinarians, poultry breeders, and others are at risk by virtue of occupation. Bird owners and even the public with casual contact with infected domestic or wild birds can also be at risk.

Clinical syndromes

Birds

In birds, psittacosis manifests as anorexia, apathy, ocular and nasal discharge, diarrhea, and conjunctivitis. The organism is present in high concentrations in the droppings of birds. A carrier state can occur and then there is intermittent shedding. Crowding and transportation of birds result in increased spread of the infection among a bird colony.

Humans

The clinical spectrum of *C. psittaci* infection in humans is wide, ranging from a subclinical illness to severe pneumonia. The incubation period ranges from 5 to 15 days. Fever, rigors, sweats, and headache are common. Cough, occurring in from 50% to 100% of patients, appears late in the course of illness and usually is nonproductive or productive of mucoid sputum. About 20% of patients have no respiratory symptoms. The wide range of clinical manifestations has led some workers in the field to indicate that there are six or seven presentations of psittacosis: (1) nonspecific manifestations consisting of fever with rigors, sweats, and constitutional symptoms but no localizing features, which occurs in 41% of patients; (2) a second form dominated by prominent cough and occasionally dyspnea in association with fever; this is the major presentation in one-third of patients; (3) a third form presents as severe headaches suggestive of meningitis; (4) a fourth, uncommon, form that presents with severe diarrhea; and (5) a form that presents as pharyngitis, which occurred in 21% of patients. An alteration of mental status was noted in 12%. A sixth presentation is that of a mononucleosis-like syndrome with fever, pharyngitis, hepatosplenomegaly, and lymphadenopathy. These distinctions serve to illustrate that the clinical spectrum of manifestations of *C. psittaci* infection is wide, and a high index of suspicion is necessary to make the diagnosis.

It is also critical to remember the extrapulmonary manifestations of psittacosis. These include Horder's spots (a pink, blanching maculopapular eruption resembling the rose spots of typhoid fever), acrocyanosis, superficial venous thrombosis, and splinter hemorrhages. Panniculitis, erythema multiforme, and erythema nodosum are other cutaneous manifestations. Neurological manifestations include encephalitis, meningitis, cerebellar involvement, cranial nerve palsies, intracranial hypertension, and transverse myelitis. Acute renal failure, interstitial nephritis, pancreatitis, and thrombocytopenic purpura have also complicated psittacosis. Other manifestations include reactive arthritis and hemophagocytosis. Rarely *C. psittaci* is a cause of endocarditis.

Psittacosis during pregnancy is uncommon, but when it occurs it may be severe.

The white blood cell count is usually normal in psittacosis. The radiographic features of pneumonia due to *C. psittaci* are not distinctive. The pleural fluid in psittacosis may have a high adenosine deaminase level. This could result in confusion with tuberculosis, since an adenosine deaminase level of >43 IU/L in pleural fluid is believed to be sensitive and specific for tuberculosis.

In a review of 57 studies of community acquired pneumonia with at least 100 cases as an inclusion criterion, the authors found that *C. psittaci* accounted for 1.03% (0.79–1.30) of cases.

In a study from the Netherlands, investigators estimated 1,640 cases of psittacosis and 9 deaths from this infection annually from 2012—2014. Using a model that estimates the burden of an infectious disease in terms of disability adjusted life years (DALY) and years of life lived with disability they found that psittacosis resulted in 222 DALY per year, a number comparable to that of rubella and shigellosis.

Chlamydophila psittaci and ocular adnexal mucosa-associated lymphoid tissue type (MALT) lymphomas

Lymphomas of the ocular adnexa (the eyelid, conjunctiva, orbit, lacrimal gland, and lacrimal sac) are not uncommon. Orbital lymphomas usually present as solitary, painless masses that cause displacement of the globe, ptosis, and diplopia. In one study 39/44 patients with such lymphomas had *C. psittaci* DNA detected by PCR. Treatment with doxycycline was associated with an improved response rate.

Diagnosis

Isolation

Chlamydiae are organisms that are easily damaged. To maximize the chance of isolating such organisms, the specimens should be

placed in transport media, kept cold, and transported to the laboratory as soon as possible. Sputum, bronchial washings, biopsy specimens, and blood are suitable specimens from which to isolate *C. psittaci*. This organism is quite infectious and has caused many laboratory-acquired infections. It should only be handled in a biocontainment level 3 laboratory. Specimens are inoculated onto cycloheximide-treated monolayers of McCoy cells in shell vials. Following incubation for 48 to 72 hours organisms are detected by staining with group-specific fluorescent monoclonal antibodies.

Serology

A fourfold increase in antibody titre between acute and convalescent serum samples is the most common method of diagnosis. The complement fixation test or the microimmunofluorescence (MIF) tests can be used. A single IgM titre of ≥1:32 by MIF is diagnostic, as is a fourfold rise in antibody titer between acute and convalescent serum samples. The MIF test has improved the sensitivity and specificity of testing for *C. psittaci.* However, cross-reactivity between *C. pneumoniae* and *C. psittaci* can be a problem. Cross-reactivity with *Legionella longbeachae* has also been reported.

Nucleic acid amplification

PCR has been used to amplify *C. psittaci* from a variety of specimens.

Therapy

Tetracyclines, macrolides, and fluoroquinolones have good activity against *C. psittaci*. Ciprofloxacin is the least active and should not be used. High-level azithromycin resistance occurs spontaneously due to a point mutation in the 23 S rRNA gene.

The treatment of choice is generally doxycycline administered in a dose of 100 mg twice daily for 14 days. Seriously ill patients should be treated with intravenous doxycycline.

Second-line therapy is with levofloxacin, moxifloxacin, or gatifloxacin.

Treatment failures are not uncommon when erythromycin is used. Azithromycin is effective probably due to its long half-life and intracellular concentration.

Prevention

All those who own pet birds or who work with birds should be familiar with the guidelines for preventing and controlling *C. psittaci* infections.

Suggested reading

De Ggier B, Hogerwerf L, Dijkstra F, van der Hoek W. Disease burden of psittacosis in the Netherlands. *Epidemiol Infect*. 2018;146:303–305.

Gherman RB, Leventis LL, Miller RC. Chlamydial psittacosis during pregnancy: A case report. *Obstet Gynecol*. 1995;86:648.

Hogerwerf L, De Grier B, Baan B, van der Hoek W. *Chlamydia psittaci* (psittacosis) as a cause of community-acquired pneumonia: A systematic review and meta-analysis. *Epidemiol Infect*. 2017;145:3096–3011.

Smith KA, Bradley KK, Stobierski MG, Tengelsen LA. Compendium of measures to control Chlamydophila psittaci (formerly Chlamydia psittaci) infections among humans (psittacosis) and pet birds 2005. *JAVMA*. 2005;226:532–539.

Wallensten A, Fredlund H, Runehagen A. Multiple human-to-human transmission from a severe case of psittacosis, Sweden, January-February 2013. *Euro Surveill*. 2014 19(42):pil=20397.

Yung AP, Grayson ML. Psittacosis: A review of 135 cases. *Med J Australia*. 1998;148:228.

Section 21

Specific organisms: Rickettsia, Ehrlichia, and Anaplasma

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Rickettsial infections

Noah Wald-Dickler and Paul D. Holtom

The family *Rickettsiaceae* are small, aerobic, gram-negative coccobacilli that are obligate intracellular parasites of eukaryotic cells. Rickettsiae are divided into three groups based on clinical presentation: the spotted fever group, the typhus group, and scrub typhus. *Coxiella burnetii*, the causal agent of Q Fever, is covered in this chapter but is now classified in the γ-proteobacteria group, together with *Legionella* and *Francisella tularensis* (Table 168.1).

Rickettsial disease pathogenesis is characterized by systemic vasculitis whereby the organisms proliferate in vascular endothelial cells of host arterioles, capillaries, and veins. In Q fever the organisms are acquired by inhalation of dust contaminated by birth fluids of domestic ungulates and proliferate in the lungs, causing inflammation and bacteremic seeding of other organs, particularly the liver. All other medically relevant rickettsial diseases are vector-borne and acquired from a variety of arthropods including ticks, fleas, mites, and lice.

In the treatment of rickettsioses, one must stress that proper therapy cannot be given unless the diagnosis is suspected. Diagnostic confirmation is usually serologic and almost always delayed because antibodies occur no earlier than the second week of illness. Arthropod-borne rickettsioses are diseases of the spring and summer in temperate climates. Q Fever can occur in any season if exposure to aerosols of the organism occurs. Given an appropriate geographic, temporal, and/or occupational history, the clinical triad of fever, headache, and rash should raise suspicion of a rickettsial disease. As early treatment is important in preventing mortality, particularly in Rocky Mountain spotted fever (RMSF), therapy should be instituted when the diagnosis is suspected, even while awaiting serologic confirmation.

Rocky Mountain spotted fever

RMSF was first described in the late 1800s in the Bitterroot Valley of Montana. Prevalence was thought to shift from the western United States to the South Central and South Atlantic, but, since 2008, more cases have been reported in Mexico and Central America with immigration and ease of travel contributing to a resurgence of cases in the US Southwest. The causative agent is *Rickettsia rickettsii*, a member of the spotted fever group of rickettsial infections. In 2009, epidemiologic reporting reclassifications resulted in changing RMSF to the more broad "spotted fever rickettsiosis" (SFR), which includes RMSF as well as diseases caused by other rickettsial species, including *R. parkeri* and *R. philipii*. Using this new definition, there were 4,269 US cases of SFR reported in 2016, the majority of which were presumed to be RMSF. SFR incidence has increased from 4 to 8 per million in 2000 to 25 per million in 2015.

Ticks are both the vectors and the main reservoirs of *R. rickettsii*; the specific tick responsible for transmission varies from region to region. The dog tick, *Dermacentor variabilis*, and the wood tick, *D. andersoni*, predominate in the eastern and western United States, respectively. Humans are infected by *R. rickettsii* either by release of organisms from the salivary glands of a feeding tick or by exposure to infected tick hemolymph, which may occur during tick removal, especially if the tick is crushed. The incubation period of RMSF ranges from 2 to 14 days (with a median of 7 days) prior to symptom onset.

TABLE 168.1 **DISEASES CAUSED BY RICKETTSIAE**

Disease	Organism	Geographic distribution	Vector
Spotted Fever Group			
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Western Hemisphere	Tick
Spotted fever	*Rickettsia parkeri*	United States	Tick
Boutonneuse	*Rickettsia conorii*	Africa, Mediterranean, India	Tick
Queensland tick typhus	*Rickettsia australis*	Australia	Tick
North Asian tick typhus	*Rickettsia sibirica*	Russia, Asia, Africa, France	Tick
Japanese spotted fever	*Rickettsia japonica*	Japan, China	Tick
Flinders Island spotted fever	*Rickettsia honei*	Australia, Thailand	Tick
African tick-bite fever	*Rickettsia africae*	Sub-Saharan Africa, West Indies	Tick
Fleaborne spotted fever	*Rickettsia slovaca*	United States	Tick
Rickettsialpox	*Rickettsia aeschlimannii*	Europe	Tick
	Rickettsia felis	Africa	Flea
	Rickettsia akari	Western Hemisphere, Europe, Russia, Korea, Africa	Mite
Typhus group			
Epidemic typhus	*Rickettsia prowazekii*	Western Hemisphere, Africa, Asia	Louse
Murine typhus	*Rickettsia typhi*	Worldwide	Flea
Scrub typhus	*Orientia tsutsugamushi*	Asia, Australia, South Pacific	Mite
Other			
Q fever	*Coxiella burnetii*	Worldwide	Airborne

Virtually all patients have fever, usually >38.9°C/102°F. The major diagnostic sign is the rash, seen in approximately 90% of patients, which usually occurs within 3 to 5 days after the onset of fever. Fewer than half of patients show the rash during the first 3 days of the illness; as a result rash is often absent when patients first seek medical care. The rash typically starts around the wrists and ankles, but it may start on the trunk or be diffuse at onset. Although involvement of the palms is considered characteristic, this does not occur in all patients and often occurs late in the course of the disease (Figure 168.1). Other common symptoms include severe headache, myalgias, and gastrointestinal complaints such as nausea, vomiting, and severe abdominal pain.

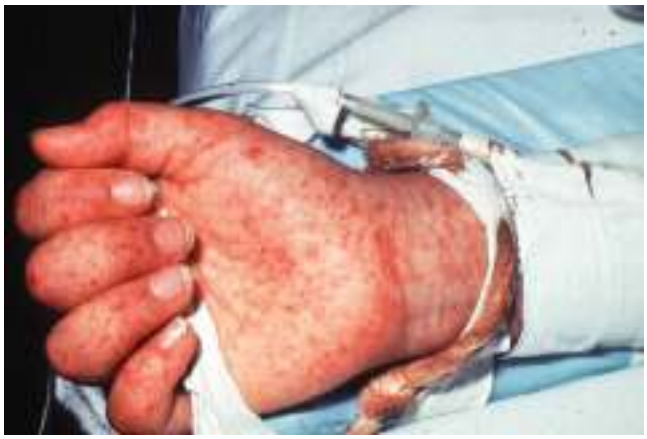

FIGURE 168.1 Petechial rash in Rocky Mountain spotted fever. Courtesy of David Schlossberg, MD.

Complications of RMSF include meningismus, meningitis, renal failure, pulmonary involvement, hepatic dysfunction with development of jaundice, splenomegaly, myocarditis, and thrombocytopenia. In early reports, RMSF case fatality rates were >20% in the absence of early therapy; in recent series, death occurs in 4% to 8% of the cases. In those with fulminant RMSF, death occurs 8 to 15 days after the onset of symptoms.

Diagnosis of RMSF is primarily based on a high clinical suspicion in the setting of a patient with fever, headache, and myalgias with exposure to ticks. A skin biopsy of a rash lesion (when present) can show *R. rickettsii* with immunohistochemistry staining or nucleic acid amplification test. This has a specificity of 100% and a sensitivity of 70% but is useful only in patients who have developed a rash. Serologic diagnosis is retrospective. The use of the polymerase chain reaction (PCR) is not well established for the diagnosis of RMSF.

Treatment of RMSF requires the administration of an effective antibiotic for 7 days, continuing for 2 days after the patient has become afebrile. Early therapy is important, as the risk of death is five times greater in patients treated after day 5 of illness. The antibiotic of choice for both adults and children is oral doxycycline, 100 mg every 12 hours for 7 days, or at least 2 days after the patient becomes afebrile. Tetracycline, 25 to 50 mg/kg/d in four doses, is also effective. In patients with hypersensitivity to tetracyclines and in pregnant patients, chloramphenicol, 50 to 75 mg/kg/d, is a

less effective alternative. Although fluoroquinolones have shown activity against *R. rickettsii*, they are not recommended because of a lack of clinical experience. Glucocorticosteroids have been given to severely ill patients in the past, but there is no documentation of their efficacy. No vaccine is currently available to prevent RMSF.

Other spotted fever group rickettsia

The SFRs include *R. rickettsiae*, but also *R. parkeri, R. felis, R. akari*, and *R. philipii*—all cause human infections in the United States. Except for *R. akari*, whose invertebrate host is a mite, all SFG rickettsiae reside in tick hosts. The change to SFR nomenclature reflects the inability to differentiate between spotted fever group *Rickettsia* spp. using commonly available serologic tests. Successful treatment for SFR members has been reported using doxycycline (200 mg/d), with alternatives including tetracycline, chloramphenicol, or ciprofloxacin for 5 to 7 days.

R. akari causes the nonfatal disease rickettsialpox, first reported in 1946 in New York but with worldwide distribution in Asia and Eastern Europe. The reservoir for *R. akari* is the house mouse, *Mus musculus*, and the vector for transmission to humans is the mouse mite (or "chigger") *Allodermanyssus sanguineus*. Clinically, a painless papule arises then ulcerates and forms an eschar at the site of the mite bite 3 to 7 days before the onset of systemic symptoms including chills, fever, headache, myalgia, backache, and photophobia. Rigors and profuse diaphoresis may be seen. Within 2 to 3 days after onset, a generalized papulovesicular rash occurs with multiple lesions leading to the term "rickettsialpox" which distinguishes the disease from other rickettsioses with only one or a few lesions. The rash begins as red papules 2 to 10 mm in diameter that vesiculate and heal by crusting. The disease is usually benign; death and complications are very rare. Mediterranean spotted fever is a similar disease caused by *R. conorii* in Italy, Greece, Turkey, and other Mediterranean regions.

Epidemic or louse-borne typhus

This classic plague of humanity is caused by *R. prowazekii* and transmitted by the human body louse *Pediculus humanus corporis*. The bacteria may remain latent in humans for many years after the initial infection and then relapse when persons are stressed by other disease or deprivations. Thus, during war and refugee exodus, where poverty, deprivation, and poor hygiene promote the spread of lice, a rickettsemic person may initiate the cycle and cause an epidemic. This relapsing disease is generally milder than an initial attack, presumably because it occurs in a person with some established immunity. This recrudescent typhus is called *Brill–Zinsser disease*. An extrahuman reservoir has been identified in southern flying squirrels, *Glaucomys volans*, throughout the eastern United States. Humans are infected by flying squirrel fleas.

The characteristic incubation period is 8 to 16 days. The onset is usually abrupt, with intense headache, progressive fever, chills, and severe myalgia. The rash begins around day 5 of illness, usually in the axillary folds and upper trunk, and spreads centrifugally. Unlike many rickettsial rashes, the rash of epidemic typhus characteristically lacks an initial eschar. Rather, the rash begins as blanching pink macules that progress to become maculopapular, darker, petechial, and nonfading on pressure. The rash may become confluent and involve the entire body, but the face, palms, and soles are spared. In the pre-antibiotic era, mortality was seen in 13%, occurring a median of 12.5 days after illness onset; survivors defervesced a median of 14 days after onset. Epidemic typhus from flying squirrel exposure is a similar but milder illness.

The established therapy for epidemic typhus is doxycycline (100 mg BID), tetracycline (25–50 mg/kg/d in four doses), or chloramphenicol (60–75 mg/kg/d in four doses) given for 7 to 10 days. In epidemic situations where the availability of doxycycline may be limited, a single dose of 200 mg of doxycycline may be effective, but a small proportion of patients may relapse. No vaccine is currently available for the prevention of typhus; the only prevention available is control of body lice by hygiene and insecticides such as permethrin.

Endemic or murine typhus

Murine typhus, caused by *R. typhi*, has worldwide distribution, especially in tropical and subtropical seaboard regions. Its most important reservoirs are *Rattus* spp. rats, and the classic vector that spreads the organisms from rats to people is the flea *Xenopsylla cheopis*. Although rats are the primary animal reservoir of *R. typhi*, other mammals (including opossums and domestic dogs and cats) can also serve as reservoirs. A recent outbreak of endemic typhus was identified in Los Angeles in 2018, primarily associated with homeless persons in downtown.

Murine (endemic) typhus is clinically less severe than epidemic typhus and often self-limited, with reported case fatality rates of 1% to 4%. Illness begins 1 to 2 weeks after an infected flea bite. Initial nonspecific symptoms of fever, headache, chills, myalgia, and nausea are accompanied by rash in about 20% of patients at presentation and in about 50% sometime during the illness. Skin lesions are macular or maculopapular. The trunk is most often involved, but extremity involvement is seen in about half of patients who develop the rash, which may also be seen on the palms and soles. The rash is usually salmon-colored and evanescent, but a frank hemorrhagic vasculitic rash may develop. Occasionally, patients develop central nervous system abnormalities, hepatic or renal failure, respiratory failure, or hematemesis. Diagnosis is suggested by risk factors and clinical findings and can be confirmed by a fourfold or greater rise in *R. typhi* antibody titers from paired serum specimens taken ≥3 weeks apart or by detection of *R. typhi* DNA in a clinical specimen (i.e., skin biopsy) by PCR.

R. typhi infection is treated with doxycycline, tetracycline, or chloramphenicol. Antimicrobial therapy should be continued for 2 to 3 days after defervescence.

Scrub typhus

Scrub typhus occurs when a larval stage trombiculid mite (chigger) infected with *Orientia tsutsugamushi* bites a susceptible human host. The disease occurs throughout the Asia-Pacific region and is endemic in Korea, China, Japan, Southeast Asia, and Australia; it is considered one of the most underdiagnosed causes of febrile illness in the Asian region.

Some 6 to 18 days after a chigger bite, patients develop high fever, severe headache, mental status changes, lymphadenopathy, and myalgia. An eschar may be found at the site of the bite. The severity of the signs and symptoms is widely variable depending on the virulence of the responsible strain and the degree of susceptibility of the host. After about 5 days, a macular rash, sometimes evanescent, may occur, beginning on the trunk and spreading to the extremities. Complications include multiple organ system dysfunction and hemorrhage, pneumonia, heart failure, respiratory failure, and renal failure. Case fatality rates as high as 30% in untreated patients have been reported, but treatment shortens the duration of illness and essentially eliminates fatalities.

Doxycycline and chloramphenicol are the recommended treatments. Doxycycline can be given as a single dose of 200 mg or for a course of 3 to 7 days. Alternative drugs include rifampin (600–900 mg/d) and azithromycin (500 mg initial dose, then 250 mg/d).

Q fever

Coxiella burnetii, the etiologic agent of Q fever, was discovered simultaneously in the 1930s in Montana as the cause of a human laboratory-acquired infection and in Australia, where researchers were investigating an outbreak of febrile illness among slaughterhouse workers they called "Query" (Q) fever. Q fever can present as an acute infection with an influenza-like illness, including pulmonary and hepatic involvement, or it can develop into a chronic infection with endocarditis and chronic granulomatous hepatitis. *C. burnetii* is an extremely infectious organism: a single inhaled organism is sufficient to initiate infection. It is endemic worldwide except in New Zealand. *C. burnetii* infects many species of animals, and the infection usually results in long-lasting parasitism. Q fever in humans is usually caused by the inhalation of aerosolized particles from infected domestic animals; these particles can be airborne over long distances. *C. burnetii* is asymptomatic in about half of those infected. Those with clinical illness most commonly have a nonspecific febrile illness, which may be associated with pneumonia, hepatitis, or meningoencephalitis. Patients can go on to develop a chronic illness characterized by endocarditis and granulomatous hepatitis.

The incubation period for Q fever can be as short as 4 to 5 days, but it typically ranges from 9 to 39 days. High fever is the most common symptom, occurring in almost all patients, with temperature often spiking to 40°C/104°F to 40.5°C/105°F). Pneumonia is the primary clinical manifestation, with a majority of patients showing abnormalities on chest radiography. Other signs and symptoms include chills, headache (often severe and debilitating), retrobulbar pain, myalgias and arthralgias, neck pain and stiffness, pleuritic chest pain, cough, nausea and vomiting, diarrhea, jaundice, hepatomegaly, and splenomegaly. Unlike the rickettsial diseases, Q fever does not usually present with a rash, although a transient erythematous macular rash has been noted in about 4% of patients. The manifestations of Q fever usually resolve within 2 to 4 weeks, although some patients have fever for as long as 9 weeks. Case fatality rates from acute Q fever are very low (none in most series), but in hospitalized patients the case fatality rate has been reported as 2.4%.

Chronic Q fever is uncommon (<5% of patients with acute infections) and usually manifested by endocarditis. Most patients have preexisting valvular heart disease, often a prosthetic valve. Other manifestations include chronic hepatitis, infections of vascular prostheses and aneurysms, osteomyelitis, and interstitial pulmonary fibrosis. The illness evolves slowly, manifesting any time from a few months to 20 years after the acute infection, and presents clinically as a culture-negative endocarditis, although fever is often absent in Q fever endocarditis. Post-Q fever fatigue syndrome, lasting for several years to life, is the most common chronic manifestation after acute infection, occurring in up to 20% of patients.

The diagnosis of Q fever is based on identifying risk factors and clinical suspicion. Culture is not recommended as it is difficult and dangerous, requiring a biosafety level 3 laboratory. Serologic testing of paired acute and convalescent sera, showing a fourfold increase of IgG to *C. burnetii* phase II antigen by an indirect immunofluorescence antibody assay, is the most common method for diagnosing acute Q fever. PCR testing of blood or tissue is another diagnostic method, but different tests vary in sensitivity and specificity.

Most acute Q fever infections resolve spontaneously, but, given concern about the development of chronic Q fever, specific antimicrobial therapy should be given. The treatment of choice is doxycycline orally for 2 weeks; some success has been reported with trimethoprim-sulfamethoxazole (TMP-SMX), chloramphenicol, rifampin, and (in vitro) telithromycin.

The treatment of chronic Q fever has never been the subject of controlled studies. Current recommendations are to give doxycycline together with hydroxychloroquine for at least 18 months, a regimen shown in retrospective data to be superior to long-term tetracycline plus a fluoroquinolone in Q fever endocarditis. A vaccine for people in at-risk professions is available in Australia but requires testing before vaccination to identify preexisting immunity, as it can lead to a severe local reaction.

Suggested reading

Bechah Y, Raoult D, et al. Epidemic typhus. *Lancet Infect Dis*. 2008;8(7):417–426.

Civen R, Ngo V. Murine typhus: An unrecognized suburban vectorborne disease. *Clin Infect Dis*. 2008;46:913–918.

Cunha BA. Clinical features of Rocky Mountain spotted fever. *Lancet Infect Dis*. 2008;8:143–144.

Luce-Fedrow A, Lehman ML, et al. A review of scrub typhus (*Orientia tsutsugamushi* and related organisms): Then, now, and tomorrow. *Trop Med Infect Dis*. 2018;3(1):8.

Million M, Raoult D. Recent advances in the study of Q fever epidemiology, diagnosis and management. *J Infect*. 2015;71(Suppl 1):S2–9.

Paddock CD, Zaki SR, Koss T, et al. Rickettsialpox in New York City: A persistent urban zoonosis. *Ann NY Acad Sci*. 2003;990:36–44.

Reynolds MG, Krebs JS, Comer JA, et al. Flying squirrel-associated typhus, United States. *Emerg Infect Dis*. 2003;9:1341–1343.

Ehrlichiosis and anaplasmosis

Johan S. Bakken and J. Stephen Dumler

Ehrlichiosis is the collective name for infections caused by obligate intracellular gram-negative bacteria in the genera *Ehrlichia*, *Anaplasma*, and *Neoehrlichia*, family Anaplasmataceae. Members of these genera cycle between invertebrate (arthropod) and vertebrate hosts, and some cause human zoonoses. At least seven species cause human tick-borne infection in the United States and Europe, including *Ehrlichia chaffeensis*, the agent of human monocytic ehrlichiosis (HME), *Ehrlichia ewingii*, the agent of human ewingii ehrlichiosis (HEE), *Anaplasma phagocytophilum*, the agent of human granulocytic anaplasmosis (HGA), an *Ehrlichia muris*-like agent (EMLA), the Panola Mountain ehrlichia, an agent phylogenetically similar to *Ehrlichia ruminantium* that has caused fever in humans in the United States, *Ehrlichia canis*, thought limited to canids but identified as an agent of human febrile illness in Venezuela, and *Candidatus* Neoehrlichia mikurensis, which has caused severe sepsis-like conditions in Europe, but mild febrile disease in Asia. While human infection by *Neorickettsia sennetsu* periodically surfaces in Asia, the transmission and disease processes are distinct and it will not be considered here.

Most Anaplasmataceae reside in ixodid (hard-body) ticks, and the bacteria are acquired during the larval stage and passed transstadially with each successive tick stage. *Amblyomma americanum* (the Lone Star tick) is the vector for *E. chaffeensis* and *E. ewingii*, and its range is throughout the south and eastern United States from Maine to Texas. In addition, all documented reports of human infections are limited to North America, although some evidence suggests that they exist in ticks in South America and Asia. In contrast, *A. phagocytophilum* and the *E. muris*-like agent cycle within *Ixodes* species ticks. *Ixodes scapularis* (the black-legged or deer tick) is found in the eastern United States and is a vector for both species. In addition, *Ixodes pacificus* (the western black-legged tick), found in regions of the US Pacific coast (northern California, Oregon, and Washington), and *Ixodes ricinus* and *Ixodes persulcatus*, found in Europe and Asia, respectively, are competent vectors for *A. phagocytophilum*. *Ixodes* species ticks are also vectors for *Borrelia burgdorferi* (the agent of Lyme borreliosis), and most cases of HGA are reported from areas where Lyme borreliosis is endemic.

Thus far, HGA has been reported in 36 US states and in countries in western and central Europe, as well as Russia, China, Korea, and Japan. Active US surveillance in southeastern Missouri identified HME incidence as high as 414 cases per 100 000 population. The incidence for HGA varies from 25 up to 58 cases per 100 000 in endemic regions of Connecticut and Wisconsin. Only a limited number of cases of HEE have been recognized in central US states, but it is anticipated to be common. Clinical cases of infection by the *E. muris*-like agent were recently recognized in up to 48 patients in Wisconsin and Minnesota, and a small fraction of healthy blood donors in Minnesota and Wisconsin have evidence of past exposure. Less than 20 Venezuelan patients with *E. canis* infection, and only a small number of infections by *Candidatus* N. mikurensis, likely transmitted by *I. ricinus* ticks in Europe, have been identified; there is only a single report of Panola Mountain ehrlichia human infection. Most cases of ehrlichiosis present during the period between April and October, and as many as 75% of patients have noted one or more tick bites 1 to 2 weeks prior to the onset of symptoms. Male patients outnumber females by a factor of nearly 3 to 2, and even though HME and HGA affect all age groups, symptomatic infection is less frequent in children. The case-fatality rate is 0.6% and 2.7% for HGA and HME, respectively. Table 169.1 summarizes some of the

TABLE 169.1 **EPIDEMIOLOGIC CHARACTERISTICS, INCIDENCE RATES AND REPORTED CASES ASSOCIATED WITH HUMAN MONOCYTIC EHRLICHIOSIS (HME), HUMAN EWINGII EHRLICHIOSIS (HEE), HUMAN GRANULOCYTIC ANAPLASMOSIS (HGA), *EHRLICHIA MURIS*-LIKE AGENT (EMLA) INFECTION AND *CANDIDATUS* NEOEHRLICHIA MIKURENSIS INFECTION**

Bacterial species	***Ehrlichia chaffeensis***	***Ehrlichia ewingii***	***Ehrlichia muris-like agent***	***Anaplasma phagocytophilum***	***Candidatus Neoehrlichia mikurensis***
Tick vector	*Amblyomma americanum*	*A. americanum*	*Ixodes scapularis*	*Ixodes scapularis* (USA) *Ixodes pacificus* (USA) *Ixodes ricinus* (Europe) *Ixodes persulcatus* (Asia) *Haemaphysalis concinna* (Asia)	*Ixodes ricinus* (Europe) *?Ixodes ovatus* (Japan)
Clinical illness	HME	HEE	EMLA infection	HGA	No name
Year first reported	1987	1999	2009	1994	2009
Known geographic distribution	Atlantic USA Southeast USA South Central USA	South Central USA	Upper Midwest (USA)	Upper Atlantic (USA) Upper Midwest (USA) Pacific coast (USA) North and central Europe Asia (China, Korea, Japan, Eastern Russia)	Central Europe Northeast China
Target leukocyte	Monocyte Macrophage	Neutrophilic granulocyte	Monocyte	Neutrophilic granulocyte	?Neutrophilic granulocyte
Incidence rate (cases/100 000)	14	Unknown	Unknown	20	Unknown
Reported cases (*n*)[a]	9411	≤50	44	12 764	15

[a] As of 09/13/2013 per MMWR Weekly Reports, CDC.

epidemiologic characteristics associated with HME, HEE, HGA, EMLA-associated illness, and *Candidatus* N. mikurensis infection.

When the tick takes a blood meal, bacteria become injected with the tick saliva into the host. Once injected, the bacteria infect specific circulating leukocytes and cause a nonspecific febrile illness. *Ehrlichia chaffeensis* and EMLA typically infect monocytes and macrophages, whereas *E. ewingii* and *A. phagocytophilum* infect neutrophilic granulocytes; *Candidatus* N. mikurensis has been observed only once in human neutrophils but its definitive target is not yet established. The bacteria adhere to leukocyte membrane receptors to enter cells by endocytosis. There are key differences in the vacuoles with *E. chaffeensis* and *A. phagocytophilum*, underscoring that the agents induce distinct pathogenetic pathways. Regardless, the bacteria reside within cytoplasmic vacuoles, where they interact with the host cell to access nutrients, delivering effector proteins to the host cytosol and nucleus that subvert host cell functions, including intracellular signaling, cell cycle regulation, innate immune responses such as respiratory burst or induction of immune activation, delayed induction of apoptosis, and subversion of autophagy, among others. During this interval, the bacteria multiply in the vacuole to form aggregates called morulae. Eventually, each morula fuses with the cell membrane through exocytosis or the cell is mechanically lysed, liberating bacteria to infect other cells. Most recent investigations of disease pathogenesis focus on the induction of innate, inflammatory, and immune-mediated injury as the major consequence of infection. This suggests that an important target for control of disease could include control of inflammatory and immune responses.

Even though they differ with respect to biology, epidemiology, and ecology, HME, HEE, HGA, and infection with EMLA present as clinically similar illnesses with characteristic, albeit nonspecific alterations in hematology and chemistry laboratory tests. The incubation period for HME, HEE, HGA, and EMLA varies between 1 and 2 weeks following tick exposure or tick bite. The symptoms and signs range from asymptomatic to fatal, and clinical severity increases with patient age and comorbid illnesses. Ehrlichiosis presents as a clinical syndrome most commonly manifest by abrupt onset of fever, shaking chills, severe headache, and myalgia (Table 169.2); a specific diagnosis can be difficult because of the undifferentiated nature of the signs and symptoms. Between one-third and one-half of symptomatic patients require hospitalization for 1 week or longer. Infection with *Candidatus* N. mikurensis can result in either a severe febrile illness that lasts for weeks in the absence of therapy, as observed in Europe where most patients had pre-existing immune compromise, or as a mild to moderate and self-limited illness, as observed in Asia where most patients were not immune compromised.

TABLE 169.2 **MEAN FREQUENCY OF SYMPTOMS AND SIGNS OBSERVED IN PATIENTS WITH HUMAN MONOCYTIC EHRLICHIOSIS (HME), HUMAN GRANULOCYTIC ANAPLASMOSIS (HGA), HUMAN EWINGII EHRLICHIOSIS (HEE), *EHRLICHIA MURIS*-LIKE AGENT (EMLA) INFECTION, AND *CANDIDATUS* NEOEHRLICHIA MIKURENSIS INFECTION AMONG PUBLISHED CASE SERIES**

Prevalence of complaint	Symptom or sign	HME (%) *n = 451*	HGA (%) *n = 750*	HEE (%) *n = 8*	EMLA (%) *n=48*	*N. mikurensis ehrlichiosis* *n = 13*
Common	Fever (T >38.0°C)	97	93	100	87	92
	Headache	76	62	63	66	62
	Myalgia/arthralgia	82	66	38	69	38
Less common	Nausea	62	40	25	na	38
	Vomiting	40	28	25	na	38
Uncommon	Pneumonitis or cough	27	25	0	na	31
	Confusion / altered	21	26	0	na	8
	mental status	33[a]	6[b]	0	0	31
	Rash					

[a] Mostly in children.
[b] All erythema migrans in Lyme borreliosis coinfected patients.
Abbreviations: T = temperature; na = data not available.

Laboratory abnormalities are nonspecific and include various leukopenia and thrombocytopenia with a differential leukocyte count that reveals increased proportions of band neutrophils and a corresponding decrease in relative and absolute lymphocyte concentrations. In addition, most patients manifest mild to moderate increases in serum transaminase activities reflecting underlying hepatocellular injury. Albeit relatively insensitive, the diagnosis can be confirmed by blood smear examination, because morulae can be observed in peripheral blood leukocytes of 1% to 20% of patients with HME and as many as 60% of patients with HGA during the first week of infection (Figure 169.1). Polymerase chain reaction (PCR) is an excellent tool for diagnosing HME, HEE, HGA, and EMLA during the early stage of infection, and sensitivity >90% and specificity >95% are regularly achieved. However, the availability of these PCR assays is limited to large commercial, academic medical, or public health reference laboratories. More than 95% of patients with HME and HGA form specific antibodies during the course of the infection, and testing of acute and convalescent sera using indirect fluorescent antibody (IFA) tests is currently the most sensitive method for laboratory confirmation of HME and HGA, even though the diagnosis is only retrospective. Antibody titers remain elevated for months to years after convalescence, and no evidence of persistent infection associated with clinical disease has ever been observed. Serologic cross-reactivity between *Ehrlichia*

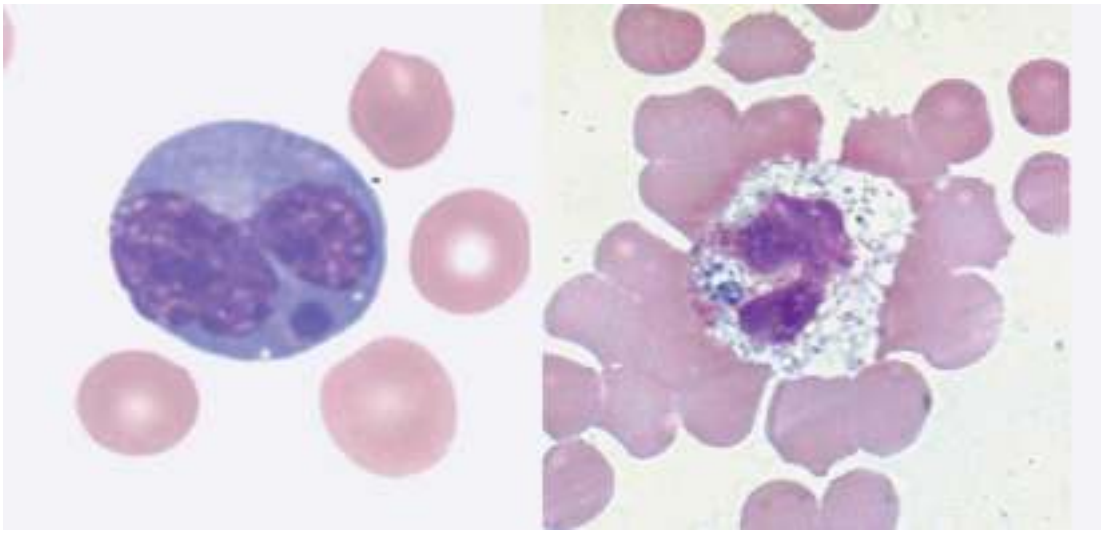

FIGURE 169.1

spp. and *Anaplasma phagocytophilum* is frequent, but differential titers can be helpful. No specific serologic tests exist for either HEE or EMLA. Most diagnoses of Panola Mountain ehrlichia and *Candidatus* N. mikurensis infections have been made by specific or broad-range PCR.

Laboratory criteria for *probable* HME and HGA include a compatible exposure history and clinical illness combined with (1) the detection of morulae in peripheral blood, (2) a single high positive IFA titer, or (3) positive PCR of acute phase blood. The criteria for a *confirmed* case of HME or HGA requires (1) demonstration of seroconversion (4-fold or greater change in serum antibody titer) with *E. chaffeensis* or *A. phagocytophilum*, (2) isolation of *E. chaffeensis* or *A. phagocytophilum* in culture from blood, or (3) a single elevated IFA titer combined with either detection of morulae in the peripheral blood smear or a positive PCR. Formal laboratory criteria for probable or confirmed HEE, EMLA or *Candidatus* N. mikurensis infection have yet to be established.

Therapy

Ehrlichia and *Anaplasma* are susceptible in vitro to tetracycline, tetracycline derivatives, and rifampin. However, no controlled clinical trials of antimicrobial agent efficacy have been conducted and treatment recommendations are therefore based on the experience from empirical antibiotic treatment of infected humans. Even though HME and HGA can manifest as self-limited febrile illnesses that resolve spontaneously without therapy, it is currently recommended that any patient diagnosed with acute infection should receive antibiotic treatment. Doxycycline, 100 mg administered twice daily (oral or intravenous route), is the treatment of choice for adults. Doxycycline, 2 mg/kg, maximum dose 100 mg, given twice daily, is the preferred treatment for children who are seriously ill. The response to doxycycline is rapid; most patients become afebrile and resolve symptoms within 24 to 36 hours. In fact, failure to respond to doxycycline should prompt further clinical evaluation of the patient for an alternative diagnosis. The optimal duration of therapy with doxycycline has not been established. Serologic surveys demonstrate that 15% to 20% of patients with active HGA also are seroreactive with *B. burgdorferi*, the agent of Lyme borreliosis. Doxycycline therapy should therefore be administered for 10 to 14 days to ensure adequate coverage for potential co-incubating Lyme borreliosis.

Treatment with rifampin can be considered for pregnant women, known hypersensitivity to tetracycline class drugs, and children younger than 8 years with mild to moderate illness suitable for outpatient management. The dose of rifampin is 300 mg given twice daily for adults and 10 mg/kg (maximum dose 300 mg) twice daily for children for 5 to 7 days. Chloramphenicol is not recommended for treatment of ehrlichiosis, since in vitro susceptibility assays with chloramphenicol demonstrate poor activity against *E. chaffeensis* and *A. phagocytophilum*, and treatment failures with fatal outcome have been noted. Fluoroquinolones have in vitro activity against *A. phagocytophilum*, but not *E. chaffeensis*; however, limited experience has shown that levofloxacin is apparently not bactericidal and should not be used to treat HGA.

Human ehrlichioses are for the most part self-limited clinical illnesses that resolve spontaneously, even without active antibiotic therapy. Unlike Lyme borreliosis and babesiosis, HME, HEE, HGA, and EMLA have not been reported to be associated with persistent infection, but several patients with *Candidatus* N. mikurensis infection had severe febrile illnesses that lasted as long as several weeks before treatment or death. The long-term prognosis after resolved HME, HEE, HGA, and EMLA appears favorable, and patients should expect to make a complete recovery.

Suggested reading

Bakken JS, Dumler JS, Chen SM, et al. Human granulocytic ehrlichiosis in the upper Midwest United States. A new species emerging? *JAMA*. 1994;272:212–218.

Buller RS, Arens M, Hmiel SP, et al. *Ehrlichia ewingii*, a newly recognized agent of human ehrlichiosis. *N Engl J Med*. 1999;341:148–155.

Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States: a practical guide for physicians and other health-care and public health professionals. *MMWR Recomm Rep*. 2006;55:1–27.

Hamburg BJ, Storch GA, Micek ST, Kollef MH. The importance of early treatment with doxycycline in human ehrlichiosis. *Medicine (Baltimore)*. 2008;87:53–60.

Li H, Jiang JF, Liu W, et al. Human infection with *Candidatus* Neoehrlichia mikurensis, China. *Emerg Infect Dis*. 2012;18:1636–1639.

Pritt BS, Sloan LM, Johnson DK, et al. Emergence of a new pathogenic *Ehrlichia* species, Wisconsin and Minnesota, 2009. *N Engl J Med*. 2011;365:422–429.

Welinder-Olsson C, Kjellin E, Vaht K, et al. First case of human "*Candidatus* Neoehrlichia mikurensis" infection in a febrile patient with chronic lymphocytic leukemia. *J Clin Microbiol*. 2010;48:1956–1959.

Section 22

Specific organisms: Fungi

170

Candidiasis

Christopher F. Carpenter and Nicholas Gilpin

Candida spp. are small, unicellular yeasts that are found in a number of environments, including soil, hospital surroundings, food, and other inanimate objects. Most species also may live as commensal organisms, colonizing the skin, gastrointestinal tract, and vagina. They become opportunistic pathogens when the host has compromised immunologic or mechanical defenses or when there are changes in the host's normal flora, such as those triggered by broad-spectrum antibiotic use and chemotherapy. *Candida* spp. are common causes of disease ranging from superficial cutaneous and mucocutaneous infections to invasive infections such as candidemia and disseminated candidiasis. There are >150 species of *Candida*, with *Candida albicans* (Figure 170.1) being the most frequently implicated in human disease processes. Over the past two decades, however, there has been a noticeable increase in disease due to non-*albicans* species. Important non-*albicans* pathogens include *C. tropicalis* (Figure 170.2), *C. parapsilosis*, *C. glabrata* (Figure 170.3), *C. krusei* (Figure 170.4), *C. kefyr*, *C. lusitaniae*, *C. dubliniensis*, *C. guilliermondii*, and *C. auris*. This latter organism, *C. auris*, is an emerging multidrug-resistant pathogen that is causing healthcare-associated outbreaks of severe infections. Less commonly isolated species with medical significance include *C. lipolytica*, *C. famata*, *C. rugosa*, *C. viswanathii*, *C. haemulonii*, *C. norvegensis*, *C. catenulate*, *C. ciferri*, *C. intermedia*, *C. utilis*, *C. lambica*, *C. pulcherrima*, and *C. zeylanoides*.

Diagnosis of *Candida* infections continues to be primarily via culture, although a number of faster and more sensitive contemporary diagnostic methods have become available, including polymerase chain reaction (PCR), CHROMagar (Figure 170.5), and T2Candida. Indirect diagnostic methods have also become more widely used in clinical practice, such as the serum or plasma (1→3)-β-D-glucan (BDG) assay, which is specific for a unique component of the cell wall in many fungi that is detectable during invasive candidiasis. Given that several *Candida* species have intrinsic or acquired resistance to antifungal agents (Table 170.1), these tests may prove to be cost-effective approaches for guiding early appropriate antifungal therapy in certain clinical settings. Newer antifungal agents have become available for the treatment of *Candida* infections, including advanced-generation triazoles and the echinocandins (Table 170.2), which are particularly useful when antifungal resistance is suspected or proved.

Infectious syndromes and treatment/prophylaxis

Mucocutaneous *Candida* syndromes

Cutaneous candidiasis

Primary cutaneous candidiasis is commonly seen in normal hosts manifesting as diaper dermatitis and intertriginous infections. Other manifestations include balanitis, folliculitis, paronychia, and onychomycosis. Cutaneous candidiasis most commonly presents in skin areas that are moist and/or occluded or in areas of impaired skin integrity, such as burns or chronic wounds. Immunocompromised patients, including patients with diabetes mellitus, are also at increased risk. Cutaneous candidiasis is generally a clinical diagnosis,

FIGURE 170.1 *Candida albicans* on CHROMagar.
Courtesy of Dr. Barbara Robinson-Dunn and Ms. Mrudula Nandwana, Beaumont Health.

FIGURE 170.2 *Candida tropicalis* on CHROMagar.
Courtesy of Dr. Barbara Robinson-Dunn and Ms. Mrudula Nandwana, Beaumont Health.

demonstrated by the presence of a confluent erythematous rash with satellite lesions in a typical warm, moist environment such as the perineum or axilla. Microscopic examination of skin scrapings revealing budding yeast cells and hyphae may be useful to confirm the diagnosis. Positive cultures for *Candida* species may also assist with diagnosis; however, positive results may occur because of colonization or contamination, and thus culture is generally not recommended. Bacterial superinfection may also coexist with cutaneous candidiasis and sometimes necessitates antimicrobial therapy. Non-antimicrobial methods are important in both prevention and treatment of cutaneous candidiasis, such as keeping skin surfaces clean and dry, frequent diaper changes, and control of hyperglycemia in patients with diabetes. Topical antifungals such as nystatin cream or an imidazole cream are the mainstay of treatment. Systemic therapy with fluconazole, itraconazole, or terbinafine is rarely required for severe or refractory cases.

Chronic mucocutaneous candidiasis

Individuals with chronic mucocutaneous candidiasis suffer from persistent and recurrent *Candida* infections of the skin, nails, and mucous membranes. It most commonly occurs within the first two decades of life. T-cell dysfunction is the primary immunologic abnormality associated with chronic mucocutaneous candidiasis, although other immune abnormalities such as immunoglobulin deficiency and cutaneous anergy have been described. Several endocrine disorders have been associated with chronic mucocutaneous candidiasis, such as hypoparathyroidism, Addison's disease, hypothyroidism, and diabetes. The disease is a complex disorder that may manifest as one of many different syndromes with variable severity, although associated invasive disease is quite rare.

Therapy for mucosal infections is typically accomplished with topical or systemic triazole antifungal agents. A significant problem with mucosal disease is its propensity for repeated relapses, particularly among immunocompromised hosts and persons with HIV infection. Chronic suppressive therapy is usually unnecessary but is occasionally employed in select cases, with the associated risk of emerging resistance.

Oropharyngeal and esophageal candidiasis

As normal members of the gastrointestinal tract flora, *Candida* spp. become pathogenic in the oropharynx and esophagus in patients with various risk factors, including impaired cell-mediated immunity (e.g., HIV infection, chronic mucocutaneous candidiasis, stem cell and solid organ transplant recipients), diabetes mellitus, extremes of age, or esophageal motility disorders. The use of certain medications, including progesterone, broad-spectrum antibiotics, or immunosuppressive agents is also a contributing factor in many cases.

Oral candidiasis most commonly presents as creamy white, plaque-like lesions on the oropharyngeal mucosa or tongue surface.

FIGURE 170.3 *Candida glabrata* on CHROMagar.
Courtesy of Dr. Barbara Robinson-Dunn and Ms. Mrudula Nandwana, Beaumont Health.

Candidiasis lesions are typically painless, but atypical and more symptomatic forms may exist, such as erythematous or pseudomembranous plaques (erythematous candidiasis), *Candida* leukoplakia, or hyperplastic candidiasis. Angular cheilitis, a painful condition with associated cracking and erythema at the oral commissure, can also be a result of *Candida* infection. As with cutaneous candidiasis, oropharyngeal candidiasis is usually a clinical diagnosis. Cultures are not usually recommended because of the potential for positive results due to colonization. For treatment of mild disease, clotrimazole troches or nystatin suspension for about 7 to 14 days are recommended first-line agents. For more moderate to severe oropharyngeal candidiasis, often seen in patients with HIV infection, systemic therapy with low-dose oral fluconazole for 7 to 14 days is generally recommended. Infections that are refractory to fluconazole should be managed with another systemic antifungal agent, such as an extended-spectrum azole or echinocandin.

FIGURE 170.4 *Candida krusei* on CHROMagar.
Courtesy of Dr. Barbara Robinson-Dunn and Ms. Mrudula Nandwana, Beaumont Health.

Esophageal candidiasis often presents as dysphagia or odynophagia, usually with retrosternal pain. Clinically, it can be difficult to distinguish *Candida* esophagitis from other causes of esophagitis, such as cytomegalovirus esophagitis, herpes simplex virus esophagitis, esophageal ulcers, eosinophilic esophagitis, or pill esophagitis. The presence of oral thrush coupled with dysphagia or odynophagia has relatively good predictive value for esophageal candidiasis, and a therapeutic trial is a reasonable alternative to endoscopy in such patients. Empirical therapy should include a systemic antifungal for about 14 to 21 days; typically, fluconazole in oral or parenteral form is prescribed. In rare circumstances, an alternative antifungal agent such as an echinocandin, extended-spectrum triazole, or low-dose amphotericin B may be required. In refractory cases, endoscopy with mucosal brushings or biopsy may be necessary to confirm the diagnosis, test for antifungal resistance, and evaluate for other potential concomitant pathogens or disorders (Figures 170.6 and 170.7).

Vulvovaginal candidiasis

Vulvovaginal candidiasis (VVC) is common in women of childbearing age and is the most common form of mucosal candidiasis. Several host risk factors can predispose to VVC, including pregnancy, oral contraceptive use, antibiotic use, diabetes mellitus, HIV infection, and the presence of an intrauterine device or a diaphragm. Often no precipitating factor can be found. The mechanism by which asymptomatic colonization transforms into symptomatic VVC remains unclear. For clinical purposes, VVC may be classified as complicated or uncomplicated (Table 170.3). About 90% of cases are classified as uncomplicated. The clinical manifestations of VVC are primarily vulvar pruritus, vaginal discharge, dyspareunia, dysuria, and vaginal irritation, although none of these symptoms is particularly sensitive or specific. Signs include erythema and edema of the vulva with erythema of the vagina and vaginal discharge of variable consistency, often described as thick and curd-like. As with other forms of mucocutaneous candidiasis, the diagnosis is typically made clinically, but confirmation is easily obtained by observing budding yeast, with or without pseudohyphae, on a wet mount or 10% potassium hydroxide preparation of vaginal secretions. Evaluation for concomitant pathogens or sexually transmitted infections is also prudent.

Uncomplicated VVC can be managed successfully with a number of topical antifungal agents, with courses ranging from single doses to short courses of 3 to 7 days. Alternatively, fluconazole as a single

FIGURE 170.5 Mixture of *Candida* species (*C. albicans, C. tropicalis, C. glabrata*, and *C. krusei*) on CHROMagar.
Courtesy of Dr. Barbara Robinson-Dunn and Ms. Mrudula Nandwana, Beaumont Health.

dose of 150 mg is also quite effective. Treatment with azoles results in symptomatic relief in about 80% to 90% of patients who complete therapy, and no agent is considered clearly superior.

Complicated VVC, including recurrent VVC (RVVC, usually defined as four or more episodes of symptomatic VVC in 1 year), affects a small percentage of women with VVC (≤5%). Vaginal cultures should be obtained to confirm the clinical diagnosis of RVVC and to identify unusual species, including non-*albicans* species such as *C. glabrata*, for which conventional antifungal therapies may not be as effective. Each individual episode of RVVC caused by *C. albicans* usually responds well to short-duration oral or topical azole therapy, but in some situations a course of induction therapy followed by a maintenance dose of suppressive antifungal therapy for several months is necessary for control of symptoms. Unfortunately, 30% to 50% of women will have recurrent disease after suppressive therapy is discontinued. For pregnant patients with VVC, topical therapy for 7 days is recommended.

Candidemia and disseminated candidiasis

Candidemia

Candida species are a significant cause of nosocomial bloodstream infections in the United States. Crude mortality rates of candidemia range from 30% to 61% with attributable mortality ranging as high as 49%. *Candida* species, like some bacterial pathogens, are capable of forming biofilms on catheters and other surfaces, leading to infections that are difficult to eradicate. Certain risk factors are known to predispose to candidemia, but it remains exceedingly difficult to clinically predict which patients will develop infection. For example, colonization with yeast remains a leading risk factor for infection in the intensive care unit (ICU). However, the prevalence of colonization in the ICU is high (50–70% or more), which corresponds to a low predictive value given the relatively low rate of invasive infection. Nevertheless, colonization in ICU patients

TABLE 170.1 *CANDIDA* SPECIES AND COMMON SUSCEPTIBILITY PATTERNS

	Triazoles		Extended-spectrum triazoles	Polyenes	Echinocandins	
Species	Fluconazole	Itraconazole	Voriconazole, posaconazole, isavuconazole	Amphotericin b	Caspofungin, anidulafungin, and micafungin	Risk factors
C. albicans	S	S	S	S	S	HIV/AIDS, surgery
C. glabrata	S-DD to R	S-I	S-I	S-I	S	Hematologic malignancies, azole prophylaxis
C. parapsilosis	S	S	S	S	S to S-I	Foreign bodies, azole prophylaxis, neonates
C. tropicalis	S	S	S	S	S	Neutropenia
C. krusei	R	S-I to R	S	S-I	S	Hematologic malignancies, azole prophylaxis
C. guilliermondii	S-I to R	S	S	R	S to S-I	Azole prophylaxis, previous amphotericin treatment
C. lusitaniae	S	S	S	R	S to S-I	Previous amphotericin treatment

Abbreviations: HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome; S = susceptible; S-DD = susceptible-dose dependent; S-I = intermediate; R = resistant.

TABLE 170.2 **ANTIFUNGAL AGENTS**

Class	Antifungal
Polyene	Conventional amphotericin B
	Lipid formulations of amphotericin B (liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloid dispersion)
Triazole	Fluconazole
	Itraconazole
	Voriconazole (extended spectrum)
	Posaconazole (extended spectrum)
	Isavuconazole (extended spectrum)
Echinocandin	Caspofungin
	Anidulafungin
	Micafungin

with unexplained fever, leukocytosis, and hypotension merits strong consideration of invasive candidiasis and candidemia as a potential cause of sepsis, as delay of antifungal treatment portends significantly high mortality. In all cases, candidemia requires antifungal treatment and removal of potential sources, such as vascular devices. Search for additional foci of infection is also critical, as dissemination to areas such as the eye, liver, spleen, kidney, heart, soft tissues, bone, central nervous system (CNS), and gastrointestinal tract may occur. This is of particular concern in patients who are immunocompromised. Given the high morbidity and mortality of candidemia and disseminated candidiasis, azole susceptibility testing is recommended for all bloodstream and invasive *Candida* isolates, and echinocandin susceptibility testing should be considered if previously treated with an echinocandin or if infected with *C. glabrata* or *C. parapsilosis*.

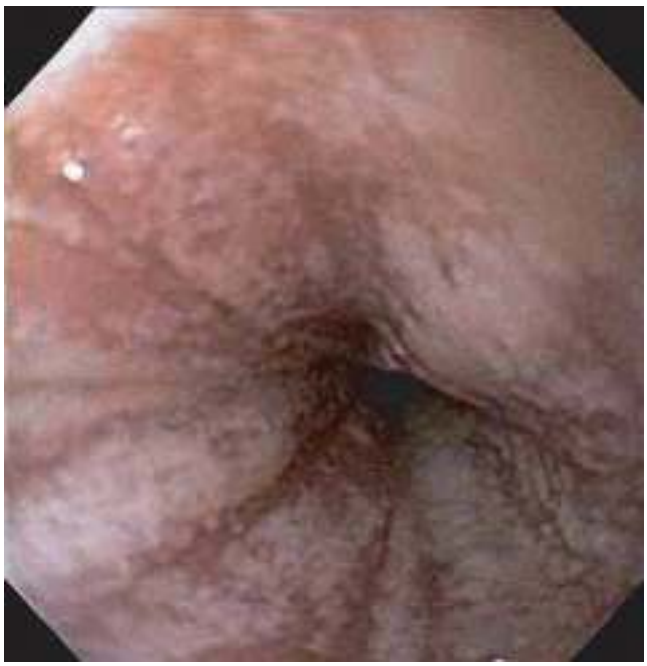

FIGURE 170.6 Endoscopic view, *Candida* esophagitis.

Echinocandins are recommended as empiric therapy for suspected invasive candidiasis, though fluconazole may be considered in select patients who are not critically ill and who are unlikely to harbor azole-resistant *Candida* spp. *C. albicans* is usually susceptible to most antifungals, including fluconazole, whereas other species are more likely to demonstrate reduced susceptibility or resistance to select antifungals. For example, *C. krusei* should be considered resistant to fluconazole and itraconazole, but it is usually susceptible to voriconazole, echinocandins (nearly 100% susceptible), and amphotericin B formulations (though higher doses may be required). *C. glabrata* has variable dose-dependent susceptibility to fluconazole and itraconazole, and it may be frankly resistant to these antifungals. It also typically shows some degree of cross-resistance to the newer triazoles, although voriconazole could be considered as step-down therapy if susceptible. The echinocandins have activity against most *Candida* spp., although *C. parapsilosis* typically has relatively higher minimum inhibitory concentrations to these antifungals. The clinical relevance of these in vitro data is not clear.

For non-neutropenic patients, potential antifungal choices include caspofungin (70 mg loading dose followed by 50 mg/d), micafungin (100 mg/d), or anidulafungin (200 mg loading dose followed by 100 mg/d). Fluconazole (800 mg [12 mg/kg] loading dose, followed by 400 mg [6 mg/kg] per day) may be considered in less ill individuals unlikely to have fluconazole-resistance. Amphotericin B or a lipid-based amphotericin B formulation is an alternative that is much less commonly used for this indication today, generally only if there is intolerance to the other antifungal agents. Most neutropenic patients should initially be managed with an echinocandin. Select circumstances may lead to use of a lipid-based amphotericin B formulation, fluconazole, or voriconazole or other extended-spectrum azole. All candidemia treatment should be extended for at least 2 weeks after clearance of candidemia and resolution of sepsis. For neutropenic patients, recovery of neutrophil counts is another important factor, and antifungal treatment should generally be continued until this occurs. Step-down oral therapy with an azole may be considered after 5 to 7 days in patients who are clinically stable with negative repeat blood cultures and who have isolates susceptible to the azole. Dilated ophthalmological examination should be performed in all patients within the first week after diagnosis, and it should be deferred until or repeated within the first week after neutrophil recovery for neutropenic patients.

Chronic disseminated candidiasis

Chronic disseminated candidiasis (CDC, formerly hepatosplenic candidiasis) is an indolent process most commonly found in patients with severe persistent neutropenia (e.g., in patients with acute leukemia or stem cell transplant recipients) that frequently becomes apparent when the neutrophil count begins to recover. It typically involves the liver and/or spleen, although other organs may be involved. CT or MR) studies are helpful in confirming the diagnosis (>90% sensitive), often by identifying small discrete lesions within the liver or spleen. Unfortunately, such lesions may be absent early in

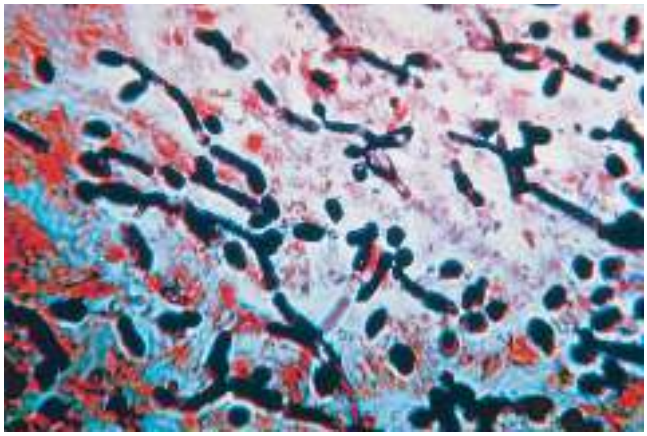

FIGURE 170.7 Photomicrograph of esophageal candidiasis (silver stain, ×100).
Courtesy of Sherry Brinkman, CDC Public Health Image Library.

the course of disease. Signs and symptoms of CDC are neither sensitive nor specific and may include right upper quadrant tenderness, elevated transaminases and alkaline phosphatase concentrations, and hepatosplenomegaly. Blood cultures are often negative, and biopsy may be required to confirm the diagnosis. Much of what is known about treatment of CDC has been gathered from case-series data. Amphotericin B, fluconazole, and echinocandins have been shown successful. Therapy should be continued until lesions appear calcified or cleared, a process which may take several months. Notably, in patients who receive repeated courses of antineoplastic therapy or who persistently remain immunosuppressed, prolonged treatment or suppression may be necessary.

Other forms of invasive candidiasis

Endocarditis and cardiac device infections

Patients with *Candida* endocarditis and patients with bacterial endocarditis share both risk factors (intravenous drug use, cardiac surgery, prosthetic heart valves, abnormal native heart valves, and central venous catheters) and clinical presentation (fever, nonspecific signs and symptoms, cardiac murmur, and congestive heart failure). Mycotic emboli to major arteries are more common in *Candida* endocarditis, and blood cultures are often negative initially. The diagnosis should be considered in all patients with candidemia. Evidence of a valvular vegetation by transthoracic or the more sensitive transesophageal echocardiogram establishes the diagnosis. Definitive treatment for native or prosthetic valve *Candida* endocarditis involves valve replacement in conjunction with a prolonged course of antifungal therapy, typically lipid-based amphotericin B formulation (3–5 mg/kg/d with or without flucytosine 25 mg/kg QID) or high-dose echinocandin (caspofungin 150 mg/d, micafungin 150 mg/d, or anidulafungin 200 mg/d) for at least 6 weeks after surgery. Chronic suppression with fluconazole is recommended if valve replacement cannot be performed and the yeast is susceptible. Following treatment, patients should be monitored closely for a minimum of 1 year due to the propensity for relapse.

Infections due to *Candida* spp. involving cardiac devices such as pacemaker and implantable cardiac defibrillator infections are fortunately uncommon. Therapy should include removal of the entire device as well as systemic antifungal therapy as recommended for endocarditis. If the infection is limited to the generator or pocket, 4 weeks of therapy is recommended. If the infection involves wires or leads, at least 6 weeks of therapy is recommended. Failure to remove the device completely should warrant long-term suppressive azole therapy.

Central nervous system infections

Meningitis is the most common form of CNS candidiasis, but numerous other forms of infection such as cerebral or epidural abscesses may occur. Low-birth-weight infants and immunosuppressed hosts are at particularly increased risk for meningitis. Nosocomial risk factors such as recent neurosurgery and the presence of ventricular shunts and drains are also significant in the development of *Candida* CNS infections. Signs and symptoms are similar to, but often less severe than, bacterial meningitis. Typically there is a more indolent and chronic course. Cerebrospinal fluid (CSF) analysis usually reveals a neutrophilic predominance, elevated protein, and either normal or depressed glucose. The diagnosis can be difficult because the organism is present in low numbers in the CSF and the yield of standard CSF cultures is poor; thus repeated CSF cultures may be required. Therapy with lipid-based amphotericin B (3–5 mg/kg/d) with or without oral flucytosine (25 mg/kg QID) is recommended

TABLE 170.3 CLASSIFICATION OF VULVOVAGINAL CANDIDIASIS (VVC)

Uncomplicated VVC	Complicated VVC
All of the following:	At least one of the following:
• Sporadic and infrequent VVC	• Recurrent VVC
• Mild to moderate VVC	• Severe VVC
• Likely to be *Candida albicans*	• Non-*albicans* VVC
• Nonimmunocompromised women	• Women with diabetes, immunocompromising conditions (e.g., HIV infection), debilitation, or immunosuppressive therapy (e.g., corticosteroids)

From Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(No. RR-3):1–137.

initially. After there is clinical response to initial therapy (usually several weeks later), treatment may be adjusted to fluconazole (400–800 mg/d) until all signs and symptoms have resolved. Removal of any ventricular shunt or drain is highly recommended to achieve eradication.

Ocular infections

Up to 15% of patients with candidemia have retinal lesions, often visible within 1 week of the onset of illness. The mortality rate in ICU patients with *Candida* endophthalmitis is considerably higher than the mortality rate in patients with candidemia alone. Symptoms may include bulbar pain, scotomas, and blurred vision. Diagnosis requires a high degree of clinical suspicion, and thus all patients with candidemia should be screened at least once for endophthalmitis by an ophthalmologist. Additional screening is discretionary and may be required in cases of persistent candidemia or in patients who are unable to communicate regarding visual disturbances. Lesions may be sight-threatening; diagnosis relies on characteristic ocular findings such as white lesions on the retina with ill-defined borders with possible vitreal extension. A diagnostic vitreal aspiration is often necessary if endophthalmitis is suspected and the etiology is unknown. The sensitivity of vitreous humor cultures remains low, ranging from 33% to 50%, and PCR may increase diagnostic yield. Recommended systemic therapy follows that for candidemia. Endophthalmitis due to fluconazole-/voriconazole-resistant isolates should be treated with an amphotericin B formulation with or without flucytosine at doses used for candidemia, particularly for sight-threatening lesions. Fluconazole or voriconazole are treatment options for fluconazole-/voriconazole-susceptible isolates. Both have good vitreal penetration and less toxicity compared with amphotericin B. Caution is advised with the use of echinocandins because of poor ocular tissue penetration. Typically, about 4 to 6 weeks of therapy is anticipated for endophthalmitis in conjunction with close ophthalmology follow-up. Intravitreal injection of amphotericin B deoxycholate or voriconazole should be considered for macular involvement and, in patients with vitreitis vitrectomy, should be considered to decrease the burden of organisms and allow removal of fungal abscesses.

Intra-abdominal candidiasis

Candida peritonitis may develop in patients on peritoneal dialysis, after gastrointestinal surgery, as a complication of candidemia, or as an extension of local organ or tissue infection. In addition, gastric and duodenal mucosal infections may develop in patients with peptic ulcer disease or mucosal neoplasm. Other rare intra-abdominal manifestations of *Candida* infection include isolated pancreatic abscess, gangrenous cholecystitis, and obstruction of the common bile duct with a *Candida* fungus ball. *C. albicans* is the predominant species isolated in intra-abdominal infections, but *C. glabrata* plays a significant role. Diagnosis is made by paracentesis or by endoscopic, percutaneous, or open biopsy. Antifungal therapy targeting *Candida* is not recommended for all patients with community-acquired intra-abdominal infection, but antifungal therapy is recommended in patients with significant risk factors for candidiasis (e.g., recent abdominal surgery or anastomotic leaks). An echinocandin or fluconazole is most commonly recommended for empiric therapy. Amphotericin B formulations are not usually recommended due to significant toxicity. As with all intra-abdominal infections, appropriate source control measures (e.g., drainage of abscesses, removal of infected material, etc.) are also crucial in management and to help define the duration of therapy.

Bone and soft tissue infection

Bone and soft tissue infections are rare complications of *Candida* dissemination or direct extension of a local *Candida* infection and are diagnosed by needle aspiration or via surgical debridement. They also may result from exogenous inoculation during trauma, intra-articular injection, a surgical procedure, or injection drug use. Treatment usually requires a combination of surgical debridement/drainage and often prolonged systemic antifungals (6–12 months for osteomyelitis, 6 weeks for septic arthritis), and fluconazole or an echinocandin is recommended for initial therapy; lipid formulation amphotericin B is an alternative. If prosthetic joint hardware or other devices are involved, removal is highly recommended to achieve cure.

Respiratory tract candidiasis

Pneumonia due to *Candida* spp. is exceedingly rare as an isolated *Candida* infection. It is also poorly defined as a clinical entity because positive cultures cannot distinguish between true infection and either colonization or contamination of samples with oropharyngeal contents. Confirming a diagnosis of *Candida* pneumonia requires histopathologic confirmation, which is rarely performed. Growth of *Candida* from respiratory secretions alone is insufficient to warrant therapy and perhaps best serves to document colonization.

Patients with empyema involving *Candida* generally have an underlying predisposing condition such as malignancy, and esophageal perforation should be considered in appropriate clinical circumstances. Most cases are nosocomially acquired, occurring frequently with concomitant bacterial infection. Diagnosis is made with isolation of a fungal species from an exudative pleural effusion in association with clinical signs of infection. Treatment via drainage and systemic antifungals with an echinocandin or fluconazole is appropriate. The newer triazoles or lipid formulation amphotericin B may also be considered.

Genitourinary *Candida* infections

The isolation of *Candida* in the urine is common in hospitalized or nursing home patients, especially in those with indwelling urinary catheters. Most often catheter-related candiduria is asymptomatic, and although it generally does not require antifungal treatment, it may occasionally be difficult to distinguish patients with asymptomatic candiduria from those with true *Candida* urinary tract infections. Infections are more common and potentially more serious in patients who are taking broad-spectrum antibiotics or immunosuppressive agents, in patients with diabetes mellitus or who are otherwise immunosuppressed, and in patients with genitourinary

abnormalities (including obstructive uropathy and renal transplant recipients). The diagnosis is problematic as high colony count is not a strong indicator of infection, and pyuria in this setting is not always helpful. Frequently, the clinical suspicion combined with signs and symptoms of infection and culture results following removal of the catheter may be all that is available for the clinician. In most episodes of candiduria, catheter removal is often all that is required. *Candida* infection of the bladder also must be distinguished from infection of the kidney, although the two entities can coexist. Invasive infection of the kidney is unusual and is more difficult to treat. Other genitourinary syndromes (e.g., epididymo-orchitis) often require percutaneous culture for diagnosis.

Antifungal treatment for asymptomatic candiduria is only recommended for high-risk patients including those with neutropenia and very low-birth-weight infants, and they should be treated as recommended for candidemia. Treatment should also be recommended for patients undergoing urologic procedures with oral fluconazole 400 mg/d for several days before and after the procedure (amphotericin B deoxycholate may also be considered). Fluconazole is recommended for symptomatic *Candida* cystitis (200 mg/d) or symptomatic ascending candida pyelonephritis (200–400 mg) for 2 weeks is recommended if fluconazole-susceptible. For *C. glabrata* (fluconazole-resistant) or *C. krusei*, amphotericin B deoxycholate or flucytosine (*C. glabrata* only) could be considered. Amphotericin B bladder irrigations are not routinely recommended due to high relapse rates but may prove useful for treatment of resistant *Candida* isolates; other systemic antifungals (e.g., the echinocandins, posaconazole, isavuconazole, and voriconazole) do not achieve adequate urine levels to be considered optimal for treatment. Infections associated with fungus balls require surgical intervention.

Suggested reading

Andes DR, Safdar N, Baddley JW, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: A patient-level quantitative review of randomized trials. *Clin Infect Dis*. 2012;54:1110–1122.

Bassetti M, Righi E, Montravers P, Cornely OA. What has changed in the treatment of invasive candidiasis? A look at the past 10 years and ahead. *J Antimicrob Chemother.* 2018;73(Suppl 1):i14–25.

Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(No. RR-3):1–137.

Clancy CJ, Nguyen MH. Diagnosing invasive candidiasis. *J Clin Microbiol.* 2018;56(5):e01909–17.

Kim J, Sudbery P. *Candida albicans*, a major human fungal pathogen. *J Microbiol*. 2011;49:171–177.

Kullberg BJ, Arendrup MC. Invasive candidiasis. *N Engl J Med.* 2015;373:1445–1456.

Pappas PG, Kauffman CA, Andes CJ, et al. Clinical practice guidelines for the management of candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;64(4):e1–e50.

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Aspergillus

Stuart M. Levitz and Sanjay Ram

Aspergillus is readily isolated from environmental samples of soil, water, and air worldwide. *A. fumigatus*, followed by *A. flavus*, *A. niger*, and *A. terreus*, are the most common species that cause human disease. Aspergillosis follows exposure of a susceptible host to the ubiquitous conidia (spores). Germinating conidia form hyphae, the invasive form of the fungus. *Aspergillus* hyphae average 2 to 4 μm in diameter and are septate, with dichotomous (Y-shaped) branching (Figure 171.1). The spectrum of diseases caused by the aspergilli is wide and profoundly influenced by the underlying immune status of the host.

Clinical manifestations and diagnosis of invasive aspergillosis

Although inhalation of conidia is common, invasive disease is relatively rare. The vast majority of affected patients are severely immunosuppressed. Major risk factors include prolonged neutropenia and macrophage dysfunction secondary to cytotoxic chemotherapy and high doses of corticosteroids, respectively. In patients who have undergone hematopoietic stem cell transplantation, additional risk factors are graft-versus-host disease and cytomegalovirus infection. Recently, invasive aspergillosis cases have been described in patients receiving small molecule kinase inhibitors such as ibrutinib. Inborn mutations of genes controlling innate immune responses, particularly chronic granulomatous disease, a rare genetic disorder characterized by a defective phagocyte respiratory burst, predispose to invasive aspergillosis. Finally, critically ill patients and persons recovering from influenza may be at increased risk even without the aforementioned risk factors.

Invasive pulmonary aspergillosis, with or without dissemination, is the most common form of disease. Signs and symptoms of invasive aspergillosis are nonspecific. Fever is generally present. Radiographic features include patchy densities or well-defined nodules that may be single or multifocal and can progress to cavitation or consolidation. High-resolution CT scanning has greater sensitivity than plain films. Macronodules (nodules >1 cm in diameter) are present in the majority of patients with invasive pulmonary aspergillosis. Nodules may be surrounded by a perimeter of ground-glass opacity, the so-called *halo sign* (Figure 171.2). Cavitation ("air-crescent sign") is less common and tends to occur as a later manifestation of disease. Tracheobronchitis without alveolar invasion may be seen, particularly in lung transplant recipients and those with advanced AIDS. Invasive *Aspergillus* sinusitis is the second most common manifestation and must be distinguished from saprophytic colonization. Its clinical features include fever, localized pain, proptosis, and visual problems. Fungal keratitis due to direct inoculation of *Aspergillus* has been increasingly recognized as an important cause of visual loss, particularly among agrarian workers in developing countries. Less common manifestations include cutaneous aspergillosis, which may be seen at intravenous (IV) catheter insertion sites in neutropenic patients or at sites of burn wounds. While disseminated aspergillosis can involve any organ, cerebral involvement is a particularly common manifestation. Endocarditis due to *Aspergillus* is relatively rare and can be difficult to diagnose as blood cultures are often negative.

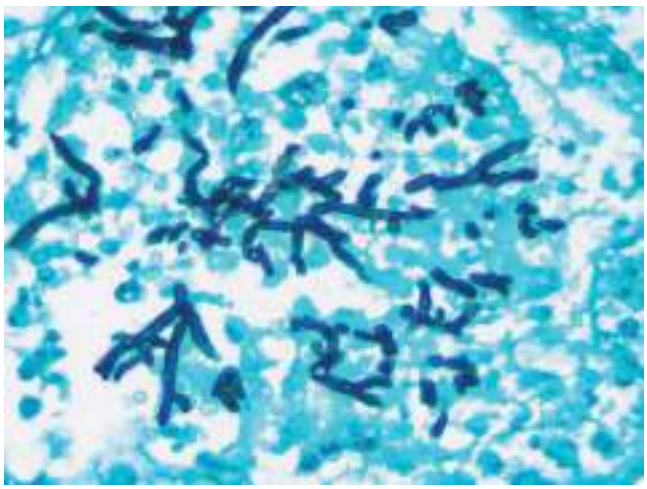

FIGURE 171.1 Photomicrograph demonstrating *Aspergillus* hyphae in a lung at autopsy in a liver transplant patient who died of systemic aspergillosis. The hyphae are stained with methenamine silver.
Courtesy of Dr. Barbara Banner, University of Massachusetts Medical School.

Invasive aspergillosis must be strongly suspected in any high-risk patient with fever unresponsive to broad-spectrum antibiotics, and empiric antifungal therapy should be considered. Although *Aspergillus* can be a laboratory contaminant or a colonizer, a positive culture for *Aspergillus* in an at-risk patient is predictive of invasive disease and should not be ignored. However, in patients with established disease, cultures and even biopsies are often negative.

To improve prognosis with earlier detection, nonculture methods have been studied to detect *Aspergillus* antigens and nucleic acids in specimens from high-risk patients. Tests to detect two cell wall antigens released by growing aspergilli, galactomannan and β-glucan, are clinically available. Serum galactomannan levels have excellent specificity but only moderate sensitivity. Sensitivity is higher in patients with hematologic malignancies, where positive results may precede clinical or radiologic manifestations, than in those with solid organ transplants. False positives have been noted in patients receiving piperacillin-tazobactam due to contamination of some lots with galactomannan. False negatives are considerably more common in patients receiving anti-mold prophylaxis. Assays to detect β-glucans in clinical specimens appear to perform comparably to those for galactomannan, with the caveat that elevated β-glucans may be seen in fungal infections other than aspergillosis. Detection of *Aspergillus* DNA by polymerase chain reaction (PCR) in clinical samples, while still investigational, has good sensitivity and specificity, especially when used in conjunction with galactomannan assays. It should be emphasized that surrogate markers cannot definitively establish or exclude a diagnosis of aspergillosis, and clinical correlation is required. Moreover, testing for antibodies, while useful for other forms of aspergillosis (see later discussion), is not helpful in invasive aspergillosis.

Treatment of invasive aspergillosis

Licensed drugs with activity against *Aspergillus* include amphotericin B (a polyene); the triazoles, itraconazole, voriconazole, posaconazole, and isavuconazole; and the echinocandins, caspofungin, micafungin, and anidulafungin. Fluconazole and ketoconazole do not inhibit *Aspergillus* at clinically obtainable concentrations and should not be used to treat aspergillosis. It is difficult to rank the active drugs in terms of relative efficacy because few randomized comparative trials have been performed. Studies based on comparisons to historical controls are problematic due to significant differences in the patient populations. A multicenter, randomized trial compared voriconazole with amphotericin B in 277 patients with definite or probable acute invasive aspergillosis. The voriconazole regimen demonstrated superior efficacy and a 22% relative survival benefit. Moreover, there were fewer treatment-related adverse events in the voriconazole group. The large survival benefit observed established voriconazole as the drug of choice for initial treatment of invasive aspergillosis. An important caveat though is that voriconazole is not effective therapy against mucormycosis (zygomycosis), which can present in a similar manner to aspergillosis.

In the preceding study, two doses of 6 mg/kg of IV voriconazole were administered on day 1, followed by 4 mg/kg/d. A switch to oral voriconazole at a dose of 200 mg twice a day was allowed after 1

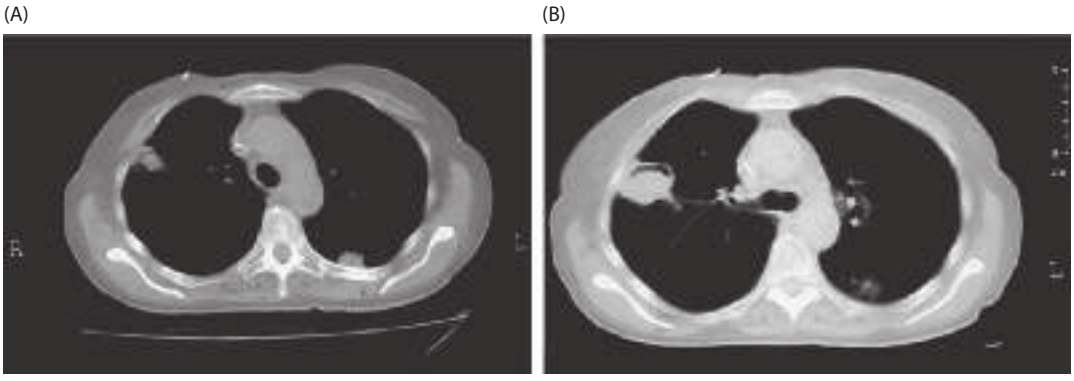

FIGURE 171.2 High-resolution CT scans from patients with invasive pulmonary aspergillosis. (A) Two pleural-based nodules can be seen. The one on the right is surrounded by a gray area of low-attenuation (halo sign). (B) Air-crescent sign in a patient recovering from neutropenia.
Courtesy of the *Aspergillus*/Aspergillosis website: www.aspergillus.org.uk. Copyright Fungal Research Trust. Used with permission.

week. Transient visual disturbances, including blurred vision, altered color perception, and photophobia, are common with voriconazole and tend to resolve without incident. Other side effects that have been observed include rash and liver function test abnormalities. Voriconazole is a substrate and an inhibitor of CYP2C19, CYP2C9, and CYP3A4. Thus, drug interactions are common and dose adjustments of voriconazole and coadministered drugs may be needed. The authors recommend obtaining steady-state trough levels and adjusting the dosing if necessary to achieve levels between 1.0 and 5.5 μg/mL. In patients with an estimated creatinine clearance of <50 mL/min, accumulation of the IV vehicle occurs; these patients should be given oral voriconazole whenever possible.

In addition to voriconazole, other licensed triazoles with activity against *Aspergillus* are itraconazole, posaconazole, and isavuconazole. Itraconazole appears to be least potent and is mainly used for the treatment of aspergillomas and allergic bronchopulmonary aspergillosis (see later discussion). Posaconazole appears more promising and, along with isavuconazole, has the added advantage of having useful activity against the agents of mucormycosis. While clinical experience with posaconazole for primary treatment of invasive aspergillosis is limited, a randomized study compared isavuconazole with voriconazole as primary treatment of invasive aspergillosis and other filamentous mold infections. The all-cause mortality was similar in the two groups; however, there were fewer treatment-related adverse events in the group that received isavuconazole. Resistance of *Aspergillus* to triazole drugs can emerge during therapy, although the extent to which this leads to clinical failure is not clear. Ominously, primary resistance has been reported worldwide in both environmental and initial clinical isolates of *Aspergillus*, perhaps as a consequence of the agricultural use of antifungal azoles.

Amphotericin B is generally used for the treatment of invasive aspergillosis in patients who cannot take voriconazole and isavuconazole because of contraindications or intolerance. (Amphotericin B should not be used to treat *Aspergillus terreus* or *Aspergillus nidulans* due to decreased susceptibilities.) However, controversy exists regarding the optimal daily dosage and formulation. For the conventional amphotericin B desoxycholate formulation, following a test dose of 1 mg, dosages ranging from 0.6 to 1.5 mg/kg/d have been recommended, with higher dosages reserved for severely ill and/or profoundly immunosuppressed patients. Fevers, chills, and rigors, observed in a significant number of patients treated with amphotericin B, may be alleviated by premedication with acetaminophen, meperidine, 25 to 50 mg given intravenously, or the addition of 25 to 50 mg of hydrocortisone sodium succinate to the infusion solution. Amphotericin nephrotoxicity has been associated with sodium-depleted states and may be reduced by giving 1 L of normal saline per day to patients with no contraindications to volume expansion. As amphotericin B causes renal tubular losses of potassium and magnesium, their levels should be monitored closely and supplementation provided as needed. The dosage of amphotericin B must be individualized depending on factors such as the expected duration and degree of immunosuppression and the extent of the disease.

To reduce the toxicity associated with the conventional amphotericin B preparation, lipid-associated formulations have been developed. Currently available formulations include amphotericin B lipid complex, amphotericin B colloidal dispersion, and a liposomal preparation. Comparisons between the different formulations of amphotericin B are difficult to make due to the lack of well-designed randomized trials. However, at the usual daily dosages recommended for the treatment of invasive aspergillosis (3 to 5 mg/kg/d), the lipid formulations appear to be at least as efficacious as amphotericin B deoxycholate. The lipid formulations are less nephrotoxic than the conventional preparation but cost considerably more, a factor that limits their use in resource-poor settings. A clinical trial comparing 3 and 10 mg/kg/d of liposomal amphotericin B as primary therapy for invasive aspergillosis found the lower dose was equally effective but less toxic.

Three members of the echinocandin class of antifungal drugs, caspofungin, micafungin, and anidulafungin, are licensed for use. All have modest activity against *Aspergillus* in vitro and in animal models, although none has been adequately studied in comparative clinical trials for primary treatment of invasive aspergillosis. In an open-label study of 83 patients with invasive aspergillosis who were refractory or intolerant to amphotericin B, a favorable response to caspofungin therapy was observed in 37 (45%) of the subjects. Due to poor oral absorption, the echinocandins must be administered intravenously. Although infusion-related reactions and liver function test elevations are relatively common, serious side effects of this class of drugs are rare.

Due to the high failure rate associated with monotherapy for invasive aspergillosis, combination regimens as initial and salvage therapy have been tried. A randomized, double-blind study comparing voriconazole and anidulafungin combination therapy with voriconazole monotherapy in the treatment of invasive aspergillosis revealed a trend, which did not reach statistical significance, toward improved overall survival in the group that received combination therapy. It is the authors' practice to treat most cases of invasive aspergillosis with voriconazole monotherapy but to add an echinocandin if progression ensues or resistance is suspected.

Regardless of whether monotherapy or combination therapy is utilized, the duration of treatment should be individualized depending on the extent of disease and degree of immunosuppression. Most patients will require several months of treatment. Surgery should be considered as an adjunct to treatment in instances where there is localized disease, particularly in cases where there is progression despite antifungal therapy or further courses of neutropenia-inducing chemotherapy are anticipated. Whenever possible, immunosuppression should be withdrawn or decreased. In neutropenic patients, recombinant granulocyte colony-stimulating factor (G-CSF) may improve outcome by decreasing the duration of neutropenia and increasing the functional activity of neutrophils. Finally, patients with filamentous fungal keratitis should be treated with 5% natamycin eyedrops initially applied every hour. Surgical intervention by ophthalmology is often required.

Prophylaxis and preemptive treatment of invasive aspergillosis

Given the high mortality associated with established disease, strategies for the prevention of invasive aspergillosis have been advocated and are summarized in Table 171.1. Numerous studies

TABLE 171.1 **PREVENTION OF INVASIVE ASPERGILLOSIS**

Preventive strategy	Comments
1. Avoidance of exposure to *Aspergillus* conidia a. Avoidance of environmental exposure b. High-efficiency particulate air (HEPA) filters or laminar air flow (LAF)	Heavily contaminated areas include compost heaps, grain silos, moldy hay, and marijuana Although expensive, HEPA and LAF may be considered for hospitalized patients at very high risk of invasive aspergillosis, particularly if mold counts are high
2. Prophylaxis of high-risk patients	Posaconazole or other mold-active antifungals should be considered in very high-risk groups[a]
3. Administration of colony-stimulating factors to neutropenic patients	Expensive and not proved to be beneficial.
4. Preemptive, empirical administration of antifungals to neutropenic patients with fevers despite broad-spectrum antibacterial agents	Strongly recommended[a]
5. Secondary prophylaxis (antifungal treatment to prevent recrudescence of invasive aspergillosis in patients who will become immunosuppressed)	Due to high relapse rates, a mold-active antifungal agent should be given at the onset of chemotherapy or neutropenia. Consider surgical resection of localized disease[a]

[a] See text for details.

have examined empiric antifungal therapy in neutropenic patients with persistent or recurrent fevers despite empiric antibacterial therapy. This group is at high risk for invasive fungal infections, particularly aspergillosis and candidiasis, but also other opportunistic mycoses, including mucormycosis and fusariosis. Thus, ideal agents will have activity against a broad spectrum of opportunistic fungi. However, for those for whom the duration of neutropenia is expected to be short, candidiasis is the main concern, with aspergillosis and other mold infections being less common.

Studies published in the 1980s established that amphotericin B deoxycholate could decrease the incidence of invasive fungal infections in patients with persistent neutropenic fevers. Subsequent noninferiority studies compared amphotericin B (either deoxycholate or lipid-based formulations) with fluconazole, itraconazole, voriconazole, and caspofungin. Later studies compared different antifungal azoles. An important caveat in interpreting these studies is the variability in inclusion criteria and endpoints defining success.

A study compared posaconazole (200 mg TID) with either fluconazole (400 mg/d) or itraconazole (200 mg/d) in 602 patients undergoing intensive chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. Patients received antifungal medications with each cycle of chemotherapy until complete remission or for up to 12 weeks. Remarkably, during the treatment phase of the study, only 2 cases of aspergillosis were seen in the posaconazole arm compared with 20 in the fluconazole-itraconazole arm. Moreover, there was a significant overall survival benefit in favor of posaconazole. Similarly, a significant reduction in cases of aspergillosis and in mortality was seen in a study comparing posaconazole with fluconazole for allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease.

Prophylaxis can be expensive, associated with side effects, and lead to antifungal drug resistance. Rather than administer mold-active prophylaxis, some centers prefer a preemptive approach whereby antifungal therapy is administered based on criteria including fevers, positive serum antigen markers (galactomannan, β-D-glucan, and/or PCR) and suggestive chest CT scans.

Aspergillomas

Pulmonary aspergillomas are the result of saprophytic colonization of *Aspergillus*, usually within preexisting lung cavities such as might result from sarcoidosis, tuberculosis, or bullous emphysema. The diagnosis is most often made by chest radiography, where a round to oval intracavitary mass partially surrounded by a radiolucent crescent of air is seen. Some patients have chronic cavitary pulmonary aspergillosis without radiographically visible intraluminal fungus balls. Serum precipitins and sputum cultures for *Aspergillus* are positive in about 90% and 50% of cases, respectively. Hemoptysis is the most common symptom and, in most cases, is mild and self-limited. Rarely, extrapulmonary aspergillomas can form, particularly in the sinuses.

Therapy for aspergillomas must be individualized according to the pulmonary and immunologic status of the host, but in most cases a conservative approach with close clinical follow-up is recommended. Resection generally is reserved for those with life-threatening hemoptysis. However, many patients are not surgical candidates due to poor baseline lung function. Bronchial artery embolization can be tried as a temporizing measure for massive hemoptysis in patients with a high operative risk. Other measures, including intracavitary instillation of amphotericin B, oral itraconazole, and oral voriconazole, have been associated with reduction in cavity size and severity of hemoptysis in case reports. In one series of 40 patients, all patients had short-term resolution of hemoptysis following instillation of a locally formulated paste consisting of amphotericin B, fatty acids, and emulsifying wax.

A subset of patients with aspergillomas tends to be chronically ill, with fever, weight loss, pulmonary symptoms, and leukocytosis. This entity, termed "subacute invasive pulmonary aspergillosis," is seen in patients with chronic pulmonary disorders; most have mild systemic immunocompromise such as diabetes mellitus, alcoholism, low-dose corticosteroids, or malnutrition. Whenever possible, host defenses should be strengthened by diminishing factors responsible for immunosuppression. Other patients have "chronic cavitary pulmonary aspergillosis" characterized by progressive expansion of *Aspergillus*-infected pulmonary cavities, often in the absence of known immunocompromise. With both entities, dramatic clinical responses have been observed in some patients following a course of antifungal therapy as is given for invasive aspergillosis. Resection may be considered in the small subset of patients with focal disease whose pulmonary function and underlying disease do not preclude surgery.

Allergic manifestations of *Aspergillus*

Extrinsic allergic alveolitis occurs in nonatopic individuals who are exposed to *Aspergillus* conidia, as in "malt-worker's lung" or "farmer's lung," following their exposure to moldy grain or hay. Spontaneous recovery usually occurs over several weeks, without the need for antifungal agents or corticosteroids. Exposure to *Aspergillus* in individuals with asthma can result in an exacerbation of their disease (extrinsic asthma).

Allergic bronchopulmonary aspergillosis (ABPA) is a syndrome characterized by asthma, proximal bronchiectasis, immediate cutaneous reactivity to *Aspergillus*, elevated serum immunoglobulin E (IgE) concentrations, and elevated serum immunoglobulin G (IgG) and IgE antibodies specific to *A. fumigatus*. An increase in T_H2 CD4+ cells that respond to *Aspergillus* antigens and generate interleukin (IL)-4, -5, and -13 may contribute to the eosinophilia and high IgE levels seen in ABPA. Pulmonary infiltrates, peripheral eosinophilia, serum precipitins against *Aspergillus* antigens, and expectoration of fungus-laden mucus plugs may also be seen. Major predisposing factors are asthma and cystic fibrosis.

The goals of therapy are to reduce acute inflammation and minimize long-term lung damage. For patients with ABPA and pulmonary infiltrates, the primary treatment is corticosteroids. Although randomized clinical trials have not been performed, a commonly used regimen is prednisone given in doses of 0.5 mg/kg/d for 2 weeks, followed by an alternate-day regimen and then a gradual taper over a 3- to 6-month period. Total IgE levels in the serum directly correlate with disease activity and response to corticosteroids. In clinical trials, itraconazole in doses of 200 mg twice daily was associated with fewer exacerbations, improved immunologic parameters, and a reduced requirement for corticosteroids. Although it has not been studied in comparative trials, based on its superiority in invasive aspergillosis plus its better tolerability, voriconazole is increasingly being used in the treatment of ABPA.

Currently, two oral formulations of itraconazole are available: capsules and an oral aqueous acidified solution in 5% hydroxypropyl-β-cyclodextrin. Absorption of the capsular form is best in an acidic environment, and in the presence of a meal. Histamine-2 blockers and antacids may interfere with absorption. In contrast, the oral aqueous hydroxypropyl-β-cyclodextrin solution should be taken without food. This preparation achieves higher peak serum concentrations compared with the capsules but is associated with a higher incidence of gastrointestinal side effects. Drugs that induce hepatic microsomal enzymes (e.g., rifampin, isoniazid, phenytoin, phenobarbital, and carbamazepine) may significantly reduce serum itraconazole levels. Itraconazole itself slows hepatic drug metabolism and may increase the toxicity of phenytoin, oral hypoglycemics, digoxin, warfarin, and cyclosporine. Plasma concentrations of itraconazole can be measured in patients for whom absorption or drug metabolism problems are suspected, although therapeutic levels have not been established. An inhaled formulation of itraconazole is under investigation.

Allergic *Aspergillus* sinusitis often responds to endoscopic surgical debridement and drainage, particularly when there are obstructive symptoms. Intranasal corticosteroids may provide symptomatic relief, but long-term use should be avoided as it can be detrimental to the nasal mucosa. There are anecdotal reports that itraconazole may be of benefit in refractory cases.

Suggested reading

Arvanitis M, Anagnostou T, Mylonakis E. Galactomannan and polymerase chain reaction-based screening for invasive aspergillosis among high-risk hematology patients: A diagnostic meta-analysis. *Clin Infect Dis*. 2015;61(8):1263–1272. doi:10.1093/cid/civ555.

Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356(4):348–359. doi:10.1056/NEJMoa061094.

Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002;347(6):408–415.

Lionakis MS, Levitz SM. Host control of fungal infections: Lessons from basic studies and human cohorts. *Ann Rev Immunol*. 2018;36:157–191. doi:10.1146/annurev-immunol-042617-053318.

Luong ML, Al-Dabbagh M, Groll AH, Racil Z, Nannya Y, Mitsani D, Husain S. Utility of voriconazole therapeutic drug monitoring: A meta-analysis. *J Antimicrob Chemother*. 2016;71(7):1786–1799. doi:10.1093/jac/dkw099.

Maertens J, Raad A II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): A phase 3, randomised-controlled, non-inferiority trial. *Lancet*. 2016;387(10020):760–769. doi:10.1016/S0140-6736(15)01159-9.

Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: A randomized trial. *Ann Intern Med*. 2015;162(2):81–89. doi:10.7326/M13-2508.

Patterson TF, Thompson GR, 3rd, Denning DW. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1–e60. doi:10.1093/cid/ciw326.

Prajna NV, Krishnan T, Mascarenhas J, et al. The mycotic ulcer treatment trial: A randomized trial comparing natamycin vs voriconazole. *JAMA Ophthalmol*. 2013;131(4):422–429.

Verweij PE, Chowdhary A, Melchers WJ, Meis JF. Azole resistance in aspergillus fumigatus: Can we retain the clinical use of mold-active antifungal azoles? *Clin Infect Dis*. 2016;62(3):362–s8. doi:10.1093/cid/civ885.

Mucormycosis (and entomophthoramycosis)

Scott F. Davies

The term mucormycosis refers to a group of highly lethal angioinvasive fungal infections, mostly in immunocompromised hosts, caused by members of the order Mucorales, which include various species of the genera *Rhizopus*, *Lichtheimia* (formerly *Absidia*), *Mucor*, and *Saksenaea*. Other genera of Mucorales have also been implicated in human disease including *Cunninghamella*, *Apophysomyces*, and *Rhizomucor*. Most infections (50%–65% of total) are caused by *Rhizopus* species.

Classification is in flux because of extensive molecular phylogenetic analysis that has been ongoing for more than 10 years. Note that it is incorrect to use the term mucormycosis to refer only to infections caused by species of the genus *Mucor*, which are only a small minority of the total number of cases. Rather, mucormycosis refers to infection by any of the organisms within the seven genera of the order Mucorales as noted.

The term entomophthoramycosis refers to infections by members of the separate genera *Conidiobolus* and *Basidiobolus*. These organisms generally occur in tropics and cause chronic subcutaneous infection mostly in immunocompetent hosts. Only rarely (less than 15 reported cases) have they ever caused clinical syndromes overlapping with mucormycosis.

For the remainder of this chapter the term mucormycosis will be used to refer to the range of clinical infections caused by organisms in the seven genera of the order Mucorales. In recent usage this term is generally preferred over the term zygomycosis, because of elimination of Zycomycetes from the taxonomic structure and the very different clinical syndrome as compared to entomophthoramycosis with virtually no clinical overlap.

Pathogenesis

The causative agents of mucormycosis are found throughout the world, associated with decaying organic matter. They grow as a mycelium (broad nonseptate hyphae with short stubby right-angle branches) in nature and in infected mammalian tissue.

Airborne spores of the fungi settle on the skin or are inhaled into the nose, the pharynx, and the lung. The organism has little chance of invading healthy tissue defended by neutrophils. *Rhizopus* organisms grow best at acid pH in a high-glucose environment. A specific enzyme, ketone reductase, plays an important role. Thus diabetic ketoacidosis provides a favorable opportunity for the fungus to locally invade tissues of the upper airway, resulting in the fulminant rhinocerebral form of mucormycosis. Once established, the fungus is angioinvasive, leading to infarction of tissues and wider areas of necrosis, in which the fungus thrives. The tissue response to the fungus includes pyogenic inflammation, but there is little tendency for granuloma formation. A second form of disease is pulmonary mucormycosis, in which infection occurs in the lung or, less commonly, in proximal airways. The disease resembles invasive pulmonary aspergillosis and occurs, although much less commonly, in the same substrate: patients with profound neutropenia and patients in whom phagocyte function is depressed by high-dose glucocorticoid therapy. Like *Aspergillus* species, agents of mucormycosis are angioinvasive in the lung, leading to tissue necrosis and eventually to pyemic spread

to distant sites, including the skin, kidney, and brain. Rare forms of mucormycosis include a direct cutaneous infection that can complicate severe burns and contaminated wounds and the gastrointestinal form of the illness, associated with profound protein malnutrition (usually in infants), in which organisms directly invade the bowel wall, causing hemorrhage, bowel infarction, peritonitis, and death.

When uncontrolled diabetes is the main predisposing factor, rhinocerebral mucormycosis is more common. When hematologic malignancy and organ transplantation are the predisposing factors, pulmonary mucormycosis is more common. Patients being treated for leukemia and bone marrow transplantation recipients appear to have an increasing risk of pulmonary mucormycosis. Early use of fluconazole for these indications reduced *Candida* infections but likely shifted what was once a reasonably even split between disseminated candidiasis and invasive aspergillosis more heavily toward aspergillosis. More recently, other triazoles, including itraconazole and now voriconazole, that are highly active against *Aspergillus* species have been used for prophylaxis, reducing *Aspergillus* infections but likely resulting in higher relative frequency of mucormycosis. There are several studies implicating itraconazole and voriconazole prophylaxis as independent risk factors for development of invasive mucormycosis.

Clinical manifestations

Rhinocerebral mucormycosis is an extremely fulminant infection. Infection begins in the nose, sometimes manifested by dark, blood-tinged discharge from one or both nostrils. Necrosis of the nasal septum and turbinates then follows, with spread to the paranasal sinuses. In sequence, the disease accelerates with ulceration and necrosis of sinus walls, periorbital cellulitis, and direct invasion of the orbit, eye, cavernous sinuses, and brain. Arterial thrombosis adds to the extent of tissue destruction. Early clinical findings include eye pain, decreased visual acuity, and cranial nerve palsies. A black eschar from ischemic necrosis, either in the nose or on the palate, is a strong signal of disease presence. Early symptoms and signs may be followed by seizures and progressive decrease in level of consciousness. Death may occur in 1 week.

Pulmonary mucormycosis is acquired by inhalation or possibly by microaspiration from colonized sinuses. The disease presents as an acute or subacute pneumonia, with fever, cough, and purulent sputum. Some patients have pleuritic pain and hemoptysis from superimposed pulmonary infarction caused by invasion of pulmonary vessels. The most characteristic finding on chest radiograph is an area of consolidation, often peripheral and sometimes wedge-shaped. Focal areas of consolidation often cavitate as the infection progresses. The spectrum of radiographic abnormalities also includes large masses (even to 6 to 10 cm in size), multiple nodules, and multiple peripheral infiltrates. The computed tomography (CT) halo sign (ground-glass changes surrounding a dense central nodule) was first reported in invasive pulmonary aspergillosis (the most common cause of this finding in immunosuppressed patients), but also occurs in mucormycosis (with similar frequency as in aspergillosis) and in other infections and conditions, including bronchoalveolar carcinoma (the most common cause in immunocompetent patients). The CT reverse halo sign (central ground-glass area surrounded by denser consolidation) seems to be relatively more common in mucormycosis (the most common cause in immunosuppressed patients) than in aspergillosis, but also occurs in other infections and conditions, including cryptogenic organizing pneumonia (the most common cause in immunocompetent patients). The CT halo signs may be helpful in individual patients, but lack great sensitivity and specificity.

Metastatic abscesses may develop in the brain, liver, spleen, kidney, and skin. Metastatic skin lesions often show extensive necrosis (ecthyma gangrenosum) and offer easy diagnosis with a simple punch biopsy. Clinically, pulmonary mucormycosis with or without pyemic dissemination cannot easily be distinguished from invasive aspergillosis. Most cases occur in patients with hematologic malignancy with prolonged neutropenia. Cases of pulmonary mucormycosis also occur in organ transplant recipients, in patients receiving prolonged courses of high-dose glucocorticoid therapy for malignant or nonmalignant disorders, and even in diabetic patients.

Deferoxamine therapy, used for chelation in some patients receiving long-term dialysis and in other iron-overloaded states, is also a risk factor for mucormycosis because it is a siderophore, mobilizing iron from peripheral storage sites and making it more available to the fungus as a growth factor.

Endobronchial mucormycosis is a rare form of pulmonary mucormycosis that has been reported mainly in patients with advanced acquired immunodeficiency syndrome (AIDS). Patients have cough, purulent sputum, and often hemoptysis. Physical findings may include a localized wheeze. The chest radiograph may be normal or may show segmental or even lobar infiltrates with significant volume loss distal to the obstructed airway. Several other unusual forms of mucormycosis have also been reported in this population. Isolated renal mucormycosis has been described in AIDS patients who abuse drugs intravenously or have long-term intravascular access catheters for various therapeutics. Nodular skin lesions have also been reported in AIDS patients who abuse drugs intravenously. Cerebral mucormycosis of the basal ganglia has also been reported in similar patients.

Cutaneous mucormycosis can also complicate contaminated wounds via direct inoculation, rather than pyemic spread. This has been reported from war theaters including those in Afghanistan. It can also complicate civilian trauma; a total of 13 cases were reported following a tornado in Joplin, Missouri, in 2011. The causative organism in all cases was an *Apophysomyces* species. There was an association between fungal infection and penetrating wounds containing wood, soil, gravel, and other foreign material. The patients developed a cutaneous necrotizing infection within a few days of the trauma; 5 of the 13 patients died.

Diagnosis

The diagnosis of rhinocerebral mucormycosis can often be strongly suspected based on the setting of diabetic ketoacidosis and the clinical features of the illness. Specific diagnosis usually depends on

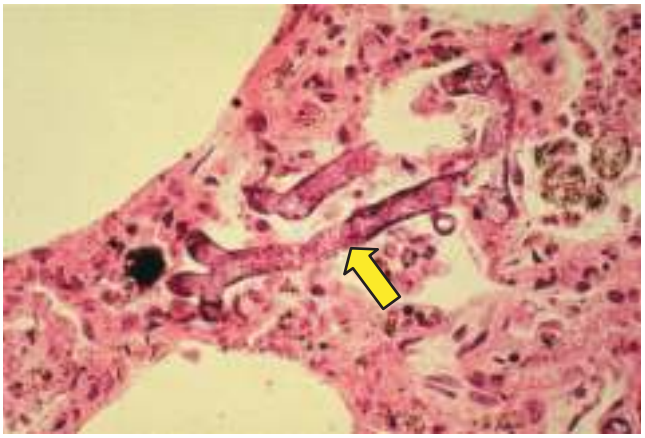

FIGURE 172.1 Mucormycosis: Hyphae (*arrow*) vary from 6 to 50 μm in diameter, are nonseptated, and typically branch at 90-degree angles. Courtesy of www.doctorfungus.org, copyright 2007.

demonstration of characteristic broad nonseptate hyphae in biopsies of diseased tissue (Figure 172.1). Positive cultures are confirmatory and also serve to define the exact species causing the infection. PCR may play an increasing role in the future for species identification. Positive cultures for causative organisms of mucormycosis must be interpreted cautiously and in clinical context because the organisms are ubiquitous in the environment and occasionally can be recovered from the skin, pharynx, and sputum of patients without disease. No useful skin tests or serologic tests are available.

The diagnosis of pulmonary mucormycosis is also highly dependent on clinical awareness in high-risk clinical settings, with leukemia and bone marrow transplantation most important predispositions, followed by organ transplantation. Prior use of itraconazole or voriconazole for prophylaxis or empiric antifungal therapy may also be a risk factor. The disease resembles invasive aspergillosis in similar hosts and can be distinguished only by histopathology or by culture.

Treatment

Rhinocerebral mucormycosis has a very high mortality, beyond 50% of cases in many series. Successful therapy is most likely if the diagnosis is made early and initiation of therapy is based entirely on clinical findings, before confirmation by histopathology or culture. There are three aspects to the treatment. First, the diabetic ketoacidosis must be controlled. Second, and most importantly, aggressive surgical debridement of all necrotic tissue must be done. Sometimes several procedures are needed as the limits of the diseased tissue become more apparent. Finally, full doses of amphotericin B (AMB) must be given quickly. Use of lipid-based formulations of AMB (AMB-L) have become standard because of lower toxicity and likely superior efficacy. Usual dose of AMB-L is 5 mg/kg/day—higher dosing to 7.5 or 10 (or even higher) mg/kg/day has been used in select cases, but has higher toxicity.

Pulmonary mucormycosis is also highly lethal. Once there is spread to distant sites and particularly to the brain, fatal outcome is nearly certain. Localized pulmonary disease can sometimes be managed successfully. Again, a three-pronged approach is necessary. First, the predisposing causes must be reversed. This means return of neutrophils (either spontaneously or aided by marrow-stimulating biologicals) and/or rapid taper of glucocorticoid therapy to the extent it is possible. Second, AMB-L should be started and escalated quickly to full dosages. Third, if the patient stabilizes, strong consideration should be given to surgical resection of necrotic lung tissue, if the lung disease is localized and the risk of thoracotomy is reasonably low. There are anecdotal reports of successful treatment of pulmonary mucormycosis by surgical resection alone. In those rare cases, the preoperative diagnosis was uncertain, total excision of all involved lung was accomplished, the diagnosis was established by histopathology of the resected tissue, and the patient recovered fully without other therapy.

When possible, isolated renal mucormycosis in patients with AIDS should be treated with nephrectomy combined with AMB-L. When nephrectomy is either not possible or is not a reasonable option given the overall condition of the patient, AMB-L alone should be used. There are some anecdotal successes using AMB-L without surgery.

Cutaneous mucormycosis is treated with aggressive surgical debridement and aggressive antifungal therapy, with AMB-L the first-line therapy.

As mentioned above, itraconazole and voriconazole are triazoles with activity against *Aspergillus* but no activity against Mucorales species. Wide use of these agents for prophylaxis and empiric antifungal therapy in patients with hematologic malignancy likely has increased the incidence of mucormycosis.

A possible advance in treatment of mucormycosis is posaconazole, the first triazole compound with activity against Mucorales species. Compassionate use in a large series of 91 patients with mucormycosis (69 proven disease, 22 probable) who had failed or were intolerant to prior antifungal treatment (usually a form of AMB) showed a success rate of 60% at 12 weeks. That exceeds historical success rates with prior standard therapy. Although posaconazole is not yet approved for use in mucormycoses, one approach pending further data might be to start patients with proven disease on AMB-L plus posaconazole until clinical response, and then extending posaconazole to 12 or more weeks. However, posaconazole is available only in oral formulation, limiting its use in critically ill patients. For now, AMB-L remains standard treatment with posaconazole used as an adjunctive, salvage, or continuation therapy on an individual case basis.

Echinocandins are another possible candidate for combination therapy. *Rhizopus oryzae* (the most common *Rhizopus* species causing infection) expresses the enzyme 1,3 β-glucan synthetase, which is the target enzyme for the echinocandins. Use of echinocandins in animal models has shown additional benefit when combined with AMB-L. There are anecdotal reports of successful use in selected cases, usually in combination with AMB-L. At present there is more experience and a larger number of positive clinical reports with posaconazole as a second agent or for salvage, and

for now echinocandins should not be used as an alternate therapy versus AMB-L.

As mentioned, iron availability is an important promoter of growth for Mucorales species and deferoxamine, which mobilizes iron and also increases availability of iron to the organisms, is a risk factor for mucormycosis. However, newer iron chelators such as desferasirox bind iron but are not used as siderophores by Mucorales and thus deprive the fungus of iron availability. In models of mucormycosis in mice, desferasirox was as effective as AMB-L and it also had additive effects when used together with AMB-L. Anecdotal reports have suggested some benefit in patients, but a very small (20 patients) randomized prospective trial showed poorer outcome (more frequent death at 30 and 90 days and lower global success) when desferasirox was used in combination with AMB-L for initial therapy of mucormycosis. At present desferasirox should not be used as combination therapy with AMB-L or other agents.

Finally, hyperbaric oxygen therapy has been proposed, based on limited and anecdotal reports, as an adjunctive therapy for some patients with mucormycosis. As for other unproven therapies, hyperbaric oxygen can be considered for selected patients.

Suggested reading

Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis PD. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. *Clin Infect Dis*. 2005;41(1):60–66.

Kontoyiannis DP, Lionakis MS, Lewis RE. Zygomycosis in a tertiary-care cancer center in the era of *Aspergillus*-active antifungal therapy: a case-control observational study of 27 recent cases. *J Infect Dis*. 2005;191(8):1350–1360.

Kwon-Chung KJ. Taxonomy of fungi causing mucormycosis and entomophthoramycosis (zygomycosis) and nomenclature of the disease: molecular mycologic perspectives. *Clin Infect Dis*. 2012;54(Suppl 1):S8–S15.

Lewandowski L, Purcell R, Fleming M, Gordon WT. The use of dilute Dakin's solution for the treatment of angioinvasive fungal infection in the combat wounded: a case series. *Mil Med*. 2013;178(4):e503–e507.

Neblett Fanfair R, Benedict K, Bos J, et al. Necrotizing cutaneous mucormycosis after a tornado in Joplin, Missouri, in 2011. *N Engl J Med*. 2012;367(23):2214–2225.

Pagano L, Cornely O, Busca A, et al. Combined antifungal approach for the treatment of invasive mucormycosis in patients with hematological diseases: a report from the SEIFEM and FUNGISCOPE registries. *Haematologica*. 2013;98(10): e127–e130.

Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41(5):634–653.

Spellberg B, Ibrahim AS, Chin-Hong PV, et al. The Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor) study: a randomized, double-blinded, placebo-controlled trial. *J Antimicrob Chemother*. 2012;67(3):715–722.

Spellberg B, Ibrahim A, Roilides E, et al. Combination therapy for mucormycosis: why, what, and how? *Clin Infect Dis*. 2012;54 (Suppl 1):S73–S78.

Van Burik JA, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. *Clin Infect Dis*. 2006;42(7):e61–e65.

173

Sporotrichum

Ronald A. Greenfield†

Sporotrichosis is a subacute or chronic fungal infection caused by *Sporothrix schenckii* and related species. It occurs most commonly in cutaneous or lymphocutaneous forms resulting from direct inoculation of the pathogen but also occurs in a variety of extracutaneous forms. Among the extracutaneous forms, a primary sporotrichotic pneumonia, presumably acquired by inhalation, occurs rarely. More commonly, musculoskeletal or osteoarticular sporotrichosis occurs, either as a result of direct inoculation into tendons, bursae, and joints or as a result of hematogenous dissemination. Hematogenous dissemination may result in disseminated cutaneous sporotrichosis and/or infection of a variety of unusual sites, including the meninges.

Epidemiology

Sporothrix schenckii is widely distributed in nature; it grows on plant debris in soil, and on the bark of trees, shrubs, and garden plants. The fungus and the disease occur in much of the world, primarily in the tropical and temperate zones. The abundance of the organism and the reported incidence of the disease show great geographic variation, perhaps related to genotypic differences between organisms in different locales. The penetrating trauma that introduces the fungal conidia into the human host is most commonly accomplished by splinters, thorns, or woody fragments of plants, but any contact with plants or plant products (e.g., sphagnum peat moss, mulch, hay, timber) accompanying minor skin trauma may initiate infection. Activities most frequently associated with acquisition of sporotrichosis include gardening (particularly rose gardening), landscaping, farming, berry-picking, horticulture, and carpentry. Skin test and serologic surveys demonstrate that most *S. schenckii* inoculations promote the development of immunity without clinically apparent infection. Zoonotic transmission also occurs from infected animals, particularly cats with extensive skin lesions, but may result from the scratch of any digging animal. Both pulmonary and disseminated sporotrichosis appear to occur more commonly in patients with a history of alcoholism.

Patients with immunosuppression due to human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) appear to more frequently develop disseminated cutaneous sporotrichosis and hematogenously disseminated sporotrichosis, including sporotrichotic meningitis, than immunocompetent hosts. Although the incidence of HIV/AIDS-associated sporotrichosis is not precisely known, it is less than that of other endemic mycoses. Patients treated with immunosuppressive agents, including tumor necrosis factor-α antagonists, have also developed disseminated sporotrichosis.

Laboratory diagnosis

Definitive diagnosis of sporotrichosis requires the isolation of *Sporothrix* spp. in culture specimens from a normally sterile body site. Occasionally, the organism can be visualized in biopsied tissue specimens stained with periodic acid–Schiff, Gomori methenamine silver, or immunochemical stains (Figure 173.1). The

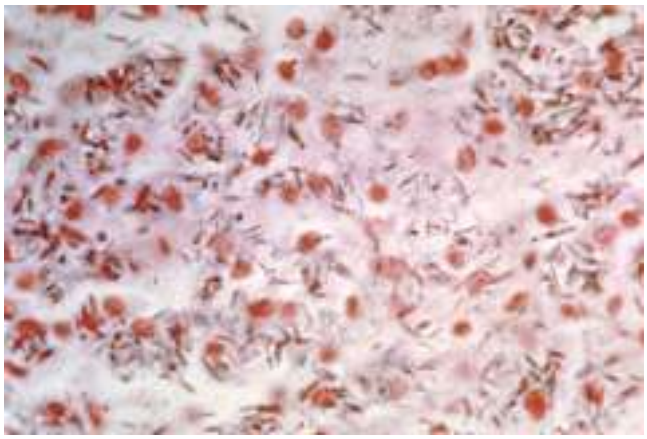

FIGURE 173.1 Histopathologic demonstration of the cigar-shaped yeasts of *Sporothrix schenckii*.
Courtesy of the CDC and Dr. Lucille K Georg, CDC Public Health Image Library.

organism can be recovered by fungal culture from sputum, pus, synovial fluid, bone drainage, and surgical specimens. Concentrations of organisms in joint fluid and particularly cerebrospinal fluid may be relatively low. Therefore, repetitive large-volume cultures may be required for diagnosis. Serologic techniques for measurement of antibody are available but exhibit significant interlaboratory variability in sensitivity and specificity; they are best used to suggest the need for more aggressive attempts at definitive diagnosis.

Clinical manifestations

Cutaneous sporotrichosis

The primary lesion develops at the site in the skin, 20 to 90 days after inoculation, most typically distally in the upper extremities. Over a few weeks, the initial small nodule enlarges, reddens, becomes pustular, and ulcerates, releasing purulent material from which the organism is readily cultured. Patients are typically afebrile and not systemically ill. In the lymphocutaneous form of the disease, an ascending chain of nodules develops along lymphatic channels of the skin, with the older distal lesions ulcerating and draining and the younger, more proximal lesions forming subcutaneous nodules that attach to the skin as they age and begin to ulcerate (Figure 173.2). The lesions are usually minimally painful, but extensive disease may result in functional impairment. Some patients exhibit no lymphangitic spread, and the disease presents as an indolent ulcerating plaque that persists for years if untreated (fixed cutaneous sporotrichosis). Patients often have received courses of antibacterial therapy without benefit before the process is recognized as sporotrichosis. The lymphocutaneous form of sporotrichosis can be mimicked by infection with *Nocardia*, *Mycobacterium marinum* and other mycobacteria other than tuberculosis, *Leishmania*, and *Francisella tularensis*.

FIGURE 173.2 Lymphocutaneous sporotrichosis.
Courtesy of the CDC and Dr. Lucille K Georg, CDC Public Health Image Library.

Pulmonary sporotrichosis

Pulmonary sporotrichosis is a subacute or chronic pneumonitis with cavitation, usually in the upper lobes, clinically indistinguishable from mycobacterial infection or chronic pulmonary histoplasmosis. Almost all patients have underlying chronic obstructive pulmonary disease. They present with productive cough, sometimes with weight loss and increasing dyspnea, but rarely with fever, chills, or sweats. Diagnosis requires isolation of *S. schenckii* from sputum cultures or its histopathologic recognition in biopsy specimens.

Osteoarticular sporotrichosis

Lesions of deeper tissues may occur in almost any organ, but there is a distinct predilection for the joints, particularly of the extremities, and the long bones adjacent to these joints. The resulting chronic arthritis is often confused with rheumatoid or other chronic inflammatory arthritis, not infrequently for 10 or more years, until destruction of adjacent bone or development of draining fistulas encourage efforts to establish the microbial etiology of the chronic osteomyelitis. Cutaneous or lymphocutaneous lesions are unusual in these patients. The process generally begins in a single joint, but additional joints may be involved successively. The patient usually has pain on motion, and the involved areas may be warm and red. Functional impairment resulting from osteoarticular sporotrichosis can become very severe.

Disseminated sporotrichosis

Sporotrichotic lesions occur infrequently in many other organs such as the eye, the prostate, the oral mucosa, and the larynx, and the clinical manifestations in these patients depend on the organ involved. Involvement of the central nervous system (CNS) and meninges, which was distinctly rare in the pre-AIDS era, has become more common but is still rare in persons living with AIDS. Patients may present with subtle changes in mental status as the only symptom and are found to have chronic lymphocytic meningitis. Recovery of the fungus from extracutaneous lesions may be difficult, particularly in meningitis.

Therapy

Spontaneous healing of the cutaneous forms of sporotrichosis has been reported, but without treatment, the lesions usually progress slowly with draining and scarring. In immunocompetent patients, the infection is not life threatening. Treatment options are presented in Table 173.1. Historically, cutaneous and lymphocutaneous sporotrichosis have been treated with saturated solution of potassium iodide (SSKI), although the mechanism of action has not been determined. An initial dose of 5 to 10 drops diluted in liquid, preferably fruit juice, is given three times daily after meals, and increased dropwise to 120 drops per day or the maximum tolerated by the individual patient (frequently <60 drops per day). Although relatively inexpensive, this form of therapy is poorly accepted by many patients due to adverse effects, including increased lacrimation, increased salivation, metallic taste perversion, salivary gland swelling, gastrointestinal upset, and frequent rash.

Itraconazole is the treatment of choice for lymphocutaneous sporotrichosis; 100 mg orally daily for 3 to 12 months, determined by continuing treatment for 2 to 4 weeks beyond resolution of all lesions. Itraconazole can be given either as capsules that must be taken with food and must not be coadministered with therapies that suppress gastric acidity and that have somewhat erratic absorption or as an itraconazole oral solution, which is less palatable and generally more expensive but avoids these drawbacks. In patients who do not respond to itraconazole initially, one can consider increasing the dosage of itraconazole to 400 mg/day. Therapy with terbinafine, 250 mg orally daily, appears to be as effective as itraconazole therapy. By historical comparison, treatment with fluconazole, 200 to 400 mg orally daily, was less effective than itraconazole. The effectiveness of higher doses of fluconazole is subject to speculation. Amphotericin B preparations should only be necessary as a treatment of last resort for patients with cutaneous or lymphocutaneous sporotrichosis. Because many strains of *S. schenckii* that cause fixed cutaneous sporotrichosis grow poorly in the laboratory at 37°C, local application of heat may be an effective adjunct to antifungal therapy.

Pulmonary sporotrichosis should be treated with either itraconazole, 200 mg orally twice daily, for patients with non-life-threatening infection or with an amphotericin B preparation (preferably a liposomal amphotericin B preparation because of better tolerability) in patients with life-threatening or extensive pulmonary infection. For the latter patients who have the lung capacity to tolerate such a procedure, treatment with an amphotericin B preparation with subsequent surgical resection of involved lung areas may be the best therapy.

Itraconazole, 200 mg orally twice daily, should be initial therapy for patients with osteoarticular sporotrichosis. As with other joint and bone infections, drainage and debridement may be important surgical adjuncts to antimicrobial therapy. Conventional amphotericin B therapy appears to be approximately as effective as itraconazole but is less convenient and associated generally with more frequent adverse reactions; therefore, it is generally used only after failed itraconazole therapy. The role of liposomal amphotericin B preparations in osteoarticular sporotrichosis has not been defined. Fluconazole has been used with only modest success in osteoarticular sporotrichosis. Itraconazole treatment should generally be continued for 12 months, therapy with amphotericin B preparations for 6 to 10 weeks. Voriconazole has poor activity in vitro against sporotrichosis and should not be used. Posaconazole has in vitro activity, but its role in vivo is undefined.

Sporotrichotic meningitis should be treated with amphotericin B, based on limited numbers of anecdotally reported cases; liposomal amphotericin B is preferred because of increased penetration into the cerebrospinal fluid. Based on possible in vitro synergy and anecdotal reports, the addition of flucytosine may be beneficial for patients with recalcitrant meningitis. Itraconazole may offer effective step-down therapy after clinical improvement.

An amphotericin B preparation should be considered initial therapy for patients with disseminated sporotrichosis with or without AIDS. Itraconazole might be used for non-life-threatening infection and in cases in which meningitis has been actively excluded. Itraconazole may also play a role in lifelong suppressive therapy for patients with disseminated sporotrichosis and AIDS after initial induction therapy with an amphotericin B preparation.

Suggested reading

de Lima Barros MB, de Almeida Paes R, Schubach AO. *Sporothrix schenckii* and sporotrichosis. *Clin Microbiol Rev*. 2011;24:633–654.

de Lima Barros MB, Schubach AO, de Oliveira R, et al. Treatment of cutaneous sporotrichosis with itraconazole—study of 645 patients. *Clin Infect Dis*. 2011;52: e200–e206.

Francesconi G, Fancesconi do Valle AC, Passos SL, et al. Comparative study of 250 mg/day terbinafine and 100 mg/day itraconazole for the treatment of cutaneous sporotrichosis. *Mycopathologia*. 2011;171:349–354.

TABLE 173.1 **TREATMENT OF SPOROTRICHOSIS**

Form of sporotrichosis	Preferred treatment	Alternative agents
Cutaneous or lymphocutaneous	SSKI, itraconazole, terbinafine	Fluconazole, posaconazole, amphotericin B
Pulmonary	Itraconazole	Amphotericin B
Osteoarticular or musculoskeletal	Itraconazole	Amphotericin B
Disseminated	Amphotericin B	Amphotericin B plus flucytosine, itraconazole step-down therapy

Abbreviation: SSKI = saturated solution of potassium iodide.

Freitas DF, de Siqueira Hoagland B, do Valle AC, et al. Sporotrichosis in HIV-infected patients: report of 21 cases of endemic sporotrichosis in Rio de Janeiro, Brazil. *Med Mycol*. 2012;50:170–178.

Kauffman CA, Bustamante B, Chapman SW, Pappas PG. Clinical practice guidelines for the management of sporotrichosis. 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45:1255–1265.

Kauffman CA, Pappas PG, McKinsey DS, et al. Treatment of lymphocutaneous and visceral sporotrichosis with fluconazole. *Clin Infect Dis*. 1996;22:46–50.

Yamada K, Zaitz C, Framil VM, Muramatu LH. Cutaneous sporotrichosis treatment with potassium iodide. A 24 year experience in Sao Paulo State, Brazil. *Rev Inst Med Trop Sao Paulo*. 2011;53:89–93.

174

Cryptococcus

William G. Powderly

Cryptococcus neoformans, which is found worldwide as a soil organism and thought to be transmitted by inhalation, most often causes disease in patients with abnormal cell-mediated immunity, notably patients with HIV infection and solid organ transplant recipients, but the infection also occurs with increasing frequency in apparently immunocompetent persons. It is the most common systemic fungal infection in patients infected with HIV. It is estimated that as many as 300,000 cases of invasive cryptococcal infection occur annually in patients with AIDS worldwide, with >150,000 deaths each year. Most of these cases occur in resource-poor settings, especially in sub-Saharan Africa. With the advent of effective antiretroviral therapy (ART), cryptococcal infections have become much less common in the United States.

Two varieties of *C. neoformans* exist, distinguishable by serology: *C. neoformans var. neoformans* (serotypes A and D) and *C. neoformans var. gattii* (serotypes B and C). Virtually all HIV-associated infection is caused by *C. neoformans var. neoformans*. *C. neoformans var. gattii* is endemic in Australia, and recent outbreaks of *C. neoformans var. gattii* infection have occurred in the Pacific northwestern parts of North America.

Presentation and diagnosis

The most common manifestation of cryptococcal infection is meningitis. Most patients develop insidious features of a subacute meningitis or meningoencephalitis, with fever, malaise, and headache, and are generally symptomatic for at least 2 to 4 weeks before presentation. In patients with a more subacute or chronic course, mental status changes such as forgetfulness and coma can also be seen. Classic meningeal symptoms and signs such as stiff neck and photophobia occur in only about one-quarter to one-third of all patients and generally are less likely to occur in HIV-positive patients. The typical pattern in the cerebrospinal fluid (CSF) is chronic meningitis with a lymphocytic pleocytosis. However, the CSF may appear normal in HIV-positive patients with cryptococcal meningitis because the usual response to infection is usually markedly blunted. In fact, fewer than half of HIV-positive patients with cryptococcal meningitis have an elevated protein level, only about one-third have hypoglycorrhachia, and only about 20% have >20 white blood cells per cubic millimeter of CSF. The opening pressure is usually elevated in patients with cryptococcal meningitis (up to 70% of patients present with pressures >20 cm H_2O), and this is an important issue associated with therapy. The cryptococcal antigen titer in the CSF is almost invariably positive with sensitivity of 93% to 100% and specificity of 93% to 98%. Serum cryptococcal antigen (sCRAG) is elevated in 95% of patients with meningitis. A positive sCRAG raises the possibility of disseminated cryptococcosis and such patients should be evaluated for possible meningeal involvement. Culture of *C. neoformans* from any body site should also be regarded as an indication for further evaluation and initiation of therapy. However, colonization of *Cryptococcus* can be found in the respiratory system. Patients with isolated positive respiratory cultures for *C. neoformans* should be carefully evaluated for disseminated infection; therapy might not

be necessary in immunocompetent patients with no symptoms and negative sCRAG, but careful follow-up is essential.

C. neoformans can invade sites other than the meninges. Isolated pulmonary disease has been well-described. It usually presents as a solitary nodule in the absence of other symptoms. Cryptococcal pneumonia has also been described. In immunocompromised patients, especially those with AIDS, disseminated disease is common. About half of HIV-positive patients with cryptococcal meningitis have evidence of pulmonary involvement at presentation, with clinical symptoms such as cough or dyspnea and abnormal chest radiographs. The chest radiographic finding is usually diffuse interstitial infiltrates in immunocompromised patients or focal lesions in immunocompetent patients. Concomitant opportunistic infections, especially with *Pneumocystis jirovecii* (*carinii*) or with *Mycobacterium tuberculosis* (especially in resource-poor settings) can occur. Cutaneous involvement is common and, with this presentation, suggests disseminated disease. The most common skin involvement resembles that of molluscum contagiosum. As many as three-quarters of patients with cryptococcal meningitis have positive blood cultures. Infection of bone, eye, adrenal glands, prostate, and urinary tract has also been described. The prostate gland represents a reservoir of infection and potential source of reinfection after completion of therapy.

Therapy

Management of cryptococcal infection depends on the extent of disease and the patient's immune status. A solitary pulmonary nodule in a normal host may not need treatment provided the patient has careful follow-up. The availability of relatively safe antifungals such as fluconazole permits a short course of therapy for most patients with localized disease. Extrapulmonary disease is generally managed in the same way as meningitis. A search for potential underlying problems should be initiated in patients who are not known to be immunosuppressed, including an HIV antibody test and consideration of undiagnosed secondary immunodeficiency including the development of auto-antibodies directed at interferon or granulocyte-macrophage colony-stimulating factor, as well as isolated cases of CD4 lymphopenias. Drugs generally used in the treatment of cryptococcal infection are summarized in Table 174.1.

Cryptococcal infection in "normal" hosts

Untreated cryptococcal meningitis is uniformly fatal, so all patients with meningitis must be treated. Indeed, the non-HIV/non-transplant population experiences poorer outcomes, including increased mortality, than traditionally immunosuppressed groups,

TABLE 174.1 **DRUGS USED IN THE TREATMENT OF CRYPTOCOCCAL INFECTION**

Drugs	Dosage	Side effects	Drug interactions	Comments
Amphotericin B	0.7–1.0 mg/kg/d; 3–6 mg/kg/d (liposomal) 5 mg/kg/d (lipid complex)	Immediate hypersensitivity reaction, fever, hypotension, nausea and vomiting during administration, hypokalemia, and nephrotoxicity	Nephrotoxic drugs (e.g., aminoglycosides, foscarnet, cidofovir)	Liposomal or lipid complex formulation are preferred in available to minimize renal toxicity
Flucytosine (5-FC)	25 mg/kg q6h	Gastrointestinal, bone marrow suppression	Nephrotoxic drugs	Dosage must be reduced in patients with renal dysfunction; drug level should be monitored
Fluconazole	400 mg/d (acute therapy), 200 mg/d (suppressive therapy)	Nausea, rash, and hepatitis	Rifabutin (increased rifabutin levels); rifampin (decreased fluconazole levels)	Dosage may need to be adjusted in renal dysfunction
Itraconazole	200–400 mg BID	Nausea, abdominal pain, rash, headache, edema, and hypokalemia	Rifamycins, ritonavir, phenobarbital, phenytoin all decrease itraconazole levels The drug should not be used concomitantly with terfenadine or astemizole Antacids, histamine blockers decrease itraconazole absorption Itraconazole itself acts as a moderate inhibitor of cytochrome P450 system and can increase levels of some protease inhibitors, cyclosporin, digoxin, and phenytoin	Absorption of itraconazole is dependent on food and gastric acid and may be erratic; newer formulations are better absorbed

in part because of delayed diagnosis. Most of the available evidence suggests that amphotericin B–based therapy remains the gold standard, and the combination of an amphotericin B preparation plus flucytosine (5-FC) should be regarded as the best initial treatment. This combination is most likely to lead to more effective and more rapid clearance of the fungus from the CSF, which is probably the best surrogate marker for ultimate successful therapy. This conceptual approach is consistent with clinical trial data in AIDS that amphotericin B–based therapy is superior to initial therapy with azoles. The different amphotericin B preparations have not been shown to have important differences in response rates of cryptococcal meningitis, although clearly the lipid-based formulations are less toxic than amphotericin B deoxycholate. Current recommendations suggest that liposomal amphotericin at a dose of 5 mg/kg is the preferred treatment for cryptococcal meningitis in normal hosts. Although it is unclear whether 5-FC is necessary in normal hosts, extrapolation from trials in patients with AIDS would suggest that it accelerates clearance of the fungus and improves mortality. The recommended dosage is 37.5 mg/kg four times daily. Levels must be measured to minimize toxicity (especially bone marrow suppression), and dosages must be adjusted for renal insufficiency.

The duration of therapy is not well defined for patients with cryptococcal infection. Normal subjects with no evident risk factors for a poor outcome respond well to 4 weeks of combination therapy, and this is often curative. Prolonged therapy should be considered for patients at risk of relapse, such as those who present with more severe neurological symptoms or those with underlying conditions such as cancer or end-stage liver disease. With current data, amphotericin B plus 5-FC is still recommended as standard therapy for cryptococcal meningitis. Fluconazole can be used to treat patients (or to complete a course of treatment) in patients who cannot tolerate amphotericin B. In many circumstances (need for intravenous access, difficulties with outpatient parenteral therapy, toxicity) a full course of parenteral amphotericin B is impractical or undesirable, and a switch to fluconazole is preferred. Timing of such a switch is uncertain. There is insufficient evidence to advocate using changes in cryptococcal antigen as a guide to making treatment decisions, but it is probably reasonable to consider using the clearance of yeast from CSF as an indicator for switching treatment from polyene to oral azole therapy. In most patients, this is likely to take 2 to 3 weeks to achieve, suggesting this is probably the minimum amount of amphotericin B therapy that should be used. Pulmonary cryptococcosis without meningeal involvement can be treated initially with fluconazole.

Once patients have been switched to fluconazole, the next question becomes how long to treat? Unfortunately, there are absolutely no well-controlled studies to answer this question. Given the potential severity of cryptococcal infection, the most prudent recommendation would be to treat with fluconazole for 6 to 12 months after clearance of CSF has been documented.

Cryptococcal infection in AIDS

In patients with AIDS, the acute mortality with cryptococcal meningitis ranges from 10% to 25%. Multiple clinical factors have been identified in studies as predictors of a poor outcome, as summarized in Box 174.1. The current recommendations for the treatment of cryptococcal meningitis in AIDS are to use a combination of amphotericin B (usually a liposomal preparation) plus 5-FC (25 mg/kg q6h) for at least 2 weeks followed by at least 8 weeks of fluconazole, 400 mg PO daily. This approach has been validated by a large randomized trial comparing amphotericin B plus 5-FC to amphotericin B plus fluconazole and to amphotericin B alone. There were fewer deaths among patients receiving amphotericin B and 5-FC compared with those receiving amphotericin B alone, whereas combination therapy with fluconazole had no significant effect on survival as compared with amphotericin B alone. In resource-poor settings, there has been considerable interest in evaluating shorter duration of amphotericin B, and a more recent trial conducted in Africa suggested that 1 week of amphotericin B plus flucytosine and 2 weeks of fluconazole plus flucytosine were effective as induction therapy.

There have been a number of controlled comparative trials of the orally active antifungal triazoles, fluconazole and itraconazole. In each trial, the azole antifungals were effective in about 50% of patients. Similarly, in a study directly comparing fluconazole and itraconazole, <50% of patients responded to either drug. Thus, at least 50% of patients treated initially with azole antifungals will fail to respond. Most studies of amphotericin B report response rates of 70% to 80% or more, reinforcing the current guidelines that recommend an initial period of amphotericin B–based treatment. Voriconazole and posaconazole are active against *C. neoformans*, but clinical experience is limited and they are rarely used.

An important aspect of management of acute cryptococcal meningitis in AIDS is the recognition that clinical deterioration may be caused by increased intracranial pressure (ICP), which may not respond rapidly to antifungal therapy. Analyses have shown a relationship between baseline opening pressure and long-term outcome, with the median survival in patients with the highest pressures being significantly less than that in patients whose pressures were normal. I believe that all patients with cryptococcal meningitis should have opening pressure measured when a lumbar puncture is performed, and strong consideration should be given to reducing such pressure if the opening pressure is high (>25 cm H_2O). Lumbar puncture with removal of 30 mL of spinal fluid daily is often effective.

BOX 174.1

Factors at baseline predictive of a poor outcome in AIDS patients with cryptococcal meningitis

Decreased mental status at diagnosis
CSF leukocyte count ≤20 cells/mm^3
High titer of CSF cryptococcal antigen
Positive blood culture for *C. neoformans*
Age ≤35 yr
Hyponatremia

Abbreviations: AIDS = acquired immunodeficiency syndrome; CSF = cerebrospinal fluid.

If elevated opening pressure persists with neurologic symptoms despite serial lumbar puncture, lumbar drainage should be considered. Some patients have required placement of lumbar peritoneal shunts for persistently elevated ICP despite successful antifungal therapy. Neither acetazolamide nor corticosteroids are effective in this situation, and may be detrimental, so they should not be used.

The advent of effective ART has changed the natural history of AIDS-related cryptococcal infection. Prior to effective HIV therapy, lifelong maintenance therapy was required in AIDS patients with cryptococcal infection to prevent relapse of infection. Relapse rates of 50% to 60% and a shorter life expectancy were reported in patients who did not receive long-term suppressive therapy. Fluconazole, 200 mg/d, is the drug of choice. Routine monitoring by measurement of sCRAG has not been shown to predict relapse. It is now clear that long-term suppressive treatment can be stopped after at least 12 months of antifungal therapy if the patient's immune system recovers with ART (usually defined as the CD4+ T-cell count increasing to >200 cells/mm^3).

All HIV-positive patients with cryptococcal meningitis should receive ART. Recent studies evaluating the timing of ART in AIDS patients with cryptococcal meningitis suggest a higher mortality if given during the acute treatment for cryptococcal infection. Consequently ART initiation should be deferred for 6 to 8 weeks after initiation of antifungal therapy.

It is thought that a likely mechanism for increased mortality with early initiation of ART is immune reconstitution inflammatory syndrome (IRIS), which is a more vigorous inflammatory response to the underlying infection associated with restoration of the immune system. The pathogenesis of IRIS is unclear but is thought to represent an overexuberant immunologic response to a high antigen load in the context of an immune response that is recovering but not yet fully normal. Clinically there can be considerable morbidity and even mortality. In the case of cryptococcal meningitis, IRIS may manifest as an apparent recurrence of meningitis, with all the features of the initial meningitis presentation. Lumbar puncture will typically show inflammation but, by definition, will remain culture negative. Rarely, the syndrome may present outside the central nervous system (CNS) as pulmonary infiltrates or hilar/mediastinal lymphadenitis due to extra-CNS *Cryptococcus*. Typically, IRIS presents following an initial clinical improvement. The majority of cases of IRIS occur within 30 days of starting ART, and the frequency of IRIS following initiation of ART in cryptococcal meningitis has varied from 10% to 50% in different series. IRIS has been found more frequently in patients who are antiretroviral naïve before ART. It is also more commonly seen in those with a higher CSF cryptococcal antigen level, probably due to increased antigen producing a greater inflammatory response. Starting ART within 30 days of diagnosis of cryptococcal meningitis is also associated with a higher likelihood of IRIS, presumably due to a greater antigenic burden. If IRIS develops in a patient receiving ART, the patient should remain on antiviral therapy and continue antifungal treatment. Anti-inflammatory treatment may be needed for symptom management, and, in some cases, immunosuppressive therapy such as corticosteroids has been used.

Fluconazole, 200 mg PO daily, has been shown to be effective as primary prophylaxis in patients with advanced HIV disease. However, this has not been regarded as cost-effective in developed countries such as the United States. However, a strategy of primary prophylaxis may be appropriate in patients with advanced HIV disease (CD4+ T-cell count <100 cells/mm^3) in resource-poor settings; alternatively, screening patients using cryptococcal antigen testing and treating asymptomatic patients with positive serum antigen tests may also be effective.

Cryptococcal infection in other immunocompromised hosts

Management of cryptococcal meningitis in the setting of organ transplantation or lymphoma has not been well studied prospectively. An approach similar to that used with AIDS patients (i.e., an initial period of treatment with amphotericin B plus 5-FC followed by fluconazole) is recommended. Because nephrotoxicity is an issue in many of these patients, liposomal amphotericin B is generally preferred, again for at least 2 to 3 weeks. However, there is very little published experience with the use of fluconazole, itraconazole, voriconazole, or fluconazole plus 5-FC in this setting, and these agents are also associated with significant drug interactions. An area of considerable uncertainty is the duration of fluconazole therapy after acute therapy. Suppressive antifungal therapy for at least 1 year after the completion of acute treatment is recommended. In some patients with persistent immunosuppression, such as solid organ transplant recipients, many clinicians continue treatment indefinitely, although again there are very limited data on which to base a recommendation. In transplant recipients and other patients on immunosuppressive therapy, consideration may be given to reduction or discontinuation of immune-modulating drugs including steroids and calcineurin inhibitors. However, there is increasing evidence that discontinuation of immunosuppressive therapy in the setting of cryptococcal infection may worsen outcomes by increasing the risk of immune reconstitution.

Finally, there is increasing attention being paid to the long-term morbidity (as opposed to acute mortality) of cryptococcal meningitis. Recent data from the Cryptococcus Infection Network in non-HIV Cohort (CINCH) study showed significant cumulative neurologic morbidity and impaired cognition at 1 year of follow-up. This remains an important area for future research.

Suggested reading

Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *N Engl J Med*. 2016;374:542–554.

Boulware D, Meya D, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. 2014;370:2487–2498.

Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med*. 2013;368:1291–1302.

George IA, Spec A, Powderly WG, Santos CAQ. Comparative epidemiology and outcomes of HIV, non-HIV non-transplant and organ transplant associated cryptococcosis: A population-based study. *Clin Infect Dis*. 2018;66:608–611.

Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. *N Engl J Med*. 2018;378:1004–1017.

Marr KA, Sun Y, Spec A, et al Cryptococcus Infection Network Cohort Study Working Group. A multicenter, longitudinal cohort study of cryptococcosis in human immunodeficiency virus-negative people in the United States. *Clin Infect Dis*. 2020;70:252–261.

Mazziarz EK, Perfect JR. Cryptococcosis. *Infect Dis Clin North Am*. 2016;30(1):179–206.

Pappas PG, Perfect JR, Cloud GA, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. *Clin Infect Dis*. 2001;33:690–699.

Perfect J, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2010;50:291–322.

Histoplasmosis

Cole Beeler and Mitchell Goldman

Introduction

Histoplasma capsulatum is a thermally dimorphic fungus found most frequently in soil in the midwestern United States. The fungus is also found in Central and South America, Africa, Asia, and Australia. Bird and bat excreta rich in organic nitrogen support the growth of the organism. Recent evidence supports an expansion of the endemic region in the United States to areas north and west of the originally described Ohio River Valley to the upper Missouri River Basin. Sites associated with blackbird roosts are the most common sources of outbreaks currently, whereas domestic chicken coops were a common source in the past. Recent outbreaks have occurred after cleaning a campsite contaminated by bat excreta, rototilling soil in a schoolyard below a bird roost, whitewater rafting, and digging for buried treasure. In the United States, workplace exposures are implicated in 40% of outbreaks. When sites are disturbed, the spores become airborne, producing an infective aerosol. The lung is the portal of entry in almost every case of histoplasmosis. Following inhalation of *H. capsulatum* spores into alveoli, the fungus converts to a yeast, the tissue-invasive form. The yeasts are then phagocytosed by alveolar macrophages that are initially incapable of killing the fungus. During the pre-immune phase of the illness, ingested yeast cells multiply inside macrophages and spread throughout the body via the lymphatics to reticuloendothelial organs. Once adequate cell-mediated immunity (CMI) develops, the now "armed" macrophages can either kill or wall off the infecting organisms. Following a strong immune response, as is seen in immunocompetent individuals, tissue necrosis occurs, which, in time, becomes calcified. These calcified granulomas are seen in the lung, hilar lymph nodes, liver, and spleen of individuals who successfully limit the infection.

Most individuals infected with *H. capsulatum* develop adequate CMI. If CMI fails to develop, progressive dissemination will occur. In the United States, histoplasmosis-associated hospitalizations have increased during the past two decades as has the proportion of hospitalizations in those with histoplasmosis associated with transplants, diabetes, and autoimmune conditions requiring biologic therapies.

Clinical manifestations

Localized pulmonary and self-limited infections

Most *H. capsulatum* infections are asymptomatic. After low-inoculum exposure, some patients develop a localized form of infection with fever, chills, headaches, myalgia, anorexia, cough, and chest pain. Erythema multiforme or erythema nodosum may develop. The incubation time following low-inoculum exposure is approximately 14 days. This form of acute localized pulmonary infection is self-limited; after 2 to 4 weeks, most immunocompetent patients will have recovered completely, and treatment is usually not necessary. Chest radiographs usually demonstrate localized pneumonitis but may be normal. Ipsilateral hilar lymph nodes are usually enlarged. Healing may be complete with normalization of the radiograph, but frequently multiple cycles of central necrosis and peripheral calcification occur, leaving the characteristic "coin" lesion as proof of prior infection.

When the infective aerosol is unusually large, fulminant infection may occur, with severe hypoxemia and respiratory failure that requires prompt and aggressive treatment. Patients who inhale a large inoculum may develop nodular lesions of variable sizes. The radiologic appearance of an overwhelming inoculum is diffuse micronodular infiltrates that may appear miliary.

Patients with emphysema may develop upper lobe infiltrates after exposure. The resultant infection may result in cavitation. The radiographic appearance of this infection mimics reactivation tuberculosis. Low-grade fever and anorexia with weight loss are common. Without treatment, most of these patients develop progressive destructive lung disease. The clinical and radiologic similarities to tuberculosis make the diagnosis challenging.

Late complications of healed and calcified histoplasmosis are related to the location of the calcified lymph nodes, which may envelop and compress various mediastinal structures. A rare late complication is the development of mediastinal fibrosis, which can lead to crippling complications, such as the superior vena cava syndrome and constrictive pericarditis.

Progressive disseminated histoplasmosis

During the pre-immune phase of the infection, the fungus disseminates widely. With the development of adequate CMI, the cells of the reticuloendothelium limit the spread of the disease.

In immunosuppressed patients or at the extremes of age this dissemination becomes progressive. This form of the disease is known as progressive disseminated histoplasmosis (PDH), and prognosis is poor without treatment. Fever and weight loss are the most common symptoms, and hepatosplenomegaly is frequent.

Dissemination to the oropharyngeal or gastrointestinal mucosa (causing ulcerations), the skin (causing a plethora of skin findings), and the adrenal glands (potentially causing adrenal insufficiency) may occur. Severe cases may be complicated by respiratory distress, hepatic failure, renal failure, coagulopathy, shock, and even hemophagocytic lymphohistiocytosis (HLH). Central nervous system (CNS) involvement occurs in% 5 to 10% of patients with disseminated disease and presents as either a chronic meningitis or focal lesion. In PDH, the mortality is close to 100% without treatment. In severely ill patients, mortality may still be high despite treatment.

Prior to the widespread use of cytotoxic agents and glucocorticoids, most patients with PDH had underlying lymphoreticular malignancies, most commonly Hodgkin's disease. Currently, the most common underlying disease of patients with PDH is AIDS. Organ transplantation and immune-modulating treatments (such as the tumor necrosis factor [TNF] blocking agents) have increasingly contributed to the pool of patients at risk for disseminated disease (Figure 175.1).

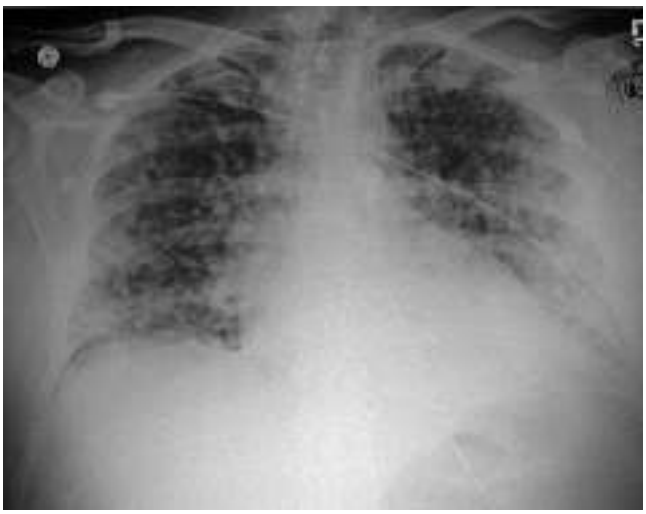

FIGURE 175.1 Chest radiograph demonstrating diffuse infiltrates in a patient with rheumatoid arthritis with progressive disseminated histoplasmosis following initiation of treatment with a tumor necrosis factor (TNF-α) inhibitor.

Diagnosis

The gold standard in diagnosis is recovery of the organism, but this is time-consuming, requiring up to 30 days for identification.

Sputum cultures are not very useful in cases of suspected acute pulmonary infection because of the low inoculum of infecting organisms and the rarity of productive cough in this syndrome. In contrast, acute disseminated histoplasmosis and chronic pulmonary or cavitary infections have a higher likelihood of positive cultures. When bronchoscopy with bronchoalveolar lavage is employed with appropriate stains, the sensitivity of respiratory cultures increases. Biopsy of accessible lesions (Figure 175.2) and bone marrow can be used in cases of disseminated infection.

Detection of histoplasma polysaccharide antigen in urine, serum, or cerebrospinal fluid offers high sensitivity and rapid diagnosis for patients with large-inoculum acute pulmonary disease, PDH, and CNS disease. Antigen sensitivity is higher in disseminated infections than in isolated pulmonary disease. The highest sensitivity of histoplasma antigen testing is in patients with AIDS and PDH when compared

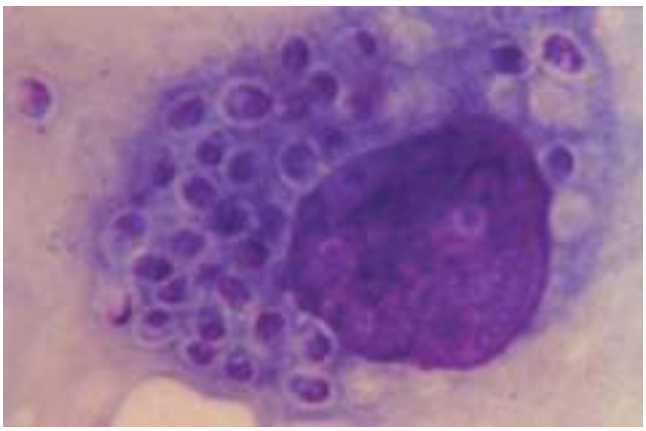

FIGURE 175.2 Histiocyte containing numerous yeast cells of *Histoplasma capsulatum*. Giemsa stain.

Courtesy of Dr. DT McClenan, Public Health Image Library, Centers for Disease Control and Prevention.

to other immunosuppressed or immunocompetent individuals with PDH. Since the levels of antigen are highest in the urine for most patients, urine testing is a helpful initial strategy. Antigen testing from blood may be particularly useful in anuric patients. Urine antigen levels correlate with disease severity and are useful when monitoring response to treatment or investigating for relapse.

Serologic testing using complement fixation and immunodiffusion is also helpful in some cases and may be the only means by which an infection can be diagnosed in immunocompetent individuals. In these patients, it frequently takes 2 to 6 weeks to develop detectable antibodies. The use of these antibodies for diagnosis of histoplasmosis is most helpful in chronic pulmonary histoplasmosis and for those with persistent symptoms following recent infection. In a recent study of those with acute pulmonary infection, a strategy of testing using serum *Histoplasma* IgM and IgG antibody detected by enzyme immunoassay (EIA*) along with* serum *Histoplasma* antigen testing appears to have the greatest diagnostic yield for this acute form of the disease.

Similar to antigen levels, there is also clinical correlation between the severity of the disease and the height of antibody response. In immunosuppressed patients, antibody response may be weaker and, in some cases, absent.

Molecular techniques like polymerase chain reaction demonstrate high sensitivities from the blood and may be an option for patients who are immunosuppressed without antigenemia or antigenuria. Unfortunately, these tests are relatively new and not currently widely available.

Treatment

The vast majority of patients with acute histoplasmosis are asymptomatic or have a mild self-limited disease and do not require antifungal treatment. In the few patients where treatment is required, therapy depends on the clinical scenario (Table 175.1).

Acute localized pulmonary infection resolves without therapy in the majority of cases, and treatment is only indicated when symptoms persist for more than 4 weeks. In these patients oral itraconazole, 200 mg three times daily for 3 days, followed by oral itraconazole, 200 to 400 mg/d for 6 to 12 weeks, is recommended. In more severe cases of acute diffuse pulmonary histoplasmosis in the immunocompetent host who requires hospitalization, lipid formulations of amphotericin B in doses of 3 to 5 mg/kg/d are recommended for up to 2 weeks, followed by oral itraconazole, 200 mg three times daily for 3 days, followed by oral itraconazole, 200 mg twice daily for an additional 12 weeks. Some studies support the use of methylprednisolone, 0.5 to 1.0 mg/kg/d intravenously in severely ill, hypoxemic, or ventilated patients for up to 2 weeks.

The treatment of chronic pulmonary histoplasmosis is oral itraconazole, 200 mg three times daily for 3 days, followed by 200 to 400 mg/d for at least a year. Therapy may be extended if resolution is slow. Amphotericin B is also effective when used for 12 to 16 weeks but is rarely necessary. Relapses after apparently successful treatment may occur, and close follow-up is essential.

The treatment of severe PDH is liposomal amphotericin B at the dose of 3 mg/kg/d for 1 to 2 weeks or until clear clinical improvement. This is followed by oral itraconazole, 200 mg three times daily for 3 days, followed by oral itraconazole, 200 mg twice daily for at least 12 months. Other lipid preparations may be substituted in appropriate doses. Mildly ill patients with PDH may be treated with itraconazole alone for at least 12 months. PDH in AIDS patients is treated in a similar fashion. Chronic suppressive therapy with itraconazole is recommended for patients who do not recover immune function. CNS histoplasmosis is treated with liposomal amphotericin B, 5 mg/kg/d, for a total of 175 mg/kg over 4 to 6 weeks, followed by oral itraconazole, 200 mg two to three times daily for at least 1 year.

Due to erratic absorption (though better with the oral suspension), itraconazole requires therapeutic drug level monitoring. Generally, itraconazole levels should be measured after 2 weeks of therapy. Many labs report both itraconazole and hydroxyitraconazole

TABLE 175.1 **RECOMMENDATIONS FOR TREATMENT OF PATIENTS WITH HISTOPLASMOSIS**

Manifestation	Treatment
Acute pulmonary: moderately severe or severe when symptoms persist for ≥4 weeks	Itraconazole, 200 mg 3× daily for 3 d, followed by itraconazole, 200–400 mg/d for 6–12 wk
Acute pulmonary with severe manifestations	Liposomal amphotericin, 3–5 mg/kg/d for up to 2 wk, followed by itraconazole, 200 mg 3× daily for 3 d, then itraconazole, 200 mg 2× daily for 12 additional wk
Chronic cavitary pulmonary	Itraconazole, 200 mg 3× daily for 3 d, followed by itraconazole, 200 mg 2× daily for at least a year. Itraconazole levels should be measured in patients where resolution is slow Amphotericin B deoxycholate may also be used at the dose of 0.7 mg/kg/d for 12–16 wk
Progressive disseminated: moderately severe/severe, with or without HIV/AIDS	Liposomal amphotericin B, 3 mg/kg/d for 1–2 wk or until stability, followed by itraconazole, 200 mg 3× daily and then 200 mg 2× daily for at least 1 yr
Progressive disseminated mild to moderate	Oral itraconazole, 200 mg daily for 3 d followed by 200 mg 2× daily for at least 1 yr
Central nervous system	Liposomal amphotericin B, 5 mg/kg/d for a total of 175 mg/kg, followed by itraconazole, 200 mg 2–3× daily for at least 1 yr

levels (an active metabolite). The sum of these two values should be at least 1 μg/mL, and drug dosing should be adjusted to achieve this value. Absorption may improve with administration of an acidic beverage like Coca-Cola.

Suggested reading

Benedict K, Derado G, Mody RK. Histoplasmosis-associated hospitalizations in the United States, 2001–2012. *Open Forum Infect Dis*. 2016;3(1):ofv219. http://doi.org/10.1093/ofid/ofv219

Dismukes WE, Bradsher RW, Cloud GC, et al. Itraconazole therapy for blastomycosis and histoplasmosis. NIAID Mycoses Study Group. *Am J Med*. 1992;93:489–497.

Hage CA, Ribes JA, Wegennack NL, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. *Clin Infect Dis*. 2011;53: 448–454.

Johnson PS, Wheat LJ, Cloud GC, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med*. 2002;137:105–109.

Maiga AW, Deppen S, Koontz B et al. Mapping *Histoplasma capsulatum* exposure, United States. *Emerg Infect Dis*. 2018;24:1835–1839.

Richer SM, Smedema ML, Durkin MM, et al. Improved diagnosis of acute pulmonary histoplasmosis by combining antigen and antibody detection, *Clin Infect Dis.* 2016;62:896–902.

Wheat J, Hafner R, Korzun AH, et al. Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trial Group. *Am J Med*. 1995;98:336–342.

Wheat J, Nyint Thein, Guo Y, et al. Central nervous system histoplasmosis: Multicenter retrospective study on clinical features, diagnostic approach and outcome of treatment. *Medicine.* 2018;97(13):e0245. http://doi.org/10.1097/MD.0000000000010245

Wheat LJ, Freifeld AG, Kleiman MB, et al. Practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45:807–825.

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Blastomycosis

Todd P. McCarty and Peter G. Pappas

Blastomycosis is a systemic pyogranulomatous disease caused by the thermally dimorphic fungus *Blastomyces dermatitidis*. While *B. dermatitidis* causes the vast majority of disease, two other species have also recently been identified as pathogenic agents: *B. gilchristii* and *B. helicus*. The disease is endemic to parts of the midwestern and south-central United States and Canada; however blastomycosis has been reported worldwide, including isolated reports from Africa, Asia, and Central and South America. Within the United States and Canada, the disease is concentrated in areas along the Mississippi and Ohio River basins and the Great Lakes. In endemic areas, small point-source outbreaks of blastomycosis have been associated with recreational and occupational activities occurring in wooded areas along waterways. Current evidence indicates that *B. dermatitidis* exists in warm moist soil enriched by organic debris, including decaying vegetation and wood.

Most infections with *B. dermatitidis* occur through inhalation of aerosolized spores, although infection through direct inoculation has been reported rarely. Primary infections are usually asymptomatic or may result in a self-limited flu-like illness. Hematogenous dissemination of organisms from the lung can result in extrapulmonary manifestations.

Blastomycosis is usually recognized as a chronic, indolent systemic fungal infection associated with various pulmonary and extrapulmonary manifestations. Pulmonary blastomycosis usually manifests as a chronic pneumonia syndrome characterized by productive cough, chest pain, hemoptysis, weight loss, and low-grade fever. There are no distinguishing radiologic features of pulmonary blastomycosis, although nodular and mass lesions, with or without cavitation, often mimicking other granulomatous diseases or bronchogenic carcinoma, are common. Hilar adenopathy and pleural effusions are uncommon. Rarely, diffuse interstitial infiltrates consistent with acute respiratory distress syndrome (ARDS) can occur secondary to blastomycosis.

Clinical manifestations of blastomycosis are highly variable. The lungs are involved in up to 90% of cases, and the skin is involved in 40% to 60% of cases. Multiple organ involvement is common, occurring in approximately 50% to 60% of cases. Osteoarticular disease is the next most common manifestation, followed by male genitourinary tract (especially the prostate and epididymis) involvement. Central nervous system (CNS) involvement occurs in fewer than 5% of patients and can present as either granulomatous meningitis or an intracerebral mass lesion. *B. dermatitidis* is an uncommon opportunistic pathogen but may cause overwhelming disease in the immunocompromised host. Among patients with predisposing factors, chronic glucocorticosteroid use, solid organ transplant, and advanced HIV disease are the most common underlying conditions.

Diagnosis

The definitive diagnosis of blastomycosis requires a positive culture for *B. dermatitidis* from clinical specimens. A presumptive diagnosis is based on the finding of classic-appearing broad-based budding yeasts with doubly refractile cell walls compatible with *B. dermatitidis* on histopathologic examination of clinical specimens (Figure 176.1). Ten percent potassium hydroxide (KOH) is used to prepare wet specimens

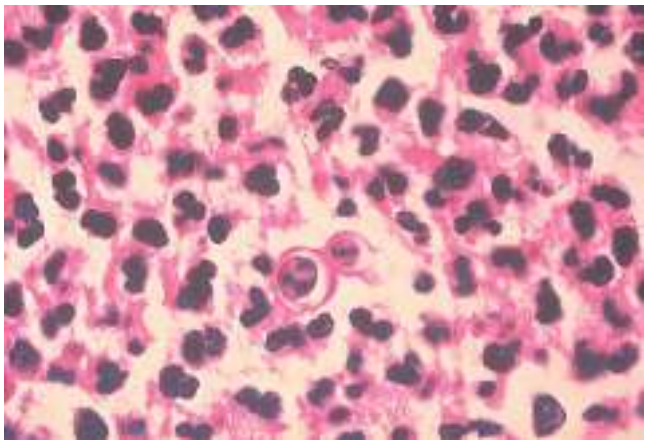

FIGURE 176.1 Histopathology of blastomycosis of skin. Cell of *Blastomyces dermatitidis* undergoing characteristic broad-based budding, surrounded by neutrophils. Multiple nuclei are visible.

Public Health Image Library, Centers for Disease Control and Prevention.

for examination, whereas fixed specimens are usually stained with hematoxylin and eosin, periodic acid–Schiff (PAS), or Gomori's methenamine silver (GMS) reagents. Serologic assays are of limited value in the diagnosis of blastomycosis. The complement fixation assay for serum antibody is highly cross-reactive and of little diagnostic value. Recent studies suggest that immunodiffusion or enzyme immunoassay (EIA) tests for A antigen of *B. dermatitidis* or antibody to more purified antigens have potential as serologic markers of disease. The *Blastomyces* EIA urine antigen assay is sensitive but nonspecific and gives false-positive results among patients with active histoplasmosis, paracoccidioidomycosis, and penicilliosis. The blastomycin skin test antigen lacks sufficient sensitivity and specificity and should not be used as a diagnostic test. Polymerase chain reaction (PCR) is being evaluated as an additional diagnostic tool, but there is not currently a commercialized assay available that is specific to blastomycosis. Universal fungal ribosomal PCR is an option when the specific fungal pathogen is not known at the time of tissue acquisition and can provide results very quickly.

Treatment

Presently, three drugs are approved for the treatment of blastomycosis: amphotericin B, itraconazole, and ketoconazole. Originally, amphotericin B was the mainstay of therapy for all forms of blastomycosis, but studies and experience gained since the early 1990s indicated that ketoconazole, itraconazole, and fluconazole are highly effective alternative oral therapies. Ketoconazole is no longer manufactured for systemic use because of hepatotoxicity concerns. Although no comparative trials have been performed, itraconazole appears to have greater efficacy and less toxicity than either fluconazole or ketoconazole and therefore is the oral agent of choice. In a published trial, 95% of patients with non–life-threatening, non-CNS blastomycosis were treated successfully with itraconazole, 200 to 400 mg/d for 2 to 6 months. This approximates the observed efficacy seen with amphotericin B. Clinical data regarding the use of fluconazole suggest similar efficacy of this agent, with at least 80% of patients responding to 400 to 800 mg/d for 6 months. Most patients with blastomycosis can be started on oral itraconazole, 200 mg/d and advanced by 100 mg increments at monthly intervals to a maximum of 400 mg/d in patients with persistent or progressive disease. In patients with more aggressive disease, an initial dose of 400 mg is appropriate. Therapy with any of the azoles should be given for a minimum of 6 months. More recently, newer mold-active triazoles (voriconazole, posaconazole, and isavuconazole) have been reported to have success in treatment when other agents are not tolerable. Voriconazole is recommended as the azole of choice for blastomycosis involving the CNS. Based on in vitro susceptibility data, one would anticipate excellent clinical activity from all of these compounds.

A formulation of amphotericin B is generally reserved for patients with overwhelming life-threatening and/or CNS disease, patients who are severely immunocompromised, and for those in whom oral therapy has failed. In selected patients, an induction dose of amphotericin B for a rapid fungicidal effect to gain control of the disease may be useful, followed by oral therapy with itraconazole for at least 6 months. For patients with CNS involvement, several reports suggest that fluconazole and voriconazole, two azoles with significant CNS penetration, are effective therapeutic agents among individuals who have had an initial favorable response to amphotericin B. There is substantial clinical experience but few published data concerning the use of the lipid formulations of amphotericin B in the treatment of blastomycosis. There are no data to suggest superior efficacy of these agents compared with conventional (deoxycholate) amphotericin B. However, the use of the lipid formulations of amphotericin B, at doses ranging from 3 to 6 mg/kg/d to treat blastomycosis has become a standard approach in many developed countries where there is broad access to these compounds. Despite their greater expense, the lipid formulations are associated with significantly less nephrotoxicity and infusion reactions than deoxycholate amphotericin B.

The treatment of acute pulmonary blastomycosis remains controversial. Many investigators suggest close observation without therapy in patients who are not immunocompromised; however, this approach has become less acceptable to many clinicians given the extensive safety and efficacy profiles of the azole compounds. Available data suggest that most cases of acute pulmonary blastomycosis resolve spontaneously without therapy, although careful long-term evaluation of these untreated patients is important to monitor for evidence of active disease.

All patients with chronic blastomycosis should receive antifungal therapy. Cure rates of at least 90% should be expected, with relapse rates of <10%. Mortality is uncommon and is usually seen among patients with extensive pulmonary involvement and acute respiratory distress syndrome (ARDS). A few patients, especially chronically immunocompromised individuals such as organ transplant recipients, patients receiving chronic glucocorticosteroid treatment,

and patients with AIDS require long-term suppressive therapy to prevent relapse.

Suggested reading

Bariola JR, Hage CA, Durkin M, et al. Detection of *Blastomyces dermatitidis* antigen in patients with newly diagnosed blastomycosis. *Diagn Microbiol Infect Dis*. 2011;69:187–191.

Bariola JR, Perry P, Pappas PG, et al. Blastomycosis of the central nervous system: A multicenter review of diagnosis and treatment in the modern era. *Clin Infect Dis*. 2010;50:797–804.

Bariola JR, Vyas KS. Pulmonary blastomycosis. *Semin Respir Crit Care Med*. 2011;32:745–753.

Brown EM, McTaggart LR, Zhang SX, et al. Phylogenetic analysis reveals a cryptic species Blastomyces gilchristii, sp. nov. within the human pathogenic fungus Blastomyces dermatidis. *PLoS One;* 2013;8:e59237.

Castillo CG, Kauffman CA, Miceli MH. Blastomycosis. *Infect Dis Clin North Am.*; 2016;30:247–264.

Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46:1801–1812.

Grim SA, Proia L, Miller R, et al. A multicenter study of histoplasmosis and blastomycosis after solid organ transplantation. *Transpl Infect Dis*. 2012;14:17–23.

McKinnell JA, Pappas PG. Blastomycosis: New insights into diagnosis, prevention and treatment. *Clin Chest Med*. 2009;30:227–239.

Proia LA, Harnisch DO. Successful use of posaconazole for treatment of blastomycosis. *Antimicrob Agents Chemother*. 2012;56:4029.

Roy M, Benedict K, Deak E, et al. A large community outbreak of blastomycosis in Wisconsin with geographic and ethnic clustering. *Clin Infect Dis*; 2013;57:655–662.

Schwartz IS, Wiederhold NP, Hanson KE, et al. Blastomyces helicus, a new dimorphic fungus causing fatal pulmonary and systemic disease in humans and animals in western Canada and the United States. *Clin Infect Dis;* 2019;68:188–195.

Thompson GR, Rendon A, Ribeiro Dos Santos R, et al. Isavcuonazole treatment of cryptococcosis and dimorphic mycoses. *Clin Infect Dis;* 2016;63:356–362.

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Coccidioidomycosis

Trung T. Vu, Jose Cadena, and Gregory M. Anstead

Introduction

Coccidioidomycosis (CM) is caused by dimorphic fungi of the genus *Coccidioides*. It typically presents as acute and chronic pulmonary disease. The infection may disseminate widely, especially to cutaneous, osseous, and central nervous system (CNS) sites. CM is a significant health problem in the southwestern United States and Latin America, with approximately 150,000 infections per year in the United States, about 50,000 of which are symptomatic.

Microbiology

In routine fungal culture, at 25°C to 30°C/77°F to 86°F, *Coccidioides* grows as a mold; colonies are usually white but may be tan to brown, pink, purple, or yellow. The hyphae are thin, septate, and hyaline. Side branches produce unicellular, barrel-shaped arthroconidia (3–4 × 3–6 μm), alternating with empty disjunctor cells. At 37°C/98.6°F, in tissue or special media, the arthroconidia become spherical, enlarge, and develop into spherules (20–60 μm) that contain many endospores (2–4 μm). Conversion to spherules is not routinely performed in the laboratory; definitive identification is established by a DNA probe or exoantigen testing. Unlike *Histoplasma capsulatum* and *Blastomyces dermatitidis*, *Coccidioides* grows rapidly (usually in 3–7 days) and sporulation may be seen after 5 to 10 days. Clinicians should notify the laboratory when CM is suspected to ensure proper infection control practices. Plates with suspected *Coccidioides* mycelia should be sealed and opened only in biohazard hoods. Careless handling of culture plates has caused CM in laboratory personnel. The risk of inadvertent exposure of laboratory staff is especially high in nonendemic areas in which *Coccidioides* is not expected.

Epidemiology

Based on molecular genetics, the genus *Coccidioides* has been divided into *C. immitis* (mostly California isolates) and *C. posadasii* (other areas); both species are similarly pathogenic, but may differ in thermo- and halotolerance. The mycelial form of the fungus grows just beneath the soil surface and is composed of arthroconidia intercalated with nonviable segments. In addition to wind-borne arthroconidia, another route of soil colonization with *Coccidioides* is the decomposition of the carcasses of small mammals that were infected with the fungus.

The endemic area of CM is the Lower Sonoran Life Zone, marked by arid or semi-arid climates (annual rainfall 5–20 inches), sandy alkaline soil, and mild winters. These conditions are found in the southwestern United States (primarily Arizona, California, New Mexico, and Texas), Bolivia, Paraguay, Argentina, and

Mexico (Figure 177.1). Cases occur infrequently in Guatemala; Honduras, Nicaragua, Venezuela, Brazil, and Colombia. Overall, the epidemiology of CM in Latin America is poorly defined and is based primarily on skin test surveys; the real incidence is unknown because it is not reportable and cases may be misdiagnosed as tuberculosis.

The incidence of CM in the United States is increasing. In Arizona, the number of cases increased 40-fold in 19 years, from 255 in 1990 (incidence 7/100,000 population) to 10,233 cases in 2009 (155/100,000). Cases in Arizona reached an all-time high in 2011 with 16,467 cases. The increasing incidence is due to soil disturbance from construction for its rising population and an influx of susceptible individuals into the state. Furthermore, the frequency of dust storms has increased in the American Southwest by 240% from the 1990s to 2000s, and this has been proposed as a factor in the rise in the incidence of CM. Arizona accounts for 60% of all US cases; the highest rates occurred in its most populous counties (Maricopa, Pima, Pimal). In Tucson, *Coccidioides* causes 29% of community-acquired pneumonia.

In California, from 1995 to 2009, the annual incidence ranged from 1.9 to 8.4 per 100,000, increasing to 13.8 per 100,000 in 2011. Cases in California reached an all-time high in 2017 of 6,925; most occur in the Central Valley and Central Coast. The reasons for the increased rates are uncertain but may be due to a period of rainfall after years of drought and soil disturbance due to construction. In 2017, there were 14,364 cases reported to the US Centers for Disease Control and Prevention, mostly among residents of Arizona and California. However, this is likely to be a significant underestimate because many individuals with apparent community-acquired pneumonia are not tested for CM.

Risk factors for increased severity of CM include receiving immunosuppressive medications (corticosteroids, transplant

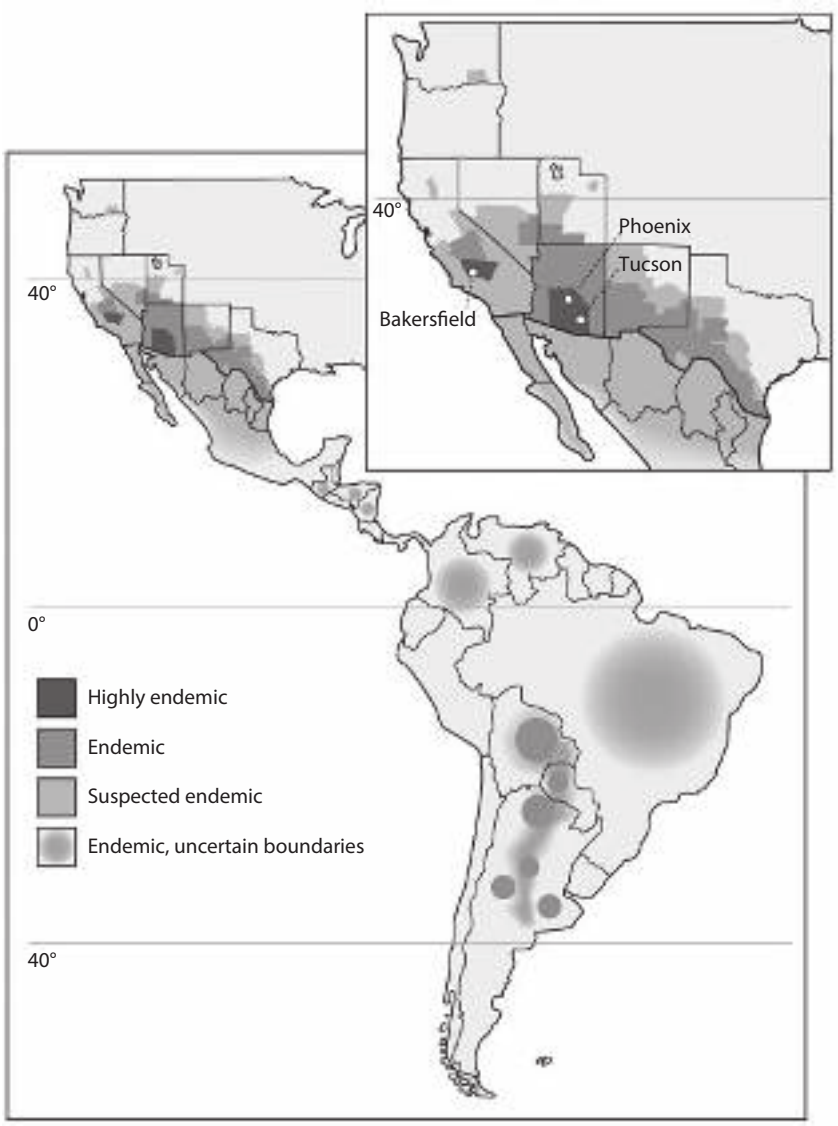

FIGURE 177.1 Map of the distribution of *Coccidioides* spp.

drugs, and tumor necrosis factor [TNF-α] antagonists), diabetes mellitus, pregnancy (especially the third trimester), genetic factors (i.e., defects in the interleukin [IL]-12/interferon-γ axis and the STAT3 pathway, certain ABO blood groups and HLA types), and specific races/ethnicities. The incidence of CM per 100,000 in Arizona in 2009 among different ethnic/racial groups was African American, 67; Asian-Pacific Islander, 36; Caucasian, 28; and Hispanic, 21. Filipinos and Native Americans are also considered to be high-risk groups. Persons with occupations with soil exposure (farm and construction workers, archeologists, military personnel, miners, and oil and gas workers) are also at risk for CM.

Natural history, pathogenesis, and pathologic findings

When the soil is disturbed, the fragile mycelia disintegrate into a cloud of conidia which may be carried for miles by the wind. Inhaled conidia are phagocytosed by alveolar macrophages and, over several days, convert into the characteristic large spherule (Figure 177.2). The spherules elaborate endospores, which multiply, and, after 3 to 4 days, hundreds of daughter cells (endospores) burst from the mature spherule. The endospores are ingested by neutrophils but not killed. These gradually enlarge into the next generation of spherules.

Arthroconidia, endospores, and spherules are resistant to killing by phagocytic cells, which may be due to components of the outer cell wall of the organism, such as spherule outer wall glycoprotein (SOWgp). Host exposure to SOWgp biases the immune response in a Th2 manner, compromising cell-mediated immune pathways. Other virulence factors of *Coccidioides* include melanin and extracellular urease. Melanin protects the fungus from the reactive oxygen species produced by leukocytes. The urease generates an alkaline microenvironment, which impairs granuloma formation and pathogen clearance. Pulmonary infection with *Coccidioides* also alters surfactant production, which promotes disease progression.

Early in the course of infection, *Coccidioides* may hematogenously disseminate to the skin, bones, and CNS. Clinical manifestations of these remote lesions may appear soon after the acute infection or months later, sometimes without evidence of the primary infection. Uncontrolled infection often presents as suppurating abscesses, with draining exudates containing abundant neutrophils and spherules, whereas chronic low-grade infection manifests as better-formed granulomas containing few organisms. Both B- and T-lymphocytes are essential for host defense, indicating that a balanced Th1/Th2 response is necessary for protective immunity.

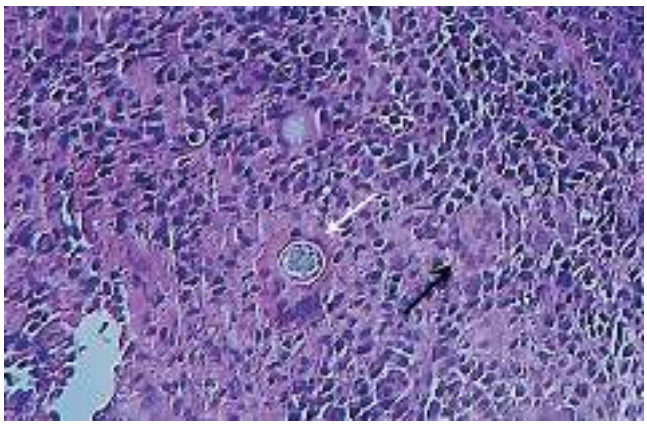

FIGURE 177.2 Hematoxylin and eosin stain of the biopsy specimen from a nodular skin lesion showing a coccidioidal spherule (*white arrow*), chronic inflammatory cell infiltrates, as well as surrounding granuloma formation with multinucleated giant cells.

Clinical features

Primary infection

CM is asymptomatic in more than half of patients. Hypersensitivity reactions may occur with primary infection, including fever, toxic erythema, erythema nodosum, erythema multiforme, arthralgias, arthritis, conjunctivitis, or episcleritis, known as "Valley Fever" after the San Joaquin Valley of California, a major endemic focus. These may be the only manifestations of primary CM, or they may blend into the invasive forms of disease. Occasional case clusters may occur 10 to 14 days after a group of susceptible persons is exposed to dust in an endemic area.

Pulmonary infection

Most symptomatic patients have a transient pulmonary infection occurring 1 to 3 weeks after exposure, manifesting as fever, dry cough, and pleuritic chest pain. This is usually indistinguishable from community-acquired pneumonia. Radiographically, there may be infiltrates, hilar adenopathy, and pleural effusions. Typically, the symptoms of acute pulmonary CM resolve spontaneously in less than a month. Alternatively, the pulmonary infiltrates may condense into nodules that may resolve or persist asymptomatically. While primary pneumonia usually resolves, in 5% to 19% of patients, the disease may linger for months, with chronic pulmonary infiltrates, cough, and pleuritic chest pain. Coccidioidal pleuritis with pleural effusion may also occur, often with spontaneous resolution. Immunocompromised patients are more likely to develop chronic progressive pulmonary infection, characterized by the presence of extensive thin-walled cavities that may be complicated by rupture, with bronchopleural fistula and empyema formation. Cavitary disease may be asymptomatic or cause chronic productive cough and hemoptysis (Figure 177.3). Cavities may also develop secondary to bacterial or *Aspergillus* (fungus ball) infection. The cavity may contract into a nodule within a year in about half of the cases. Small cavities (<5 cm in diameter) are more likely to resolve spontaneously

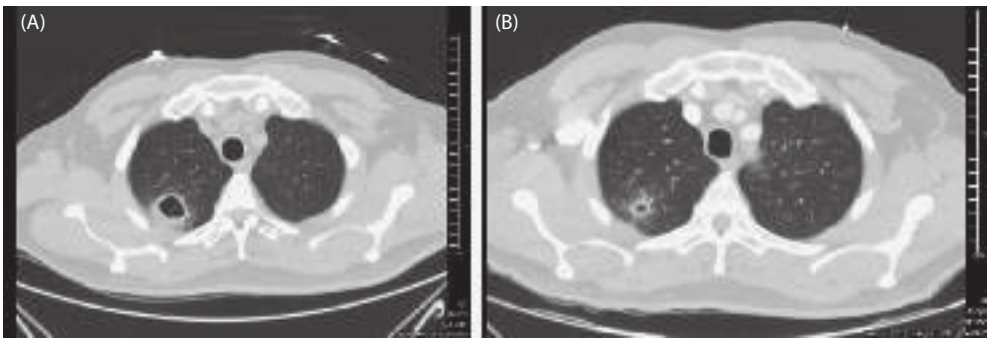

FIGURE 177.3 A 50-year-old Hispanic man presented with a 5-day history of productive cough, chills, and night sweats. (A) Chest CT with contrast showed a single thick-walled right upper lobe cavitary lesion with surrounding ground-glass opacities. A fungal culture of the bronchoalveolar lavage fluid yielded *Coccidioides* spp. (B) Six weeks after receiving daily fluconazole (800 mg), the patient's symptoms resolved, and a repeat chest CT with contrast showed a contracting cavitary lesion.

than larger ones. Chronic pulmonary CM may follow a waxing and waning course or be slowly progressive over years. Uncommonly, patients have fulminating pneumonia, with diffuse reticulonodular infiltrates, fever, and hypoxia. Aggressive pulmonary disease can occur in pregnancy, especially the last trimester, and in other immunocompromising conditions.

Extrapulmonary disease

Disseminated CM occurs in about 1% of those infected, with a fatal course in one-third of these patients. Extrapulmonary CM usually presents as skin lesions, lymphadenitis, deep abscesses, osteoarticular disease (which presents as lytic bone lesions and thickened synovia), or CNS disease, but nearly any organ can be involved. Dissemination may occur years after an apparently resolved primary infection if the individual becomes immunocompromised.

Meningitis and other CNS disease

CNS manifestations of CM include meningitis, encephalitis, mass lesions, and vasculitis (Figures 177.4 and 177.5). Coccidioidal meningitis presents as progressive headache, cranial neuropathies, and altered mental status. Typical CSF findings include a lymphocytic or eosinophilic pleocytosis (100–500 cells/mm^3), hypoglycorrachia, and elevated protein (>150 mg/dL). Elevated opening pressure of >20 cm H_2O may be observed, often associated with hydrocephalus. Granuloma formation may cause focal neurologic signs. CSF eosinophilia is a helpful diagnostic clue, and the CSF is usually positive for immunoglobulin (IgG) antibody. CSF cultures are positive in <50% of cases. Untreated, coccidioidal meningitis is fatal within 2 years. CNS vasculitis due to CM may present as a stroke-like syndrome. Not all patients with CM require a lumbar puncture; however, for those with headache or other CNS signs or symptoms, a lumbar puncture is necessary.

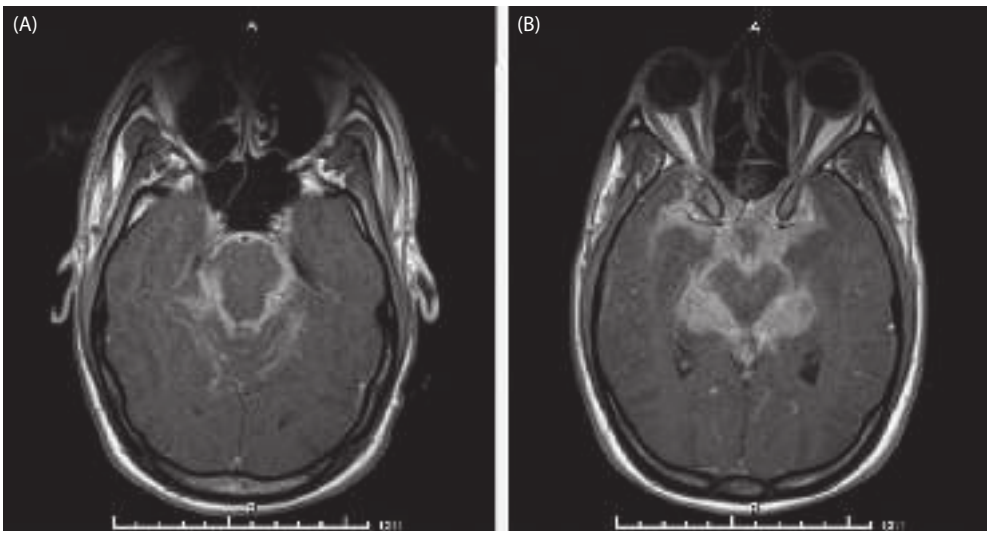

FIGURE 177.4 The patient is a 30-year-old African American man with disseminated coccidioidomycosis. Four weeks after visiting the Grand Canyon, he was treated for an upper respiratory infection. Two months after the trip, he developed a headache and was diagnosed with aseptic meningitis. He later developed a nodule near his left nasolabial fold. Four months after the trip, he presented with altered mental status. Clinical evaluation revealed coccidioidal meningitis with obstructive hydrocephalus, vertebral osteomyelitis, and fungal septic arthritis of his knee.

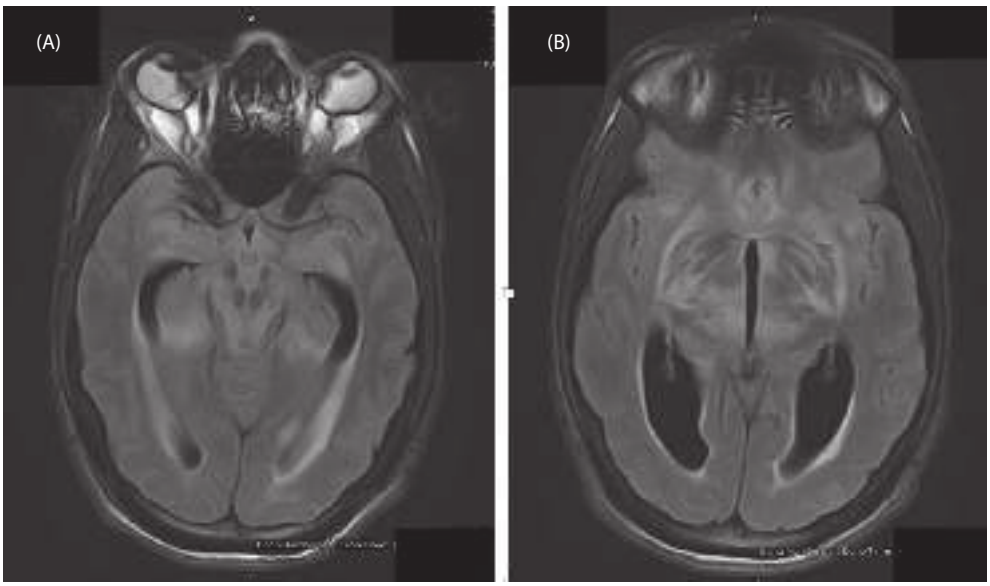

FIGURE 177.5 (A and B) These images are from the same patient as described in Figure 177.4. T2-weighted MRI axial images showing enlarged lateral and third ventricles in obstructive hydrocephalus, a dreaded complication of coccidioidomycosis. Also note the surrounding white matter edema. The patient was not shunted but responded to liposomal amphotericin B, followed by voriconazole.

Soft tissue and osteoarticular disease

Soft tissue involvement in disseminated CM includes papules, nodules, abscesses, and ulcers that may drain purulent fluid or verrucous lesions that may progress to ulceration. In general, lesions with purulent drainage are associated with a worse prognosis.

Osteoarticular involvement accounts for 20% to 50% of extrapulmonary CM. Axial skeletal structures (vertebrae, skull, sternum, and ribs) are more commonly affected than is the appendicular skeleton. The spine is the most frequent site of osteoarticular dissemination (Figure 177.6). Vertebral infection starts in the central cancellous bone of the vertebral body and then may invade into the periosteum and adjacent soft tissue. Vertebral CM may be confused with Pott's disease (vertebral tuberculosis), and, like Pott's disease, it can cause vertebral collapse and spinal cord compression. In appendicular skeletal infection with *Coccidioides*, the ends of long bones, especially at bony prominences, are most commonly involved. Radiographically, there are typically lytic lesions with osteopenia. Technetium bone scans are considered 100% sensitive for the identification of areas of coccidioidal osteomyelitis. Joint involvement is less common than osteomyelitis; it is usually mono-articular and most commonly involves the leg, especially the knee (Figure 177.7). Arthrocentesis reveals an exudative synovial fluid and the synovium shows granulomata with spherules. A synovial specimen is more likely to yield a positive culture for *Coccidioides* than is joint fluid.

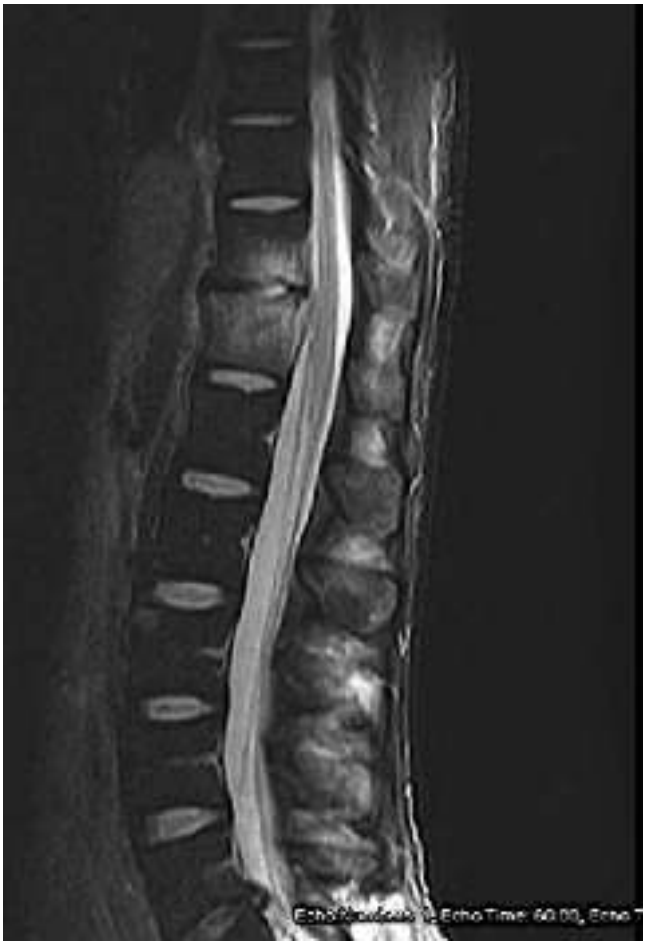

FIGURE 177.6 This image is from the same patient as described in Figure 177.4. T2 MRI sagittal image showing T11-T12 osteomyelitis and discitis with extension of infection into the anterior epidural space.

Fungemia

Coccidioides fungemia, which manifests as a systemic inflammatory response syndrome with progressive cardiorespiratory failure,

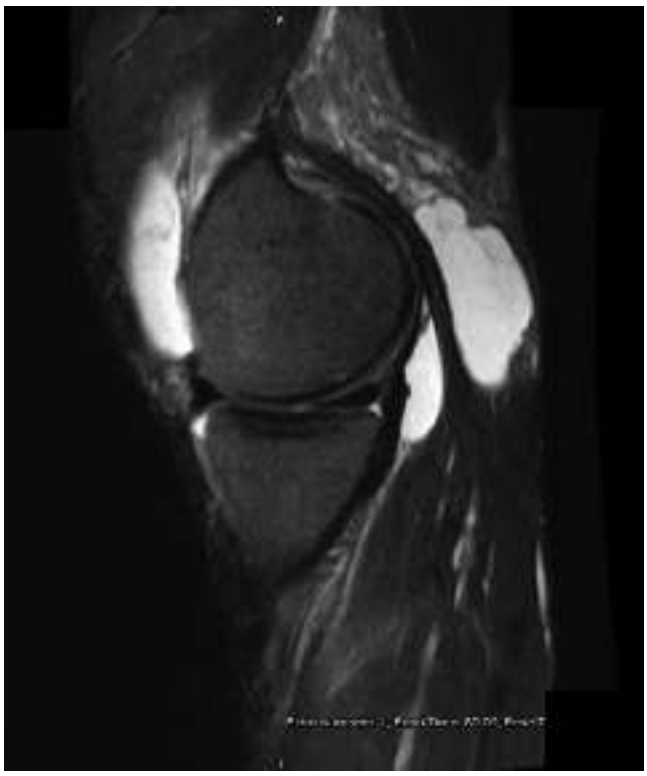

FIGURE 177.7 This image is from the same patient as described in Figure 177.4. T2 MRI sagittal image showing left knee synovial enhancement. Synovial fluid culture grew *Coccidioides* spp.

has been described in immunocompromised patients and carries a high mortality rate. In one series of 33 patients with coccidioidal fungemia, 73% died within 28 days of the diagnosis.

Coccidioidomycosis, the "great imitator"

CM has been termed a "great imitator" disease and has many diverse disease manifestations. In addition to the usual pulmonary, cutaneous, osteoarticular, and nervous system manifestations of CM, various uncommon presentations are listed in Table 177.1. In general, unusual manifestation most often occur in the immunosuppressed host or in those prone to dissemination such as African Americans, Filipinos, and pregnant women.

Coccidioidomycosis in children

Children are susceptible to CM, with a reported incidence of hospitalization in endemic regions of 8 to 12/100,000. In one series, 56% of hospitalized children had pulmonary disease, 14% had progressive disease, and 7% had meningitis. About one-third of pediatric CM patients had underlying conditions, usually immunodeficiency or malignancy; none died during their first hospitalization. Coccidioidal serologic tests are not reliable for the evaluation of infants during the first 3 months of life and positive tests must be interpreted cautiously during the first year. Breastfeeding is not recommended for mothers with CM taking azoles other than fluconazole. It uncertain if transplacental infection of the fetus occurs, and the very rarely observed neonatal infections are likely the result of aspiration of amniotic fluid or vaginal secretions.

TABLE 177.1 **UNUSUAL MANIFESTATIONS OF COCCIDIOIDOMYCOSIS**

Site or organ system	Manifestation
Skin and soft tissue	Purpura; bullae; subcorneal pustulosis; mesh infection; tenosynovitis
Neurologic	Brain aneurysms; brain abscess; cerebral arteritis and infarction
Hematologic	Immune thrombocytopenia; hemophagocytic lymphohistiocytosis
Head and neck	Massive cervical lymphadenopathy; laryngeal abscess; retropharyngeal abscess; thyroiditis; preauricular cyst; glossitis
Ocular	Endophthalmitis; iridocyclitis; granulomatous conjunctivitis; choroiditis; uveitis
Cardiac	Endocarditis, pericarditis, myocarditis
Intra-abdominal	Peritonitis; hepatitis; pelvic mass; adrenal mass; duodenitis
Female genital/ reproductive system	Placentitis with or without fetal demise; salpingitis; uterine involvement
Male genital/ reproductive system	Prostatitis, epididymitis, orchitis

Diagnosis

CM should be considered in the differential diagnosis of a compatible illness occurring in a resident or visitor to an endemic area. Rapid diagnostic methods include examination of sputum or exudates from purulent lesions for spherules or detection of spherules on histopathologic exam of cutaneous lesions, bronchoscopy specimens, or lymph nodes. The morphology of *Coccidioides* spherules is nearly pathognomonic.

The gold standard technique for the diagnosis of CM is culture of the organism from clinical specimens. The spherules in sputum, exudates, or tissue convert to mycelia in culture, which usually grow in 3 to 7 days.

The immunodiffusion (ID) technique detects IgG and IgM antibodies indicating exposure to *Coccidioides* with high specificity. IgM antibodies develop within weeks after infection but are not sustained. IgG antibodies take 1 to 2 months to appear (in blood and CSF) and persist for many months. Complement fixation (CF) tests detect IgG and are useful for both diagnosis and monitoring

the activity of the infection; CF titers of >1:16 suggest disseminated infection. Antibody concentrations may decrease over time to undetectable levels upon resolution of the infection. Thus, a positive antibody assay indicates recent infection, chronic disease, or reactivation. There may be false-negative serologic studies early in the course of infection, in localized disease (i.e., a pulmonary nodule), or in immunocompromised patients. Serologic assays may be applied to blood, CSF, and pleural and synovial fluid. Enzyme immunoassays (EIA) are available outside of reference laboratories and detect both IgM and IgG. There is controversy regarding the false-positivity rates of isolated EIA IgM measurements; serial measurements have been used to differentiate false-positive from true-positive results. A positive EIA IgG, either alone or with a positive EIA IgM, should be sent to a reference laboratory for confirmation.

A urinary antigen test is available from MiraVista Laboratories (Indianapolis, IN), with 71% sensitivity in moderate to severe disease versus 87% for culture. The urinary antigen test has some cross-reactivity with *Histoplasma* antigens. There is a commercially available PCR test (Mayo Medical Laboratories, Rochester, MN) that can utilize either body fluids or tissue.

Treatment

Treatment guidelines for CM were published in 2016. *Coccidioides* isolates are generally susceptible to amphotericin B and azoles in vitro, but treatment responses are highly dependent on host factors (immunocompetence and race/ethnicity). In a study of the in vitro susceptibility of 581 *Coccidioides* isolates, elevated MIC values were observed for 37% of isolates to fluconazole (≥16 g/mL) versus 1% of isolates for itraconazole, posaconazole, and voriconazole. However, studies of the relationship between MIC values and patient outcomes are necessary to determine the relevance of these data in antifungal selection. Clinical experience with echinocandins is limited.

Treatment courses for any form of CM are prolonged and should continue for months after improvement. Because some lesions can progress while others wane, a scoring system was developed by the Mycosis Study Group (Catanzaro, Galgiani, and coworkers) that incorporated signs and symptoms, cultures, radiographically apparent lesions, and serologic titers with a reduction of a cumulative score to <50% of baseline considered as response to therapy. As cultures are often not repeated (especially if invasive methods are required) and serologic titers change slowly, the total burden of disease has recently been measured using clinical signs and symptoms and radiographic evaluation of lesion size. In coccidioidal meningitis, normalization of CSF findings indicates an appropriate treatment response.

Selection of the antifungal agent depends in part on the involved site and the severity of disease. No treatment is recommended for asymptomatic coccidiomas (noncalcified nodular densities) which are often resected incidentally by a biopsy for presumed lung cancer. The nephrotoxicity of amphotericin B initially discouraged physicians from treating primary coccidioidal pneumonia, which usually resolves spontaneously. However, all patients require observation for at least 2 years to document resolution of infection and promptly identify complications. Liposomal amphotericin B (AmBisome) has several advantages over amphotericin B deoxycholate, including lower nephrotoxicity, attainment of higher levels in the reticuloendothelial system, and better CNS penetration. Fluconazole has been increasingly deployed to treat primary coccidioidal pneumonia. Nevertheless, there are no clear data to indicate its efficacy in this setting or in the prevention of dissemination.

For patients at risk for disseminated disease, antifungal treatment of primary coccidioidal pneumonia is appropriate. Other indications for treatment are severe disease: infiltrates involving both lungs or more than half of one lung, hilar or mediastinal lymphadenopathy, IgG titers of >1:16, and highly symptomatic disease (weight loss >10%, night sweats >3 weeks, symptoms >2 months). Patients with signs of chronic pulmonary infection, such as weight loss, night sweats, and multilobar infiltrates and symptoms for more than 2 months should also be treated.

Based on its excellent tolerability, linear renal clearance, limited drug interactions, and efficacy, fluconazole is the drug of choice for less severely ill patients. In one trial, the response rate in chronic pulmonary and disseminated disease was 50% for fluconazole versus 63% for itraconazole. Fluconazole doses of 400 mg/d are often used initially, but slow responses and failures in meningitis may necessitate doses as high as 1,000 to 1,200 mg/d. Treatment for 6 months has been suggested for primary pneumonia and >12 months after response for severe or chronic pulmonary or disseminated disease.

Although itraconazole is superior to fluconazole in patients with skeletal disease, its less predictable pharmacokinetics and more frequent adverse events have demoted itraconazole to a second-line drug. Itraconazole is administered orally either as capsules with a fatty meal or as a cyclodextrin solution (Sporanox) in the fasted state, at 400 to 600 mg/d. The larger studies have been conducted with the capsules, which are better tolerated but less predictably absorbed. Itraconazole inhibits and is metabolized by cytochrome 3A4, so its drug interactions are extensive. There is limited experience with itraconazole in the treatment of meningitis.

For life-threatening CM, amphotericin B or a lipid formulation is recommended. The latter is preferred because of its decreased risk of nephrotoxicity. There is no evidence that high doses of the lipid formulations (e.g., 10 mg/kg) are more effective than doses of 3 to 6 mg/kg. Responses to amphotericin-based therapy on the order of 50% to 70% are seen. When the patient has improved or when nephrotoxicity occurs, treatment is shifted to azoles for ongoing therapy. Because the azoles may be teratogenic, amphotericin B is preferred during the first trimester of pregnancy. If nephrotoxicity develops, azole treatment may be necessary for at least a limited time, preferably later in pregnancy.

A challenge in the management of CM is the selection of a salvage agent when initial therapy fails or when the patient relapses (which may be years later). For azole failures, the 2016 guidelines recommend amphotericin B. However, voriconazole or posaconazole may also be considered. Voriconazole, at doses of 400 to 600 mg/d, has proved successful in some patients with refractory disease. Another salvage option is posaconazole. Published clinical experience for posaconazole is limited to its suspension form, given 200 mg four times per day with a fatty meal. More than half of salvage patients responded to posaconazole. Posaconazole has also

been used as primary therapy with responses of 85% in 20 patients. Unfortunately, relapses occurred in a third of patients who initially responded. Both voriconazole and posaconazole show high in vitro activity against *Coccidioides*, but the posaconazole suspension has variable oral bioavailability. A posaconazole tablet with improved oral bioavailability and an intravenous preparation are now available, and these new forms may prove to be more efficacious. Experience with isavuconazole is limited; in a series of nine patients with pulmonary CM, complete or partial success was observed in 56% of patients, but only 22% had complete resolution.

For meningitis, treatment has changed dramatically with the availability of fluconazole; previously, intrathecal amphotericin B was required. However, intrathecal amphotericin B can cause arachnoiditis and vasculitis and should be administered with corticosteroids to suppress these adverse events. It is seldom used in the post-fluconazole era except for coccidioidal meningitis in the first trimester of pregnancy. There are concerns that intravenous amphotericin B has poor CNS penetration. However, intravenous AmBisome has been used successfully in the treatment of other CNS mycoses. Further data are required to define its role in the management of coccidioidal meningitis. Posaconazole and voriconazole have also been used with success in meningitis. For patients with increased intracranial pressure at the time of meningitis diagnosis, repeated lumbar punctures are recommended. Hydrocephalus may require ventriculoperitoneal shunting. In patients with CNS vasculitis with cerebrovascular accident due to CM, those who received corticosteroids were less likely to develop additional infarcts compared to those who did not.

Reduction of immunosuppression is an important adjunct to antifungal therapy, including the initiation of antiretroviral therapy in HIV patients. In patients with AIDS and non-meningeal CM, antifungal therapy can be discontinued when the CD4 count exceeds 250 cells/mm^3. All patients with coccidioidal meningitis require lifelong antifungal therapy. Vertebral osteomyelitis may require surgical stabilization or spinal cord/nerve root decompression. For patients with a ruptured coccidioidal cavity, resection and decortication are recommended. For chronic coccidioidal arthritis, synovectomy may be beneficial.

Prevention

Vaccines. Among the endemic mycoses, CM has generated the most interest for the development of a vaccine, because (1) prior infection engenders immunity, (2) it produces a considerable burden of morbidity, and (3) it exists in a defined endemic zone, growing in population. Multiple vaccine candidates have been evaluated since the 1960s, but no vaccine has been approved for human use. These vaccine candidates have included inactivated spherules, spherule extracts, individual antigens (proline-rich antigen [Ag2/PRA], β-glucanosyltransferase, calnexin, aspartyl protease, phospholipase, and α-mannosidase, among others, using multiple different adjuvants), and live attenuated mutants (inactivated by radiation or by deletion of genes required for sporulation). Recombinant proteins, such as Ag2/PRA were found to be protective in some mouse studies, but the protection is variable, likely due to a lack of standardization of testing. One clinical trial of a killed spherule vaccine involving 2,867 persons was conducted from 1980 to 1985, with no significant reduction in the incidence of positive coccidioidin skin reaction or CM between the vaccine and control groups.

A recent study in mice compared the effectiveness of killed *Coccidioides* spores to mutant avirulent spores (*Δcps1*) in which the virulence gene CPS1 was replaced with the hygromycin resistance cassette. The attenuated strain produced long-term immunity whereas the killed spores failed to do so. The mice immunized with the *Δcps1* mutant spores had increased IFN-γ production and an enhanced Th1 response, and they were protected from lethal challenge with *C. posadasii*.

Antifungal prophylaxis. CM has been described among transplant patients in endemic regions, with an incidence of 1.4% to 6.9%. Risk factors include pre-transplant seropositivity, a history of CM, and African American race; disease can result from either primary infection or reactivation. During pre-transplant evaluation, patients should be queried about a history of traveling to or living in an endemic region and may require clinical assessment, serological testing, and chest radiography. If serologic studies are positive, transplant candidates should be evaluated by an infectious diseases specialist, and clearance for transplantation should be determined on a case-by-case basis. In endemic areas, postoperative prophylaxis with fluconazole is recommended (200 mg/d if seronegative pre-transplant, and 400 mg/d if seropositive). Duration of prophylaxis is usually 6 to 12 months. If the organ donor is seropositive, then azole prophylaxis is also warranted. Lung transplant recipients of infected or seropositive donors require life-long suppression with fluconazole 400 mg/d, and other organ recipients should receive at least 6 to 12 months of therapy, followed by the option to decrease to 200 mg/d or discontinuation after 6 to 12 months based on clinical assessment and with subsequent clinical and serological monitoring.

For patients with HIV infection and low CD4 counts living in endemic areas, primary prophylaxis against CM is not recommended. However, for HIV patients living in endemic regions, annual or biannual serologic screening for CM is recommended. If the patient is seropositive and asymptomatic (with no abnormalities consistent with active disease), and has a low CD4 count (<250 cells/mm^3), antifungal therapy with fluconazole 400 mg/d should be prescribed and continued until the HIV viral load is suppressed and the CD4 count increases to ≥250 cells/mm^3. For patients living in endemic areas, in which TNF-α antagonist therapy is planned, screening for asymptomatic coccidioidomycosis before the patients begin TNF-α antagonist therapy decreases the risk of developing symptomatic CM.

Occupational prevention. Occupational CM outbreaks in California from 2007 to 2014 have led to prevention strategies to reduce the infection among at-risk workers. Work practices to limit occupational exposure to dust include safer project design, frequent soil wetting during dust-generating activities, enclosed cabs on construction equipment with HEPA-filtered air conditioning, suspending work during periods of excessive dust, having onsite personnel able to implement additional control measures during dusty conditions, and necessary respiratory protective equipment. At-risk workers should have access to occupational medicine providers; ill workers should be advised to promptly report concerning symptoms

to supervisors and physicians. The systematic collection and analysis of occupational CM cases by public health authorities may prevent future workplace-associated outbreaks.

Conclusion

CM is a mycosis geographically restricted to arid areas of the New World. Nevertheless, it exacts a great toll of human suffering from acute and chronic respiratory disease, osteoarticular destruction, and neurologic invasion. The severity of CM is highly dependent on host factors (immunocompetence and race/ethnicity). Due to travel and the influx of susceptible persons into the American Southwest, the incidence is increasing. Diagnostic methods include culture, serologic testing, histopathologic exam, and antigen detection, but all have limited sensitivity. CM can be successfully treated with azoles and amphotericin B; however, the duration of treatment is prolonged, relapse is common, and permanent disability or death may occur despite aggressive treatment. Additional resources are needed to develop more effective therapeutic modalities and to conduct randomized, controlled clinical trials for the treatment of this potentially devastating disease.

Suggested reading

Adam RD, Elliott SP, Taljanovic MS. The spectrum and presentation of disseminated coccidioidomycosis. *Am J Med*. 2009;122(8):770–777.

Anstead GM, Corcoran G, Lewis J, et al. Refractory coccidioidomycosis treated with posaconazole. *Clin Infect Dis.* 2005;40(12):1770–1776.

Anstead GM, Graybill JR. Coccidioidomycosis. *Infect Dis Clin N Amer.* 2006;20(3):621–643.

Awasthi S, Magee DM, Coalson JJ. *Coccidioides posadasii* infection alters the expression of pulmonary surfactant proteins (SP)-A and SP-D. *Respir Res.* 2004;5(1):28.

Blair JE, Ampel NM, Hoover SE. Coccidioidomycosis in selected immunosuppressed hosts. *Med Mycol.* 2019;57(Suppl 1):S56–S63.

Brown J, Benedict K, Park BJ, Thompson GR 3rd. Coccidioidomycosis: epidemiology. *Clin Epidemiol*. 2013;5:185–197.

Catanzaro A, Cloud GA, Stevens DA, et al. Safety, tolerance, and efficacy of posaconazole therapy in patients with nonmeningeal disseminated or chronic pulmonary coccidioidomycosis. *Clin Infect Dis*. 2007;45(5):562–568.

Catanzaro A, Galgiani JN, Levine BE, et al. Fluconazole in the treatment of chronic pulmonary and nonmeningeal disseminated coccidioidomycosis. *Am J Med.* 1995;98:249–256.

Centers for Disease Control and Prevention. Increase in reported coccidioidomycosis—United States, 1998–2011. *MMWR*. 2013;62(12):217–221.

Centers for Disease Control and Prevention. Fungal diseases. Statistics. How common is Valley Fever? https://www.cdc.gov/fungal/diseases/coccidioidomycosis/statistics.html

Choi K, Deval N, Vyas A, et al. The utility of screening for coccidioidomycosis in recipients of inhibitors of tumor necrosis factor α. *Clin Infect Dis*. 2019;68(6):1024–1030.

Cooksey GS, Nguyen A, Knutson K, et al. Notes from the field: increase in coccidioidomycosis—California, 2016. *MMWR*. 2017;66(31):833–834.

Crum NF, Lederman ER, Stafford CM, Parrish JS, Wallace MR. Coccidioidomycosis: A descriptive survey of a re-emerging disease. Clinical characteristics and emerging controversies. *Medicine (Baltimore*). 2004;83(3):149–175.

de Perio MA, Materna BL, Sondermeyer Cooksey GL, et al. Occupational coccidioidomycosis surveillance and recent outbreaks in California. *Med Mycol.* 2019;57(Suppl 1):S41–S45.

Durkin M, Connolly P, Kuberski T, et al. Diagnosis of coccidioidomycosis with use of the *Coccidioides* antigen enzyme immunoassay. *Clin Infect Dis*. 2008;47(8):e69–73.

Freifeld A, Proia L, Andes D, et al. Voriconazole use for endemic fungal infections. *Antimicrob Agents Chemother.* 2009;53(4):1648–1651.

Fisher BT, Chiller TM, Prasad PA, et al. Hospitalizations for coccidioidomycosis at forty-one hospitals in the United States. *Ped Infect Dis J.* 2010;29(3):243–247.

Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. *Clin Infect Dis.* 2016;63(6):e112–146.

Galgiani JN, Catanzaro A, Cloud GA, et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis: A randomized, double-blind trial. *Ann Intern Med*. 2000;133(9):676–686.

Hector RF, Rutherford GW, Clarisse A, et al. The public health impact of coccidioidomycosis in Arizona and California. *Int J Environ Res Public Health.* 2011;8(4):1150–1173.

Hung C-Y, Xue J, Cole GT. Virulence mechanisms of C*occidioides*. *Ann NY Acad Sci.* 2007;1111:225–235.

Kirkland TN. The quest for a vaccine against coccidioidomycosis: A neglected disease of the Americas. *J Fungi (Basel).* 2016;2(4):E34.

Kuberski T, Myers R, Wheat LJ, et al. Diagnosis of acute coccidioidomycosis by antigen detection using cross-reaction with a *Histoplasma* antigen. *Clin Infect Dis.* 2007;44(5):e50.

McHardy IH, Dinh BN, Waldman S, et al. Coccidioidomycosis complement fixation titer trends in the age of antifungals. *J Clin Microbiol.* 2018;56(12):pii: e01318–18.

Mirbod-Donovan F, Schaller R, Hung C-Y, et al. Urease production by *Coccidioides posadasii* contributes to the virulence of this respiratory pathogen. *Infect Immun.* 2006;74(1):504–515.

Moore JN, Healy JR, Kraft WK. Pharmacologic and clinical evaluation of posaconazole. *Expert Rev Clin Pharmacol*. 2015;8(3):312–334.

Muñoz-Hernández B, Martínez-Rivera MA, Palma Cortés G, Tapia-Diaz A, Manjarrez Zavala ME. Mycelial forms of *Coccidioides* spp. in the parasitic phase associated to pulmonary coccidioidomycosis with type 2 diabetes mellitus. *Eur J Clin Microbiol Infect Dis.* 2008;27(9):813–820.

Nguyen C, Barker BM, Hoover S, et al. Recent advances in our understanding of the environmental, epidemiological, immunological, and clinical dimensions of coccidioidomycosis. *Clin Microbiol Rev*. 2013;26(3):505–525.

Odio CD, Marciano BE, Galgiani JN, Holland SM. Risk factors for disseminated coccidioidomycosis, United States. *Emerg Infect Dis.* 2017;23(2):308–311.

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of HIV-infected adults and adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

Pappagianis D. Evaluation of the protective efficacy of the killed *Coccidioides immitis* spherule vaccine in humans. The Valley Fever Vaccine Study Group. *Am Rev Respir Dis.* 1993;148(3): 656–660.

Parish JM, Blair JE. Coccidioidomycosis. *Mayo Clin Proc.* 2008;83(3): 343–348.

Porte L, Valdivieso F, Wilmes D, et al. Laboratory exposure to *Coccidioides*: Lessons learnt in a non-endemic country. *J Hosp Infect*. 2019;Mar 16:S0195-6701(19)30110-0.

Schein R, Homans J, Larsen RA, Neely M. Posaconazole for chronic refractory coccidioidal meningitis. *Clin Infect Dis*. 2011;53(12): 1252–1254.

Stewart ER, Eldridge ML, McHardy I, Cohen SH, Thompson GR 3rd. Liposomal Amphotericin B as monotherapy in relapsed coccidioidal meningitis. *Mycopathologia*. 2018; 183(3):619–622.

Stockamp NW, Thompson GR. Coccidioidomycosis. *Infect Dis Clin N Am.* 2016;30(1): 229–246.

Shubitz LF, Powell DA, Trinh HT, et al. Viable spores of *Coccidioides posadasii* Δcps1 are required for vaccination and provide long lasting immunity. *Vaccine.* 2018;36(23):3375–3380.

Thompson GR 3rd, Barker BM, Wiederhold NP. Large-scale evaluation of in vitro amphotericin B, triazole, and echinocandin activity against *Coccidioides* species from US institutions. *Antimicrob Agents Chemother.* 2017;61(4):e02634–16.

Thompson GR 3rd, Blair JE, Wang S, et al. Adjunctive corticosteroid therapy in the treatment of coccidioidal meningitis. *Clin Infect Dis.* 2017;65(2):338–341.

Thompson GR 3rd, Rendon A, Ribeiro Dos Santos R, et al. Isavuconazole treatment of cryptococcosis and dimorphic mycoses. *Clin Infect Dis.* 2016;63(3):356–362.

Tong DQ, Wang JXL, Gill TE, Lei H, Wang B. Intensified dust storm activity and Valley fever infection in the southwestern United States. *Geophys Res Lett.* 2017;44:4304–4312.

Tsang CA, Anderson SM, Imholte SB, et al. Enhanced surveillance of coccidioidomycosis, Arizona, USA, 2007–2008. *Emerg Infect Dis.* 2010;16(11):1738–1744.

Valdivia L, Nix D, Wright M, et al. Coccidioidomycosis as a common cause of community-acquired pneumonia. *Emerg Infect Dis*. 2006;12(6):958–962.

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Pneumocystis jirovecii (carinii)

Shelley A. Gilroy and Nicholas J. Bennett

Background

Pneumocystis jirovecii (pronounced "yee-row-vet-zee"), formerly known as *Pneumocystis carinii*, is an opportunistic pathogen that causes pneumonia in the immunocompromised individual. The initials "PCP" stood for *Pneumocystis carinii* pneumonia but were kept for a while for ease of use after the organism was renamed (PneumoCystis Pneumonia). The condition is more correctly abbreviated as PJP. Disease occurs when both cellular and humoral immunity are impaired. Serologic studies have shown that *Pneumocystis* has a worldwide distribution, but the prevalence of antibodies to specific antigens varies among different geographic regions. PJP first came to attention when it caused interstitial pneumonia in severely malnourished and premature infants in Central and Eastern Europe during World War II. Prior to the AIDS epidemic in the 1980s, <100 cases were reported annually in the United States. PJP is one of several life-threatening opportunistic infections in patients with HIV infection worldwide and is still the most common AIDS-defining illness in patients with advanced HIV infection. The decline in the number of PJP cases in the United States occurred after the introduction of anti-pneumocystis prophylaxis in 1989 and highly active antiretroviral therapy (HAART) in 1992. In patients without HIV infection, the incidence of PJP has increased in those being treated with immunosuppressive and chemotherapeutic agents and in hematopoietic stem cell (HSCT) and solid organ transplant recipients.

The taxonomic classification of the *Pneumocystis* genus and the organism's name has changed throughout the years. In the 1980s, biochemical analysis identified the organism as a unicellular fungus. *P. jirovecii* is found in three distinct morphologic stages: the trophozoite, in which it often exists in clusters; the sporozoite (precystic form); and the cyst, which contains several intracystic bodies (spores). The cyst is the diagnostic form of *P. jirovecii* and stains with Giemsa, Papanicolaou, and Grocott methenamine silver nitrate (GMS) and immunocytochemical techniques using monoclonal antibodies. Giemsa- and Papanicolaou-stained smears show indirect evidence of *P. jirovecii* infection by the demonstration of foamy exudates in the form of alveolar casts.

The environmental source for *Pneumocystis* is unknown. Studies in animals and humans suggest that it is transmitted by the airborne route. The organism can be found in the respiratory tracts of hospitalized patients with viral or bacterial infections and healthy individuals without pneumonia. These individuals may serve as a reservoir for infection to susceptible hospitalized patients. The time necessary from colonization to infection is unknown. Once *Pneumocystis* enters the lungs it attaches to the alveoli. Alveolar macrophages are the first line of defense and are responsible for clearing the organism from the lung. This function is impaired in patients with HIV or cancer and in transplant recipients receiving immunosuppressive therapy. Tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), proinflammatory cytokines, have been shown to be important in host defenses against the organism in the early stages of infection. As the host defenses become compromised, *Pneumocystis* organisms proliferate and fill alveolar lumens, subsequently leading to interstitial plasma pneumonia.

Extrapulmonary *Pneumocystis* infection is rare. Dissemination may occur via direct spread, hematogenous spread, or via lymphatic vessels in the absence of pneumonia. It can occur in HIV-infected patients receiving

aerosolized pentamidine for prophylaxis. The most common organs or tissues infected are the lymph nodes, spleen, liver, bone marrow, and the small intestine.

Clinical manifestations

PJP is an AIDS-defining illness, typically occurring in HIV-infected patients not taking HAART, with a T-helper cell count (CD4) of <200 cells/mm^3. Symptoms include insidious onset of dyspnea with a dry cough, fever, diarrhea, and weight loss. Acute dyspnea with chest pain may indicate a pneumothorax. Physical examination typically reveals tachypnea, tachycardia, and fever with normal findings or mild crackles or rhonchi on lung auscultation. Oral thrush or oral hairy leukoplakia may also be present. A resting PaO_2 of <80 mm Hg occurs in 80% of cases. Desaturation with exercise is a highly sensitive marker of PJP, even if the PaO_2 is normal. A clinical picture of PJP in HIV-infected patients with a high CD4 count should prompt consideration of immune reconstitution inflammatory syndrome (IRIS), defined as a clinical deterioration caused by restoration of a patient's capacity to mount an inflammatory immune response against infectious and noninfectious agents once HAART has begun.

In children, early signs are poor feeding, diarrhea, and coryza. Physical findings include nasal flaring, intercostal retraction, and cyanosis.

Immunocompromised patients without AIDS typically present with acute respiratory insufficiency or shorter duration of illness and fewer days of dyspnea and fever. PJP can occur with or without lymphopenia or low CD4 counts.

The most significant risk factors for PJP are defects in cell-mediated immunity, prolonged glucocorticoid use, cancer (particularly hematologic malignancies), HSCT, rheumatologic diseases, severe combined immunodeficiency, and severe malnutrition. The most common chemotherapeutic drugs associated with increased risk of PJP are fludarabine, temozolomide, vincristine, temsirolimus, and cyclophosphamide. Patients receiving biologic agents, particularly alemtuzumab and the TNF inhibitor infliximab, and kinase inhibitors (ibrutinib, idelalisib) are also at risk for infection.

In early mild disease the chest radiograph will be normal. High-resolution CT scanning (HRCT) is more useful. Typical findings are diffuse micronodules, patchy ground-glass, symmetric or asymmetric opacities, reticulation, septal thickening, and/or airspace consolidation (Figure 178.1). Apical interstitial infiltrates and pneumothorax occur more often in patients receiving prophylactic treatment with aerosolized pentamidine. Solitary or multiple nodules, which may cavitate, and pneumatoceles are less common. Pleural effusions and intrathoracic adenopathy are rare.

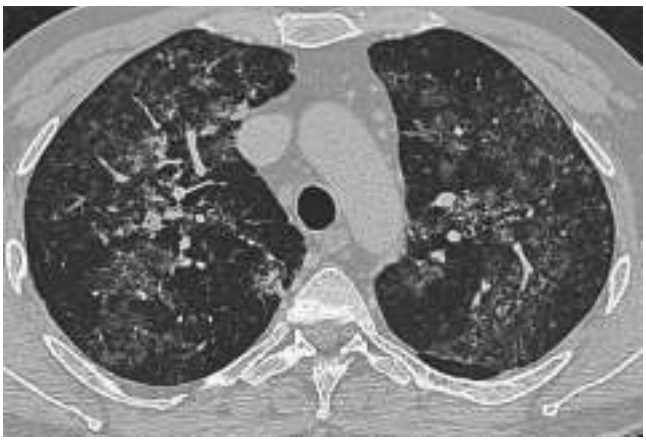

FIGURE 178.1 High-resolution CT image of the upper lung zones demonstrates diffuse micronodules and patchy ground-glass opacities, as well as some fine reticulation, all suggestive of an interstitial process consistent with *Pneumocystis* pneumonia.

Courtesy of Frederic Hellwitz, MD. Department of Radiology, Albany Medical College, Albany, New York. Reprinted with permission from Thieme Publishers.

Diagnosis

Pneumocystis has no effective culture-based test and the diagnosis, if suspected on clinical grounds, usually relies on obtaining invasive respiratory specimens. Tests on routine sputum specimens are insensitive and should not be performed, although induced sputum (performed with a respiratory therapist after inhalation of nebulized hypertonic saline) is about 50% sensitive. The sensitivity varies but approaches 90% in some institutions depending on technique proficiency and the experience of the laboratory. A negative result would not rule out PJP. Optimal testing requires bronchoscopy and bronchiolar lavage (BAL). Lung biopsy is diagnostic.

The classic histology findings are "foamy alveolar casts," in which there is proteinaceous fluid within the alveoli (Figure 178.2). With a silver stain such as GMS, pneumocystis can be visualized as teacup-shaped organisms (Figure 178.3). Immunofluorescence techniques, such as direct fluorescent antigen (DFA), can also be employed and are sensitive and specific. Single-copy real-time polymerase chain reaction (PCR) assays rapidly identify patients with infection rather than colonization and are more useful in clinical settings. PCR of BAL fluid or induced sputum can increase the diagnostic yield over conventional staining alone in HIV-uninfected immunocompromised patients.

In certain clinical settings, it may not be practical or safe to obtain invasive specimens, and noninvasive specimens are preferred. Serologic testing specific to PJP is available but cannot reliably distinguish between past and present infection. The majority of people will, at some point, become colonized with *Pneumocystis* and seroconvert, although some efforts have been made toward using the specific antibody titers or responses to specific proteins as being more indicative of active infection.

The *Pneumocystis* cell wall contains the same 1–3 β-D-glucan (BDG) as *Candida* and *Aspergillus*, and an assay for serum levels of BDG (known as Fungitell commercially) has proved to be sensitive and specific for PJP when appropriate cutoff levels are used. It can be used as an adjunct to the diagnosis of PJP. It has a high negative predictive value, making it unlikely that a patient with a negative β-D-glucan result has PJP. Although the assay is not specific for PJP

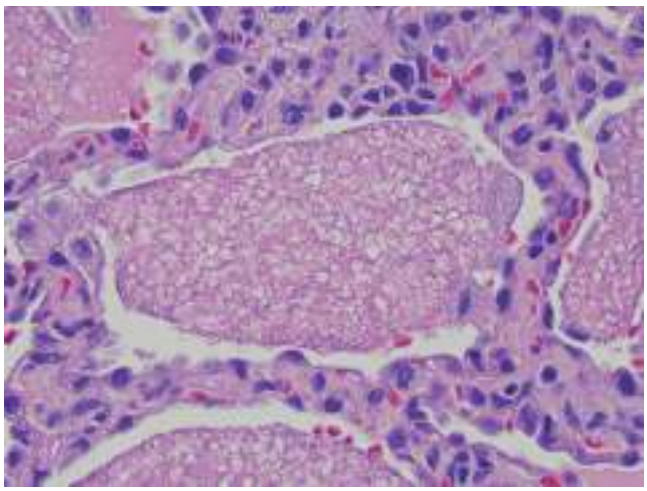

FIGURE 178.2 Hematoxylin and eosin stain of lung alveolae showing foamy infiltrates (foamy alveolar casts).

Courtesy of Anna-Luise Katzenstein, MD. Department of Anatomic Pathology, State University of New York Upstate Medical University, Syracuse, New York. Reprinted with permission from Thieme Publishers.

it may be useful in certain settings where BAL sampling cannot be safely performed. Because of the cross-reactivity of the assay to multiple fungi, bacteria (*Pseudomonas*), or exposure to intravenous immunoglobulin, interpretation of assay results should be done in the clinical context of the patient. PJP may be associated with somewhat higher levels of BDG than are seen in invasive candidiasis or aspergillosis. In patients with non-HIV PJP, and in children with PJP, levels tend to be higher than in HIV-associated PJP but there are no levels at which PJP can be reliably ruled in or out. In all cases, serum levels can be used to track response to treatment.

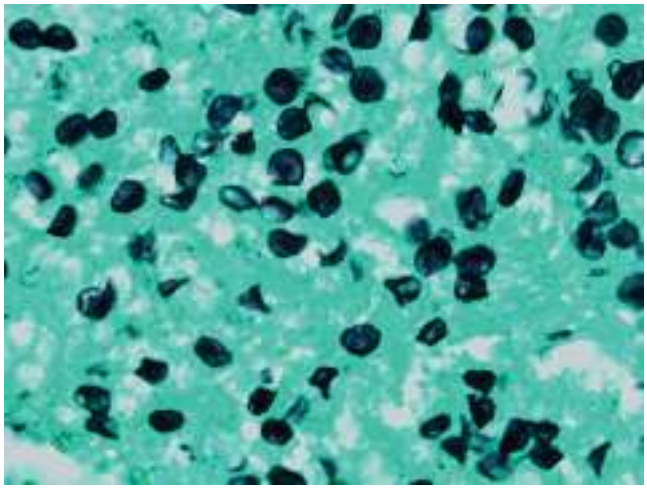

FIGURE 178.3 Grocott's methenamine silver stain of lung alveolae, highlighting the *Pneumocystis* organisms in black.

Courtesy of Anna-Luise Katzenstein, MD. Department of Anatomic Pathology, State University of New York Upstate Medical University, Syracuse, New York. Reprinted with permission from Thieme Publishers.

Treatment and prophylaxis

Recommended antimicrobial regimens are detailed in Table 178.1. The mainstay treatment of PJP is TMP-SMX. The dosing is usually 15 to 20 mg/kg/d in three divided doses for 14 to 21 days, orally or intravenously depending on severity of illness. Adjunct corticosteroids have been shown to have benefit in HIV-associated PJP with significant hypoxemia (an alveolar–arterial oxygen gradient of >35 mm Hg, or an arterial oxygen partial pressure of 70 mm Hg on room air). The role of steroids is in blunting the immune reaction to microorganism degradation which can result in an acute respiratory distress syndrome-like process. Guideline dosing for methylprednisolone is 40 mg twice daily on days 1 to 5, 40 mg once a day on days 6 to 10, 20 mg once a day on days 11 to 21.

Alternative medications, for instance in the case of allergy to sulfa-based antibiotics, include atovaquone, pentamidine, clindamycin-primaquine, and dapsone, of which the latter is usually given in combination with trimethoprim or pyrimethamine and leucovorin. A glucose-6-phosphate dehydrogenase (G6PD) level should be tested when using a regimen that contains dapsone or primaquine since a G6PD deficiency can lead to hemolytic anemia when such patients are exposed to these agents. Certain patients with severe PJP whose sulfa allergy is non–life-threatening can be "desensitized" using a gradual dose escalation of TMP-SMX. Of note, in one study assessing salvage therapy after failing initial treatment, the combination of clindamycin and primaquine appeared to be inferior to TMP-SMX.

TMP-SMX, pentamidine, or dapsone can all be used for prevention of PJP (Table 178.2). Prophylaxis is recommended for high-risk individuals, particularly those with HIV infection and CD4+ T-cell counts of <200 (or a history or previous PJP regardless of CD4 count). Other causes of immune suppression or deficiency also increase the risk of *Pneumocystis* to varying degrees. Neonates with severe combined immune deficiencies (SCID) and recipients of bone marrow transplants are at particularly high risk. Individuals with CD40 ligand deficiency are associated with an increased risk of PJP and should be placed on prophylaxis. Interestingly, although the 22q11 deletion syndrome (also known as *DiGeorge* or *velocardiofacial syndrome*) is primarily a T-cell deficiency and may result in CD4 counts similar to those seen in end-stage HIV infection, PJP has not been convincingly reported in patients with 22q11del. In these patients T-cell function is often intact and the CD4/CD8 ratio is preserved, whereas in HIV infection T-cell responses are blunted and the CD4/CD8 ratio is inverted. Nevertheless, some experts recommend PJP prophylaxis in individuals with 22q11del and very low CD4+ T-cell counts (<500), especially if T-cell function has not yet been assessed or if any form of immune modulation or suppression is also present.

The use of steroids and other immunosuppressive agents is associated with varying levels of risk for PJP, and the indications for

TABLE 178.1 **TREATMENT**

Drug	Adult dose	Pediatric dose	Notes
Trimethoprim-sulfamethoxazole (TMP-SMX)	15–20 mg/kg/d trimethoprim IV or PO in 4 divided doses for 21 d	As adult dose. Off-label use <2 mo of age	Drug of choice. Risk of anemia, kernicterus in neonates under 28 d old
Pentamidine	4 mg/kg/d IV for 21 d	≥4 mo of age, as adult dose	
Dapsone	100 mg PO once daily, in combination with trimethoprim 15 mg/kg/d PO in 3 divided doses for 21 d	No pediatric data for treatment	
Atovaquone	1,500 mg PO daily (or divided twice daily) for 21 d	Age >13 dose as adult	Take with food
		Age 3–24 mo 45 mg/kg/d (max 1,500 mg/d) in 2 divided doses PO for 21 days	
		Other ages 30–40 mg/kg/d (max 1,500 mg/d) in 2 divided doses	
Methylprednisolone	40 mg BID on days 1–5, 40 mg once a day on days 6–10, 20 mg once a day on days 11–21; begin as early as possible and within 72 h of PCP therapy	<12 yr 1 mg/kg every 6 h on days 1–7, 1 mg/kg twice daily on days 8–9, 0.5 mg/kg twice daily on days 10–11, 1 mg/kg once a day on days 12–16; begin as early as possible and within 72 h of PCP therapy	Best evidence in patients with moderate to severe HIV-related PCP
Clindamycin with Primaquine	1,800 mg/d PO clindamycin divided 3–4 times a day *Plus* 30 mg primaquine base PO once daily	Not studied in pediatrics, but equivalent doses are 10 mg/kg/dose clindamycin 3–4 times daily and 0.5 mg/kg/dose primaquine base once daily	Patients who fail TMP-SMX may be more likely to fail Clindamycin and Primaquine

TABLE 178.2 **PROPHYLAXIS**

Drug	Adult	Pediatric	Notes
Trimethoprim–sulfamethoxazole	One DS tab (160 mg trimethoprim) PO daily or 3 days a week (may be consecutively or every other day)	(≥2 months of age) 150 mg/m^2/d trimethoprim (max 320 mg/d) in 2 divided doses PO 3 times a week	Drug of choice
Pentamidine	300 mg by inhalation, monthly	≥5 yrs, same as adult	May require specialized equipment and respiratory therapists to administer
Dapsone	100 mg PO daily or 200 mg PO weekly	(≥1 month) primary and secondary prophylaxis, 2 mg/kg PO once a day (max 100 mg/d); or 4 mg/kg PO once weekly (max 200 mg/dose)	
Pyrimethamine	50 mg PO once weekly *Plus* leucovorin 25 mg PO once weekly *Plus* dapsone 50 mg PO once daily *Or* 75 mg PO once weekly *Plus* leucovorin 25 mg PO once weekly *Plus* dapsone 200 mg PO once weekly		
Atovaquone	1,500 mg PO daily	Age >13, dose as adult. Age 3–24 mo, 45 mg/kg PO daily (max 1,500 mg/d) Other ages, 30 mg/kg PO daily (max 1,500 mg/d)	Take with food

prophylaxis are often dictated by the specific combination and duration of therapy rather than the use of any one particular drug.

Suggested reading

Alanio A, Hauser PM, Lagrou K, et al.; 5th European Conference on Infections in Leukemia (ECIL-5), a joint venture of The European Group for Blood and Marrow Transplantation (EBMT), The European Organization for Research and Treatment of Cancer (EORTC), the Immunocompromised Host Society (ICHS) and The European LeukemiaNet (ELN). ECIL guidelines for the diagnosis of Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother*. 2016 Sep;71(9):2386–2396.

Bodro M, Paterson DL. Has the time come for routine trimethoprim-sulfamethoxazole prophylaxis in patients taking biologic therapies? *Clin Infect Dis*. 2013;56(11):1621–1628.

Doyle L, Vogel S, Procop GW. *Pneumocystis* PCR: It is time to make PCR the test of choice. *Open Forum Infect Dis.* 2017;1–5.

Fauchier T, Hasseine L, Gari-Toussaint M, Casanova V, Marty PM, Pomares. Detection of *Pneumocystis jirovecii* by quantitative PCR to differentiate colonization and pneumonia in immunocompromised HIV-positive and HIV-negative patients. *J Clin Microbiol.* 2016;4(6):1487–1494.

Gilroy SA, Bennett NJ. Pneumocystis pneumonia. *Semin Respir Crit Care Med*. 2011;32(6):775–782.

Leoung GS, Stanford JF, Giordano MF, et al.; American Foundation for AIDS Research (amfAR) Community-Based Clinical Trials Network. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for Pneumocystis Carinii pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis*. 2001;184(8):992. Epub 2001 Sep 4.

McKinnell JA, Canella DF, Kunz EW, et al. Pneumocystis pneumonia in hospitalized patients: A detailed examination of symptoms, management, and outcomes in human immunodeficiency virus (HIV)-infected and HIV-uninfected persons. *Transpl Infect Dis*. 2012;14:510–518.

Mocroft A, Reiss P, Kirk O, et al. Is it safe to discontinue primary *Pneumocystis jirovecii* pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? *Clin Infect Dis*. 2010;51(5):611–619.

Pennington K, Wilson J, Limper AH, Escalante P. Positive *Pneumocystis jirovecii* sputum PCR results with negative bronchoscopic PCR results in suspected pneumocystis pneumonia. *Can Respir J.* 2018;Article ID 6283935:1–5.

Sistek CJ, Wordell CJ, Hauptman SP. Adjuvant corticosteroid therapy for *Pneumocystis carinii* pneumonia in AIDS patients. *Ann Pharmacother*. 1992;26(9):1127–1133.

Wazir JF, Ansari NA. *Pneumocystis carinii* infection. *Arch Pathol Lab Med*. 2004;128:1023–1027.

Wilson JW, Limper AH, Grys TE, Karre T, Wengenack NL, Binnicker MJ. Pneumocystis jirovecii testing by real-time polymerase chain reaction and direct examination among immunocompetent and immunosuppressed patient groups and correlation to disease specificity. *Diagn Microbiol Infect Dis*. 2011;69(2):145.

Miscellaneous (emerging) fungi and algae

Obinna N. Nnedu and George A. Pankey

Many nonendemic fungi and algae cause disease among an increasing population of individuals at risk. These microorganisms, known as *opportunistic agents*, can cause disease if two major criteria are met: (1) the patient suffers from some predisposing factor that has mechanically or immunologically decreased the capacity to resist infection, and (2) the infecting agent can survive and multiply at body temperature. At present, >200 of these opportunists have been reported to cause infection.

Some opportunistic fungal infections are associated with predisposing factors such as ketoacidosis, iron overload state, neutropenia, and defects in cell-mediated immunity. However, any trauma or pharmacologic insult to the host's defenses increases the chance of fungal invasion, even from the patient's own resident flora.

The microorganisms considered here are ubiquitous in nature but uncommon causes of disease in humans. Therefore, the diagnosis is usually made in one of the following scenarios: (1) a patient with an infection does not respond to antibacterial therapy; (2) the microbiology laboratory isolates one of these agents; or (3) the pathologist identifies a fungus or algae in tissue, bronchoalveolar lavage, or cerebrospinal fluid. When a physician suspects a fungal pathogen, the laboratory should be informed and special requests made, such as for lysis centrifugation to maximize the yield from blood cultures or for specific fungal media to be inoculated.

Diagnosis

Identification of these pathogens requires cultures. Some species require special media or conditions for culture. Virtually all these species grow readily at 25°C/77°F to 30°C/86°F. Most of these opportunistic fungi can be identified down to the genus name in the clinical microbiology laboratory. Treatment for all species within a genus is usually the same. Molecular methods such as polymerase chain reaction (PCR) and matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry are new techniques for species identification, but further work is needed to standardize these procedures. Reliable serologic tests are not available for these pathogens.

Isolating these pathogens does not prove causation of the disease process. To prove causation, the culture must be associated with tissue invasion as seen on biopsy or repeated positive cultures from sterile body fluid. The appearance of these agents in tissue is extremely variable and is typically broken down into hyalohyphomycoses (Table 179.1), phaeohyphomycoses (Table 179.2), opportunistic yeasts (Table 179.3), and protothecosis (Table 179.4). Hyalohyphomycoses generally have long septate hyphae in tissue. They include *Fusarium* spp., *Talaromyces marneffei, Scedosporium* spp., and *Lomentospora prolificans*. Phaeohyphomycoses (dematiaceae) are pigmented environmental molds with irregular septated hyphae. These include *Exserohilum rostratum*, *Exophiala,* and *Cladosporium*. Opportunistic yeasts include *Candida auris*, *Pichia (Hansenula) anomala*, *Rhodotorula*, *Saccharomyces cerevisiae*, *Malassezia furfur*, and *Trichosporon beigelii*. Protothecosis are achlorophyllic algae that are pervasive in nature. They look like fungi microscopically. Only two species are known to infect humans: *Prototheca wickerhamii* and *Prototheca zopfii*.

TABLE 179.1 **HYALOHYPHOMYCOSES**

Pathogen	Characteristics	Diagnosis	Therapy
Fusarium spp.	Purpuric skin lesions with central necrosis, keratitis, pulmonary disease	Blood cultures (positive in 50% of cases) Histopathology	Reversal of immunosuppression or correction of neutropenia LAmB + voriconazole Duration dependent on site of infection
Talaromyces (Penicillium) marneffei	Endemic in Southeast Asia, Southern China, Taiwan, and Hong Kong Pulmonary disease, osteomyelitis, adenitis, skin lesions, AIDS-defining illness	Cultures of tissue samples and BAL Histopathology from biopsy	LAmB for 2 weeks, followed by itraconazole
Scedosporium spp,	Normal host by traumatic implantation Mycetoma, meningitis, osteomyelitis, pneumonia (near drowning), sinusitis, endocarditis, spondylodiskitis, keratitis	Culture from tissue Histopathology Molecular: cross-reactivity with *Aspergillus* galactomannan	Surgical resection No optimal antifungal agent Voriconazole LAmB is not effective Isavuconazole has some in vitro activity against some isolates
Lomentospora prolificans	Causes similar spectrum of diseases as *Scedosporium* spp.	Culture from tissue Histopathology	Surgical resection No optimal antifungal agent Voriconazole

Abbreviations: AIDS = acquired immunodeficiency syndrome, BAL = bronchoalveolar lavage, LamB = liposomal amphotericin B.

Therapy

Treatment of these infections can be challenging. Total excision, whenever feasible, should accompany any treatment regimen. No solid data on optimal drug therapy for many of these fungal infections are available because of the lack of controlled randomized trials, and the relatively low number of clinical cases make it difficult to conduct a randomized clinical trial. When possible, antifungal therapy should be guided by results of susceptibility testing. An infectious diseases consultation should be obtained when treating these infections.

Antifungal therapy may fail for one of the following reasons: (1) the drug has no in vivo activity, (2) neutropenia or other immunosuppressed state could not be reversed, (3) oral itraconazole

TABLE 179.2 **PHAEOHYPHOMYCOSES (DEMATIACEAE)**

Pathogen	Characteristics	Diagnosis	Therapy
Exserohilum rostratum	Skin and subcutaneous tissue, sinusitis, occasional dissemination Local infection from skin and eye trauma in immunocompetent host Responsible for multistate meningitis outbreak from contaminated steroid injection	Molecular PCR Culture of tissue	LAmB for 6 weeks, then voriconazole for 4 months
Exophiala	Inhalation or traumatic implantation, subcutaneous nodules, keratitis, and/or skin abscess	Melanin in dematiaceous fungi with Fontana-Masson staining	Surgical excision 12-week therapy with voriconazole or posaconazole or itraconazole ± LAmB for first 2 weeks
Cladosporium	Distributed in air or as rotten organic material and contaminant on food Keratitis, onychomycosis, skin abscesses, chromoblastomycosis	Molecular: antigen cross-reacts with *Aspergillus* galactomannan	Surgical excision 6 months of itraconazole or voriconazole

Abbreviations: LamB = liposomal amphotericin B, PCR = polymerase chain reaction.

TABLE 179.3 **YEAST OR YEAST-LIKE FUNGI**

Pathogen	Characteristics	Diagnosis	Therapy
Candida auris	Invasive healthcare-associated infections Outbreaks reported at healthcare centers	Culture Some automated systems may misidentify *C auris* If suspected, contact CDC or local health department	Echinocandins such as micafungin, anidulafungin, or caspofungin are preferred If no response to echinocandin, may switch to LAmB Resistance has been reported to azoles and to LAmB Susceptibility should be performed Remove intravascular catheters
Pichia (Hansenula) anomala	Catheter-related fungemia, prosthetic valve endocarditis, NICU outbreaks	Culture	LAmB, if unresponsive: voriconazole or itraconazole + flucytosine Remove intravascular catheters
Rhodotorula "red yeast"	Contaminant of air, soil, lakes, and dairy products Colonizes plants and humans Fungemia, meningitis, peritonitis	Culture Molecular: cross-reacts with *Aspergillus* latex agglutination test	LAmB or posaconazole Remove intravascular catheters
Saccharomyces cerevisiae	Colonizer of mucosal surfaces Fungemia, prosthetic valve endocarditis, liver abscess, oral leukoplakia Associated with probiotic use	Culture	LAmB ± flucytosine Resistant to fluconazole and itraconazole Remove intravascular catheters
Malassezia furfur	Lipophilic fungus Fungemia associated with lipid infusion, folliculitis in AIDS, tinea versicolor	Culture in lipid-rich media Potassium hydroxide	Bloodstream infection should be treated with LAmB, with voriconazole as an alternative Remove intravascular catheters in bloodstream infection Folliculitis may be treated with voriconazole or itraconazole
Trichosporon beigelii	Fungemia, prosthetic valve endocarditis, chronic meningitis, peritonitis	Cross-reacts with cryptococcal latex agglutination	LAmB Voriconazole for LAmB-resistant strains Correct neutropenia

Abbreviations: AIDS = acquired immunodeficiency syndrome, CDC = Centers for Disease Control and Prevention, LAmB = liposomal amphotericin B, NICU = Neonatal Intensive care unit.

or posaconazole were taken while fasting or with antacids, (4) adequate blood levels were not obtained, (5) the dosage was too low or combination therapy was not used, (6) the drug is fungistatic rather than fungicidal, and (7) the drug is unable to concentrate in the area of concern, such as the brain. Voriconazole, itraconazole, and posaconazole trough levels must be monitored to ensure that therapeutic blood levels are achieved. Liposomal formulations of amphotericin B allow much higher dosages without increasing toxicity.

TABLE 179.4 **PROTOTHECOSIS**

Pathogen	Characteristics	Diagnosis	Therapy
Prototheca	Systemic infection, algaemia, peritonitis	Culture	Excise isolated lesion Remove intravascular catheter Optimal therapy is unclear LAmB and/or voriconazole

Abbreviations: LamB = liposomal amphotericin B.

Prevention

Immunocompromised patients should be educated on preventive measures regarding the risk of fungal infection from the environment. Prompt recognition of these pathogens in infected skin lesions after trauma is necessary for early therapy. Proper intravascular catheter care and neutropenia precautions are critical for hospitalized patients.

Candida auris has been associated with outbreaks in hospitals. Patients with *C. auris* should be placed in a single-patient room with standard and contact precautions observed. Hand hygiene is critically important. The patient care environment and any reusable devices should be disinfected daily.

Suggested reading

Centers for Disease Control and Prevention (CDC). Interim treatment guidance for central nervous system and parameningeal infections associated with injection of contaminated steroid products. October 29, 2015. www.cdc.gov/hai/outbreaks/clinicians/index.html

Centers for Disease Control and Prevention. Candida auris. December 21, 2018. www.cdc.gov/fungal/candida-auris/health-professionals.html.

Huprikar S, Shoham S; AST Infectious Diseases Community of Practice. Emerging fungal infections in solid organ transplantation. *Am J Transplant*. 2013;13(Suppl 4):262–271.

Kauffman CA, Pappas PG, Patterson TF. Fungal infections associated with contaminated methylprednisolone injections. *N Engl J Med*. 2013;26:2495–2500.

Lass-Florl C, Mayr A. Human protothecosis. *Clin Microbiol Rev*. 2007;20(2):230–242.

Li JY, Yong TY, Grove DI, Coates PT. Successful control of *Scedosporium prolificans* septic arthritis and probable osteomyelitis without radical surgery in a long-term renal transplant recipient. *Transpl Infect Dis*. 2008;10:63–65.

Mayorga J, Barba-Gomez JF, Verduzco-Martinez AP, Munoz-Estrada VF, Welsh O. Protothecosis. *Clin Dermatol*. 2012;30:432–436.

Nucci M, Anaisse E. Fusarium infections in immunocompromised patients. *Clin Microbiol Rev*. 2007;20:695–704.

Pfaller MA, Messer SA, Rhomberg PR, et al. In vitro activity of isavuconazole and comparator antifungal agents tested against a global collection of opportunistic yeasts and molds. *J Clin Microbiol*. 2013;51:2608–2616.

Schieffelin J, Garcia-Diaz JB, Loss GE, et al. Phaeohyphomycosis fungal infections in solid organ transplant recipients: Clinical presentation, pathology, and treatment. *Transpl Infect Dis*. 2014;16:270–278.

Skiada A, Pavleas I, Drogari-Apiranthitou M. Rare fungal infectious agents: A lurking enemy. *F1000Res*. 2017;6:1917.

Section 23

Specific organisms: Viruses

180

Cytomegalovirus

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Human cytomegalovirus (CMV) is a member of the herpesvirus family and only replicates in humans. Once a person is infected with CMV, they are forever carriers of the virus. Past or recent CMV infection is marked by presence in serum of immunoglobulin G (IgG) antibody against CMV. The proportion of people having CMV IgG varies according to age, socioeconomic status, sexual activity/practice, and race/ethnicity. In the United States, 55% of women are CMV-seropositive by age 30 and >90% of all persons are seropositive by age 80. Women of reproductive age have an annual CMV seroconversion rate of approximately 2%. Maternal–fetal transmission of CMV afflicts 1 out of 154 babies born. CMV is the leading infectious cause of birth defects and the most common nongenetic cause of sensorineural hearing loss. Preexisting immunity to CMV even in healthy people does not fully protect from reinfection with a different CMV strain.

Close mucosal contact with infectious body fluids is the most common way CMV is acquired. Infectious virus is shed into saliva, urine, breast milk, semen, and cervical secretions. Adults intermittently shed virus with a frequency that depends on body site, the person's age, a recent versus past CMV infection, and predisposing factors such as pregnancy, immunosuppression, and critical illness. Condom use decreases CMV transmission risk from sexual contact. Healthy infants and young children typically shed CMV into urine and saliva for weeks to months after the first (primary) CMV infection. Breast milk of CMV-seropositive mothers commonly contains CMV DNA, and breast milk is a potential source of CMV transmission. Primary CMV infection during pregnancy carries a risk of maternal–fetal CMV transmission that is 10-fold greater than the risk of maternal–fetal CMV transmission from CMV reinfection or reactivation. CMV resides in a latent state in virtually all tissues and in circulating cells of myeloid lineage. This makes viable tissues and blood leukocytes from CMV-seropositive donors potential sources of CMV transmission.

Most primary CMV infections in healthy people go unnoticed. When illness develops, it often manifests as self-limited heterophile-negative mononucleosis, a nonspecific viral syndrome, or fever with hepatitis. In rare cases, a protracted illness or tissue-invasive disease results. Rare cases of CMV colitis in the "immunocompetent" host are associated with older age or having received a corticosteroid or blood transfusion. A mother acquiring a primary CMV infection in the first trimester of pregnancy is at greater risk of having a baby with symptomatic congenital CMV infection than if the maternal infection occurred after the first trimester of pregnancy. Approximately 13% of all congenitally infected newborns will have sensorineural hearing loss.

Profound impairment of cellular immunity allows unchecked CMV replication that damages tissue and produces end-organ disease. This situation is more often encountered in people having AIDS, receiving hematopoietic stem cell transplantation (HSCT) or solid-organ transplantation (SOT), or treated with potent immunosuppressive drugs for reasons other than transplantation. CMV end-organ disease manifests with clinical symptoms and signs and laboratory testing and/or medical imaging abnormalities attributable to the specific organ affected. Common presentations include retinitis, upper or lower gastrointestinal disease, hepatitis, pneumonia, and encephalitis. In transplantation, CMV may also indirectly promote allograft dysfunction, superinfection, and posttransplant lymphoproliferative disorder. CMV decreases survival of people living with HIV who are receiving effective antiretroviral treatment (ART) and have not had overt CMV disease.

Diagnosis

The tentative diagnosis of primary CMV infection in an acutely ill immunocompetent person is based on evidence of serum IgM antibody reacting to CMV antigen. However, CMV IgM positivity by itself does not prove primary CMV infection because CMV reactivation and reinfection also elicits CMV IgM, and false-positive IgM results are common. Primary Epstein–Barr virus (EBV) infection in children is an example of a condition that commonly produces false-positive CMV IgM results. A very high level of CMV IgM may better predict a primary CMV infection. CMV IgG is usually detectable when a person first seeks medical attention for a primary CMV infection. These newly induced CMV IgG antibodies bind to CMV antigens with low avidity. Documenting a low-avidity CMV IgG index confirms a primary CMV infection diagnosis should CMV IgG be initially detected. If CMV IgG is not initially detectable, the primary CMV infection diagnosis can be confirmed by documenting the seroconversion to CMV IgG positivity during convalescence. The probability of a primary CMV infection is strengthened by having the combined findings of CMV DNA in blood plasma or serum (CMV DNAemia) and CMV IgM positivity. CMV DNAemia is not generally present in the plasma or serum of CMV-seropositive immunocompetent persons experiencing a mono-like illness from another cause. Pregnant women suspected of having a primary CMV infection should be referred to an obstetrician for further evaluation. The pretransplant assessment of CMV IgG status of donor and recipient determines posttransplant risk of CMV disease and the management strategy going forward. Serology has no role in the diagnosis of active CMV infection or disease in immunocompromised persons.

CMV end-organ disease is proved by documenting presence of active CMV infection in tissue of the diseased organ producing clinical, laboratory test, or medical imaging abnormalities that are consistent with the diagnosis. The histological finding of an enlarged "cytomegalic" cell containing intranuclear and intracytoplasmic inclusions (Figure 180.1) is pathognomonic of an active CMV infection. Tissue-invasive infection is usually determined from histopathological findings combined with immunohistochemical detection of CMV replication proteins. Less commonly, viral culture or CMV nucleic acid detection is used to document CMV replication in tissue. Proof of CMV retinitis does not require evidence of CMV in tissue. Experienced ophthalmologists accurately diagnose CMV retinitis based on funduscopic findings of characteristic retinal changes that include perivascular infiltrate, atrophy, and hemorrhage. Detection of CMV DNA in vitreous fluid aids in the diagnosis of atypical or unclear presentations of CMV retinitis. The diagnosis of probable CMV syndrome is unique to SOT recipients and is defined as evidence of CMV DNAemia (or CMV antigenemia) together with at least two of the following: (1) fever ≥38°C/100.4°F for ≥2 days, (2) new or increased malaise or fatigue, (3) leukopenia or neutropenia, (4) thrombocytopenia, (5) ≥5% atypical lymphocytes, or (6) elevation of liver enzymes. Probable CMV disease is defined as illness and organ dysfunction likely attributed to CMV and supported by evidence of CMV in blood, bronchoalveolar lavage fluid (BALF), or cerebral spinal fluid (CSF). For example, the diagnosis of probable CMV pneumonia is based on detection of CMV by culture or CMV DNA in BALF from a patient with clinical and radiographic findings of pneumonia. A high CMV viral load in BALF increases the probability of CMV pneumonia, whereas the absence of detectable CMV DNA in BALF by quantitative nucleic acid testing (QNAT) rules out CMV pneumonia. Detection of CMV DNA in CSF supports the diagnosis of probable CMV encephalitis, polyradiculopathy, or myelitis if the clinical context is appropriate. Importantly, not all patients with detectable levels of CMV in tissue, blood, BALF, or CSF have CMV disease.

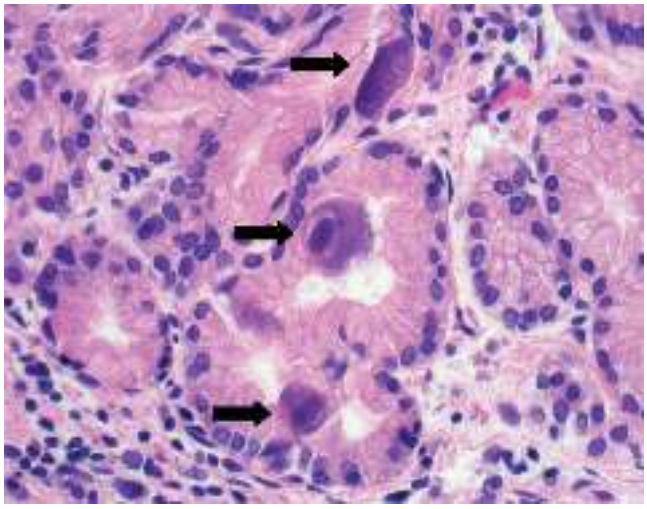

FIGURE 180.1 Cytomegalic inclusion disease. Arrows point to characteristic cytomegalovirus (CMV) infected cells, which contain intranuclear and ground-glass cytoplasmic inclusions. Hematoxylin and eosin staining.

* DIC: Disseminated intravascular coagulation.

Use of QNAT to determine CMV DNA level in blood enables diagnosis and monitoring of CMV infection and disease in HSCT and SOT recipients. While QNAT calibration with the WHO International Standard and the IU/mL report improves agreement of viral load values, different QNATs and methods produce significant interlaboratory variability in the results. CMV DNAemia does not accompany all CMV end-organ disease and is commonly absent in gastrointestinal CMV disease. Regardless of the type of patient population, QNAT detection of CMV DNA in blood, CSF, BALF, vitreous fluid, or amniotic fluid signals CMV replication because the level of latent viral DNA is below the threshold of detection by these assays. In the setting of AIDS, the monitoring of CMV DNAemia is not recommended for diagnosing CMV disease because CMV DNAemia has poor predictive value for end-organ disease and does not help predict progression or relapse of AIDS-associated CMV retinitis, the most common AIDS-associated CMV disease. In the pivotal clinical trial comparing oral valganciclovir with IV ganciclovir for treatment of AIDS-associated CMV retinitis, half of the CMV retinitis cases did not have CMV DNAemia. Detection of CMV DNA in amniotic fluid or in a newborn's saliva, urine, or blood indicates congenital CMV infection. The CMV pp65 antigen assay of CMV antigen-positive leukocytes in blood has largely been supplanted by QNAT because the latter is more sensitive, less labor-intensive, and not affected by neutropenia. Assessment of

CMV-specific T-cell response (e.g., interferon [IFN]-γ release in response to CMV antigens) is useful for predicting CMV DNAemia and disease in HSCT and SOT but should be combined with viral load monitoring.

Therapy

The US Food and Drug Administration (FDA) has approved use of ganciclovir, valganciclovir, foscarnet, and cidofovir for various CMV treatment indications. Ganciclovir and valganciclovir are also approved for prophylaxis in SOT recipients. Letermovir is approved for prophylaxis to prevent CMV replication and disease in adult CMV-seropositive allogeneic HSCT recipients. First-line treatment of an active CMV infection usually consists of either intravenous (IV) ganciclovir or oral valganciclovir. Table 180.1 summarizes the recommended dosing schedules for these agents and their use in clinical practice. Fomivirsen, a therapeutic antisense oligonucleotide administered by intraocular injection, and the intraocular ganciclovir implant are no longer manufactured. Oral ganciclovir is not available in the United States. Investigational anti-CMV drugs (e.g., maribavir) are in the clinical stage of development.

AIDS

In HIV/AIDS, CMV end-organ disease usually does not develop until the $CD4^+$ T lymphocyte count falls below ≤50 cells/μL in conjunction with an uncontrolled HIV viral load. CMV retinitis accounts for 85% of all AIDS-associated CMV disease. Initial treatment of CMV retinitis is selected from options of oral valganciclovir alone, oral valganciclovir plus intravitreal injection with foscarnet or ganciclovir, or IV ganciclovir. IV foscarnet and IV cidofovir are also effective but risk greater toxicity. Treatment selection is based on individual patient characteristics (ability to absorb oral medication, adhere to treatment, achieve immune recovery, etc.) and extent/location of the retinal lesion. Systemic anti-CMV therapy prevents CMV disease from developing in the contralateral eye and in other organs. Treatment of HIV with ART results in immune recovery that controls the CMV infection. CMV retinitis is treated for 14 to 21 days at induction therapy dosing. Maintenance therapy (secondary prophylaxis) is continued for at least 3 to 6 months after the CD4+ count is >100 cells/μL. Ophthalmology follow-up looking for relapse of retinitis and post-retinitis sequela is also important. Immune recovery uveitis may develop as an ART–induced inflammatory response to CMV, which can be managed with periocular, intravitreal, or oral corticosteroids. Secondary prophylaxis is resumed when the CD4+ count falls below 100 cells/μL. An early first relapse (≤3 months) of CMV retinitis will often respond to reinstituting the same initial treatment regimen. Ganciclovir-resistant CMV may emerge with prolonged use of ganciclovir/valganciclovir. Genotypic resistance testing of CMV in blood enables determination of mutations in the viral phosphotransferase (UL97) and polymerase (UL54) genes that confer antiviral resistance. A virus with mutations conferring low-level ganciclovir resistance may be contained by intravitreal injection of ganciclovir, whereas a virus with mutations conferring high-level ganciclovir resistance requires treatment with a different class of anti-CMV drug.

CMV esophagitis and colitis are treated initially with IV ganciclovir (or IV foscarnet). Oral valganciclovir is an option if absorption is not a concern. Treatment duration is 21 to 42 days or until the disease resolves. Secondary prophylaxis is not always needed. CMV pneumonitis is treated with IV ganciclovir, oral valganciclovir, or IV foscarnet. CMV neurological disease may initially require double therapy with IV ganciclovir and IV foscarnet; both agents fall short in achieving target drug levels in CSF.

Transplantation

SOT patients at highest risk for CMV disease are CMV-seronegative recipients of organs of CMV-seropositive donors (D+/R−) and recipients of CMV-positive donor lung, heart, or intestine. In contrast, CMV-seropositive HSCT recipients of cells from CMV-seronegative donors are at highest risk of CMV disease. Use of either chemoprophylaxis or preemptive therapy in the first 3 to 6 months after transplant prevents CMV disease in at-risk HSCT and SOT recipients. Chemoprophylaxis entails giving the antiviral drug to all patients to suppress CMV replication. Preemptive therapy involves monitoring of CMV DNAemia at regular intervals (usually weekly) and beginning valganciclovir/ganciclovir treatment when CMV DNAemia exceeds a threshold level. The viral load threshold differs among the different at-risk groups. Oral valganciclovir is administered at treatment dose for at least 2 weeks and until the CMV DNAemia has resolved. Viral load monitoring is resumed after the treatment because nearly one-third of these patients will have a second episode of CMV DNAemia. Published guidelines on prevention and management of CMV infection and disease in HSCT and SOT recipients have helped standardize approaches, but practice varies between centers and continues to evolve with advances in transplant medicine. Chemoprophylaxis is usually preferred over preemptive therapy in the highest risk patients. Oral valganciclovir/IV ganciclovir is commonly used for chemoprophylaxis in HSCT and SOT recipients. Letermovir (IV or oral) is effective chemoprophylaxis in allogenic HSCT recipients but does not have activity against herpes simplex virus (HSV) and varicella-zoster virus (VZV). High-dose acyclovir or valacyclovir is less effective than ganciclovir for chemoprophylaxis, although it is sometimes used in low-risk renal transplant recipients. Late-onset CMV disease in HSCT and SOT recipients is more likely to occur in patients having received chemoprophylaxis or experiencing graft-versus-host disease. CMV replication during or after having received ganciclovir/valganciclovir for ≥6 weeks increases probability that the virus has become resistant to ganciclovir.

CMV disease in HSCT and SOT recipients is treated with IV ganciclovir or oral valganciclovir. IV ganciclovir is preferred in patients having life-threatening CMV disease and when absorption of oral valganciclovir is compromised. Immune suppression should be decreased if possible. Weekly measurements of the level of CMV DNAemia provides an assessment of treatment response and guides duration of treatment. Treatment is continued until CMV

TABLE 180.1 **PREVENTIVE AND TREATMENT REGIMENS FOR CYTOMEGALOVIRUS (CMV) INFECTION**

Agent	Indications	Dosing regimen	Toxicities	Monitoring	Comments
Intravenous					
Ganciclovir	Treatment of visceral or disseminated disease Preemptive therapy in transplant recipients Prophylaxis therapy in transplant recipients	Treatment: 5 mg/kg q12h × 14–21 d or until disease resolves. Maintenance: 5 mg/kg qd (modify dose in renal failure) 5 mg/kg qd (modify dose in renal failure)	Catheter-related complications, neutropenia, thrombocytopenia, renal failure Causes infertility, teratogenicity, and embryotoxicity in animals	Treatment: CBC 2×/wk, Cr weekly Maintenance: CBC every wk, Cr q1–3wk	Adjust dosage for reduced renal function. If ANC 500–750, consider SQ G-CSF If ANC ≤500 or platelets ≤25 K, hold ganciclovir.
Foscarnet	Treatment of visceral or disseminated disease	Treatment: 90 mg/kg q12h (or 60 mg/kg q8h) × 14–21d or until disease resolves. Maintenance: 90–120 mg/kg qd (modify dose in renal failure) Maximum dose is 120 mg/kg qd	Catheter-related complications, nephrotoxicity, paresthesia, cation chelation, genital ulcerations, nausea, marrow suppression	Treatment: CBC, Cr, cations (K^+, Mg^{2+}, Ca^{2+}), and phosphate 2–3× every wk Maintenance: Cr, cations, and phosphate every wk, CBC q2wk	Adjust dosage for reduced renal function If Cr >2.8, hold foscarnet until Cr ≤2.1 mg/dL. Hydration reduces renal toxicity. Caution if seizures.
Cidofovir	Treatment of retinitis (limited experience with use for salvage therapy for CMV disease in other viscera)	Treatment: 5 mg/kg/wk × 2; infuse over 1 h Maintenance: 5 mg/kg q2wk; infuse over 1 h (reduce dose to 3 mg/kg if Cr increase 0.3 mg/dL)	Nephrotoxicity with Fanconi syndrome, neutropenia, uveitis, ocular hypotony, probenecid rash Probenecid contraindicated in persons with severe sulfa allergy	Treatment: Cr and UA every dose Maintenance: Same plus intraocular pressure every mo	1–2 L saline hydration, with 1 L given before cidofovir infusion; probenecid, given 3 h before (2 g), at 3 h (1 g) and 8 h (1 g) after cidofovir infusion Caution if diabetes mellitus Do not use if Cr >1.5 mg/dL CrCl ≤55 mL/min, ≥100 mg/dL proteinuria or receiving other nephrotoxic agents.
Letermovir	Prophylaxis in allogeneic HSCT recipients (up to day 100 post-transplantation)	480 mg/d. 240 mg/d when used with cyclosporin. Data lacking in patients with CrCl ≤10 mL/min	Accumulation of IV vehicle, hydroxypropyl betadex, with CrCl <50 mL/min. Not recommended for patients with severe hepatic impairment.	Closely monitor Cr in patients with CrCl <50 mL/min	Potential for drug–drug interaction; inhibitor of OATP1B1/3 transporters and CYP34A. Not active against HSV and VZV.
Intraocular					
Foscarnet intravitreal injection	Treatment of CMV retinitis	2.4 mg every week for up to 4 weeks	Transient blurred vision, hemorrhage, infection	Experienced Ophthalmologist	Requires addition of systemic therapy to reduce CMV disease risk in contralateral eye and other organs.

TABLE 180.1 CONTINUED

Agent	Indications	Dosing regimen	Toxicities	Monitoring	Comments
Ganciclovir intravitreal injection	Treatment of CMV retinitis	2–3 mg every week for up to 4 weeks	Transient blurred vision, hemorrhage, infection	Experienced Ophthalmologist	Requires addition of systemic therapy to reduce CMV disease risk in contralateral eye and other organs.
Oral					
Valganciclovir	Treatment of visceral or disseminated disease Prophylaxis or preemptive therapy in transplant	Induction: 900 mg BID × 14–21 d or until disease resolves. Maintenance: 900 mg/d (modify dose in renal failure 900 mg/d or BID, with food (modify dose in renal failure)	Neutropenia, thrombocytopenia Causes infertility, teratogenicity, and embryotoxicity in animals	Induction: CBC 2×/wk, Cr weekly Maintenance: CBC every wk, Cr q1–3wk	If ANC 500–750, consider SQ G-CSF If ANC ≤500 or platelets ≤25 K If Hg<8 mg/dL consider holding dose.
Letermovir	Prophylaxis in allogeneic HSCT recipients (up to day 100 post-transplantation). Not active against HSV and VZV.	480 mg/d. 240 mg/d when used with cyclosporin. Data lacking in patients with CrCl ≤10 mL/min.	Not recommended for patients with severe hepatic impairment.	Closely monitor Cr in patients with CrCl <l50 mL/min	Potential for drug–drug interaction; inhibitor of OATP1B1/3 transporters and CYP34A.
Valacyclovir	Prophylaxis in solid organ transplant recipients	2 g QID (modify dose in renal failure)	Hallucinations, confusion, marrow toxicity	CBC and Cr q2wk	Less effective than ganciclovir; therefore, use limited to low-risk patients
CMV Hyperimmunoglobulin					
CMV immunoglobulin intravenous (Cytogam)	Treatment of CMV pneumonitis in bone marrow transplant recipient Prophylaxis in solid organ transplant recipients	400 mg/kg days 1, 2, and 7 200 mg/kg day 14 plus IV ganciclovir (see IV ganciclovir) 50–150 mg/kg q2–4wk (various dosing regimens have been used) until delivery	Fever, myalgia, arthralgia, nausea, wheezing, hypotension, aseptic meningitis	Vital signs before, during, and after infusion	Derived from pooled adult human plasma Increase infusion rate as tolerated, 15–60 mg/kg/h Caution if IgA deficiency

Abbreviations: SQ = subcutaneous injection; CBC = complete blood count; Cr = serum creatinine; CrCL = creatinine clearance; ANC = absolute neutrophil count; CMV = cytomegalovirus; UA = urine analysis; AIDS = acquired immunodeficiency syndrome; G-CSF = granulocyte colony- stimulating factor.

DNAemia ceases or is at very low level and the CMV end-organ disease resolves. Genotypic antiviral resistance testing of CMV phosphotransferase (UL97) and DNA polymerase (UL54) genes should be done if persistent or recurrent CMV DNAemia develops against a background of extensive exposure history to valganciclovir/ganciclovir. A higher dose of IV ganciclovir may be effective against a virus with phosphotransferase gene mutations conferring low-level ganciclovir resistance. Most ganciclovir-resistant CMV strains are susceptible to IV foscarnet. IV cidofovir may be an option when the virus is resistant to both ganciclovir and foscarnet but is susceptible to cidofovir. The use of letermovir for treatment of CMV disease has not been adequately studied and may be compromised by CMV's greater tendency to develop resistance to this drug.

Other immunocompromising conditions

Treatment of CMV end-organ disease in other immunocompromised patient populations largely follows the strategy applied to transplant recipients. Patients with inflammatory bowel disease (IBD) are prone to developing active CMV infection in colonic

mucosa that is fueled by corticosteroid or thiopurine therapy for IBD. Tumor necrosis factor antagonists do not appear to increase risk of CMV infection in IBD. Low-level CMV activity commonly accompanies IBD flares and may resolve without antiviral treatment. Moderate to high levels of CMV activity in colonic tissue or blood of hospitalized patients is generally treated initially with IV ganciclovir for 3 to 5 days while IBD therapy is continued. The IV ganciclovir is then changed to oral valganciclovir for a total treatment duration of 2 to 3 weeks.

Congenital infection

Routine screening of pregnant women for CMV infection is not standard of care in the United States. There is no antiviral treatment or passive immunization for prevention of intrauterine fetal CMV infection. Ganciclovir should not be used in pregnancy because it causes birth defects in animals. While anecdotal reports suggest that fetal abnormalities do not result from use of ganciclovir/valganciclovir in humans during pregnancy (including the first trimester), rigorous studies are needed to evaluate safety and outcome. Six weeks of IV ganciclovir therapy given to neonates with symptomatic congenital CMV infection appears to decrease risk of hearing impairment, but dose-limiting bone marrow toxicity is common.

The otherwise normal host

Symptomatic CMV illness in otherwise healthy people is usually self-limiting (e.g., heterophile-negative mononucleosis, viral syndrome, or hepatitis). Sometimes, symptoms resolve slowly over several weeks, and relapsing symptoms may occur until the illness abates. Use of IV ganciclovir or oral valganciclovir is reserved for debilitating protracted illness or tissue-invasive disease. CMV is a potential cause of anterior uveitis in immunocompetent people, as well as the Posner-Schlossman and Fuchs iridocyclitis syndromes. These ocular infections are generally treated with oral valganciclovir. Low-level CMV DNAemia is common in critically ill patients and not an indication for antiviral treatment.

Antiviral agents

Ganciclovir and valganciclovir

Ganciclovir is a guanosine analog that must be phosphorylated by the CMV phosphotransferase (UL97 gene product) to be active. The CMV phosphotransferase adds the first phosphate to ganciclovir and then cellular enzymes add two more phosphates to produce ganciclovir triphosphate. The ganciclovir triphosphate inhibits CMV DNA polymerase (UL54 gene product) function and disrupts viral DNA chain elongation via ganciclovir incorporation into the new viral DNA strand. Ganciclovir also has activity against HSV-1, HSV-2, VZV, EBV, human herpesvirus 6 (HHV-6), HHV-8, and herpes B virus. The intracellular half-life of the ganciclovir triphosphate is 16.5 hours. Ganciclovir concentration in vitreous fluid and CSF is somewhat lower and more variable than in serum. Valganciclovir is an orally administered prodrug of ganciclovir that attains levels similar to that of the standard IV dose of ganciclovir. Oral ganciclovir and the ocular ganciclovir implant are no longer available. Intravitreal ganciclovir is used off-label for treatment of CMV retinitis at a reduced-dose to decrease risk of adverse effects.

Circulating ganciclovir metabolites are cleared by the kidneys, requiring adjustment of ganciclovir dose according to creatinine clearance (CrCl). Granulocytopenia is a common adverse effect that can be managed with avoidance of other marrow-suppressive agents and, if severe, use of granulocyte colony-stimulating factor. Thrombocytopenia, anemia, CNS toxicity (e.g., headache, seizures, and confusion), and renal failure may also be observed. Ganciclovir caused infertility, teratogenicity, and embryotoxicity in animal studies. The IV route of administration risks catheter-related infection. The intravitreal injection risks subconjunctival hemorrhage, pain, transient visual loss, and, rarely, endophthalmitis and permanent visual loss.

Foscarnet

Foscarnet (phosphonoformic acid) selectively inhibits CMV DNA polymerase activity and is administered by IV or intravitreal injection. Foscarnet also inhibits the replication of HSV, VZV, EBV, HHV-6, and HHV-8. The drug is cleared by the kidneys and requires dose adjustment according to CrCl. Foscarnet is toxic to kidneys, and hydration may aid in reducing this toxicity. Use of other nephrotoxic agents (e.g., amphotericin B and aminoglycosides) should be avoided. Mineral and electrolyte abnormalities are also common and include hypocalcemia, hyperphosphatemia, hypophosphatemia, hypokalemia, and hypomagnesemia. Although manageable, these abnormalities can precipitate seizures. Symptoms of numbness, tingling, and other abnormal sensations signal the chelation of ionized calcium by the IV foscarnet that can be mitigated by slowing the infusion rate of foscarnet. Other notable adverse effects include anemia, granulocytopenia, genital ulcers, and IV catheter-related sepsis.

Cidofovir

Cellular enzymes add two phosphates to cidofovir that enables cidofovir to inhibit the CMV DNA polymerase and terminate viral DNA chain elongation. Cidofovir is administered IV, and its active form has an intracellular half-life of 17 to 65 hours. Cidofovir is nephrotoxic and contraindicated in persons with renal insufficiency (CrCl ≤55 mL/min, or ≥2+ proteinuria) or receiving other nephrotoxic agents. Nephrotoxicity is minimized by IV prehydration and administration of probenecid. Probenecid is contraindicated in persons with history of a severe sulfa allergy. Neutropenia, ocular hypotony, and metabolic acidosis (Fanconi's syndrome) are other potential toxicities of the drug. Cidofovir is gonadotoxic, embryotoxic, and carcinogenic in animals.

Letermovir

Letermovir selectively inhibits the CMV terminase complex to block packaging of the viral DNA genome into the viral capsid.

Letermovir is not active against the other herpesviruses. The drug is administered by either the oral or IV route and mostly cleared unchanged in stool through the hepatobiliary system. Letermovir should not be used in severe hepatic impairment or if CrCl is ≤10 mL/min. The IV vehicle, hydroxypropyl betadex, may accumulate when CrCl is <50 mL/min. Letermovir is an inhibitor of OATP1B1/3 transporters and a moderate inhibitor of CYP34A. This increases the number of drug–drug interactions that are possible when adding letermovir to other medications. Letermovir dose reduction is required when given with cyclosporin. Letermovir is generally well tolerated and does not have significant renal or bone marrow toxicity.

Cytomegalovirus hyperimmune globulin

CMV hyperimmune globulin IV (CMVIG) is pooled human IgG enriched four- to eightfold in anti-CMV antibody compared with standard preparations of IV immunoglobulin. CMVIG is used at some centers for passive immunoprophylaxis to prevent or attenuate CMV disease in high-risk (D+/R−) lung, heart, and intestine transplant populations or in transplant recipients who have developed hypogammaglobulinemia. Clinical trial results do not support the use of CMVIG for prevention of CMV transmission from mother to fetus or in the treatment of fetal infection.

Primary prevention

Primary prevention strategies target CMV-seronegative persons who, if become infected by CMV, risk passing the virus on to their unborn baby or themselves developing serious CMV disease. CMV vaccines in development are not likely to be a prevention option in the near future. Use of CMV-seronegative or leukocyte-depleted donor blood products prevents CMV transmission by blood product transfusion. Abstinence and condoms prevent sexual transmission of the virus. Breastfeeding premature (<30 weeks gestational age) and low-birth weight (<1500 g) infants risks development of a CMV-related sepsis-like syndrome as a result of CMV transmission via breast milk. Pasteurization of breast milk eliminates the CMV transmission risk associated with breast milk. Because young children are a common source of CMV, measures taken to lessen CMV transmission include use of good hand hygiene after changing diapers and wiping oral secretions and avoidance of close mucosal contact with the child's saliva that occurs during kissing or immediate sharing of utensils or food.

Suggested reading

Chou S. Approach to drug-resistant cytomegalovirus infection in transplant recipients. *Curr Opin Infect Dis*. 2015;28:293–299. PMID: 26098499. PMCID: PMC4522269.

Hirsch HH, Lautenschlager I, Pinsky BA, Cardenoso L, Aslam S, Cobb B, Vilchez RA, Valsamakis A. An international multicenter performance analysis of cytomegalovirus load tests. *Clin Infect Dis*. 2013;56:367–373. PMID: 23097587.

Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S Danziger-Isakov L, Humar A, on behalf of the Transplantation Society International CMV Consensus Group. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*. 2018;102:900–931. PMID: 29596116.

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. https://HIVinfo.nih.gov

Society of Maternal-Fetal Medicine, Hughes BL, Gyamfi-Bannerman C. Diagnosis and antenatal management of congenital cytomegalovirus infection. *Am J Obstet Gynecol*. 2016;214:B5–B11. PMID: 26902990.

Wreghitt TG, Teare EL, Sule O, Devi R, Rice P. Cytomegalovirus infection in immunocompetent patients. *Clin Infect Dis*. 2003;37:1603–1606. PMID: 14689339.

181

Dengue

Nguyen Thanh Hung

Dengue is caused by any of four closely related viruses or serotypes (dengue 1–4). Dengue viruses are small, single-stranded RNA viruses belonging to the genus *Flavivirus*, family *Flaviviridae*. Dengue is transmitted between people by the mosquitoes *Aedes aegypti* and *A. albopictus*, which are found throughout the world. In the past 50 years, there has been a dramatic increase in the global incidence of dengue virus infections. It is estimated that 3 billion people live in areas at risk of contracting dengue, and some 390 million infections (96 million symptomatic) and 20,000 deaths from dengue occur every year. Dengue virus infections may cause symptomatic infections or asymptomatic seroconversion. Symptomatic dengue infection has a wide range of clinical presentations which include severe and nonsevere manifestations. Two major pathophysiological features are associated with severe dengue infection: plasma leakage leading to hypovolemic shock and/or abnormal hemostasis (thrombocytopenia, vasculopathy, disseminated intravascular coagulation) leading to hemorrhage (Figure 181.1). While most patients recover following a self-limiting nonsevere clinical course, a small proportion progress to severe disease, mostly characterized by plasma leakage with or without hemorrhage.

Clinical manifestations

After an incubation period of 3 to 7 days, the illness begins abruptly and is followed by three phases: a febrile phase, a critical phase, and a recovery phase.

Febrile phase

The febrile phase is characterized by high temperature (≥38.5°C/101.3°F) accompanied by headache, vomiting, myalgia, joint pain, and a transient macular rash. High fever may cause neurologic disturbances and febrile seizures in young children. Hemorrhagic manifestations include a positive tourniquet test, easy bruising and bleeding at venipuncture sites, fine petechiae, epistaxis, gingival bleeding, and mild gastrointestinal bleeding (Figure 181.2, Panels A, B, and C). A palpable liver may be noted, especially in young infants and children. The CBC reveals leukopenia, mild to moderate thrombocytopenia, and normal hematocrit value. This acute febrile phase usually lasts 2 to 7 days, and most patients recover spontaneously after this phase.

Critical phase

During the transition from the febrile to afebrile phase, patients without an increase in capillary permeability will improve uneventfully. In a small proportion of patients, systemic vascular leak syndrome becomes apparent, evidenced by increasing hemoconcentration, pleural effusions, and ascites (Figure 181.3, Panel A). The degree of increase above the baseline hematocrit often reflects the severity of plasma leakage. A right lateral decubitus chest radiograph or ultrasound detection of free fluid in the chest or abdomen or gall bladder

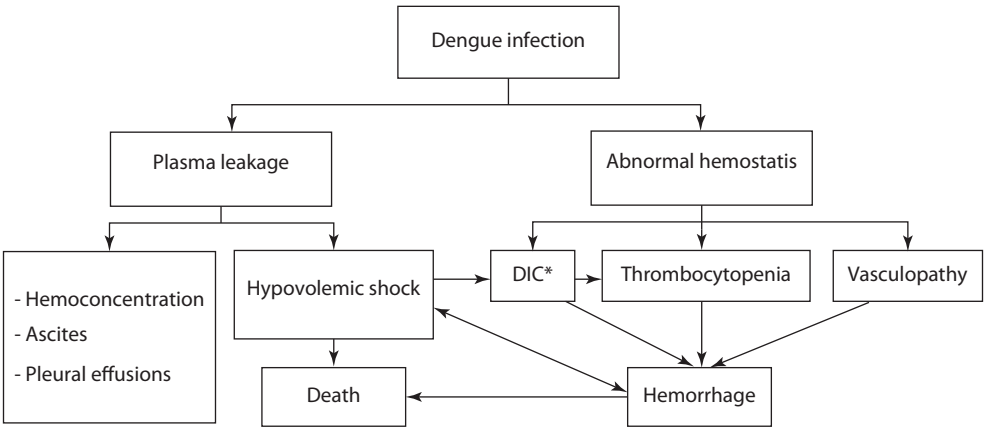

FIGURE 181.1 The correlation between pathophysiology and clinical manifestations of severe dengue.

wall edema may precede clinical detection of pleural effusion and ascites (Figure 181.3, Panels B, C, and D). In less severe cases, these changes are minimal and transient, reflecting a mild degree of plasma leakage, and patients will recover spontaneously. In more severe cases, when plasma loss is critical, hypovolemic shock ensues. Shock (dengue shock syndrome) is often preceded by warning signs. The warning signs of impending deterioration include intense abdominal pain or tenderness, persistent vomiting, mucosal bleeding, lethargy or restlessness, liver enlargement >2 cm, fluid accumulation (ascites, pleural effusion, pericardial effusion), and progressive increase in hematocrit concurrent with a rapid decrease in platelet count.

The patient in shock may die within 12 to 24 hours if appropriate treatment is not promptly administered, or they may recover rapidly following proper intravenous (IV) fluid therapy. Uncorrected shock can lead to severe complications with development of multiple organ dysfunctions, respiratory failure, metabolic acidosis, severe gastrointestinal bleeding, and a poor prognosis.

Hemorrhagic manifestations are most common during this critical period. In children, significant bleeding is usually associated with profound and prolonged shock. However, major skin bleeding and/or mucosal bleeding may occur in adults with only

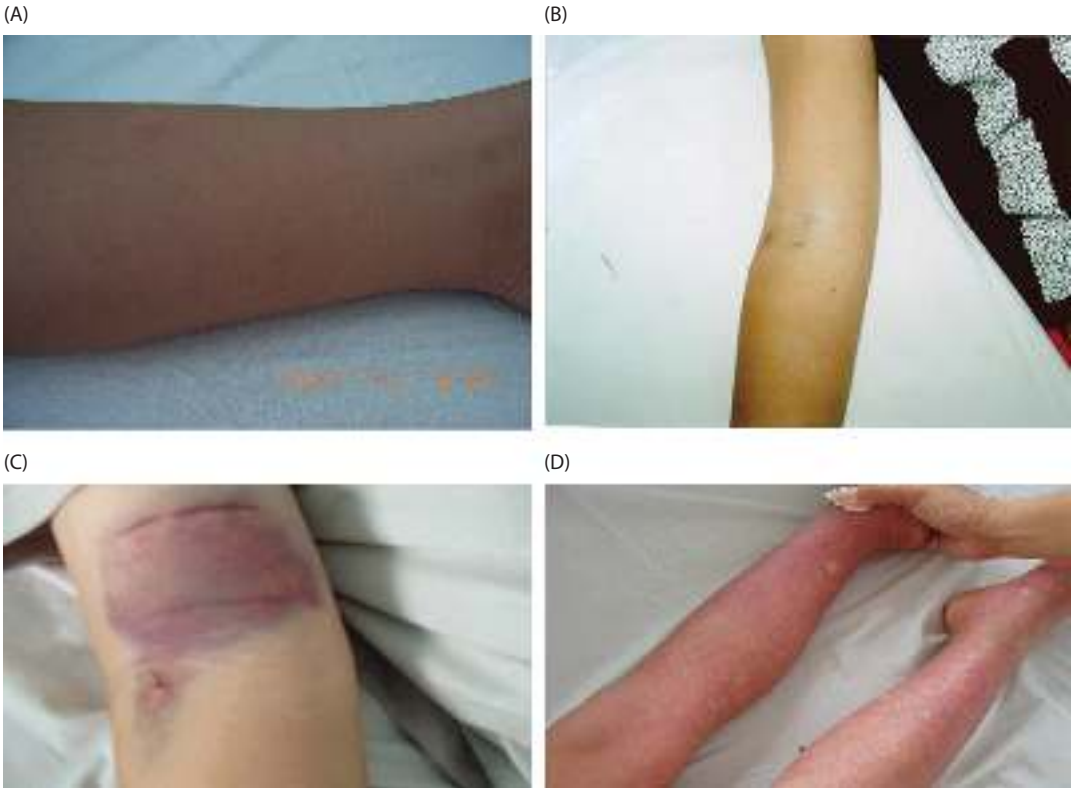

FIGURE 181.2 Hemorrhagic manifestations in dengue patients. (A) Petechial rash in a child with dengue. (B) Minor bleeding around injection sites. (C) Hematoma in a patient with severe dengue. (D) Characteristic confluent petechial rash in the recovery phase.

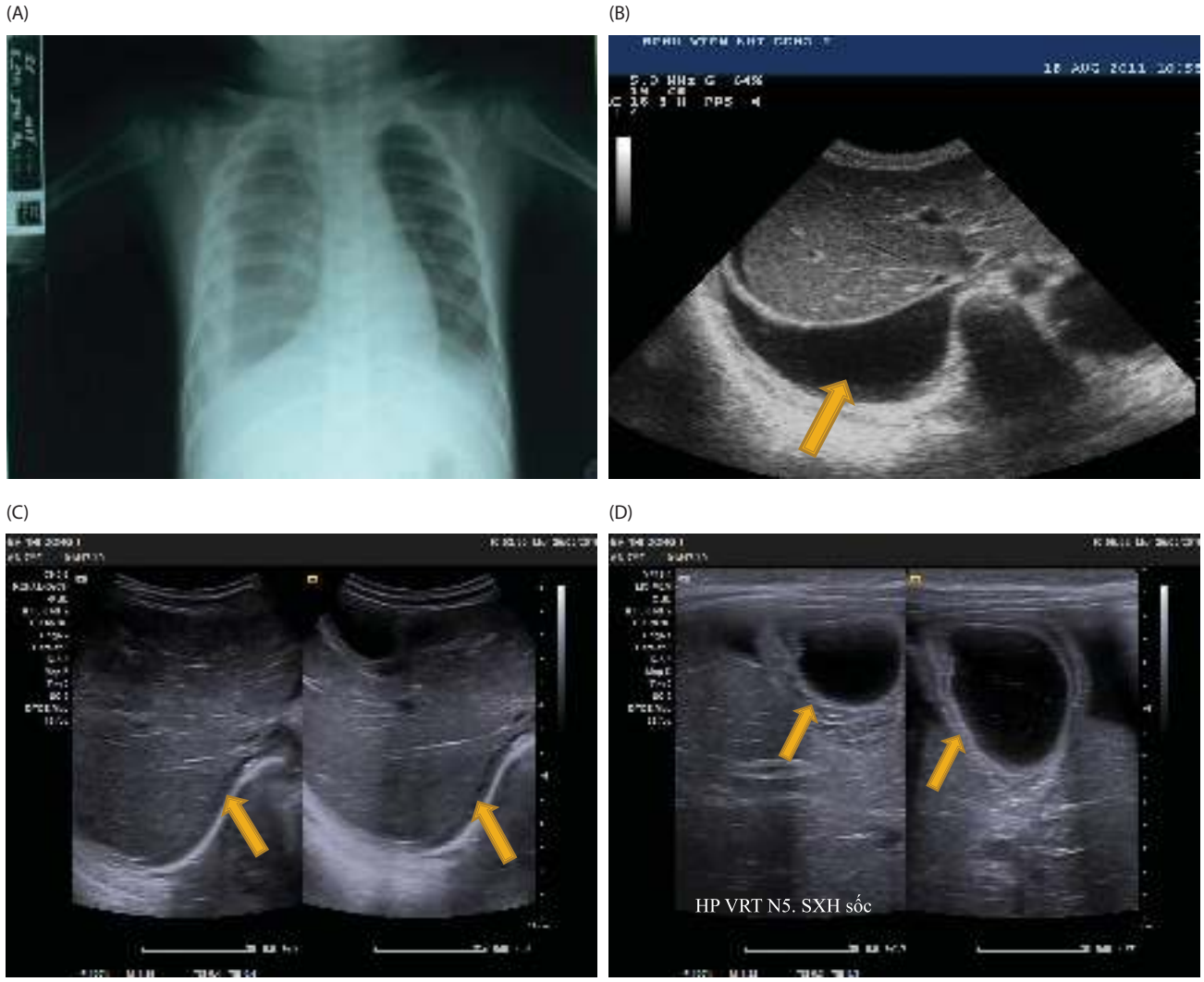

FIGURE 181.3 Systemic vascular leak syndrome in dengue patients. (A) Pleural effusion through chest X-ray in an infant dengue patient. (B) pleural effusion through ultrasound scan of the abdomen in a 7-year-old patient with dengue shock syndrome. (C) Hepatic subcapsular fluid collections through ultrasound scan of the abdomen in a 7-year-old patient with dengue shock syndrome. (D) Edematous gall bladder wall thickening through ultrasound scan of the abdomen in a 7-year-old patient with dengue shock syndrome.

minor plasma leakage (Figure 181.2, Panel C). Moderate to severe thrombocytopenia, transient increase in the activated partial thromboplastin time, and a decrease in fibrinogen levels are frequently noted.

Severe organ impairment such as acute liver failure, encephalitis, myocarditis, kidney failure, and/or severe bleeding may infrequently occur without obvious plasma leakage or shock.

Convalescent phase

Most dengue patients will recover rapidly and uneventfully within 24 to 48 hours after shock has been reversed. Indicators of recovery include improved general condition, stable vital signs, and the return of appetite, diuresis, and sinus bradycardia. Some patients develop a characteristic confluent petechial rash with small round areas of normal skin on their lower extremities (Figure 181.2, Panel D). Some patients have signs of fluid overload (respiratory distress, pulmonary edema, or heart failure associated with gross peripheral edema, large pleural effusions, and ascites) due to excessive IV therapy and reabsorption of extravasated plasma from the interstitial compartment.

Diagnosis

Clinicians should suspect dengue in persons who live in or travel to a dengue-endemic area (South-East Asia, the Americas, the Western Pacific, and the Eastern Mediterranean) with acute febrile syndromes associated with two of these signs/symptoms: nausea or vomiting, rash, aches and pains, a positive tourniquet test, leukopenia, and any warning sign mentioned earlier. Laboratory diagnosis of dengue is made by detecting the virus and/or any of its components, such as virus genome and dengue antigen, or by investigating the serologic

responses present after infection. Clinicians should keep in mind that laboratory diagnosis is usually not necessary for clinical management except in atypical cases or when constructing a differential diagnosis. A diagnosis of dengue infection is confirmed by the detection of the virus, the viral genome, or nonstructural protein 1 (NS1) antigen in the acute sera, which are collected during the febrile phase, or seroconversion of immunoglobulin (IgM/IgG) from negative to positive or a fourfold increase in antibody titer in paired sera. A positive IgM serology or a hemagglutinin inhibition test (HIA) antibody titer of ≥1,280 are considered a probable dengue infection. Both probable and confirmed dengue cases should be notified to health authorities.

Dengue case classification

Patients were previously classified as having either dengue fever or dengue hemorrhagic fever. Dengue hemorrhagic fever was further classified into four severity grades, with grades III and IV being defined as dengue shock syndrome. There have been many reports of difficulties in the use of this classification. With the 2009 revision of the World Health Organization dengue classification scheme, patients are now classified as having either dengue with/without warning signs or severe dengue. Patients who recover without major complications are classified as having dengue, whereas those who have any of the following conditions are classified as having severe dengue: severe plasma leakage leading to shock (dengue shock syndrome), accumulation of serosal fluid sufficient to cause respiratory distress, severe bleeding, and severe organ impairment (Figure 181.4).

Differential diagnosis of dengue

Early in the febrile phase, the differential diagnosis of dengue includes other arboviral infections, measles, rubella, enterovirus infections, adenovirus infections, and influenza. Depending on local frequency and epidemiologic characteristics of febrile diseases, other diseases such as typhoid, malaria, leptospirosis, viral hepatitis, rickettsial diseases, bacterial sepsis, and meningococcal disease should be considered as part of the differential diagnosis. Clinicians should also remember that some dengue patients with liver enlargement and severe abdominal pain may mimic surgical conditions such as acute appendicitis and hepatic abscess. Misdiagnosing and performing unnecessary surgery will put these dengue patients at risk of severe hemorrhage.

Management

Treatment is supportive, with special emphasis on careful fluid management. Patients without complications can be managed as outpatients and followed closely every day from day 3 of their illness until they have been afebrile for more than 48 hours without the use of antipyretics. Practically the hematocrit and platelet count should be determined at the first visit and then checked once to twice daily. Oral rehydration should be encouraged with oral rehydration solution (ORS), fruit juice, and other fluids containing electrolytes and sugar. Give acetaminophen/paracetamol for high fever if the patient is uncomfortable. Do not give acetylsalicylic acid (aspirin), ibuprofen, or other nonsteroidal anti-inflammatory agents (NSAIDs) because of the risks of gastritis or bleeding. Instruct the

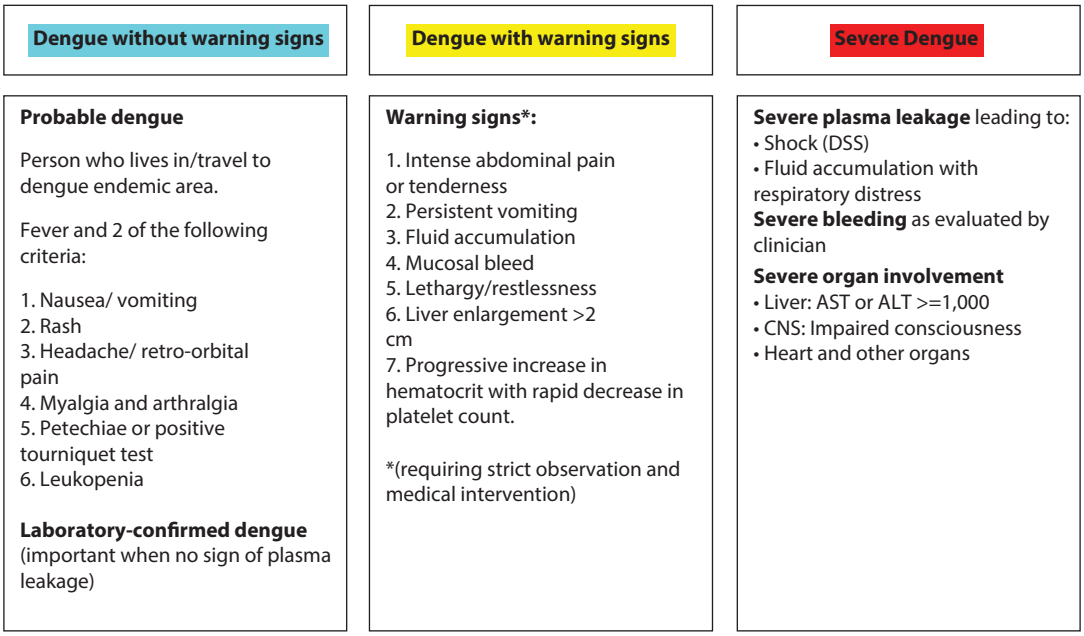

FIGURE 181.4 Dengue severity classification.
Adapted from the World Health Organization and Pan American Health Organization.

patients or caregivers to return to the nearest hospital immediately if the patients have any of the warning signs.

For those patients with warning signs, judicious volume replacement of lost plasma by IV fluid therapy with isotonic crystalloid solutions from this early stage may modify the course and severity of disease. Parenteral fluid therapy is only required for 24 to 48 hours in most patients since the capillary leak resolves spontaneously after this time.

Patients with dengue shock syndrome need emergency treatment with fluid resuscitation. The recommended regimen for the treatment of dengue shock patients is the immediate and rapid replacement of the plasma loss with isotonic crystalloid solutions or, in the case of profound shock, colloid solutions; continued replacement of further plasma losses to maintain effective circulation for 24 to 48 hours; correction of metabolic and electrolyte disturbances; and blood transfusion in patients with severe bleeding. Platelet concentrates, fresh frozen plasma, and cryoprecipitate may also be used in cases of severe bleeding. Dengue shock patients should be under close observation around the clock until it is certain that danger has passed. Generally, the duration of IV therapy should not exceed 24 to 48 hours after the patient is out of shock. Electrolyte levels and blood gases should be determined periodically in severe cases. In patients with severe and complicated dengue, mechanical ventilation, vasopressor and inotropic therapies, renal replacement therapy, and other treatment of organ impairment may be required.

Currently, efficacious and safe antiviral agents and immunomodulatory therapies for dengue have not yet been developed. Careful clinical detection and improvement of case management of dengue patients can significantly reduce case fatality rates among hospitalized cases from 20% to <0.5% in many endemic countries.

Prevention

Vaccination should be considered as part of an integrated dengue prevention and control strategy. The live attenuated dengue vaccine CYD-TDV (Dengvaxia) is currently licensed in 20 countries for use in endemic areas in persons ranging from 9 to 45 years of age. CYD-TDV has been shown in clinical trials to be efficacious and safe in persons who had exposure to dengue before vaccination (seropositive individuals), and there was evidence of a higher risk of severe dengue in vaccinated persons who had not been exposed to dengue (seronegative individuals). The World Health Organization position is that for countries considering vaccination as part of their dengue control program, pre-vaccination screening is the recommended strategy. With this strategy, only persons with evidence of a past dengue infection would be vaccinated.

Dengue is transmitted between people by the mosquitoes *A. aegypti* and *A. albopictus*, so the best measure to prevent dengue is to reduce mosquitoes and avoid mosquito bites. Eliminating the places where the mosquito lays her eggs, such as artificial containers that hold water in and around the home, and cleansing water containers, help reduce mosquitoes. The adult mosquitoes like to bite indoors during the day and at night when the lights are on. Travelers in dengue-endemic areas should avoid mosquitoes during the day by using insect repellents and sleeping under a mosquito bed net or using air conditioning. Improving community participation and mobilization for sustained vector control, applying insecticides as space spraying during outbreaks as one emergency vector-control measure, and active monitoring and surveillance of vectors should be carried out to determine effectiveness of control interventions.

Suggested reading

Alexander N, Balmaseda A, Coelho ICB, et al. Multicentre prospective study on dengue classification in four South-east Asian and three Latin American countries. *Trop Med Int Health*. 2011;16:936–948.

Cameron P, Simmons CP, McPherson K, Chau NVV, et al. Recent advances in dengue pathogenesis and clinical management. *Vaccine.* 2015;33:7061–7068.

Kalayanarooj S, Rothman AL, Srikiatkhachorn A. Case management of dengue: Lessons learned. *J Infect Dis.* 2017;215(S2):S79–88.

Pan American Health Organization. *Dengue: Guidelines for patients care in the region of the America.* 2nd ed. Washington: PAHO; 2016.

Sridhar S, Luedtke A, Langevin E, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. *N Engl J Med.* 2018;379:327–340.

World Health Organization. *Handbook for clinical management of dengue*. Geneva: WHO; 2012.

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Enteroviruses

Penelope Dennehy

Introduction

Enterovirus is derived from the Greek word "enteron" meaning intestine. Enteroviruses (EV) are so named because they infect the gastrointestinal tract and are shed in the feces. These viruses are found worldwide and can cause a wide variety of illnesses, ranging from asymptomatic infection to severe illness and death. Infection occurs in all age groups. Non-polio EVs cause about 10 to 15 million infections and tens of thousands of hospitalizations each year in the United States.

Virology

The human EVs belong to the family *Picornaviridae* which also includes rhinoviruses, hepatitis A, and parechoviruses. EVs are small (~27 nm), spherical, non-enveloped viruses with icosahedral symmetry. These viruses have a linear single-stranded, positive-sense RNA of approximately 7.5 kB which functions as mRNA. The RNA genome is surrounded by a protein shell consisting of 60 subunits. Each subunit is formed from four virus-encoded structural proteins (VPs 1–4).

EVs are relatively acid resistant and stable over a wide range of pH (3–10) which allows passage through the gastrointestinal tract. They are resistant to alcohol but are inactivated by phenol and formaldehyde and by temperatures >50°C/122°F. They retain infectivity for days at room temperature.

EVs replicate intracellularly. Viruses attach to specific cell membrane receptor proteins which determine host cell susceptibility (Table 182.1). Some serotypes have more than one receptor. Attachment is followed by penetration and uncoating with release of viral RNA into the cytoplasm of the cell. Rapid replication over 5 to 10 hours follows. Inside the cytoplasm of the cell the viral genome is translated to a single polyprotein which is cleaved by viral-encoded proteases into structural proteins VPs 1–4, an RNA polymerase, proteases, and other nonstructural proteins. These proteins are assembled into new viruses producing about 10^4 to 10^5 progeny viruses per infected cell. Only 0.1% to 10% of these progeny viruses are infectious.

Classification

Originally serotypes were distinguished by their host range and neutralization with specific antisera (Table 182.2). By 1969, 67 serotypes had been described. These serotypes were assigned to five subgroups: polioviruses, group A Coxsackieviruses, group B Coxsackieviruses, echoviruses, and EVs. All serotypes discovered after 1970 are simply designated as EV and are numbered sequentially beginning with serotype 68. Multiple new serotypes have been identified, with the number of known serotypes now >100.

In 2013, reclassification of EVs was done based on molecular serotyping determined by the RNA sequence encoding the VP1 protein. Molecular serotyping led to several new genera being named and viruses being reassigned. Echovirus serotypes 22 and 23 were reclassified as parechoviruses, enterovirus 72 became

TABLE 182.1 **ENTEROVIRUS RECEPTORS**

Host protein	EV serotype
Poliovirus receptor (PVR/CD155)	Poliovirus 1-3
Coxsackie and adenovirus receptor (CAR)	Coxsackie B 1-6
Decay accelerating factor (DAF)	Coxsackie A 21 Coxsackie B 1, 3, 5 Echovirus 3, 6, 7, 11, 12, 13, 19, 20, 21, 25, 29, 30
Scavenger receptor B2 (SCARB2)	Coxsackie A 7, 14, 16 Enterovirus A 71
P-selectin glycoprotein ligand 1 (PSGL1)	Coxsackie A 2, 7, 10, 14, 16 Enterovirus A 71
Kringle containing transmembrane protein 1 (KREMEN1)	Coxsackie A 10
Sialic acid	Enterovirus A 71
Intercellular adhesion molecule 5 (ICAM5)	Enterovirus D 68
Integrin a_2b_1 (VLA-2)	Echovirus 1
Neonatal Fc receptor (FcRn)	Echoviruses

hepatitis A, and a new genus, *Cardiovirus* was described. EVs are now grouped into 4 species (*Enterovirus A, B, C*, and *D*) on the basis of genetic similarity (Table 182.3) although traditional serotype names are retained for some individual serotypes.

Epidemiology

Enterovirus infections are common and have a worldwide distribution. Humans are the only known reservoir for human EVs, although some primates can become infected. The majority of infections are asymptomatic.

In the United States, one to three serotypes predominate each year. A small number of serotypes are seen every year while others emerge to cause widespread outbreaks and then disappear before reemerging years later. Recent serotypes that have emerged include Coxsackie A6, causing hand-foot-mouth disease (HFMD), and EV-D68, associated with respiratory disease and acute flaccid myelitis.

The occurrence of enteroviral infections varies by season, climate, and with the age and socioeconomic status of the population. In temperate climates infections are seen in the summer and early fall. In tropical and semitropical regions infections are seen throughout the year. Infection incidence, clinical attack rates, and disease severity are greatest in infants and young children. Infections occur more frequently in areas where poor sanitation, poor hygiene, and high population density are present. In the United States, geographic and socioeconomic factors affect the prevalence of enteroviral infections. Enterovirus isolation rates from young children are two- to threefold higher in southern than in northern cities and three- to sixfold higher in lower than in middle and upper socioeconomic areas.

EVs are transmitted person to person either directly by the fecal-oral route or less often by virus shed in respiratory secretions. EVs may survive on environmental surfaces, allowing transmission from fomites. Transmission via contaminated water and food can occur. The respiratory route is the principal mode of transmission for some serotypes including Coxsackie A21 and EV-D68. EV 71 is an exception as the virus is shed in tears and spread by fingers or fomites.

Viral shedding occurs after both asymptomatic and symptomatic infection. Virus is shed from 2 to 8 weeks in the feces and 1 to 3 weeks in respiratory secretions. Infants, especially those in diapers, are effective vehicles for transmission. Secondary infections occur at high rates in susceptible household contacts.

The usual incubation period for enterovirus infections is 3 to 6 days, except for acute hemorrhagic conjunctivitis (AHC), where the incubation period is 24 to 72 hours. The prevalence of unrecognized infection far exceeds that of clinical disease.

Pathogenesis

Enteroviral infection begins by ingestion of fecally contaminated material (Figure 182.1). After an incubation period of 1 to 3 days, limited replication occurs in the mucosa and lymphoid tissue of the tonsils and pharynx. Virions, which are impervious to stomach acid, proteases, and bile, are able to pass through the stomach and small bowel to the primary site of infection, lymphoid cells of Peyer's patches, which underlie the intestinal mucosa of the terminal ileum. One to two days after ingestion, virus is released from these initial sites of replication

TABLE 182.2 **CONVENTIONAL HUMAN ENTEROVIRUS CLASSIFICATION AND HOST RANGE**

		Host range		
Group	**Serotypes**	**Primates**	**Newborn mice**	**Cell culture**
Coxsackie A viruses	1–22, 24	0	+++	±
Coxsackie B viruses	1–6	0	+++	++
Echoviruses	1–9, 11–27, 29–33	0	0	++
Polioviruses	1–3	++	0	++
Enteroviruses	68–72	variable	variable	Variable

TABLE 182.3 **2013 HUMAN ENTEROVIRUS CLASSIFICATION BASED ON PARTIAL SEQUENCING OF VP1 RNA**

Species	Number of serotypes infecting humans	Serotypes included
Group A enteroviruses	21	Coxsackie A 2–8, 10, 12, 14, 16 Enterovirus A 71, 76, 89–92, 114, 119–121
Group B enteroviruses	59	Coxsackie A 9 Coxsackie B 1–6 Echovirus 1–7, 9,11–21, 24–27, 29–33 Enterovirus B 69, 73–75, 77–88, 93, 97, 98, 100, 101, 106, 107, 111
Group C enteroviruses	23	Poliovirus 1–3 Coxsackie A 1, 11, 13, 17, 19–22, 24 Enterovirus C 95, 96, 99, 102, 104, 105, 109, 113, 116- 118
Group D enteroviruses	4	Enterovirus D 68, 70, 94, 111

into the bloodstream, causing a transient minor viremia which infects regional lymph nodes. In most cases, infection is contained at this stage by host defense mechanisms with no further progression, resulting in asymptomatic infection. In a minority of infected persons, replication takes place in the regional lymph nodes with subsequent dissemination of virus into the bloodstream causing a heavy sustained viremia ("major viremia"). During the major viremia, which usually occurs by the fifth day of infection, nonspecific symptoms of fever may be seen. The major viremia disseminates large amounts of virus to target organs bearing receptors for the infecting serotype. Target organs include the spinal cord, brain, meninges, heart, skeletal muscles, and skin. The tissue targeted by the particular enterovirus determines the predominant clinical illness caused by that virus. Further virus replication results in cell necrosis in target tissues. In most patients, host defense mechanisms quickly terminate the major viremia and halt virus replication in target organs; only rarely is virus replication in target organs extensive enough to be clinically apparent.

Serotype-specific neutralizing antibodies may be detected in the serum within 4 or 5 days of infection and generally persist for life. These antibodies play a critical role in terminating infection, which is highlighted by the occurrence of chronic persistent enteroviral infections in children with agammaglobulinemia. Host defenses do not terminate virus replication in the intestine, and fecal shedding continues for weeks after both symptomatic and asymptomatic enteroviral infections.

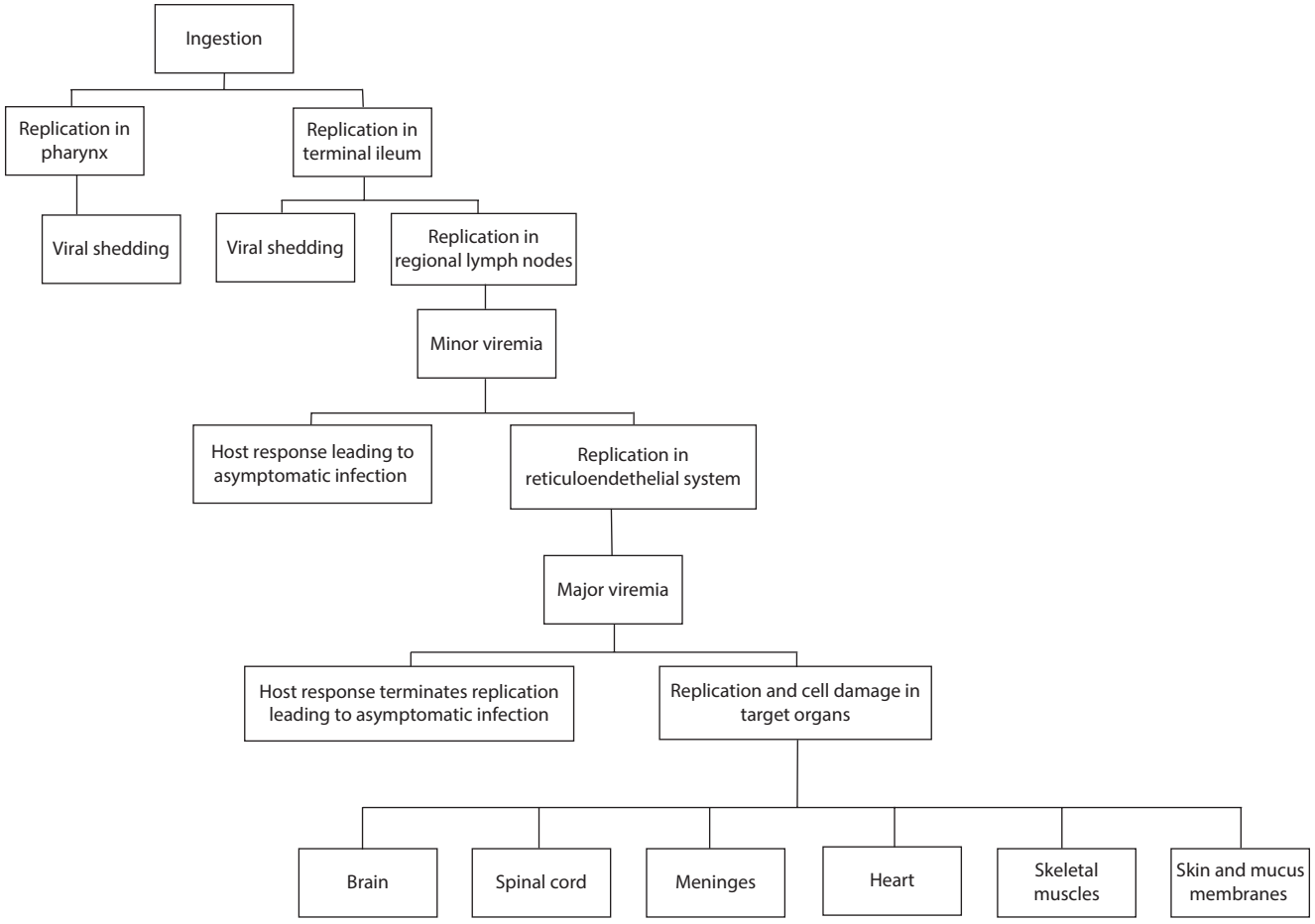

FIGURE 182.1 Pathogenesis of enteroviral infections.

Immunity to enteroviral infection is serotype-specific, with neutralizing antibodies in the blood preventing enteroviral dissemination and disease. Reinfection is relatively uncommon and is generally asymptomatic. Infection is most often confined to the gastrointestinal tract, and the duration of virus shedding is markedly reduced.

Clinical presentation

EVs cause a wide spectrum of diseases in all age groups, with infection and illness occurring most commonly in infants. When more serious disease occurs, the clinical spectrum and disease severity vary with the age, gender, and immune status of the host. The majority (50–80%) of infections caused by EVs are asymptomatic. Most symptomatic infections consist of undifferentiated febrile illnesses often accompanied by upper respiratory symptoms. Other manifestations are uncommon and can include (1) respiratory: coryza, pharyngitis, herpangina, stomatitis, parotitis, croup, bronchiolitis, pneumonia, and bronchospasm; (2) skin: HFMD, onychomadesis (shedding of nails), and nonspecific exanthems; (3) neurologic: aseptic meningitis, encephalitis, and acute flaccid myelitis; (4) gastrointestinal/genitourinary: vomiting, diarrhea, abdominal pain, hepatitis, pancreatitis, and orchitis; (5) eye: AHC and uveitis; (6) heart: myopericarditis; and (7) muscle: pleurodynia and other skeletal myositis. Some syndromes are associated with certain EV serotypes or subgroups, but even these associations are not specific. The same syndrome may also be caused by a number of enteroviral serotypes, and a single enteroviral serotype may cause several different syndromes, even within the same outbreak.

Nonspecific, febrile illness

Most EVs cause a brief febrile illness with no other symptoms or signs. Usually, there is a sudden onset of fever which may last up to 3 days. Biphasic illness, characterized by an initial day of fever and a recurrence 2 to 3 days later for 2 to 4 days, can also be seen. Younger children can have malaise and older children can experience headache or a sore throat. Physical findings are those of a general viral illness, and mild pharyngeal erythema or conjunctivitis may be seen.

Central nervous system infections

Aseptic meningitis

EVs are responsible for >80% of cases of aseptic meningitis, with almost every EV serotype implicated. Although attack rates are generally highest in children, cases also occur in adults. Symptoms of fever, headache, malaise, myalgia, and sore throat are usually followed within a day by signs and symptoms of meningitis, including a more severe headache, photophobia, and stiffness of the neck and back. Nausea and vomiting may occur, especially in children.

The cerebrospinal fluid (CSF) in enteroviral meningitis is usually clear, with a total cell count varying from <10/mm^3 to >3,000/mm^3, but usually averaging 50 to 500/mm^3. Initially neutrophils predominate but are quickly replaced by mononuclear cells within the second day of illness. Pleocytosis may persist for ≥2 weeks or more. Pleocytosis may be absent in up to 30% of infants and children with positive enteroviral reverse transcription-polymerase chain reaction (RT-PCRs) from the CSF. The glucose concentration in CSF is usually normal, although levels of <40 mg/dL are occasionally seen. The protein concentration is normal or slightly elevated but rarely exceeds 100 mg/dL. Fever and signs of meningeal inflammation subside in 3 to 7 days in most children, although symptoms often persist longer in adults. Some cases may be accompanied by a rash, which may be petechial and resemble that of meningococcemia. Most children and adults recover fully without sequelae.

Acute flaccid myelitis

Acute flaccid myelitis (AFM) may occur with nonpolio enteroviral infections. It is similar to but usually less severe than that caused by poliovirus. Muscle weakness is more common than paralysis, and recovery is usually complete, although an occasional patient may develop cranial nerve palsies or severe, sometimes fatal, bulbar involvement. In contrast to paralytic poliomyelitis, which in the prevaccine era occurred in epidemics, cases of paralysis associated with nonpolio EVs are generally sporadic. However, several nonpolio EVs can cause local outbreaks and epidemics of AFM. A variant of Coxsackievirus A7 has caused outbreaks as well as numerous sporadic cases of AFM. Paralytic disease resembling poliomyelitis, with a significant incidence of residual paralysis and muscle atrophy, has been observed in patients with AHC caused by EV-70. EV-A71 has been responsible for large outbreaks of AFM in Eastern Europe, Russia, and Asia.

Since 2014, there have been seasonal, biennial increases in the incidence of AFM cases in the United States. The CDC has reported >600 confirmed cases over that time period. The nationwide increases in AFM in 2014, 2016, and 2018 have coincided temporally and geographically with outbreaks of EV-D68 and EV-A71 infections. Despite the temporal association between EV-D68 and EV-A71 outbreaks and AFM and a mouse model of spinal cord infection and paralysis caused by clinical isolates of EV-D68, the etiology of AFM has been difficult to confirm. Fewer than half of children with AFM have had EV detected in a non-sterile specimen (nasopharyngeal or oropharyngeal swabs most commonly, rectal and stool samples less commonly). In addition, only 2% of children with AFM have EV nucleic acid detected in CSF.

Encephalitis

Encephalitis is an uncommon manifestation of EV infection. Enteroviral infection accounts for only 10% to 20% of the cases of encephalitis of proven etiology in the United States. In most cases, encephalitis complicates the course of aseptic meningitis, with 5% to 10% of patients with aseptic meningitis developing encephalitis. Manifestations range from lethargy, drowsiness, and personality change to seizures, paresis, coma, motor seizures, hemichorea, and acute cerebellar ataxia. Cerebral involvement is usually generalized, but focal encephalitis does occur and may be clinically indistinguishable from herpes simplex encephalitis. Recovery from enteroviral

encephalitis is usually complete, although neurologic sequelae and deaths do occur, especially in young infants and during EV-71 epidemics.

Other reported neurologic complications

EVs, particularly Coxsackie A viruses, appear to be an important cause of febrile seizures in children during EV season. Other neurologic syndromes, including Guillain–Barré syndrome, transverse myelitis, and Reye's syndrome, have been reported in patients with EV infections caused by a number of different serotypes.

Epidemic pleurodynia

Pleurodynia is an acute illness characterized by fever and paroxysmal spasms of the chest and abdominal muscles. Group B Coxsackieviruses, particularly B3 and B5, are the most important causes of epidemic pleurodynia. Clinically, pleurodynia presents with sudden onset of fever accompanied by pain in the chest and abdominal muscles. The chest pain is spasmodic in nature, with spasms lasting 15 to 30 minutes and worsening during inspiration or coughing. The paroxysmal pain is characteristically associated with fever that peaks within 1 hour after onset of each paroxysm and subsides with the subsequent paroxysm. Headache, nausea, and vomiting are also frequently reported.

Acute hemorrhagic conjunctivitis

AHC is an acute, highly contagious, self-limited disease of the eye characterized by sudden onset of pain, photophobia, conjunctivitis, swelling of the eyelids, and prominent subconjunctival hemorrhages. AHC has occurred in explosive epidemics worldwide. During epidemics, all age groups are affected. The most frequent causes of AHC, EV-70 and the Coxsackie A24, are temperature-sensitive and replicate optimally at 33°C/91°F to 35°C/95°F, the temperature of the conjunctivae.

AHC is highly contagious. In contrast to most enteroviral infections, it is transmitted by direct inoculation of the conjunctivae with virus-contaminated fingers or ophthalmologic instruments. Transmission can be prevented by careful handwashing, avoidance of contaminated washcloths and towels, and sterilization of all ophthalmologic instruments.

AHC begins with the sudden onset of eye pain and foreign-body sensation, lacrimation, photophobia, blurred vision, and bulbar conjunctivitis. Signs and symptoms rapidly increase in severity with the development of palpebral conjunctivitis, conjunctival edema, swelling of the eyelids, subconjunctival hemorrhages in the bulbar conjunctivae, and a serous or seromucoid ocular discharge containing large numbers of polymorphonuclear leukocytes. Subconjunctival hemorrhages are the hallmark of the disease. Preauricular lymphadenopathy is an associated finding. AHC often begins unilaterally, but it rapidly spreads to the other eye. Signs and symptoms peak within 24 to 36 hours of onset.

Poliomyelitis-like motor paralysis occurs as a rare complication of AHC caused by EV-70, but not in AHC caused by Coxsackie A24. Paralysis occurs predominantly in adult males and generally does not occur until 2 to 5 weeks after onset of AHC.

Mucocutaneous disease

Enteroviral lesions in the oropharyngeal mucosa and skin are manifestations of a systemic virus infection. Almost all EVs can cause maculopapular eruptions, and most serotypes may cause petechial or papulovesicular exanthems and enanthems. EVs may cause more than one pattern of mucocutaneous disease, even within a single household. Consequently, except for HFMD, which is usually caused by Coxsackie A16 or EV-71, there are no clinical or epidemiologic characteristics of any given EV rash that point to a specific EV as its cause. The vast majority of EV exanthems and enanthems occur during the summer and early fall. The incidence of enanthems and exanthems varies among different EVs and even among different strains of the same EV. Host factors, especially age, are important. Infants and young children are more likely to develop mucocutaneous lesions.

Enanthems

The oropharyngeal mucosa is involved to some degree during most symptomatic enteroviral infections. This is usually manifest by mild pharyngitis and mucosal erythema, but it may also result in a variety of enanthems. These may consist of macules, papules, vesicles, petechiae, or ulcers, and they may occur alone or in association with exanthems and other manifestations of systemic enteroviral infection. They are often transient and frequently unrecognized.

Two unique enanthems are caused by enteroviral infections.

Herpangina

Herpangina is characterized by sudden onset of fever, sore throat, pain on swallowing, and a vesicular enanthem of the posterior pharynx. Outbreaks are common during the summer, and sporadic cases are also observed. Group A Coxsackieviruses account for the majority of outbreaks. Herpangina is most often seen in children between ages 3 and 10 years.

Herpangina begins abruptly with fever, sore throat, and pain on swallowing. Anorexia, vomiting, and abdominal pain may also be seen. Fever tends to be greater in younger children. Older children and adults frequently complain of headache and myalgia.

On examination there is pharyngeal erythema but little or no tonsillar exudate. The characteristic lesions are discrete 1 to 2 mm vesicles and ulcers surrounded by 1 to 5 mm zones of erythema. Lesions are few, averaging 4 to 5 per patient, with a range of 1 or 2 to 20. They occur on the anterior tonsillar pillars, the posterior edge of the soft palate, and the uvula, and, less frequently, on the tonsils, the posterior pharyngeal wall, and the posterior buccal mucosa. They begin as small papules, progress to vesicles, and ulcerate within 24 hours. The shallow ulcers, which are moderately painful, may enlarge over the next 1 or 2 days to a diameter of 3 to 4 mm. Symptoms generally disappear in 3 or 4 days, but the ulcers may persist for up to a week. Most cases are mild and resolve without complications, but herpangina is occasionally associated with exanthems, aseptic meningitis, or other serious manifestations of systemic EV infection.

Herpangina is most often confused with bacterial pharyngitis, tonsillitis, or pharyngitis caused by other viruses. Other considerations include HFMD and primary herpes simplex virus (HSV) infections, particularly acute herpetic pharyngotonsillitis.

Hand-foot-mouth disease

HFMD is a common illness typically affecting children <10 years during the late summer and fall months. It presents as a self-limited febrile illness with malaise, oral ulcerations causing throat or mouth pain, and a vesicular rash on the hands and feet. HFMD begins with fever, malaise, and sore throat. Fever is typically low-grade and resolves in 48 hours. Painful oral lesions begin to appear within 1 to 2 days after onset of fever and are usually located on the tongue, palate, and buccal mucosa. Erythematous oral macules evolve into vesicles that rupture and cause painful ulcerations. Patients may develop dehydration because of refusal to eat and drink because of pain. A vesicular rash subsequently develops on the palms and soles, and also on the buttocks and in the genital region. The skin lesions are often painful. The illness typically resolves within 7 to 10 days. Some patients may exhibit only one or two of the classic findings, such as the oral-cutaneous findings without fever or systemic symptoms.

In children with atopic dermatitis, a vesicular rash concentrated in areas previously or currently affected by the dermatitis has been called *eczema coxsackium*. Eczema coxsackium is clinically indistinguishable from eczema herpeticum. HSV testing should be performed to rule out herpes infection requiring treatment with acyclovir.

Onychomadesis, separation of the proximal nail plate from the nail matrix and nail bed due to arrest of nail matrix growth, was first reported in association with HFMD in 2000. It most often occurs 3 to 8 weeks after HFMD onset. The pathogenesis of onychomadesis in HFMD is not known and may be a direct effect of the viral infection or due to a post viral immunological mechanism. Onychomadesis is usually asymptomatic, and the nails regrow normally within several months.

The vesicular lesions of HFMD resemble those caused by herpes simplex and varicella-zoster viruses. Patients with primary herpetic gingivostomatitis usually have more toxicity, cervical lymphadenopathy, and more prominent gingivitis. Their cutaneous lesions are usually perioral but may occasionally involve a finger, especially in thumb suckers. Recurrent herpes simplex (herpes labialis) usually involves the vermillion border of the lip or the adjacent skin, is rarely accompanied by lesions on the hands or feet, often has a neuralgic prodrome, and frequently has a history of recurrent episodes. The cutaneous lesions of varicella are generally more extensive and are centrally distributed, sparing the palms and soles. Oral lesions are far less prominent in varicella, and its prevalence in winter and spring further distinguish it from HFMD.

In the United States, Coxsackie A16 and EV 71 have been the most common causes of HFMD. Recently Coxsackie A6 has emerged in Asia and in Europe (2008) and in the United States (2011) as a cause of outbreaks of HFMD characterized by an atypical presentation. Patients with Coxsackie A6 HFMD usually have more severe cutaneous involvement, with vesiculobullous lesions involving the dorsum of hands and feet, calves, forearms, trunk, and neck. Involvement of the perioral area is common. Young adults may present with erythematous papulovesicular lesions on the face, oral mucosa, extensor surfaces of the upper and lower extremities, and palms and soles. Confluent, hemorrhagic, and crusted lesions can also be seen on the extremities.

Exanthems

The most common cutaneous manifestation of an enteroviral infection is an erythematous maculopapular rash that appears with fever and other manifestations of systemic infection. Only certain EVs, such as echovirus 9, frequently cause this syndrome, but almost all EVs can cause it occasionally. The rash begins on the face and quickly spreads to the neck, trunk, and extremities. It consists of 1 to 3 mm erythematous macules and papules that may be discrete (*rubelliform*, resembling rubella) or confluent (*morbilliform*, resembling measles). The rash usually lasts for 2 to 5 days and does not itch or desquamate. Enteroviral exanthems are generally not accompanied by significant lymphadenopathy. Enteroviral rashes are sometimes petechial and occasionally purpuric, most frequently in echovirus 9 and Coxsackievirus A9 infections.

Vesicular exanthems are most often seen as a component of HFMD, but several EVs, including echovirus 11, Coxsackievirus A9, and EV-71, may cause vesicular exanthems without an associated enanthem. The lesions resemble those caused by varicella-zoster and HSV. In contrast to varicella, however, vesicular rashes caused by EV are usually peripheral in distribution and consist of relatively few lesions that heal without crusting. When they are not associated with HFMD, vesicular lesions caused by EV are often confused with insect bites or poison ivy. Echovirus 11 and several Coxsackievirus serotypes have been associated with skin lesions resembling papular urticaria.

Enteroviral rashes are generally accompanied by fever and develop at the time of or within 1 or 2 days of fever onset. In some cases, the rash does not develop until the fever subsides, a pattern resembling that of *roseola infantum* (exanthem subitum) caused by human herpesvirus 6.

Enteroviral enanthems and exanthems are generally benign, self-limited illnesses that require only symptomatic therapy for headache and sore throat. While EV exanthems are benign, they may be confused with other diseases that may have more serious consequences and require specific control measures and/or anti-infective therapy. When enteroviral rashes are maculopapular they may be confused with drug reactions; when they are petechial, they may be confused with bacterial or rickettsial rashes. When enteroviral rashes are petechial or purpuric, it is impossible to rule out meningococcemia on clinical grounds alone, and when the rash is associated with aseptic meningitis, it is clinically indistinguishable from meningococcal meningitis.

Maculopapular exanthems caused by EV are distinguished from measles and rubella by their summertime occurrence; the usual absence of posterior cervical, suboccipital, and postauricular lymphadenopathy; and their relatively short incubation period. The absence of significant coryza and conjunctivitis further distinguishes the typical enteroviral exanthem from measles. In addition, the probability of measles and rubella is markedly reduced by appropriate immunization. When illness mimics meningococcemia or meningococcal meningitis, antimicrobial chemotherapy should be initiated until bacterial infection is ruled out.

Myocarditis/Pericarditis

EVs are a major infectious cause of myocarditis and pericarditis. Age is an important factor in disease presentation. Neonatal infections frequently result in severe myocarditis, widespread involvement of other organs, and high mortality. In older children and adults, pericarditis often predominates, and the disease is generally benign and self-limited. Most cases occur in males, but in females the risk of cardiac involvement is increased during pregnancy and immediately postpartum.

The most common symptoms of enteroviral myopericarditis are dyspnea, chest pain, fever, and malaise. Precordial pain may be sharp or dull and is often exacerbated by lying down. A pericardial friction rub, if present, is transient. Signs of congestive heart failure are present in 20% of cases.

Endomyocardial biopsy, with in situ hybridization and RT–PCR, has improved identification of the infectious etiology of myocarditis and pericarditis. The group B Coxsackieviruses have been the most common etiologic agents identified, accounting for 50% of sporadic cases of acute myocarditis and for all cases in epidemics. Human adenoviruses, dengue, and parvovirus B19 are other important causes of myocarditis. Group B Coxsackieviruses account for 30% or more of sporadic cases of acute nonbacterial pericarditis.

Treatment of EV myopericarditis is supportive. It includes control of pain and monitoring for arrhythmias, heart failure, and hemodynamic compromise. Bed rest is an important component of therapy because of evidence in mice with Coxsackievirus B3 myocarditis that exercise increases myocardial necrosis and mortality during the acute disease. Corticosteroids should not be administered since their use during the acute phase of viral myocarditis has been associated with rapid clinical deterioration.

The majority of children and adults with enteroviral myopericarditis recover without sequelae. Acute mortality is low (0–5%), and deaths result from arrhythmias or congestive heart failure in patients with myocarditis. Cardiac tamponade is extremely rare in enteroviral pericarditis.

Approximately 20% of patients experience one or more episodes of recurrent myopericarditis within 1 year of their initial illness, and persistent electrocardiographic (ECG) abnormalities are observed in 10% to 20% of patients. Cardiomegaly persists in 5% to 10% of patients, and long-term follow-up suggests that ≥10% may develop chronic cardiomyopathy. Constrictive pericarditis rarely occurs following enteroviral pericarditis.

Respiratory infections

A number of EVs have been associated with mild upper respiratory tract illness in children and adults, especially Coxsackieviruses A21, A24, and B1 through B5 and echoviruses 9 and 11. Many produce illnesses that resemble the common cold. In contrast to most other EVs, Coxsackievirus A21 is shed primarily from the upper respiratory tract rather than in feces. EVs have also been associated with tracheitis, bronchitis, croup, bronchiolitis, and pneumonia in children. Surveillance data indicate that EVs account for 2% to 10% of viral respiratory disease and that 10% to 15% of symptomatic EV infections are associated with respiratory symptoms. The respiratory illnesses caused by EVs are clinically indistinguishable from similar illnesses caused by viruses more commonly considered to be respiratory tract pathogens, such as rhinoviruses, influenza viruses, parainfluenza viruses, respiratory syncytial virus, and adenoviruses. However, infections with these viruses occur most frequently during the winter, whereas EV infections occur primarily in the summer and early fall.

EV-D68 was responsible for a large multinational outbreak of respiratory disease in 2014. Disease was characterized by exacerbation of preexisting asthma or new-onset wheezing in children without any history of asthma, often requiring hospitalization and, in some patients, intensive care.

Infections in special hosts

Neonatal infections

Neonates whose mothers develop an enteroviral infection in the perinatal period are at high risk for disseminated disease, especially if this is the mother's primary infection with the infecting serotype. Most neonatal infections are caused by Echoviruses 6, 9 and 11, or Coxsackievirus B 1–5. Neonatal enteroviral infections present in the first week of life and can cause a wide range of clinical disease. Milder infections may present as a nonspecific febrile illness, rash, or aseptic meningitis. More severe manifestations of neonatal infection include viral sepsis, meningoencephalitis, myocarditis, hepatitis, coagulopathy, and pneumonitis. The outcome is influenced by the presence or absence of maternal antibody to the infecting serotype. Lack of antibody is associated with severe disease. Neonatal enteroviral infections must be distinguished from neonatal bacterial sepsis and disseminated neonatal herpes simplex infections.

Infection in immunocompromised hosts

Patients with humoral and combined immune deficiencies can develop persistent central nervous system (CNS) infections, a dermatomyositis-like syndrome, and/or disseminated infection. Severe neurologic and/or multisystem disease is reported in hematopoietic stem cell and solid organ transplant recipients, children with malignancies, and patients treated with anti-CD20 monoclonal antibody. ECHO 11 is responsible for most chronic infections. Clinically, these infections most often manifest as chronic meningoencephalitis. The presentation is often insidious, with initial symptoms of headache, fatigue, and mild neck stiffness or seizures. Symptoms may fluctuate in severity and may disappear completely or slowly progress. CSF studies show persistent pleocytosis with a high protein. The prognosis is poor.

Maintenance administration of intravenous immunoglobulin (IVIG) in patients with severe combined immunodeficiency syndrome or X-linked agammaglobulinemia may prevent chronic enterovirus infection of the CNS.

Diagnosis

Diagnosis of enteroviral disease is often clinical. Laboratory diagnosis is usually unnecessary but is warranted when identification of the causative organism has management implications, as in some CNS infections, myopericarditis, neonatal infection, and infections in immunocompromised patients, or when there are public health implications.

RT-PCR is the most frequently used modality for enterovirus detection. PCR is more sensitive than isolation of EVs in cell culture for CSF and respiratory secretions. Depending on the symptoms, other specimen types such as blister fluid and blood can be collected for testing. PCR can detect all serotypes of EVs, including serotypes that are difficult to cultivate in viral culture. A positive PCR test for EVs from specimens, such as stool or respiratory secretions, does not necessarily mean the virus is the cause of infection because EVs can be shed for several weeks after the symptoms have resolved.

RT-PCR assays for detection of enterovirus RNA are available at many reference and commercial laboratories for CSF, blood, and

other specimens. There are four commercially available multiplex PCR assays for respiratory secretions which identify rhino and EVs. However, these assays do not distinguish EVs from rhinoviruses and at least one identifies rhinoviruses only. EV-D68 is demonstrated primarily in respiratory tract specimens and can be detected with most multiplex respiratory RT-PCR assays. Definitive identification of EV-D68 requires partial genomic sequencing or amplification by an EV-D68-specific RT-PCR assay.

In the past, viral culture was used for isolation of EVs from tissues or body fluids. Currently, cell culture–based methods are useful when isolate serotyping is important for investigation of disease clusters or outbreaks. Most hospital laboratories no longer maintain cell culture capability so viral culture is done primarily at state public health laboratories or the US Centers for Disease Control and Prevention (CDC). EVs grow rapidly in culture and exhibit a cytopathic effect in 3 to 8 days. The serotype of enterovirus may be identified either by partial genomic sequencing or by serotype-specific antibody staining or neutralization assay of a viral isolate. A variety of specimens, including stool, rectal swabs, throat swabs, nasopharyngeal aspirates, conjunctival swabs, tracheal aspirates, blood, urine, and tissue biopsy specimens, and CSF may be used for culture. Sensitivity of culture ranges from 0% to 80% depending on serotype and cell lines used. Many group A Coxsackieviruses grow poorly or not at all in vitro.

Serology is of limited use in diagnosing enteroviral infections.

Treatment

There are no specific antiviral agents available to treat enteroviral infections. The mainstay of therapy continues to be supportive care. Pleconaril, an antiviral developed to treat enteroviral and rhinoviral infections, has been evaluated in studies treating neonatal enteroviral sepsis and meningitis in adults but is currently not licensed or available in the United States. Pocapavir, another antiviral drug being developed primarily for the treatment of polioviruses, has activity against some EVs, but it also is not commercially available.

IVIG, administered intravenously or via intraventricular administration, may be beneficial for chronic enterovirus meningoencephalitis in immunodeficient patients. IVIG also has been used for life-threatening neonatal enterovirus infections (maternal convalescent plasma has also been used), severe enterovirus infections in transplant recipients and people with malignancies, suspected viral myocarditis, and EV-71 neurologic disease, but proof of efficacy for these uses is lacking.

The CDC has developed a comprehensive website for assessing and managing patients with acute flaccid myelitis (www.cdc.gov/acute-flaccid-myelitis/hcp/index.html).

Infection control and prevention

Simple measures, such as hand washing, are important to prevent the spread of EVs. As with other non-enveloped viruses, alcohol-based hand sanitizers may not be optimally effective.

In hospitalized patients, standard precautions are indicated. Contact precautions are indicated for infants and young children for the duration of enterovirus illness. Droplet precautions also are indicated for EV-D68 respiratory infections.

Hand hygiene, especially after diaper changing, and respiratory hygiene/cough etiquette (particularly for EV-D68) are important in decreasing the spread of EVs within families and institutions. Other measures include avoidance of contaminated utensils and fomites and disinfection of surfaces. Chlorination of drinking water and swimming pools may help prevent transmission.

Effective vaccines against non-polio EVs are not yet clinically available outside of China. Three inactivated EV-A71 vaccines are licensed in China and have demonstrated high efficacy in randomized clinical trials against the predominant genotype circulating in that country. The efficacy of these vaccines in other parts of the world, where other genotypes predominate, is unknown. Vaccines for other enterovirus serotypes associated with more severe disease are under investigation.

Suggested reading

Cherry JD, Krogstad P. Enteroviruses, parechoviruses, and saffold viruses. In Cherry JD, Gail J. Harrison GJ, Kaplan SL, Steinbach WJ, Hotez PJ eds. *Feigin and Cherry's textbook of pediatric infectious diseases*, 8th ed. Elsevier; 2019:1499–1544.

Cohen JI. Enterovirus, parechovirus, and reovirus infections. In Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. *Harrison's principles of internal medicine*, 20th ed. McGraw-Hill; 2018.

Hixon AM, Frost J, Rudy MJ, Messacar K, Clarke P, Tyler KL. Understanding enterovirus D68-induced neurologic disease: A basic science review. *Viruses*. 2019;11(9):821.

Kimmis BD, Downing C, Tyring S. Hand-foot-and-mouth disease caused by coxsackievirus A6 on the rise. *Cutis*. 2018;102(5):353–356.

Lin JY, Kung YA, Shih SR. Antivirals and vaccines for Enterovirus A71. *J Biomed Sci*. 2019;26(1):65.

Messacar K, Modlin JF, Abzug MJ. Enteroviruses, parechoviruses. In Long SS, Prober CG, Fischer. eds. *Principles and practice of pediatric infectious diseases*, 5th ed. Elsevier; 2018:1205–1213.

Messacar K, Abzug MJ, Dominguez SR. 2014 outbreak of enterovirus D68 in North America. *J Med Virol*. 2016;88(5):739–745.

Pons-Salort M, Grassly NC. Serotype-specific immunity explains the incidence of diseases caused by human enteroviruses. *Science*. 2018;361(6404):800–803.

Pons-Salort M, Oberste MS, Pallansch MA, et al. The seasonality of nonpolio enteroviruses in the United States: Patterns and drivers. *Proc Natl Acad Sci U S A*. 2018;115(12):3078–3083.

Romero JR. Coxsackieviruses, echoviruses, and numbered enteroviruses (EV-A71, EVD-68, EVD-70). In Bennett JE, Dolin R, Blaser MJ. eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 9th ed. Elsevier; 2020:2227–2237.

Romero JR. Introduction to the human enteroviruses and parechoviruses. In Bennett JE, Dolin R, Blaser MJ. eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 9th ed. Elsevier; 2020:2213–2219.

Suresh S, Forgie S, Robinson J. Non-polio enterovirus detection with acute flaccid paralysis: A systematic review. *J Med Virol*. 2018;90(1):3–7.

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Epstein-Barr virus and other causes of the infectious mononucleosis syndrome

Jeffrey L. Meier

Epstein–Barr virus (EBV) is a gammaherpesvirus that will infect nearly everyone at some point during his or her lifetime. In a representative cohort of the United States population from 2003 to 2010, approximately 85% of non-Hispanic black and Mexican American children and 52% of non-Hispanic white children had already acquired EBV by age 14. An estimated 90% to 95% of all persons will have acquired EBV by the end of their third decade of life. Lower socioeconomic status increases likelihood of acquiring EBV in childhood.

Oropharyngeal epithelial cells (e.g., in tonsillar crypts) are the source of infectious EBV in saliva. Close oral contact with infectious saliva is the primary mode of EBV transmission. Deep kissing during sexual intimacy that ordinarily begins in adolescence and early adulthood increases EBV transmission risk. Casual contact does not transmit the infection. EBV-seropositive donor blood products and tissues may transmit infection when EBV reactivates from latently infected B lymphocytes.

Infectious mononucleosis

Presentation

Most EBV infections go unnoticed. EBV-related disease, should it develop, varies in presentation (Box 183.1). Infectious mononucleosis (IM) is the paradigmatic illness most commonly ascribed to EBV. This is an acute or subacute illness occurring 5 to 7 weeks after EBV is initially acquired (primary infection) and corresponds to an overly exuberant immunologic reaction. Rates of IM are highest for adolescents and young adults aged 15 to 25, and 50% to 80% of susceptible college students experience an IM-like illness after a primary EBV infection. Infants and young children seldom exhibit a classical IM illness after a primary EBV infection. Older adults retain the ability to develop the illness, but most persons in this age group have already been EBV-infected.

The EBV IM diagnosis generally rests on identifying a distinctive combination of clinical symptoms and signs, characteristic abnormalities on a CBC with differential, and presence of heterophile antibody in blood (Table 183.1). EBV is highly likely to be the cause of the IM syndrome in patients presenting with the clinical triad of fever, pharyngitis, and cervical lymphadenopathy; absolute peripheral lymphocytosis; atypical lymphocytosis that is >10% of the differential; and heterophile antibodies that are detected by the mononucleosis spot (Monospot) test. As these criteria are relaxed, the probability of EBV as the cause of the illness decreases commensurately. Notably , the acute illness from a primary EBV infection commonly does not fulfill all these criteria. The IM case definitions applied in contemporary prospective studies of primary EBV infection and EBV candidate vaccines have been fashioned to only require the presence of two or more typical symptoms (e.g., sore throat, cervical lymphadenopathy, fever, or fatigue) in conjunction with EBV-specific serological evidence of an acute EBV infection. Although the result of a heterophile antibody

BOX 183.1

Epstein–Barr virus (EBV)-related disease

Acute
- Infectious mononucleosis (IM)
- Atypical IM presentations or complications

Chronic
- Chronic active infection (rare)
- Oral hairy leukoplakia

Lymphoproliferative disorders
- From congenital or acquired immunosuppression
- X-linked (Duncan disease)

Other disorders
- African Burkitt's lymphoma
- Nonkeratinizing nasopharyngeal carcinoma
- Primary central nervous system lymphoma in AIDS
- Rare types of smooth muscle cell tumors and thymomas
- Hodgkin's disease (EBV DNA in 40%–65% of tumors)

Abbreviations: EBV = Epstein–Barr virus; AIDS = acquired immunodeficiency syndrome.

test is commonly sought in clinical practice to support the clinical diagnosis of EBV IM, heterophile antibodies are not detected in 5% to 20% of EBV IM cases, may not become detectable until later in the illness, and are rarely detected in non–EBV-related medical conditions. Atypical lymphocytosis may also not be appreciable until later in the illness. Unusual clinical presentations are more likely to occur in infants, young children, older adults, and immunosuppressed persons.

Malaise and fatigue are often prominent IM symptoms, may take more time to resolve than other symptoms, and tend to linger for longer periods in patients having higher severity of acute illness. Fatigue and impaired functional status occasionally extend to 6 months after the acute illness. The chronic fatigue is not because of ongoing EBV activity or reflected in findings on physical examination, EBV-specific serologies, or other clinical laboratory tests. Sore throat and enlarged cervical lymph nodes are also very common in IM. Mild retro-orbital headache is common and short-lived. Body aches and upper respiratory tract symptoms may be present.

Fever in the range of 38°C/100.4°F to 39.5°C/103°F (+/− sweats and chills) is common, subsides in 1 to 2 weeks, and rarely persists for up to 4 weeks. Fever >40°C/104°F should prompt a search for superimposed bacterial infection (i.e., bacterial pharyngitis or peritonsillar abscess). The physical exam finding of exudative tonsillopharyngitis is a common in EBV IM and usually resolves in the first 2 weeks of illness. Petechiae may appear on the uvula and at the junction of soft and hard palates. The detection of bilateral posterior cervical lymphadenopathy elevates EBV IM in the differential diagnosis, whereas a wide variety of etiologies produce anterior cervical lymphadenopathy. EBV IM-related lymphadenopathy may take several weeks to resolve. Splenomegaly is common. Mild abdominal discomfort may be present. Severe abdominal pain or left upper quadrant abdominal pain radiating to the left shoulder raises concern of splenic rupture or infarction. Rash is infrequent in adolescents and adults unless they are given ampicillin. The EBV IM rash typically appears as a faint morbilliform eruption. Periorbital or eye lid edema may also be observed but occurs infrequently. Laboratory findings of mild to moderate hepatitis are common, and transaminase levels of >500 IU/L and jaundice are possible. Peripheral blood lymphocytosis often peaks during the second or third week of illness. Mild neutropenia and thrombocytopenia are also common.

In elderly persons, the illness of primary EBV infection is less likely to include pharyngitis, lymphadenopathy, splenomegaly, and atypical lymphocytosis and is more likely to have unusual features (i.e., jaundice or prolonged febrile course). Infants and young children are more likely to have a heterophile-negative illness with coryza, exudative pharyngitis, rash, and hepatosplenomegaly.

TABLE 183.1 **CLINICAL AND LABORATORY FINDINGS IN UNCOMPLICATED EPSTEIN–BARR VIRUS (EBV) INFECTIOUS MONONUCLEOSIS**

Percentage of patients	>50%	10–50%	≤10%
Symptoms	Sore throat, malaise, fatigue, swollen lymph nodes in neck, headache, sweats	Decreased appetite, body aches, chills	URI symptoms, cough, arthralgias, abdominal discomfort
Signs	Lymphadenopathy, fever, pharyngitis	Splenomegaly, hepatomegaly,	Rash, jaundice, palatal petechiae, periorbital edema, oral or genital ulcers
Labs	>50% mononuclear cells	Mild neutropenia	Bilirubinemia >3 mg/100 mL
	>10% atypical lymphocytes	Antinuclear antibodies	Hematuria
	Heterophile antibodies	Rheumatoid factor	Pyuria
	Mild LFT increase	Cardiolipin antibodies	Proteinuria
	Mild thrombocytopenia		
	Cold agglutinins		

Abbreviation: LFT = liver function test.

Complications

Approximately 1% of persons with EBV IM experience a complication. Various types of complications are possible (Box 183.2). In some cases, the complication overshadows the other IM features or is not accompanied by typical IM symptoms or signs. Most complications resolve without sequelae. Rare fatalities have resulted from encephalitis, splenic rupture, hepatic failure, myocarditis, or neutropenia-associated sepsis. Impending airway obstruction results from tonsillar lymphoid hyperplasia and edema. Enlarged spleens are susceptible to traumatic rupture; spontaneous rupture or infarction is rare. Hemolytic anemia, thrombocytopenia, or neutropenia may develop in relation to autoantibody production. Cytopenia is usually self-limiting. Aplastic anemia and hemophagocytic lymphohistiocytosis (HLH) are rare, life-threatening complications. Neurologic complications take on forms of encephalitis, cerebellitis, meningitis, optic neuritis, peripheral neuritis, facial nerve palsy, and Guillain–Barré syndrome. Chronic fatigue syndrome may sometimes follow an acute EBV IM episode, but this is not driven by ongoing EBV activity.

BOX 183.2

Complications of infectious mononucleosis

Neurologic
Encephalitis, meningitis, cerebellitis, Guillain–Barré syndrome, Bell's palsy, optic neuritis, psychosis, polyradiculitis, transverse myelitis, Reye's syndrome

Splenic
Rupture of enlarged spleen (traumatic or spontaneous), splenic infarction

Respiratory
Upper airway obstruction from hypertrophy of lymphoid tissue, interstitial pneumonitis

Hematologic
Autoimmune hemolytic anemia, severe thrombocytopenia, agranulocytosis, aplastic anemia, hemophagocytic syndrome

Hepatic
Fulminant hepatitis, hepatic necrosis

Cardiac
Myocarditis, pericarditis

Immunologic
Anergy, lymphoproliferative syndromes, hypogammaglobulinemia

Dermatologic
Cold-mediated urticaria, leukocytoclastic vasculitis, ampicillin-associated rash, erythema multiforme, erythema nodosum

Other
Chronic fatigue syndrome

EBV IM may evolve into a life-threatening lymphoproliferative disorder in solid organ and hematopoietic stem cell transplant recipients with profound cellular immunodeficiency. In a rare inherited X-linked lymphoproliferative disease, young males with a mutated signaling lymphocyte activation molecule-associated protein gene develop fulminant EBV IM or HLH. Survivors may be afflicted with aplastic anemia, hypogammaglobulinemia, and lymphoma. Other rare genetic defects have also been linked to life-threatening EBV-associated lymphoproliferative disorders or HLH. EBV very rarely causes a chronic active infection that results in interstitial pneumonitis, massive lymphadenopathy, hepatosplenomegaly, bone marrow failure, dysgammaglobulinemia, Guillain–Barré syndrome, and uveitis. These patients have high EBV burden in blood or tissues, as well as very high titers of EBV-specific antibodies.

Laboratory testing

Serum heterophile immunoglobulin M (IgM) antibodies of the Paul–Bunnell–Davidsohn type are a proxy indicator of EBV IM. These antibodies are distinguishable from Forssman and serum sickness heterophile antibodies (that also bind to animal red blood cell components), may not be detected until the second or third week of illness, and fade away in 3 to 6 months. Their levels do not correlate with severity of illness. Rarely do present-day heterophile antibody tests yield false-positive results, which have been reported to occur in settings of viral hepatitis, primary HIV infection, malaria, babesiosis, autoimmune diseases, and lymphoma.

EBV-specific antibody testing is how EBV IM is definitively diagnosed in the immunocompetent patient population. Measurements of antibodies against viral capsid antigen (anti-VCA) and EBV nuclear antigens (anti-EBNA) usually provide the information needed to confirm or reject the primary EBV infection diagnosis. Detection of anti-VCA IgM supports the diagnosis because it is present in 85% to 95% of acute EBV IM cases, fades away in weeks to months after the acute illness, and generally does not re-present once gone. The occasionally encountered false-positive anti-VCA IgM result makes this assay an imperfect stand-alone test for the definitive diagnosis of a primary EBV infection. Primary cytomegalovirus (CMV) infection is another cause of the mononucleosis syndrome in a normal host that sometimes produces EBV VCA IgM positivity as a result of either nonspecific IgM reactivity or EBV immune-reactivation. Finding undetectable levels of anti-EBNA antibodies in conjunction with presence of anti-VCA IgM substantiates the primary EBV infection diagnosis because anti-EBNA antibodies usually do not become detectable until convalescence and then persist for life. Seroconversion in anti-VCA IgG status from negative to positive between the times of acute illness and convalescence, respectively, is confirmation of the diagnosis. However, anti-VCA IgG is often near peak level during the acute illness and persists for life. This renders the detection of anti-VCA IgG seroconversion an uncommon option. Presence of VCA IgM, VCA IgG, and anti-EBNA antibodies is consistent with EBV immune reactivation or prior EBV infection with a false-positive VCA IgM result.

Interpret the levels of EBV-specific antibodies cautiously because these values differ by method used and are confounded by certain

types of preexisting or coincident conditions. Performing EBV-specific antibody tests in immunosuppressed patient populations may produce misleading or ambiguous results.

When the acute EBV infection of an immunocompetent person yields inconclusive EBV-specific serology results, the detection of EBV DNA in serum or plasma by quantitative nucleic acid testing (QNAT) may aid in arriving at an EBV IM diagnosis. This is because EBV IM releases EBV DNA in serum or plasma that does not circulate for long in otherwise healthy people, unlike the EBV DNA in whole blood that also consists of latent EBV genomes that persist. Although an international World Health Organization (WHO) standard reference for EBV DNA quantification has helped standardize results of different EBV QNAT methods, major questions remain about the positive and negative predictive values of the different EBV QNATs used in clinical practice. QNAT-based measurements of EBV DNAemia levels are commonly used in immunocompromised patients to predict presence of or manage EBV-related lymphoproliferative disorders.

Other causes of mono syndrome

An infectious mononucleosis-like (mono) syndrome may result from other etiologies. This is reflected in the International Classification of Diseases (ICD-10, 2019) Diagnosis Codes of Other infectious mononucleosis (B27.8), Infectious mononucleosis, unspecified (B27.9), and Cytomegalovirus mononucleosis (B27.1). EBV IM is coded as Gammaherpesviral mononucleosis (B27.0). Acute infections with CMV, toxoplasma, HIV, rubella, hepatitis viruses, and other etiologies of acute pharyngitis are often considered in the list of possible causes of the mono syndrome. Clinical and nonspecialized laboratory findings may help distinguish these other etiologies from EBV (Table 183.2). However, the definitive diagnosis usually rests on the results of pathogen-specific laboratory tests (Table 183.3). EBV should be included in the differential diagnosis of a heterophile-negative mono syndrome.

Primary CMV infection accounts for the majority of heterophile-negative mono episodes (see Chapter 180, "Cytomegalovirus"). CMV mono may closely resemble EBV IM. Both CMV and EBV characteristically produce fever, hepatitis, and atypical lymphocytosis. In CMV mono, cervical lymphadenopathy and pharyngitis tend to be milder, and exudative tonsillitis is uncommon. Atypical lymphocytosis is more common in EBV IM than in CMV mono. Primary CMV infection in the immunocompetent person is confirmed by serologic evidence of a positive anti-CMV IgM plus low-avidity anti-CMV IgG index or CMV IgG seroconversion. Detection of CMV DNA in peripheral blood also supports the diagnosis.

TABLE 183.2 **DIFFERENTIAL DIAGNOSIS OF MONONUCLEOSIS-LIKE SYNDROME**

Variables	EBV	CMV	Toxoplasma	HIV	Bacterial[a] and respiratory virus[b] pharyngitis	Rubella	HAV, HBV, HCV
Fever	++	++	+	++	++	+	++
Sore throat	++	+	+	++	++ Abrupt	+/− Coryza	−
Exudative pharyngitis	+	+/−	−	+/− Aphthous ulcers	+	−	−
Anterior cervical LN	++	+	++	++	++	+	+/−
Posterior cervical LN	++	+	++	++	+/− Mild	++	+/−
Rash	+/− But common with ampicillin	+	+/−	++	+/− Scarlatiniform	++	+/−
Hepatitis	++	++	+	+	−	+/−	++
Jaundice	+/−	+/−	−	−	−	−	++
Splenomegaly	++	+	+/−	+/−	−	+/−	+
Atypical lymphs	++	++	+ ≤10% of cells	+/− ≤10% of cells	−[a] +/− ≤10% of cells[b] (adenovirus, parvovirus B19)	+/− ≤10% of cells	+ ≤10% of cells
Heterophile antibodies	++ absent in ≥10%	−	−	−	−	−	−

Key: ++ = , present in >50% of cases; + = , present in 10% to 50% of cases; +/− = , present in <10% of cases; − = , absent or rare.
Abbreviations: EBV = Epstein–Barr virus; CMV = cytomegalovirus (glandular fever); HIV = human immunodeficiency virus (acute retroviral syndrome); HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; LN = lymphadenopathy; lymphs = peripheral lymphocytes.
[a] Primarily β-hemolytic streptococci (group A, C, and G); consider diphtheria, *Arcanobacterium haemolyticum*, *Neisseria gonorrhoeae*, mycoplasma, fusobacterium, and Vincent's angina.
[b] Influenza, adenovirus, parainfluenza, rhinovirus, metapneumovirus, and coronavirus.

TABLE 183.3 **DIAGNOSTIC STUDIES IN MONONUCLEOSIS-LIKE SYNDROME**

Variables	EBV	CMV	Toxoplasma	HIV	Bacterial[a] and respiratory virus[b] pharyngitis	Rubella	HAV, HBV, HCV
Antibody response: acute[c]	+ Heterophile + IgM VCA +/− anti-EA − anti-EBNA	+ IgM CMV, low-avidity CMV IgG	+ IgM Toxo, low-avidity Toxo IgG	− HIV Ab	None	+ IgM rubella	+ IgM HAV, + IgM HBc, − HCV Ab
Antibody response: convalescent	+/− fourfold increase IgG VCA +/− anti-EA (EIA) + anti-EBNA (EIA)	+ fourfold increase IgG CMV	+ IgG Toxo seroconversion (several test-types available)	+ HIV Ab +Confirmatory immunoblot or multispot	+ Elevated or rising ASO or anti-DNase B[a] + fourfold increase IgG influenza[b]	+ Fourfold increase IgG rubella	+ IgG HAV, + or − anti-HBs + IgG HBc, + HCV Ab
Nucleic acid or antigen detection	None	+/− CMV DNA in blood WBC or DNA in plasma	None	+ plasma HIV RNA PCR +/− p24 Ag	+ Rapid Strept test[a], N. gonorrhea PCR, Respiratory virus panel PCR[b] Influenza antigen	None	+ HBs Ag + plasma HCV RNA PCR
Culture	Impractical	+ Urine, saliva	Impractical	Impractical	+ Throat swab, blood agar[a]	Impractical	None

Key: + = typically present; +/− = sometimes present; − = usually absent.
Abbreviations: EBV = Epstein–Barr virus; CMV = cytomegalovirus; Toxo = toxoplasma; HIV = human immunodeficiency virus; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; VCA = EBV viral capsid antigens; EA = EBV early antigens; EBNA = EBV nuclear antigens; EIA = enzyme-linked immunoassay; HBc = HBV capsid antigens; HBs = HBV surface antigen; p24 = HIV core protein; PCR = polymerase chain reaction.
[a] Applies primarily to group A streptococcus; special media required to culture *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae*, and *Arcanobacterium haemolyticum*.
[b] Applies primarily to influenza virus, adenovirus, metapneumovirus, picornaviruses (non-polio enteroviruses and rhinovirus), and parainfluenza viruses.
[c] IgM and heterophile status determined with acute serum. Paired acute and convalescent sera are best analyzed simultaneously to accurately determine change in antibody titer but this is usually not practicable.

Acute retroviral syndrome (ARS) caused by primary HIV infection may manifest as a mono syndrome. In ARS, rash is anticipated, exudative pharyngitis is infrequent, tonsillar hypertrophy is minimal, and oral or genital ulcers are sometimes observed. A transient peripheral lymphopenia may be followed 2 to 3 weeks later by lymphocytosis, in which a small proportion of cells may be reactive. Detection of HIV RNA or p24 antigen in blood in conjunction with a negative or indeterminate HIV antibody result is indicative of a primary HIV infection.

Streptococcal pharyngitis is more frequently abrupt in onset compared to that of EBV pharyngitis. Viruses of various types, such as respiratory viruses and non-polio enteroviruses, are the most common cause of acute pharyngitis. These viral etiologies, like the bacterial causes of acute pharyngitis, do not typically produce hepatosplenomegaly, atypical lymphocytosis, or prominent posterior cervical lymphadenopathy. Adenovirus is an exception in causing of mono-like symptoms in young children that can be accompanied by atypical lymphocytosis. Toxoplasma-induced mono syndrome is uncommonly encountered in the United States and does not produce exudative pharyngitis or peripheral atypical lymphocytosis exceeding 10% of the differential. Rubella also presents with fever and lymphadenopathy, but the characteristic combination of rash, coryza, arthralgias, and minimal atypical lymphocytosis helps distinguish the German measles from EBV IM. The hepatitis viruses A to E are usually not accompanied by a bothersome pharyngitis or a marked lymphadenopathy. Acute mono-like illness has also been described for etiologies of human herpesvirus 6 (HHV-6), herpes simplex virus, parvovirus B19, West Nile virus, tick-borne diseases, lymphohematologic disorders, and systemic drug reactions (e.g., phenytoin, carbamazepine, minocycline, and sulfa drugs).

Management

Epstein–Barr virus

The management of EBV IM rarely demands more than general supportive care, which includes adequate rest, hydration, antipyretics, and analgesics. Acetaminophen is commonly used. Aspirin should be avoided because of the potential risk of bleeding or thrombocytopenia. Complications of IM may require additional supportive measures (e.g., maintenance of airway during obstructive tonsillar enlargement or encephalitis, transfusions for severe hemolytic anemia or thrombocytopenia, splenectomy for splenic rupture_. Activity should be restricted in proportion to the degree of symptoms and any splenomegaly. Most students can return to school in less than 2 to 3 weeks.

Enlarged spleens are structurally weakened by mononucleosis and at risk of rupture by trauma. Reported cases of splenic

rupture have almost always occurred within the first month after illness onset, though splenic rupture at 7 weeks has been reported. Ultrasonography detects splenomegaly that is not appreciated on physical examination, and nonpalpable splenomegaly usually resolves in 4 to 6 weeks. This supports expert opinion that contact sports should be avoided for 4 to 6 weeks after symptom onset or until absence of splenomegaly is verified. A 2008 consensus statement in sports medicine warns against using one-time ultrasonography imaging for determining presence of splenomegaly and risk of rupture. Normal spleen size may be larger for tall athletes, and spleen size in IM-associated splenomegaly may not exceed the normal range. In a prospective study, serial use of ultrasonography in 17 college-aged athletes with EBV IM revealed splenic enlargement in all subjects that peaked within 23 days from time of symptom onset (mean 12.3 days; standard deviation [SD] 5.3 days), and subsequently decreased in size at approximately 1% per day on average. While serial use of ultrasonography may increase accuracy in determining the time-frame for resolution of splenomegaly, the cost-effectiveness and reliability of this strategy have been questioned. The athlete (or legally authorized representative) should be informed about issues pertaining to risk of splenic rupture when deciding together whether he or she can return to contact sports.

EBV IM-associated exudative tonsillopharyngitis commonly leads to a search for β-hemolytic streptococci. Anywhere from 3% to 30% of surveillance throat cultures obtained during IM grow group A streptococci, reflecting the range in prevalence of community streptococcal carriage. Up to 30% of individuals harboring this bacterium eventually show serologic evidence of streptococcal infection. Streptococcal pharyngitis is treated with penicillin V (500 mg BID) for 10 days or an alternative antibiotic selected according to recommendations issued by the Infectious Disease Society of America (IDSA) Practice Guidelines, which are publically accessible. This treatment also prevents poststreptococcal sequelae. One retrospective study concluded that EBV IM does not increase the risk of rash from oral amoxicillin, unlike early reports for ampicillin.

Acyclovir, ganciclovir, and foscarnet inhibit EBV replication during lytic infection but do not inhibit amplification of latent EBV genomes in proliferating B cells. Acyclovir and valacyclovir, an orally administered prodrug of acyclovir, inhibit oropharyngeal shedding of EBV in persons with IM, but the shedding resumes after discontinuation of the antiviral agent. Antiviral therapy is not clinically beneficial in acute EBV IM, and the proportion of circulating B cells containing EBV is not consistently reduced. Some clinicians may use antiviral therapy as an adjunct to corticosteroid therapy for life-threatening complications of EBV IM.

Use of a corticosteroid for treatment of uncomplicated IM is not recommended. Several small controlled trials of varying design have not consistently found corticosteroids to be clinically beneficial and have not fully addressed their potential adverse effects. Studies showing benefit reveal modest reduction in duration of fever and tonsillopharyngeal symptoms. In a double-blinded, placebo-controlled study, the combination of prednisolone and acyclovir did not significantly decrease duration of IM symptoms. Corticosteroids have not been shown to decrease lymphadenopathy or hepatosplenic disease. Rare anecdotal reports have associated corticosteroid use with encephalitis, myocarditis, and peritonsillar abscess. The possibility of corticosteroid adversely affecting long-term immunity or number of latently infected cells with malignancy potential is a theoretical concern that has not been adequately addressed.

Corticosteroids appear to be useful in the management of certain IM complications. Corticosteroids may quickly ameliorate impending airway obstruction from tonsillar enlargement. A short course of a corticosteroid may also be considered in exceptional situations of severe protracted IM (i.e., fever, prostration, weight loss). Corticosteroids may reduce the severity of autoimmune thrombocytopenia and hemolytic anemia, and their use can be considered for intractable cases of encephalitis, myocarditis, and pericarditis. When used, corticosteroid therapy is given for a short course and commonly initiated at a dose of 40 to 60 mg of prednisone equivalent per day. Treatments of complications of EBV-associated lymphoproliferative disorders and HLH are beyond the scope of this chapter.

Therapy of other causes of mono syndrome

The mono-like symptoms of acute infections with CMV, toxoplasma, HIV, rubella, and the hepatitis viruses are usually self-limiting. Additional details about individual case are sought to determine whether interventions other than supportive care should be applied. Pregnancy and cellular immunodeficiency are important factors to consider in the decision. Profound cellular immune deficiency usually requires use of antiviral and antiparasitic treatments for acute CMV (see Chapter 180, "Cytomegalovirus") and toxoplasma (see Chapter 198, "Toxoplasma") infections, respectively. Primary CMV, toxoplasma, and rubella infections in pregnancy pose a risk to the baby (TORCH syndrome), warranting a consultation with an obstetrician with expertise in this area. Primary toxoplasmosis of pregnancy necessitates antimicrobial therapy (see Chapter 198, "Toxoplasma"). Immediate antiretroviral therapy is recommended in persons with acute HIV infection (see Chapter 98, "HIV-1 infection: Antiretroviral therapy"). Antiretroviral therapy given during pregnancy can substantially reduce perinatal HIV transmission, but its use requires knowledge of the attendant toxicities and risks (see Chapter 94, Infections in pregnancy and the puerperium").

Prevention

There is no vaccine for prevention of EBV infection or disease. Hospitalized patients with IM need not be isolated. Asymptomatic viral shedding long after the acute illness remains a potential risk for EBV transmission. Restricting intimate contact can decrease EBV transmission but is not practical unless the EBV infection would be intolerable.

Suggested reading

Chervenick PA. Infectious mononucleosis: The classic clinical syndrome. In Schlossberg D, ed. *Infectious mononucleosis*, 2nd ed. New York: Springer-Verlag; 1989: 29–34.

Cohen JI. Epstein-Barr virus infection. *N Engl J Med*. 2000;343:481–492. PMID: 10904566.

Dunmire SK, Hoquist KA, Balfour HH. Infectious mononucleosis. *Curr Top Microbiol Immunol*. 2015;390:211–240. PMID: 26424648 PMCID: PMC4670567.

Luzuriaga K, Sullivan JL. Infectious mononucleosis. *N Engl J Med*. 2010;362:1993–2000. PMID: 20505178.

Rezk E, Nofal YH, Hamzeh A, Aboujaib M, AlKehder MA, Al Hammad MF. Steroids for symptom control in infectious mononucleosis. *Cochrane Database Syst Rev*. 2015 (11):CD004402. PMID: 26558642 PMCID: PMC7047551.

Shepard RJ. Exercise and the athlete with infectious mononucleosis. *Clin J Sport Med*. 2017;27:168–178. PMID: 27347865.

Hantavirus cardiopulmonary syndrome

Gregory Mertz

Introduction

Hantavirus cardiopulmonary syndrome (HCPS), also called hantavirus pulmonary syndrome, is a viral zoonosis that may result in cardiogenic shock and respiratory failure with significant associated mortality. Hantavirus infections in humans have been identified throughout much of North, Central, and South America. In the United States approximately 25 cases (range 11–48) are reported annually, with an overall case fatality rate of 35%. Most cases occur west of the Mississippi River, with more half reported in New Mexico, Colorado, Arizona, and California. Case fatality rates are similar in South America, in particular in Argentina, Brazil, and Chile, but the number of cases reported annually in each of these countries exceeds the number reported in the United States.

Virology

Hantaviruses are enveloped, single-stranded, negative-strand RNA viruses. More than 20 New World hantaviruses have been identified since HCPS was first recognized in 1993. Although there is some overlap, the cardiopulmonary disease caused by New World hantaviruses differs from the disease with predominant renal manifestations—hemorrhagic fever with renal syndrome—that results from infection with Old World hantaviruses and occurs primarily in Asia and Europe. New World hantaviruses include highly pathogenic hantaviruses with high case fatality rates such as Sin Nombre virus (SNV) and Andes virus (ANDV); viruses such as Choclo virus, which largely causes a febrile illness and uncommonly causes fatal infection; and viruses such as Prospect Hill virus that do not cause disease in humans. The most common hantavirus causing HCPS in Canada and the United States is SNV, whereas hantaviruses that cause significant disease in South America include ANDV in Chile and Argentina and Laguna Negra virus in Paraguay.

Epidemiology

Although there is some spillover between rodent species, each hantavirus is associated with a primary rodent host that sheds the virus in urine, feces, and saliva. Humans are thought to be infected when the aerosolized excreta are inhaled, often when cleaning enclosed, rodent-infested areas. Less commonly, infection may result from rodent bites and exposures in research laboratories. Human-to-human transmission has only been documented with ANDV infections in Chile and Argentina, largely in family clusters. In a prospective study of household contacts of patients with HCPS in Chile, Ferrés et al. reported a significantly higher risk of HCPS in sex partners and other close household contacts as compared to members of the

household who slept in different rooms and denied sexual contact. Human infections in the Americas with the Old World hantavirus, Seoul virus, have also been reported in isolated outbreaks in persons working in rodent breeding facilities as well as in persons living in or near seaports.

Clinical syndrome

Most human cases lack a defined exposure, and the incubation period generally cannot be determined. However, in a series from Chile where individuals had brief periods of exposure in high-risk areas, the median incubation period between exposure and onset of clinical disease was 18 days, with a range of 11 to 32 days. Incubation periods were also determined in the Yosemite National Park outbreak in 2012 among visitors who stayed in the high-risk "signature tents" in Curry Village for only a few days. In the Yosemite outbreak, the median incubation period was 30.5 days with a range of 20 to 49 days.

Clinical disease begins with a febrile prodrome with 2 days to a week of fevers and myalgias, often with associated headache, backache, abdominal pain, nausea, and diarrhea. After several days with nonspecific prodromal symptoms, the cardiopulmonary phase starts abruptly with cough and dyspnea. This stage of disease may be mild, requiring only supplemental oxygen, or severe, causing rapid pulmonary edema and respiratory failure requiring mechanical ventilation. Severe disease is also characterized by cardiogenic shock, hemoconcentration, and lactic acidosis that may result in profound shock, cardiac arrhythmias, and death. The cardiopulmonary phase usually lasts 2 to 4 days. The cardiopulmonary phase is followed by a diuretic phase with rapid resolution shock and the pulmonary edema. Convalescence may be prolonged and may include weakness, fatigue, and impaired exercise tolerance with abnormal diffusion capacity.

Diagnosis

Early presumptive diagnosis is critical because patients with severe disease typically progress to shock and death before results of serologic testing are available. An exposure history may helpful but is usually absent. Clinical diagnosis during the febrile prodrome is exceedingly difficult since there is no cough, the chest radiograph is normal, and there are no routine laboratory abnormalities other than thrombocytopenia. In an unpublished series in Chile conducted when there was high awareness of hantavirus infections among clinicians, almost half of patients with hantavirus infection sought medical evaluation during the febrile prodrome. None had serologic testing for hantavirus infection, and none was admitted to the hospital until they returned during the cardiopulmonary phase (P. Vial, personal communication). In the controlled trial of ribavirin conducted in North America reported by Mertz et al., patients from rural areas who had thrombocytopenia and symptoms consistent with the febrile prodrome of HCPS were eligible for enrollment in the trial. None of the subjects with suspected hantavirus infection in the febrile prodrome phase had hantavirus infection, whereas hantavirus infection was confirmed in 23 of 24 subjects enrolled in the cardiopulmonary phase.

A definitive diagnosis of HCPS is based on serologic testing for hantavirus-specific immunoglobulin G (IgG) and IgM antibodies, which first become detectable during the febrile prodrome. The serologic tests available in the United States include enzyme-linked immunosorbent assay (ELISA), which are available at many state health departments and in commercial laboratories. An acute infection is characterized by a positive IgM and IgG antibody results; IgM-positive/IgG-negative results commonly represent a false-positive result, in particular if repeat testing after 24 to 48 hours still lacks detectable IgG antibody. In most commercial and state laboratories in the United States, there is an interval of approximately 7 days between the time the sample is drawn and the results are reported.

More specific Western immunoblot assays are currently restricted to research laboratories, as is nested reverse transcription–polymerase chain reaction (RT-PCR) detection of hantavirus RNA in peripheral mononuclear cells and serum. Hantavirus RNA has been detected in peripheral blood cells up to 2 weeks before the onset of symptoms or detection of anti-hantavirus antibodies and for up to 13 weeks after onset of illness. Postmortem diagnosis may also be established by detection of hantavirus antigens in tissue by immunohistochemistry.

A presumptive diagnosis can generally be made at the onset of the cardiopulmonary phase on the basis of the clinical presentation, radiologic findings, and a review of the peripheral blood smear (Figure 184.1). Characteristic hemodynamic findings may also be helpful in establishing a diagnosis. The chest radiograph will show findings consistent with pulmonary edema, including bilateral pulmonary infiltrates, Kerley B lines, indistinct hilar borders, and peribronchial cuffing, which progress rapidly over the next 12 hours. A CBC should be obtained, and the peripheral blood smear should be evaluated by an experienced pathologist. Criteria suggesting hantavirus infection in the cardiopulmonary phase include (1) thrombocytopenia (platelet count $\leq 150 \times 10^3$ mm^3), (2) left-shift (presence of myeloblasts), (3) lack of toxic granulation in neutrophils, (4) hemoconcentration (hematocrit >50 in men and >48 in women), and (5) >10% immunoblasts among lymphocytes.

When evaluating a patient in whom there is a high clinical suspicion of HCPS, the presence of four of five of these criteria has a sensitivity of 96% and a specificity of 99%. Unfortunately, these criteria apply only once the patient is already in the cardiopulmonary phase and therefore cannot be used for diagnosis in the prodromal stage. Other findings in the cardiopulmonary phase include a low cardiac index associated with a high systemic vascular resistance, in contrast to parameters found in septic shock. Alanine aminotransferase and aspartate aminotransferase levels, while often normal or slightly elevated during the prodrome, are generally abnormal at the onset of the cardiopulmonary phase and often peak during the diuretic and convalescent phases as the patient is improving.

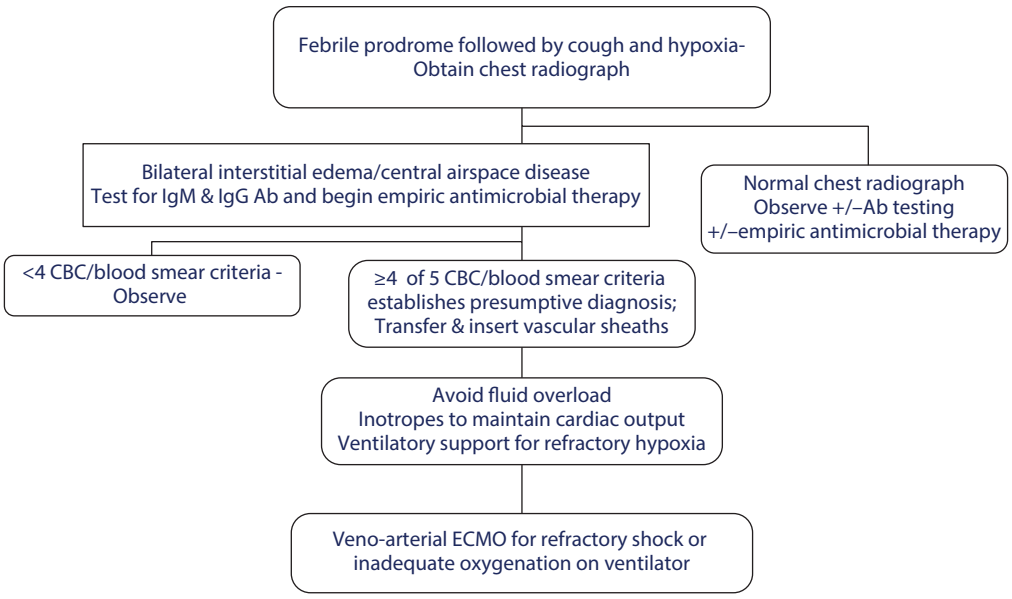

FIGURE 184.1 Flow diagram for diagnosis and management of hantavirus cardiopulmonary syndrome. See Hallin et al. for a description of characteristic hemodynamic findings, Ketai et al. for radiologic findings, Koster et al. for CBC and peripheral smear evaluation and criteria for presumptive diagnosis, and Wernly et al. for extracorporeal membrane oxygenation (ECMO) management.

Treatment

When there is clinical suspicion of HCPS (Figure 184.1), the patient should be admitted to a center in which cardiovascular and ventilatory support, including extracorporeal membrane oxygenation (ECMO) when feasible. Volume resuscitation should be avoided as this can exacerbate the pulmonary edema. Supplemental oxygen should be provided, including ventilatory support if necessary. Pending serologic confirmation, antibiotic therapy should be initiated for other infections in the differential diagnosis.

Cardiac output should be monitored either directly via thermodilution or approximated by methods such as arterial pulse waveform analysis. Echocardiography is less useful because cardiac output may drop precipitously during the cardiopulmonary phase. Early use of pressors should be utilized when appropriate. Norepinephrine is preferred as the initial agent in patients with hypotension, whereas dobutamine is preferred when there is a decrease in cardiac output but blood pressure is maintained. High-dose norepinephrine can be used in addition to dobutamine, if necessary.

If ECMO is available, the patient should be evaluated by the critical care and ECMO team, including cardiothoracic or vascular surgery, as soon as a presumptive diagnosis is made. The University of New Mexico Hospital (UNMH) in Albuquerque, New Mexico, other hospitals in the United States, and several hospitals in Santiago, Chile, have substantial experience with treatment of HCPS with veno-arterial ECMO for HCPS. Among 51 patients treated with ECMO at UNMH between 1994 and 2010, 34 (67%) survived to discharge. Furthermore, survival was 80% among the 25 patients treated between 2003 and 2010 who underwent elective insertion of arterial and venous vascular sheaths once a presumptive or definitive diagnosis of HCPS was established, were intubated nearly concurrently with vascular sheath placement, and then placed on ECMO if decompensation occurred.

For patients admitted to a medical facility without ECMO capability, immediate consultation should be sought with the nearest ECMO center as soon as hantavirus infection is considered. A listing of ECMO centers, including contact information, is maintained by the Extracorporeal Life Support Organization at www.elso.org/Membership/CenterDirectory.aspx. In practice, hantavirus infection is rarely considered prior to the onset of the cardiopulmonary phase, and progression to shock and death may occur within hours of the onset of this stage. As such, the window of opportunity for transfer to an ECMO center is generally measured in hours. Factors that may be discussed with the ECMO center include the likelihood of hantavirus infection, the patient's clinical status, distance to the ECMO center, availability of a mobile ECMO team that can initiate ECMO at the referring hospital prior to transportation to the ECMO center, and experience at the ECMO center with veno-arterial ECMO in the patient's age group.

There is no approved therapy for the treatment of HCPS. Intravenous ribavirin did not lead to survival benefit in a small placebo-controlled trial in North America, and treatment with high-dose methylprednisolone was ineffective in a randomized, placebo-controlled trial in patients with HCPS in Chile. An open, phase 1 trial of treatment with fresh frozen plasma containing anti-ANDV neutralizing antibodies was conducted in Chile, but no controlled trial of neutralizing antibody treatment has been performed, and there are no neutralizing antibody products available at this time for any of the major pathogenic hantaviruses in North or South America.

Suggested reading

Ferres M, Vial P, Marco C, et al. Prospective evaluation of household contacts of persons with hantavirus cardiopulmonary syndrome in Chile. *J Infect Dis*. 2007;195:1563–1571.

Hallin GW, Simpson SQ, Crowell RE, et al. Cardiopulmonary manifestations of hantavirus pulmonary syndrome. *Crit Care Med*. 1996;24:252–258.

Ketai LH, Williamson MR, Telpak RJ, et al. Hantavirus pulmonary syndrome: radiologic findings in 16 patients. *Radiology* 1994;191:665–668.

Koster F, Foucar K, Hjelle B, et al. Presumptive diagnosis of hantavirus cardiopulmonary syndrome by routine complete blood count and blood smear review. *Am J Clin Pathol*. 2001;116:665–672.

Jonsson CB, Hooper J, Mertz G. Treatment of hantavirus pulmonary syndrome. *Antiviral Res.* 2008;78:162–169.

Mertz GJ, Miedzinski L, Goade D, et al. Placebo-controlled, double-blind trial of intravenous ribavirin for hantavirus cardiopulmonary syndrome in North America. *Clin Infect Dis*. 2004;39:1307–1313.

Nunez JJ, Fritz CL, Knust B, et al. Hantavirus infections among overnight visitors to Yosemite National park, California, USA, 2012. *Emerg Infect Dis* 2014;20:386–393.

Vial PA, Valdivieso F, Calvo M, et al. A non-randomized multicentre trial of human immune plasma for treatment of hantavirus cardiopulmonary syndrome by ANDV. *Antivir Ther*. 2015;20(4):377–386.

Vial PA, Valdivieso F, Ferres M, et al. High-dose intravenous methylprednisolone for hantavirus cardiopulmonary syndrome in Chile: A double-blind, randomized controlled clinical trial. *Clin Infect Dis*. 2013;57:943–951. doi:10.1093/cid/cit394.

Vial PA, Valdivieso F, Mertz G, et al. Incubation period of hantavirus cardiopulmonary syndrome. *Emerg Infect Dis*. 2006;12:1271–1273.

Wernly JA, Dietl CA, Tabe CE, et al. Extracorporeal membrane oxygenation support improves survival of patients with hantavirus cardiopulmonary syndrome refractory to medical treatment. *Eur J Cardiothorac Surg.* 2011;40:13334–13340.

Herpes simplex 1 and 2

Richard J. Whitley and Abdulsalam Alsulami

The virus

Herpesviruses are generally defined as large, enveloped virions with an icosapentahedral nucleocapsid consisting of 162 capsomeres arranged around a double-stranded DNA core. The two antigenically distinct types of herpes simplex virus (HSV) are HSV-1 and HSV-2. Considerable homology exists between the HSV-1 and HSV-2 genomes, with most of the polypeptides specified by one viral type being antigenically related to polypeptides of the other viral type. Although this results in considerable cross-reactivity between HSV-1 and HSV-2, glycoproteins G (gG) are unique antigenic determinants that allow for differentiation between these two viruses (e.g., gG-1 and gG-2). Surrounding the viral genome and nucleocapsid is a tightly adherent membrane known as the *tegument*. A lipid envelope containing the viral glycoproteins loosely surrounds the tegument.

Pathology and pathogenesis

Cutaneous HSV infection causes ballooning of infected epithelial cells, with nuclear degeneration, loss of intact cellular membranes, and the formation of multinucleated giant cells. Ultimately, cells lyse and release clear fluid containing large quantities of virus, with subsequent accumulation of cellular debris and inflammatory cells between the epidermal and dermal layers. Multinucleated giant cells are usually present at the base of the vesicle. An intense inflammatory response extends from the base of the vesicle into the dermis, producing the erythema that classically surrounds a cluster of HSV vesicles. With lesion healing, vesicular fluid becomes purulent as more inflammatory cells are recruited to the site of infection. Scab formation then follows. Scarring is uncommon.

When infection involves mucous membranes, shallow ulcers are more common than vesicles because of rapid rupture of the very thin cornified epithelium present at mucosal sites. Nevertheless, the histopathologic findings of mucosal lesions are similar to those of skin lesions.

Epidemiology

Although HSV-1 is found most commonly in the oropharynx, it is an increasingly common cause of first-episode genital herpes, accounting for at least half of all new infections, and, additionally, can infect any organ system. Factors that influence the frequency of primary HSV-1 infection include geographic location, socioeconomic status, and age. The US seroprevalence of HSV-1 infection during childhood and adolescence is around 27% (age 14–19 years). This prevalence increases with age to 59.7% in people 40–49 years of age, and is generally higher in females than males (50.9% vs. 45.2%). HSV-1 antibody prevalence is highest

among Mexican Americans (71.7%) followed by non-Mexican blacks (58.8%), and is lowest in non-Hispanic whites (36.9%). HSV-1 remains a common infection despite recent decreases in prevalence (overall prevalence of 59.4% in 1999–2004 decreasing to 48.1% in 2015–2016).

Recurrences of herpes labialis have been associated with physical or emotional stress, fever, exposure to ultraviolet light, tissue damage, and immune suppression. As with primary infections, recurrent disease may occur in the absence of clinical symptoms. At any given time, 1% of healthy children and 1% to 5% of normal adults asymptomatically excrete HSV-1, as demonstrated by viral culture. Recent studies employing polymerase chain reaction (PCR) suggest that these numbers may be at least threefold higher.

Although HSV-2 causes the majority of recurrent genital HSV infections in the United States, recent data show that HSV-1 is increasingly responsible for more primary genital herpes infections; however, recurrences are less common than those infections caused by HSV-2. As would be expected, antibodies to HSV-2 are rarely found before the onset of sexual activity. Among adolescents and adults, factors that correlate with HSV-2 seroprevalence include sex (higher for women than for men), race (higher for African Americans than for whites), marital status (higher for persons previously married than for single or married persons), number of sexual partners (increasing likelihood with increasing number of partners), and income level (higher probability for those persons earning lesser amounts of money).

The propensity for recurrence of genital HSV infection depends on a variety of factors, including sex (more common in men), viral type (more common with HSV-2), and the presence and titer of neutralizing antibodies (more common in the presence of high neutralizing antibody titers). Overall, 60% to 90% of patients with primary genital HSV-2 infection will experience clinically apparent recurrence of infection.

Clinical manifestations

Oropharyngeal HSV infection

Primary oropharyngeal infection with HSV-1 occurs most commonly in young children between 1 and 3 years of age and is usually asymptomatic. The incubation period ranges from 2 to 12 days, with an average of 4 days. Symptomatic disease is characterized by fever to 40°C/104°F, oral lesions, sore throat, fetor oris, anorexia, cervical adenopathy, and mucosal edema. Oral lesions initially are vesicular but rapidly rupture, leaving 1- to 3-mm shallow gray-white ulcers on erythematous bases. These lesions are distributed on the hard palate, the anterior portion of the tongue, along the gingiva, and around the lips (Figure 185.1). In addition, the lesions may extend down the chin and neck due to drooling. Total duration of illness is 10 to 21 days.

Primary infection in young adults has been associated with pharyngitis and often a mononucleosis-like syndrome. In such patients, ulcerative lesions on erythematous bases frequently are apparent on the tonsils.

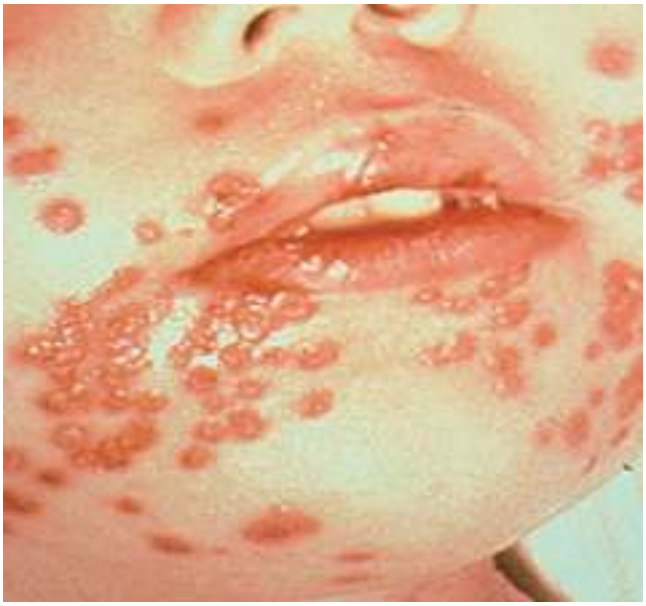

FIGURE 185.1 Herpes simplex gingivostomatitis.

Primary gingivostomatitis results in viral shedding in oral secretions for an average of 7 to 10 days. Virus is also shed in the stool.

Recurrent herpes labialis

Recurrent orolabial HSV lesions are often preceded by a prodrome of pain, burning, tingling, or itching. These symptoms generally last for <6 hours, followed within 24 to 48 hours by the appearance of painful vesicles, typically at the vermillion border of the lip (Figure 185.2). Lesions usually crust within 3 to 4 days, and healing is complete within 8 to 10 days. Recurrences occur only rarely in the mouth or on facial skin of immunocompetent patients.

Genital HSV infection

Genital HSV disease (Figure 185.3) is acquired by sexual contact with an infected partner. Historically, virtually all cases of genital herpes were caused by HSV-2 but, with changing sexual behavior, at least 50% of cases today are the consequence of HSV-1. The incubation period of primary disease ranges from 2 to 12 days. Lesions with primary infection persist for an average of 21 days. In 70% of patients, symptomatic primary infections are associated with fever, malaise, myalgias, and inguinal adenopathy, as well as other signs and symptoms of systemic illness. Complications include extragenital lesions, aseptic meningitis (which could be recurrent and known as *Mollaret's meningitis*), and sacral autonomic nervous system dysfunction with associated urinary retention. Women tend to experience more severe primary infections and are more likely to develop complications.

In males, primary genital HSV infection usually manifests as a cluster of vesicular lesions on erythematous bases on the glans or shaft of the penis. In females, primary genital HSV lesions usually involve the vulva bilaterally. Concomitant HSV cervicitis occurs in 90% of women with primary HSV-2 infection of the external

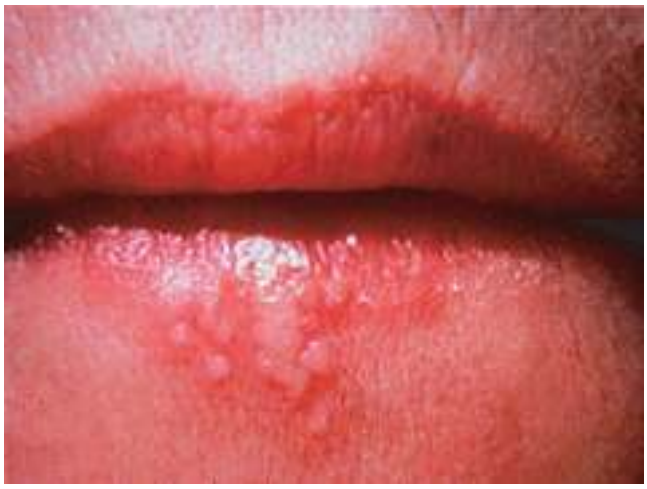

FIGURE 185.2 Recurrent herpes labialis.

genitalia. In women, the lesions rapidly ulcerate and become covered with a gray-white exudate. Lesions may be exquisitely painful. Recurrent genital HSV-2 infection can be either symptomatic or asymptomatic. A prodrome of itching, burning, tingling, or tenderness may be noted several hours before a recurrence. The duration of disease is shorter during recurrent infection (7 to 10 days), and fewer lesions are present. In men, lesions usually appear on the glans or shaft of the penis. In women, lesions occur most commonly on the labia minora, labia majora, and perineum. Cervical excretion of HSV occurs in 10% of women with recurrent genital lesions. Systemic symptoms are uncommon in recurrent genital HSV disease. Genital HSV-1 infections are much less likely to recur.

Transmission usually occurs in the absence of clinical symptoms and occurs more often from men to women. Importantly, HSV-2-seropositive but asymptomatic individuals are just as likely to transmit infection as those who are symptomatic.

Other primary HSV skin infections

Alteration in the barrier properties of skin, as occurs in atopic dermatitis, can result in localized HSV skin infection (eczema herpeticum). Most cases resolve over a 7- to 9-day period without specific therapy. Localized cutaneous HSV infection after trauma is known as *herpes gladitorium* (wrestler's herpes or traumatic herpes). HSV infection of the digits results in *herpetic whitlow*. Such lesions may be the result of autoinoculation, as in the case of infants, or exogenous exposure, as occurs among medical and dental personnel who fail to wear gloves.

Ocular HSV infection

Herpetic infection of the eye usually presents as either a blepharitis or a follicular conjunctivitis. As disease progresses, branching dendritic lesions develop. Symptoms include severe photophobia, tearing, chemosis, blurred vision, and preauricular lymphadenopathy. An ophthalmologist should always be involved in the care of such patients.

Central nervous system HSV infection

Central nervous system (CNS) signs and symptoms of HSV disease in older children and adults can begin suddenly or can follow a 1- to 7-day period of nonspecific influenza-like symptoms. Prominent CNS features include headache, fever, altered consciousness, and focal neurologic findings such as focal seizures. Clinical signs and symptoms may reflect the characteristic frontal and temporal lobe localization, such as memory loss,

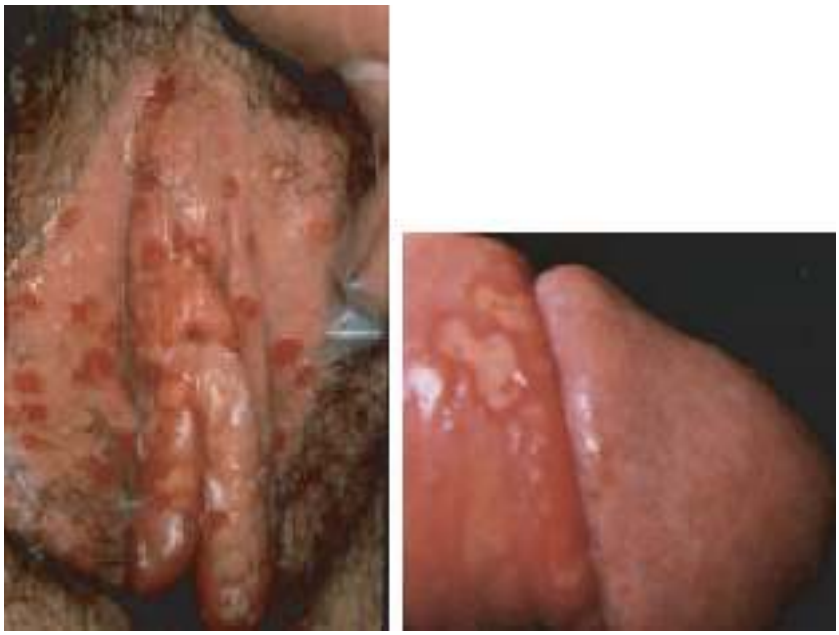

FIGURE 185.3 Genital herpes simplex infection in woman (primary infection) and man (recurrence).

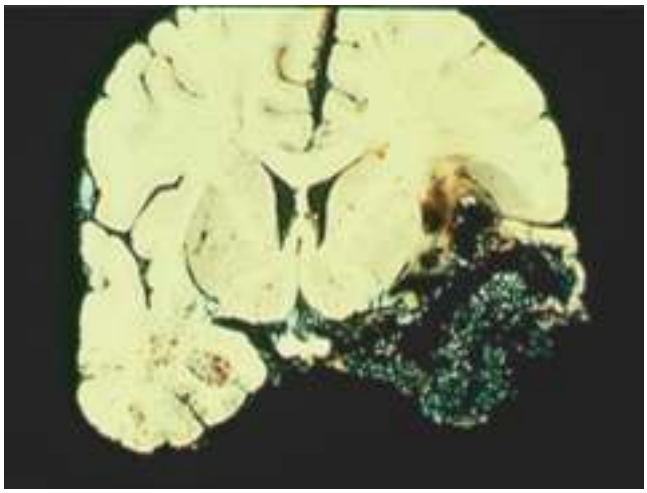

FIGURE 185.4 Brain with temporal lobe necrosis.

anosmia, olfactory hallucinations, speech disorders, and behavioral disturbances, often accompanied pathologically by focal necrosis (Figure 185.4).

Neonatal HSV infections

Neonatal HSV infection can be classified as (1) disease localized to the skin, eye, and/or mouth (SEM) (45% of cases); (2) encephalitis, with or without SEM involvement (30% of cases); and (3) disseminated infection that involves multiple organs, including the CNS, lung, gastrointestinal tract, liver, adrenals, skin, eye, and/or mouth (25% of cases). Infants with disseminated and SEM disease usually present for medical attention within the first 2 weeks of life, whereas infants with disease localized to the CNS usually present between the second and third weeks of life. Presenting signs and symptoms can include any combination of irritability, seizures (both focal and generalized), lethargy, tremors, poor feeding, temperature instability, bulging fontanelle, respiratory distress, jaundice, disseminated intra-vascular coagulopathy, shock, and cutaneous vesicles. It is important to note that >40% of infants with disseminated disease and >30% of infants with encephalitis will never develop skin vesicles during the course of illness. Even in cases of SEM disease, almost 20% of neonates do not have skin lesions. Intrapartum acquisition of the virus is responsible for approximately 85% of cases and usually occurs in the absence of symptoms. Less commonly, neonates acquire the infection postnatally (10%) or rarely (~5%) in utero, which is associated with distinctly worse disease and outcome.

HSV in the immunocompromised host

Patients compromised by immunosuppressive therapy, underlying disease, or malnutrition are at increased risk for severe HSV infection. Disseminated disease may occur with widespread dermal, mucosal, and visceral involvement. Alternatively, disease may remain localized but persist for much longer periods of time than would be evident in immunocompetent hosts.

Diagnosis

Type-specific serologic tests allow the distinction between HSV-1 and HSV-2. Such tests distinguish between gG-1 and gG-2. These tests can be utilized to determine those people at risk for infection or those previously infected but who remain unaware of their status. The diagnosis of HSV is best achieved by either the isolation of HSV by culture or the detection of viral DNA by PCR. If skin lesions are present, a scraping of the vesicles should be transferred in appropriate viral transport medium on ice to a diagnostic virology laboratory. Other sites from which virus may be isolated include the cerebrospinal fluid (CSF), though rarely, and the urine, throat, nasopharynx, conjunctivae, and duodenum. The presence of intranuclear inclusions and multinucleated giant cells on a Tzanck prep are indicative of, but not diagnostic for, HSV infection. The application of PCR to lesion scrapings is the most sensitive test for detection of HSV, especially late in the course of vesicular evolution and in the CSF. Of note, if resistance testing is necessary, a culture is essential.

In HSV encephalitis, CSF findings are variable but often include a moderate pleocytosis with a predominance of mononuclear cells, elevated protein level, and normal or slightly decreased glucose. The electroencephalogram (EEG) generally localizes spike and slow wave activity to the temporal lobe, even when obtained very early in the disease course. CT of the brain may initially be normal or reveal only edema, but, as the disease progresses, temporal lobe involvement becomes prominent. MRI of the brain is more helpful in delineating the degree and extension of CNS disease. Detection of HSV DNA in the CSF by PCR has become the diagnostic method of choice; however, it must be performed only by a reliable laboratory. Rarely, an initial early negative CSF PCR does not exclude HSV encephalitis and should be repeated especially if the clinical suspicion remains high.

Treatment

Herpes labialis

The treatments of choice for herpes labialis are acyclovir, valacyclovir, or famciclovir. Orally administered acyclovir at a dosage of 400 mg five times daily for 5 days reduces the duration of pain and time to the loss of crusts by about one-third, but only if treatment is started during the prodromal or erythematous stage of recurrent infection. Similar benefit is achieved with valacyclovir (2 g BID for 1 day, taken about 12 hours apart). Clinical benefit is achieved only if therapy is initiated very early after recurrence. Recently, 1-day therapy with famciclovir was approved by the US Food and Drug Administration. When administered during prodrome, 1,500 mg administered once accelerates healing.

Topical therapies provide little benefit in the management of herpes labialis. Although these therapies are licensed, the authors do not recommend their use. Similarly, data do not support the use of long-term suppressive treatment with acyclovir for the prevention of herpes labialis.

Genital herpes

The treatments of choice include acyclovir (oral or intravenous [IV]), valacyclovir (oral), or famciclovir (oral). Although topical acyclovir is approved for treatment of genital herpes, it is not recommended. Treatment of primary genital herpes in the normal host decreases the duration of symptoms, viral shedding, and time to healing of lesions (Table 185.1). However, neither systemic nor topical treatment of primary HSV lesions reduces the frequency or severity of recurrences. Episodic administration of oral or topical acyclovir for the treatment of recurrent genital HSV lesions provides only a modest benefit, with duration of lesions being shortened at most by 1 to 2 days. However, daily administration of oral acyclovir, valacyclovir, or famciclovir can effectively suppress recurrences of genital herpes in 60% to 90% of patients. Importantly, suppressive therapy does not totally prevent reactivation; thus, transmission can occur, albeit less frequently. Treatment should be interrupted approximately yearly to reassess the need for continued suppression.

Both valacyclovir and famciclovir are now licensed for the treatment and suppression of genital HSV. There is a pharmacokinetic advantage with these medications. For recurrent infection, valacyclovir is usually administered at 500 mg twice daily for 3 days, and famciclovir is administered at 1 g twice daily for 1 day.

The transmission of genital HSV infection can be decreased but not eliminated by administration of valacyclovir (500 mg once daily) to the infected partner.

Mucocutaneous HSV infections in immunocompromised patients

In immunocompromised patients, the three aforementioned antiviral drugs all diminish the duration of viral shedding as well as substantially accelerate the time to cessation of pain and to total healing of HSV lesions. In addition, prophylactic administration of these drugs to such patients significantly reduces the incidence of symptomatic HSV infection (see Table 185.1).

Herpes simplex keratoconjunctivitis

Idoxuridine (Stoxil), trifluridine (Viroptic), and vidarabine ophthalmic drops all are effective and licensed for treatment of HSV

TABLE 185.1 **ANTIVIRAL THERAPY IN HERPES SIMPLEX VIRUS (HSV) INFECTIONS**

Type of infection	Drug	Route and dosage[a]	Comments
Genital HSV	Acyclovir	200 mg PO 5×/d ×10 d	Preferred route in normal host
Initial episode		5 mg/kg IV q8h ×5 d	Reserved for severe cases
Recurrent episode	Valacyclovir	500mg PO BID ×3 d	
Suppression	Famciclovir Acyclovir	250 mg PO TID ×10 d 200 mg PO 5×/d ×5 d	
	Valacyclovir	500 mg PO BID × 3 d	
	Famciclovir	1 g PO BID × 1 d	
	Acyclovir	400 mg PO BID	
	Valacyclovir	500 mg or 1 g PO qd	
	Famciclovir	250 mg PO BID	
Herpes labialis	Acyclovir	400 mg PO 5×/d × 5 d	
	Valacyclovir	2 g PO BID for 1 d, taken about 12 h apart	
	Famciclovir	1500 mg administered once	
Mucocutaneous HSV in immunocompromised patient	Acyclovir	200–400 mg PO 5×/d ×10 d 5–10 mg/kg IV q8h ×7–10 d	
	Valacyclovir	500 mg BID PO	
	Famciclovir	500 mg TID PO	
HSV encephalitis	Acyclovir	10–15 mg/kg IV q8h ×14–21 d	
Neonatal HSV	Acyclovir	20 mg/kg IV q8h ×14–21 d	14 days for SEM. Minimum of 21 days in disseminated and CNS disease
Suppression		300 mg/m^2 q8h × 6 mo	
Herpetic conjunctivitis	Trifluridine	1 drop q2h while awake × 7–14 d	Alternative: vidarabine ointment

[a] The dosages are for adults with normal renal function unless otherwise noted.
SEM: Skin, eye and mouth disease.
Adapted from Workowski KA, Bolan G. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(3):1–137; and American Academy of Pediatrics. Non-HIV Antiviral Drugs. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018: 966–984.

keratitis. Trifluridine is the most efficacious and the easiest to administer and, as such, is the drug of choice for HSV ocular disease (see Table 185.1). Involving an ophthalmologist in managing HSV eye infections is essential.

Herpes simplex encephalitis

In patients with HSV encephalitis, acyclovir administration reduces mortality and has a modest impact on morbidity. Dosage and length of therapy are shown in Table 185.1. Outcome is more favorable when therapy is instituted early in the disease course.

Neonatal HSV infections

IV acyclovir is the drug of choice in the treatment of neonatal HSV infection (see Table 185.1). Therapy is most efficacious if instituted early in the course of illness. Because of the exceptional safety profile of acyclovir, an IV dosage of 60 mg/kg/d divided every 8 hours should be given. Duration of therapy is 14 days if the disease is limited to skin, eye, and mouth. The minimum duration of IV therapy is 21 days in neonatal disseminated and CNS disease. Confirming negative CSF HSV PCR before the end of the initial 21 days should be established before switching to suppressive therapy. Consultation with a pediatric infectious disease specialist is strongly recommended. Suppressive therapy with acyclovir is indicated after completion of IV therapy. The dosage is 300 mg/m^2 every 8 hours for 6 months.

Infants with ocular involvement caused by HSV should receive topical antiviral medication in addition to parenteral therapy. Trifluridine is the treatment of choice for ocular HSV infection in the neonate (see Table 187.1).

Suggested reading

Bodilsen J, Nielsen H, Whitley RJ. Valaciclovir therapy for herpes encephalitis: caution advised. *J Antimicrob Cherother*. 2019 Jan 18; epub ahead of print. doi:10.1093/jac/dky568

Gnann JW, Whitley RJ. Evaluation and management of genital HSV infections. *N Engl J Med.* 2016 Aug;375:666–674. doi:10.1056/NEJMcp1603178, PMID 27532832. Editorial Response published October, 2016.

James SH, Kimberlin DW. Neonatal herpes simplex virus infection. *Infect Dis Clin North Am*. 2015;29(3):391–100.

Kleinstein SE, Shea PR, Allen AS, Koelle DM, Wald A, Goldstein DB. Genome-wide association study (GWAS) of human host factors influencing viral severity of herpes simplex virus type 2 (HSV-2). *Genes Immun*. 2018. doi:10.1038/s41435-018-0013-4. [epub ahead of print].

Pinninti SG, Kimberlin DW. Neonatal herpes simplex virus infections. *Semin Perinatol*. 2018;42(3):168–175.

Roizman B, Knipe DM, Whitlely RJ. Herpes simplex viruses. In Knipe DM, Howley PM, eds. *Fields virology*, 6th ed. Philadelphia: Wolters Kluwer Health/LWW; 2015: 1823–1897.

Whitley RJ, Roizman B. Herpes simplex viruses. In Richman DD, Whitley RJ, Hayden FG, eds.: *Clinical virology*, 4th edi. Washington, DC: ASM Press; 2017: 415–445.

Human herpes virus 6, 7, 8

Eleni E. Magira

Introduction

Of the >100 known herpesviruses, eight types of herpesviruses infect humans: herpes simplex virus types 1 and 2 (HSV-1, -2), varicella-zoster virus or human herpesvirus-3 (VZV/HHV-3), Epstein–Barr virus or human herpesvirus-4 (EBV/HHV-4), cytomegalovirus or human herpesvirus-5 (CMV/HHV-5), human herpesvirus-6 (HHV-6) (variants A and B), human herpesvirus-7 (HHV-7), and Kaposi's sarcoma virus or human herpesvirus-8 (KSV/HHV-8). Herpesviruses consist of large double-stranded DNA packaged inside an icosahedral capsid. The capsid is surrounded by a mixture of protein tegument and an outer lipid envelope where the viral glycoprotein spikes. The diameter of complete virions is about 200 nm. These herpesviruses produce lytic and latent infection of lymphocytes and other cell types. When latency is established, these cells serve as reservoirs for endogenous viral reactivation during times of immune suppression or as potential vectors of transmission to susceptible individuals. HHV-6, HHV-7, and HHV-8 constitute a diverse group concerning their biology, pathogenesis, and the diseases they produce; HHV-6 and HHV-7 are able to infect a broader array of cell types than HHV-8. Clinical presentation of these herpesviruses ranges from asymptomatic infection or mild illnesses febrile exanthems extending to life-threatening disease in the immune compromised host.

Human herpesvirus-6 (HHV-6)

HHV-6 is a globally dispersed linear, double-stranded DNA molecule that encompasses two distinct variants, the HHV-6A and the HHV-6B. In 2012, the International Committee on Taxonomy of Viruses (ICTV) classified HHV-6A and HHV-6B as separate viruses, replacing species *human herpesvirus-6* with HHV-*6A* and *HHV-6B* in the genus *Roseolovirus*, family *Herpesviridae,* order Herpesvirales. Distinct and common immunological properties and diseases association exist among the two variants (Table 186.1).

Genomic sequencing of these two viruses has shown an overall genetic identity of 90%, with high divergence and functional differences of specific genetic sequences. Interestingly, HHV-6A and HHV-6B demonstrate a unique ability to integrate into human chromosomes in the subtelomeric region (inherited chromosomally integrated HHV-6 [iciHHV-6]). This allows the virus to continue to replicate while other human herpesviruses maintain their genome as a circular episome in latently infected cells. HHV-6 DNA integration is associated with persistent high-level viremia. High-level viremia is uncommon but not rare as it was reported in 3% of blood donors in a British study. One percent of newborns suffer congenital HHV-6 infection; the majority of instances occur in the setting of maternal chromosomal integration. If viral integration occurs in immunocompetent patients, elevated levels of viral DNA in blood, sera, and hair follicles will be found.

TABLE 186.1 **DISTINCT AND COMMON IMMUNOLOGICAL PROPERTIES AND DISEASES ASSOCIATION AMONG THE HHV-6 VARIANTS (A, B)**

	HHV-6A	HHV-6B
CD4+T-lymphocyte tropism	+	+
Neurotropism	+	+
Detection in vitreous fluid samples	+	+
CD8+ T, natural killer, gamma/delta T cells tropism	+	-
Associated more with multiple sclerosis	+	-
Associated more with rhombencephalitis	+	-
Resistant to the antiviral effects of interferon-α and -β	-	+
Most primary infections	-	+
Associated with temporal lobe epilepsy/ status epilepticus	-	+
Associated with Hashimoto's thyroiditis	+	-
Associated with hepatitis in liver transplant patients	+	-
Associated with exanthema subitum	-	+

Epidemiology, shedding, and tissue tropism of HHV-6

HHV-6 maintains a worldwide distribution, and 70% to 100% of adults possess serologic evidence of HHV-6 infection. Seroprevalence is almost 100% in Europe and the United States but in Morocco, seroprevalence comprises 20%. Infection follows 10 to 15 days after the incubation period, and it is generally acquired between the ages of 6 and 15 months. After primary infection, HHV-6A and HHV-6B remain in the host lifelong and viral replication may occur in salivary glands. Shedding of the virus from this site is considered the principal route of transmission. Although different cell surface receptor the CD46 and the CD134 serve as essential entry receptors for HHV-6A and HHV-6B, respectively, other proteins (e.g., GP96), are involved in HHV-6 infection. The cell surface receptors determine the fate of the virus inside the host (e.g., endocytosis). In addition to saliva, HHV-6 DNA could be identified in cord blood, peripheral blood, nasal mucosa, and olfactory bulb specimens, urine, and hair. The HHV-6 can infect a variety of cells like $CD8^+$/CD4+ T lymphocytes, natural killer, liver, endothelial, astrocytes, oligodendrocytes, and microglial cells. Although seroepidemiologic data indicate that breast milk constitutes a not significant source of HHV-6 infection in infancy in the United States, investigators from India found HHV-6 in breast milk in either healthy or HIV-positive women. Saliva remains the presumptive vehicle of transmission from mother to child. The HHV-6 virus may cause serious diseases, particularly in immunocompromised individuals but in immunocompetent as well.

HHV-6 infections in immunocompetent hosts

Primary infection. Primary infection with HHV-6 is experienced by up to 90% of children by the age of 3 years. It is a leading cause of skin rash and fever in children <2 years. Up to 20% of those children will develop an infection associated with high fever (40°C/104°F) for 3 to 5 days. At that point, suddenly the child will experience a rapid defervescence with an accompanying nonpruritic pink papular or maculopapular rash (exanthema subitum, roseola infantum, or sixth disease) on the trunk, face, and neck. The most likely complication from infection with HHV-6 is febrile seizures due to the ability of the virus to pass the blood–brain barrier. Malaise, otitis media, and gastrointestinal and respiratory symptoms are equally common.

Encephalitis. HHV-6 encephalopathy/encephalitis with rash can occur at primary infection in children and adults. It is intriguing that molecular testing revealed HHV-6 DNA in the CSF of 40% of 35 immunocompetent patients with encephalitis of unknown etiology. The spectrum of clinical presentations is broad and could include an altered level of consciousness, seizures, psychosis, acute cerebellar ataxia, and cranial nerve deficits or hemiparesis. Both HHV-6 variants can be recovered from cerebrospinal fluid (CSF), although the A variant is thought to be more neurotropic.

Opsoclonus-myoclonus syndrome (OMS) associated with human herpesvirus-6 rhomboencephalitis. Immunocompetent pediatric patients have been diagnosed with HHV-6 rhombencephalitis. Opsoclonus-myoclonus syndrome characterized by opsoclonus and arrhythmic-action myoclonus predominantly involving the trunk, limbs, and head has been described in adults.

POLG mutations (Alpers-Huttenlocher syndrome). POLG mutations are associated with Alpers-Huttenlocher syndrome, which is an uncommon mitochondrial disease reported in two previously healthy young boys with HHV-6–associated encephalitis. They gradually developed encephalopathy with a refractory movement disorder concurrent with the acquisition of acute HHV-6 infection.

Tick-borne encephalitis and enteroviral meningoencephalitis. In a small recent study of laboratory-proved tick-borne encephalitis, HHV (HSV1, HSV2, VZV, and HHV6) DNA was found in the CSF. This finding implied a possible impact of herpesviruses coinfection on the clinical course and patient outcomes.

Severe, infectious, mononucleosis-like syndrome resulting from a primary HHV-6 infection in immunocompetent adults. As in many other viral illnesses, the severe complications are more common in adults with primary infection; these include a mononucleosis-like syndrome, hepatitis, hemophagocytosis, thrombocytopenia, encephalitis, and/or fatal disseminated disease. HHV-6 may influence the occurrence of demyelinating diseases such as multiple sclerosis and Guillain–Barré syndrome, but a causal role has not been proved and research findings are often contradictory.

HHV-6 infections in immunocompromised hosts

Cytomegalovirus-like illness. Active HHV-6B replication is frequently detected in immunocompromised hosts, such as hematopoietic cell

and solid organ transplant recipients. Most infections are identified 2 to 4 weeks posttransplantation. Clinical syndromes result from reactivation and replication of the HHV-6. These syndromes mimic cytomegalovirus (CMV) infection, including pneumonitis, colitis, hemorrhagic cystitis, encephalitis (most frequently involving the temporal lobe), hepatitis, bone marrow suppression, and graft-versus-host disease. HHV-6 contributes to the frequent occurrence of a skin rash after bone marrow grafting as histology can demonstrate lymphocytic basophilic inclusions and viral DNA. HHV-6 is associated with bronchiolitis obliterans among lung transplant recipients and eventually linked with graft failure. Inherited chromosomally integrated HHV-6 (iciHHV-6) can cause a confusing clinical picture resembling HHV-6 activity concurrently with CMV or HHV-7, making the distinction of the clinical manifestations due to each virus complex.

Viremia in patients with serologic evidence of prior infection. The intensity of HHV-6 viremia is related to the occurrence of clinical manifestations and graft-versus-host disease in allogeneic bone marrow transplant recipients. The extent of viremia is linked to graft failure after solid organ transplantation. Viremia may be extremely common following hematopoietic cell transplantation.

HHV-6 as an opportunistic pathogen in AIDS. HHV-6 could be identified as an opportunistic pathogen in AIDS patients with reported cases of encephalitis, pneumonitis, and retinitis. Combination antiretroviral therapy (cART) appears to have reduced the incidence of serious HHV-6 infections in AIDS.

Drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS) in either immunocompromised or immunocompetent patients. Drugs associated with HHV-6 reactivation causing DIHS/DRESS (possibly through various mechanisms) are variable (e.g., carbamazepine, dapsone, allopurinol, trimethoprim-sulfamethoxazole, vancomycin, and naproxen). The skin reaction is characterized by acute, widespread erythema with high fever and multiorgan dysfunction. HHV-6 reactivation associated with DIHS/DRESS may respond to antiherpes treatment although definitive studies have not been performed.

Detection of HHV-6 infection

Detection of HHV-6 DNA in serum or CSF generally means that the patients acquired an active infection. Identification of immunoglobulin M (IgM) antibodies by enzyme-linked immunosorbent assay (ELISA) or indirect immunofluorescence assay (IFA) can differentiate active from latent infection because these antibodies appear during an active infection or 2 to 3 months after. Chronic infections in various tissues can persist with no evidence of IgM antibodies. Primary infection can be demonstrated by serologic conversion in children and adults or by the presence of IgM antibodies in children. The presence of IgM in adults may indicate either primary infection or reactivation from latency. A fourfold increase in serum IgG by IFA indicates recent infection. In classic childhood exanthema subitum, etiologic diagnosis is seldom necessary.

Quantitative polymerase chain reaction (PCR) DNA testing on whole blood can differentiate active from latent infection. An active infection results when the viral load is >200 copies/mL or 20 copies/microgram of DNA. A quantitative tissue biopsy can differentiate between low-level latent virus and active virus. Immunohistochemistry can detect cells with active infection in biopsy or cytologic specimens. While viral culture from peripheral blood remains the gold standard for viral detection, it is not routinely performed. Physicians need to be aware that a negative finding in the serum does not exclude a localized infection in an organ. Additionally, 1% of the population might have iciHHV-6 and therefore, even if they are asymptomatic, a positive HHV-6 DNA test by PCR is crucial.

Treatment of HHV-6 infection

Treatment is recommended for virologically confirmed infection in the setting of posttransplant bone marrow suppression, encephalitis, or pneumonitis. Therapy is usually unnecessary for primary infection in immunocompetent hosts, whereas in infants with exanthema subitum treatment is mainly supportive. The International Herpesvirus Management Forum and American Society of Transplantation Infectious Disease Community of Practice have recommended the initiation of foscarnet therapy in cases of HHV-6 encephalitis. Administration of ganciclovir constitutes an additional risk of hematological toxicity. Because CMV is closely related to both HHV-6A and HHV-6B, clinicians utilize anti-CMV agents such as ganciclovir, cidofovir, and foscarnet against both HHV-6 variants. Another drug with anti-HHV-6 variants activity is artesunate (used for the treatment of malaria), which recently has indicated excellent efficacy against HHV-6 in vitro. Also, brincidofovir (CMX001), a derivative of cidofovir, increased in vitro activity against HHV-6 by a factor of 100. Reduction in the intensity of immunosuppression is recommended when possible. Immunotherapies, such as transfer of HHV-6-specific T cells, proved useful in life-threatening infections among bone marrow transplant recipients. A bank of virus-specific T cells that recognized EBV, adenovirus, CMV, BK virus, and HHV-6 has been developed as an effective approach to combat severe and drug-refractory infections in hematopoietic cell transplant recipients.

Human herpesvirus-7 (HHV-7)

HHV-7 is, in addition, a member of the genus *Roseolovirus*, subfamily *Betaherpesvirinae*, family *Herpesviridae*, and order Herpesvirales. Is similar in terms of morphology and genome sequence to HHV-6; the viruses resemble each other more than they do CMV.

Epidemiology, shedding, and tissue tropism of HHV-7

Infection with HHV-7 predominantly occurs during childhood, and HHV-7 is shed throughout life in saliva. Salivary shedding occurs even more frequently than in the case of HHV-6, and exposure to oral secretions is likely the major mode of transmission. The virus can be detected in breast milk, CSF, cervical tissue, and peripheral blood lymphocytes. Congenital infection is rare if it occurs at all.

HHV-7 infects CD4+ T lymphocytes and, less frequently, CD8+ and immature T cells; it produces latent infection. Reactivation of the virus results from macrophages and/or CD4+ T cells.

HHV-7 infections

Primary infection occurs predominantly in young children, but delayed primary HHV-7 infection can also present in adolescent (e.g., associated with encephalitis or to Guillain-Barré syndrome). The virus has also been linked to febrile seizures and in rare cases with seizures and acute hemiplegia. Coinfection with HHV-6 may play a role in the pathogenesis of this clinical manifestation. Cases of acute encephalitis rarely occur in immunocompetent adults. Exanthem subitum has also been linked to HHV-7 that presented with several days of fever followed by a exanthem subitum pink macular rash that was lighter than that seen with HHV-6, and finally with defervescence. Some evidence indicates that asymmetric periflexural exanthema (atypical exanthem subitum), a unilateral maculopapular eruption mostly seen in children, is associated with HHV-7 infection. An association of HHV-7 with pityriasis rosea and lichen planus has also been suggested.

The detection of HHV-7 DNA in transplant recipient serum is reported variably, and the role of this virus in posttransplant morbidity is not clear. This is because the majority of infections are transient, low-level, and not associated with any clinical manifestations. While HHV-7–related disease in hematopoietic cell transplant recipients is considered rare, the virus has been implicated in fever, rash, bone marrow suppression, thrombocytopenia, acute myelitis, and organ involvement.

Detection of HHV-7 infection

Infection is ubiquitous; serum antibodies can be identified in >85% of adults. Also, cross-reactivity between HHV-6 and HHV-7 in some assay systems may have complicated early studies of the viruses. A multiplex PCR method was developed and indicated a marked distinction between the amplicons of HHV-6 and HHV-7 without loss of sensitivity or specificity. ELISA might remain a valuable tool for the serological study of HHV-7 infection since the glycoprotein of the HHV-7 is highly conserved and induces a specific human immune response.

Treatment of HHV-7 infection

Few research data are available to guide treatment. Foscarnet or cidofovir are recommended for the clinically evident disease. HHV-7 appears resistant to ganciclovir, acyclovir, and penciclovir.

Human herpesvirus-8 (HHV-8)

HHV-8 is a member of the *Gammaherpesviruses* family along with HHV-4. HHV-8 or Kaposi's sarcoma–associated herpesvirus (KSHV) causes Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD).

Epidemiology, shedding, and tissue tropism of HHV-8

HHV-8 DNA has been recovered in semen and prostate samples as well as from oropharyngeal secretions. Transmission via blood products and tissue grafts is possible. For example, HHV-8 is transmitted to 25% to 33% previously uninfected recipients of solid organ grafts taken from an HHV-8-seropositive donor. Moreover, HHV-8 can be identified in blood from healthy donors, thus implying transmission from blood products, but this did not appear to occur commonly. The virus targets a variety of cell types, including B lymphocytes and Langerhans, monocyte-derived dendritic, and vascular endothelial cells. Lytic and latent infections occur. Lytic infection is characterized by the transcription of a wide array of viral genes producing gene products with immunomodulatory functions that participate in the pathogenesis of HHV-8–related conditions. Relatively few viral gene products are expressed in latently infected cells. In 2010, HHV-8 was declared a Group 1 carcinogenic agent by the International Agency for Research on Cancer, highlighting its public health significance. HHV-8 seroprevalence varies among geographic regions; for example, prevalence is high in Uganda (50%) and relatively low in the United States or Switzerland (6%). In central Africa, where KS was common before the HIV epidemic, the prevalence of HHV-8 infection increased from 39% to 48% in adolescents. In the United States, men who had sex with men and persons with HIV infection were at increased risk for HHV-8 infection.

In the absence of deficiencies of T-lymphocyte function, HHV-8 infection is clinically unremarkable. A viral version of interleukin-6 (*v*IL-6) appears to carry out a particularly important role in the inflammatory nature of HHV-8–related malignancies. The prevalence of HHV-8 infections in various populations and geographic regions is summarized in Table 186.2.

TABLE 186.2 **ESTIMATED PREVALENCE OF HHV-8 INFECTION IN VARIOUS GEOGRAPHIC REGIONS AND POPULATIONS**

Population	Prevalence[a]
General population in United States	1–5%
General population in sub-Saharan Africa	50%
General population in the Mediterranean	10–40%
General population in most parts of Asia	0–20%
MSM in United States and Europe	20–60%
Women in the general population in Nigeria	46.02%
Women in the general population in Spain	3.65%
FSWs in Central Africa	51%
FSWs HIV-positive in Honduras	36%
HIV pregnant women in Central Africa	37%
General population HIV-negative in Cameroon	80%
General population HIV-positive in Cameroon	81%
Solid organ recipients	5–10%

[a] Prevalence rates depend on type of diagnostic test, are higher with lytic antigen.
FSWs, female sex workers; MSM, men who have sex with men.

HHV-8–associated malignancies

Kaposi's sarcoma. Moritz Kaposi first described classic KS in 1872 as a rare skin tumor seen primarily in elderly men of Mediterranean or Ashkenazi Jewish origin. KS could present as (1) indolent classic KS that typically affects elderly men from the Mediterranean region with slow-growing lesions confined to the skin, (2) endemic KS in men and women from sub-Saharan African regions that is very aggressive and not related to HIV infection, and (3) AIDS-related or epidemic KS that can range from isolated skin lesions to more aggressive and rapidly disseminated disease. AIDS-related KS is more prevalent among men who have sex with men than in other HIV exposure groups (injection drug users). cART plays a protective role in the development of KS. An immune reconstitution phenomenon occurs either by the onset of KS or in worsening of existing KS lesions after initiation of cART. Generally, cART can be continued through immune reconstitutional KS but fatal disease has been reported. The incidence of KS among HIV-infected persons has considerably decreased in recipients of cART. Finally, KS could present as iatrogenic-associated KS occurring primarily in solid organ transplant recipients due to corticosteroids and/or cyclosporine A and/or other immunosuppressive drugs.

The occurrence of KS is associated with impaired natural killer lymphocyte responses characterized by altered surface receptor expression; resolution of this immune impairment can result in clinical regression. Early KS lesions appear as painless, faint red-violet or brown macules on legs, feet, or face that increase in size. Typically, untreated KS evolves from the skin to mucosal tissues; to lymphatics, often with lymphedema; and then to internal organs (e.g., colon and lungs). While KS remains a relatively typical form of cancer among solid organ transplant recipients, it occurs infrequently.

Multicentric Castleman's disease (MCD and MCD-associated plasmablastic lymphoma). MCD is a rare lymphoproliferative B-cell condition characterized by multicentric angiofollicular hyperplasia. It is associated with fever, lymphadenopathy, weight loss, and hepatosplenomegaly. Laboratory abnormalities include polyclonal hypergammaglobulinemia, hypoalbuminemia, cytopenias, elevated C-reactive protein, and high serum levels of IL-6. HHV-8–related MCD appears to be distinct from types unlinked to the virus and virtually inevitably occurs with HIV infection. By contrast with KS, the occurrence of MCD has not declined in the era of potent antiretroviral treatment. HHV-8 DNA sequences are found in the polyclonal plasmacytoid cells within lymph nodes that are diagnostic for HHV-8–associated MCD. The unique microRNA signatures of the virus sequences in patients with MCD may contribute to viral pathogenesis. Survival with MCD is variable, and the clinical course is remissive with severe flares associated with the intensity of HHV-8 viremia. No standard therapy exists for HHV-8 MCD though responses to antiretroviral and antiherpes drugs, humanized monoclonal anti-IL-6 receptor antibody, cytotoxic chemotherapies, anti-CD20 monoclonal antibody (rituximab), and/or glucocorticoids do occur. MCD can transition to a large B-cell non-Hodgkin's lymphoma. MCD has also been reported in allograft recipients.

Primary effusion lymphomas (PEL) or body cavity-based lymphoma (BCBL). This is a rare non-Hodgkin's lymphoma of B-cell origin occurring among persons with marked immunologic dysfunction, most commonly due to HIV infection. It is also involved in the posttransplantation setting and in elderly patients in areas where HHV-8 is endemic. PELs present as a neoplastic effusion of the pleural (most common site), pericardial, and peritoneal cavities in the absence of a solid tumor mass. PEL diagnosis requires typical body cavity malignant effusions and the presence of HHV-8; no other lymphomatous effusion expresses HHV-8. Solid lymphomas have been reported prior to and subsequent to PEL. In general, the prognosis of PEL is poor, though some HIV-infected patients demonstrate improvement after initiation of cART. In addition, noncurative but significant responses have been reported after the intracavitary administration of cidofovir, an antiviral drug with broad efficacy. PEL has also been reported in allograft recipients.

Detection of HHV-8 infection

Immunohistochemical staining of tumors with antibodies recognizing the HHV-8–encoded latency-associated nuclear antigen (LANA) and tissue examination are needed for the diagnoses of KS, MCD, and PEL. Also, molecular techniques can identify HHV-8 DNA within tumor tissue. Standardized methods for the detection of HHV-8 infections have yet to be established. Prevalence rates depend on the testing method as well as the population being evaluated. Indirect immunofluorescence and enzyme immunoassays have been developed for the detection of antibodies to lytic and latent HHV-8 antigens. Antibody assays range from 80% to 98% sensitivity in KS patients when compared to molecular techniques. The pattern of reactivity to lytic versus latent antigens does not appear to impart much clinical information.

Treatment of HHV-8 infection

Traditional treatment for KS, MCD, and PEL include reduction or elimination of any immunosuppressive treatment, chemotherapy, and/or radiation therapy. cART should be administered to all patients with HIV and KS, PEL, or MCD, although insufficient evidence exists. The clinical course of AIDS-related KS has improved considerably in the years since the introduction of cART, especially in patients with visceral or disseminated cutaneous KS involvement. Also, liposomal doxorubicin is preferred as first-line therapy for KS. Although limited data are available for PEL treatment, a combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) with ART chemotherapy should be administered. For patients with concurrent diagnoses of KS and MCD, use of both rituximab and liposomal doxorubicin is recommended. Therapeutic monoclonal antibodies targeting either IL-6 or the IL-6 receptor have also proved effective for some MCD patients. Ganciclovir, cidofovir, and foscarnet effectively inhibit HHV-8 and may be used with modifications of immune suppression.

Suggested reading

HHV-6 Foundation. Home page. https://hhv-6foundation.org/

International Agency for Research on Cancer (IARC). *Monographs on the evaluation of carcinogenic risks to humans. Biological agents, Volume*

100 B: A review of human carcinogen. Lyon, France: International Agency for Research on Cancer; 2012.

Labská K, Roubalová K, Pícha D, Marešová V. Presence of herpesvirus DNA in cerebrospinal fluid of patients with tick-borne encephalitis and enteroviral meningoencephalitis. *J Med Virol.* 2015;87:1235–1240.

National Institutes of Health. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. https://aidsinfo.nih.gov/guidelines/

Nzivo MM, Lwembe RM, Odari EO, Budambula NLM. Human herpes virus type 8 among female-sex workers. *J Hum Virol Retrovirol.* 2017;5(6):00176.

Pellett PE, Ablashi DV, Ambros PF, et al. Chromosomally integrated human herpesvirus 6: questions and answers. *Rev Med Virol*. 2012;22:144–155.

Polizzotto MN, Uldrick TS, Hu D, Yarchoan R. Clinical manifestations of Kaposi sarcoma herpesvirus lytic activation: Multicentric Castleman disease (KSHV-MCD) and the KSHV inflammatory cytokine syndrome. *Front Microbiol*. 2012;3:73.

Razonable RR. Human herpesviruses 6, 7 and 8 in solid organ transplant recipients. *Am J Transplant*. 2013;13(Suppl 3): 67–77; quiz 77–78.

Tzannou I, Papadopoulou A, Naik S, et al. Off-the-shelf virus-specific T cells to treat BK virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol*. 2017;35(31):3547–3557.

Influenza

Ramin Sedaghat Herati and Harvey M. Friedman

Influenza infections have caused significant morbidity and mortality throughout recorded human history. Each year, seasonal influenza is estimated to cause around 500,000 excess deaths worldwide. At least 32 pandemics have occurred since 1580 in addition to the seasonal waves of influenza infection. In 1918, a particularly severe pandemic, dubbed the "Spanish flu," led to the rapid spread of influenza and resulted in at least 20 million deaths worldwide. Recently, the possibility of a worldwide pandemic due to pathogenic avian influenza viruses has become of great concern. Significant resources worldwide have been dedicated to the detection and containment of influenza outbreaks and the development of response plans to influenza epidemics at international, national, and local levels.

Influenza viral structure

Influenza viruses are enveloped, single-stranded, negative-sense RNA viruses in the family Orthomyxoviridae, which include the genera Influenzavirus types A, B, and C. Influenza viruses are spherical and 80 to 120 nm in diameter. Influenza A and B viruses cause the majority of human infections with influenza, whereas influenza C virus causes only sporadic upper respiratory infections. Influenza A viruses can cause infections in birds as well as humans, swine, and other mammals.

Influenza virus has an envelope composed of a lipid bilayer, with a layer of matrix protein on the inner surface and spike-like surface projections of glycoproteins on the outer surface. These glycoproteins include hemagglutinin and neuraminidase. Hemagglutinin is responsible for binding to those cells of the respiratory tract expressing sialic acid. Once endocytosed, hemagglutinin then fuses with the endosome membrane and releases viral ribonucleoproteins into the cytoplasm, which leads to viral replication. In contrast, neuraminidase primarily functions in the last stage of cellular infection by enzymatic cleavage of sialic acid and release of mature virions from the cell surface. Within the envelope of influenza A and B are eight segments of viral RNA encoding polymerase proteins A, B1, and B2; hemagglutinin; neuraminidase; matrix proteins M1 and M2; nucleocapsid protein; and nonstructural proteins NS1 and NS2.

Epidemiology

Antigenic drift and shift

One of the most remarkable features of influenza virus is the frequency of its antigenic changes, known as *antigenic drift* and *antigenic shift*, which contribute to incomplete immunity to future influenza viral infections. Antigenic shift and antigenic drift principally involve the two external glycoproteins of the virus, hemagglutinin and neuraminidase. Antigenic drift occurs commonly and is due to point mutations in the hemagglutinin or neuraminidase genes, which may result in alteration of the immunological targets

for antibodies generated by prior infections. Antigenic shift, on the other hand, occurs infrequently and results from major genetic reassortments between human and animal viral strains. Antigenic drift is primarily seen in influenza A viruses but can be seen in influenza B viruses as well.

Antigenic shifts can produce immunologically novel strains of influenza A that herald the epidemics and worldwide pandemics. In 2009, infections with a novel H1N1 virus, thought to derive from reassortment of avian, swine, and human influenza viruses, resulted in a pandemic. First recognized as a major threat in April 2009, the virus spread rapidly and may have resulted in >300,000 deaths within 15 months worldwide. Three subtypes of hemagglutinin, H1 (variants H0, H1, Hsw1), H2, and H3, and two subtypes of neuraminidase, N1 and N2, are recognized among human influenza A viruses. Only a few strains of influenza A or B virus tend to dominate during each annual influenza season. The World Health Organization (WHO) is leading the global effort to detect and characterize influenza outbreaks before they become pandemics.

Pathogenic avian influenza strains can sometimes cross species and cause human infections. For example, avian H5N1 was originally thought to be endemic in many wild bird populations and not pathogenic in humans. However, beginning in 1997, multiple cases of laboratory-confirmed human H5N1 infection have been reported annually. Unfortunately, humans have little preexisting immunity to H5N1, and an overall case fatality rate of 60% has been observed. Isolated human-to-human transmission has been observed, but the vast majority of cases have occurred in individuals in close contact with infected birds without subsequent human-to-human transmission. In 2013, another avian-origin virus, H7N9, was identified in China as a cause of severe respiratory tract infections with a 39% case fatality rate. In contrast to H5N1, infected birds are asymptomatic and thus environmental surveillance has been challenging. For both H5N1 and H7N9, significant effort has been placed into surveillance and rapid culling of bird populations as a means to limit spread.

Transmission

Most influenza infections are acquired through human-to-human transmission of small-particle aerosols. Localized clusters of infection begin rather abruptly, reach a sharp peak in 2 to 3 weeks, and wane in incidence over the subsequent 5 to 6 weeks. Attack rates during such outbreaks can approach 10% to 40%. Although influenza is virtually always active somewhere in the world, seasonal influenza is most common during the winter months. The peak influenza season typically extends from December through April in the Northern Hemisphere. *Influenza season* is defined by viral isolation, whereas an *epidemic* is defined by a rise in pneumonia and influenza deaths above the epidemic threshold in the US Centers for Disease Control and Prevention (CDC)'s nationwide mortality surveillance system. Although influenza can affect all individuals in a population, severe infections resulting in hospitalization during most influenza seasons generally occur among adults >65 and children aged 0 to 4 years.

Immunology

Influenza infection results in activation of the innate and adaptive arms of the immune system. Upon initial infection, innate pattern-recognition receptors including Toll-like receptor 7 (TLR7) "sense" the infection and lead to pro-inflammatory cytokine production. Dendritic cells acquire and present influenza antigens to T cells, which leads to stimulation of the adaptive immune system. Naïve and memory T cells, including CD4 and CD8 subsets, then mediate a variety of responses including recruitment of additional immune effectors, direct killing of infected cells, and B-cell help. Neutralizing antibodies are produced by B cells and block the ability of free influenza virions from infecting additional cells. After a successful immune response, tissue repair takes place and inflammation returns to baseline, along with the death or egress of most of the responding immune cells. Memory T and B cells are established that respond more quickly to subsequent infections. For many decades, neutralizing antibody titers have been used as a strain-specific correlate of protection against future infections. A titer of ≥1:40 indicates that an individual is likely protected. However, this correlate has limitations. Some individuals with low titers of neutralizing antibodies are resistant to infection in experimental challenge models, whereas some with very high titers become infected. Work to develop better correlates of protection is ongoing.

Clinical manifestations

Uncomplicated influenza

Classic influenza is characterized by the abrupt onset of symptoms including fever, headaches, and myalgias after an incubation period of 1 to 4 days. Systemic symptoms predominate initially, including chills or rigors, malaise, and anorexia. Severe intraocular muscle pain can often be elicited on lateral gaze. Calf muscle myalgia may be particularly prominent in children. The systemic symptoms usually persist for approximately 7 days and then wane. Respiratory symptoms, such as dry cough and nasal discharge, emerge early during the illness and begin to dominate the clinical presentation as fever resolves. Cough is the most common symptom and can take several weeks to resolve.

Complications of influenza

The complications of influenza can be classified as pulmonary and nonpulmonary and result either from progression of the viral process itself or from secondary bacterial infections. Influenza can be associated with a primary influenza viral pneumonia and/or a secondary bacterial pneumonia (Table 187.1). Nonpulmonary complications of influenza occur less often and are most prevalent during large outbreaks. These include myositis (more common with influenza B infection), myocarditis, pericarditis, transverse myelitis, encephalitis, and Guillain–Barré syndrome. A toxic shock–like syndrome has occurred in previously healthy children and adults during outbreaks of influenza A or B. This syndrome has been attributed to

TABLE 187.1 **PULMONARY COMPLICATIONS OF INFLUENZA**

Feature	Primary viral pneumonia	Secondary bacterial pneumonia
Setting	Cardiovascular disease, pregnancy, young adults (in large outbreaks)	Age >65 years, chronic pulmonary, cardiac, or metabolic disease
History	Rapid progression after typical onset	Biphasic illness, with worsening after initial clinical improvement
Physical examination	Diffuse crackles	Diminished breath sounds, egophony, bronchophony
Sputum culture	Normal oral flora	Streptococcus pneumoniae Staphylococcus aureus *Haemophilus influenzae*
Isolation of influenza virus	Yes	No
Chest radiograph	Diffuse bilateral interstitial disease	Lobar consolidation
Response to antibiotics	No	Yes
Mortality	Variable, high during some pandemics	Variable, generally low

the effects of the viral infection on the colonization and replication characteristics of toxin-producing staphylococci. Reye's syndrome has also been described in children treated with aspirin during influenza outbreaks. The major causes of death are pneumonia and exacerbation of chronic cardiopulmonary conditions. Of those who die, 80% to 90% are aged 65 years or older.

H5N1 infection

Most cases of H5N1 have occurred in healthy young adults, approximately 2 to 4 days after exposure to infected birds. Initial symptoms include high fever and an influenza-like illness. In contrast to infection with human influenza viruses, lower respiratory tract involvement and clinically apparent pneumonia are almost universal. Watery diarrhea may be present before the development of respiratory symptoms. Progression to multiorgan failure, including respiratory, renal, and cardiac failure is common. Atypical presentations, such as encephalopathy, gastroenteritis, and mild respiratory disease, have been reported, but frequencies of such presentations are unknown. Death occurs on average 9 to 10 days after the onset of illness. Asymptomatic infection likely occurs as well, as indicated by antibody screens in populations at risk, but the true incidence is unknown.

Diagnosis

A clinical diagnosis based on fever, headache, myalgias, and cough during influenza season has an accuracy of 60% to 85%. However, influenza cannot be distinguished from other respiratory viruses by symptoms alone, and typically other respiratory viruses are often in circulation concurrently during the winter months. Reverse transcriptase-polymerase chain reaction (RT-PCR) assays are extremely sensitive, specific, and rapid, which has made them the standard for diagnosis. Other rapid assays include immunofluorescence, which requires skilled expertise and has lower sensitivity than RT-PCR, and viral antigen studies that are rapid but typically do not give information on the specific viral strain. Viral culture is utilized in some areas but can take days for a result. Serologic tests to measure hemagglutinin neutralizing antibody titers in acute and convalescent sera are not recommended by the CDC for diagnosis due to difficulty in obtaining a convalescent serum and the delay required to establish the diagnosis.

Therapy

Multiple classes of antiviral drugs are available for treatment of influenza. Zanamivir and oseltamivir are two neuraminidase inhibitors (NIs) approved for treatment of both influenza A and B infection by inhibiting neuraminidase activity and thereby preventing viral particle release from infected cells. Zanamivir has poor oral bioavailability and is formulated for oral inhalation using a disk inhaler. Oseltamivir is the ethyl-ester prodrug of the active compound and is well absorbed orally. A third NI is peramavir, which is available as an intravenous formulation. When given within 48 hours after the onset of symptoms, NI decrease the duration of symptoms by about 24 hours. Meta-analyses indicate a reduction in the incidence of influenza-related complications including pneumonia and bronchitis when administered early during the course of an infection. There are insufficient data as to whether NIs are effective treatment of these complications once they occur, but they may have some modest benefit. These agents are generally well tolerated, although zanamivir can cause bronchospasm and respiratory compromise in patients with chronic respiratory diseases. Despite resistance developing during treatment with oseltamivir in up to 25% of individuals, transmission of resistant strains is uncommon.

The M2 inhibitors, amantadine and rimantadine, are an older class of drugs used for treatment of influenza A. The M2 inhibitors prevent viral replication by blocking the M2 protein ion channel, thus preventing fusion of the virus and host cell membranes. Both drugs have been shown to reduce the duration of symptoms of clinical influenza but have been associated with several adverse effects. For example, amantadine causes reversible central nervous system

(CNS) toxicities, including insomnia, dizziness, nervousness, and difficulty concentrating, especially in the elderly. Viral resistance to M2 inhibitors has increased over time among influenza A isolates, and their use has not been recommended during recent influenza seasons.

Baloxavir represents the first drug in a new class of influenza antivirals. Approved in 2018 for the treatment of influenza A, baloxavir inhibits influenza cap-dependent endonuclease. In the studies that led to its approval, a single dose of baloxavir reduced duration of symptoms by 1 day compared to placebo and was similar in effect to oseltamivir. Moreover, baloxavir has shown activity against avian H7N9 and H5N1 strains. Other agents in development include the polymerase basic protein 1 (PB1) inhibitor favipiravir, and the polymerase basic protein 2 (PB2) inhibitor pimodivir.

Prevention

Vaccine

Vaccination is the mainstay of influenza prevention. Because influenza viruses undergo frequent antigenic alterations, the vaccine is reformulated annually with strains predicted to predominate in the upcoming winter epidemic. The CDC, in conjunction with the WHO, tracks influenza activity throughout the world to predict the components of the annual influenza vaccine. Vaccines generally target two strains of influenza A and one or two strains of influenza B. The protective efficacy of influenza vaccination depends on the similarity between the viruses used in the vaccine and those in circulation, as well as an individual's age and immune status. In young healthy adults, a well-matched vaccine is 60% to 70% effective at preventing influenza illness. During poorly matched seasons, efficacy decreases substantially. In adults >65, efficacy is often much lower than in young healthy adults. Among people living with HIV, efficacy is lowest among those with low CD4 counts (≤200/mm^3) and uncontrolled HIV viremia. Individuals receiving antiretroviral therapy probably derive protection from vaccination but not as effectively as HIV-uninfected adults. Similarly, solid organ transplant recipients likely also derive less benefit from vaccination. However, vaccination may still be effective at decreasing hospitalization, secondary complications, and death due to influenza even if efficacy against primary infection is poor.

Several options exist for influenza vaccination. The inactivated influenza intramuscular vaccine (IIV) is the most commonly administered version and is more immunogenic in adults, whereas the live attenuated intranasal vaccine (LAIV) is less frequently used and is more immunogenic in children. Several options for IIV exist, including a high-dose IIV vaccine that is more immunogenic in older adults than conventional IIV and a recombinant IIV that reduces vaccine production time and eliminates the need for eggs. Influenza vaccines are generally unadjuvanted, but a new vaccine combining the oil-in-water adjuvant MF59 with three inactivated strains was approved in 2015 for adults ≥65 years.

Contraindications to influenza vaccination are few. Individuals who have a severe allergic reaction to influenza vaccination should not be vaccinated, although such cases are exceedingly rare. Individuals with moderate or severe acute febrile illnesses usually have vaccination delayed until their symptoms have abated, due to likely reduced effectiveness. However, minor illnesses with or without fever are not a contraindication. The LAIV is approved only for healthy, nonpregnant individuals between ages 2 and 49 years. Although a history of Guillain–Barré syndrome after vaccination and egg allergies is not a formal contraindication to vaccination, extra precautions should be taken when vaccinating these individuals. The optimal time for organized vaccination campaigns for persons in high-risk groups is typically October through December. Recommendations for the use of influenza vaccine are listed in Table 187.2.

Chemoprophylaxis

Chemoprophylaxis is an important adjunct to vaccination. Vaccination-induced neutralizing antibodies to influenza peak

TABLE 187.2 **AVAILABLE SEASONAL INFLUENZA VACCINES.**

Vaccine	Recommended recipients	Contraindications
Inactivated influenza vaccine (IIV)	All individuals >6 months of age	History of severe allergic reaction to this vaccine[a]
Inactivated influenza vaccine (IIV), high dose	Age 65 and older	History of severe allergic reaction to this vaccine[a]
Live attenuated influenza vaccine (LAIV)	Healthy, nonpregnant, ages 2–49 years	History of severe allergic reaction to this vaccine[a] Immunosuppressed patients, healthcare personnel in close contact with immunosuppressed populations, children with history of asthma or severe wheezing
Recombinant influenza vaccine	Ages 18–49	History of severe allergic reaction to this vaccine[a]
Adjuvanted influenza vaccine	Age 65 and older	History of severe allergic reaction to this vaccine[a]

[a] Individuals with active moderate or severe febrile illness usually should not be vaccinated until symptoms have abated. Individuals with a history of egg allergy may receive these vaccines if administered with additional observation and safety measures. History of Guillain–Barré syndrome within 6 months of receipt of an influenza vaccine is considered to be a precaution for future vaccinations.
Adapted from Interim Recommendations: Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2013.

at 2 to 3 weeks after vaccination. Thus chemoprophylaxis may be considered in high-risk individuals until immunity develops. Some high-risk individuals, such as organ transplant recipients, have poor responses to vaccination and should be considered for additional protection with chemoprophylaxis. Chemoprophylaxis may also be effective at controlling outbreaks in chronic care settings.

Oseltamivir and zanamivir are available for prophylaxis of influenza A and B for patients at high risk of influenza complications or those who cannot receive influenza vaccine. Zanamivir, at a dosage of 10 mg/d over a 4-week period, and oseltamivir, at 75 mg/d over a 6-week period, reduced laboratory-confirmed cases in healthy adult volunteers by 82% and 84%, respectively. Both drugs are also effective at decreasing secondary spread of influenza. Lower rates of influenza among household contacts of suspected cases of influenza were documented in patients who took zanamivir for 10 days or oseltamivir for 7 days compared with placebo. In addition to neuraminidase inhibitors, baloxavir marboxil has been approved for chemoprophylaxis as well.

Pandemic preparedness

The emergence of the avian influenza virus, H5N1, has raised awareness of the possibility of a severe, worldwide influenza pandemic. By some estimates, 30% or more of individuals could become ill during a pandemic. Healthcare systems will likely become overwhelmed, and supplies such as vaccines, antivirals, antibiotics, ventilators, and personal protective equipment will be in short supply. Very likely, there will not be adequate hospital beds to meet healthcare needs. Public health measures, including school closings, travel bans, and individual quarantine, may cause significant social disruption. Absenteeism could exceed 40% and have profound effects on commerce, the economy, and the supply of goods and services.

Proper planning could lessen the effects of a pandemic on society. Preparedness on federal, state, and local levels is crucial, but business and healthcare sectors as well as individuals must also prepare. Hospitals, clinics, and long-term care facilities are encouraged to develop pandemic preparedness plans that include the development of surveillance systems for identifying potential outbreaks, plans for communication (i.e., with public officials, employees, and patients), strategies for dealing with surges in patient volume (including triage, admissions, cohorting, and facility access), and protocols for dealing with sick and exposed employees and the reassignment of worker duties. Other important issues include developing guidelines for the distribution of antivirals, vaccines, and medical supplies that may be limited. Healthcare workers should also encourage patients to develop their own pandemic preparedness plans with their families.

The CDC provides checklists, guidelines, and suggestions for pandemic planning in healthcare, family, school, business, and community, state, and local government settings. Given the likely limited availability of vaccine and antiviral medication during the initial waves of a pandemic, the CDC is also promoting nonpharmacologic interventions to limit transmission of the virus. This strategy has been termed *targeted layered containment* and includes isolation of ill persons and voluntary quarantine of household contacts, social distancing measures (i.e., school closure, increased use of telecommuting in the workplace, and masks in public settings), cancellation of public events and public gatherings (including closure of houses of worship), and individual infection control measures (such as hand hygiene and cough etiquette). These measures may help limit viral spread during a pandemic and reduce morbidity and mortality. The COVID-19 pandemic has demonstrated the value of public health measures to help mitigate morbidity and mortality during a pandemic.

Suggested reading

Cavallazzi R, Ramirez JA. Influenza and viral pneumonia. *Clin Chest Med*. 2018;39(4):703–721.

Centers for Disease Control and Prevention (CDC). Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2018-19 influenza season. *Morb Mortal Wkly Rep*. 2018;67(3):1–20.

Davidson S. Treating influenza infection, from now and into the future. *Front Immunol*. 2018;9:1946.

Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12(1):36–44.

Treanor JJ. Chapter 167: Influenza viruses including avian influenza and swine influenza. In Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* 8th ed. New York: Churchill Livingstone; 2014: 2000–2024.e7.

World Health Organization. *Pandemic influenza risk management: WHO interim guidance*. Geneva: World Health Organization; 10 June 2013.

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Coronavirus-19

Smitha Gudipati, Gina Maki, Marcus Zervos, and Mayur Ramesh

Overview

Coronaviruses are a large group of viruses that can infect humans as well as many animal species. They result in a wide range of primarily respiratory illnesses in humans. Coronavirus epidemics first originated in 2002, with the severe acute respiratory syndrome coronavirus (SARS-CoV), first reported in Guangdong Province and thought to have originated in bats. The second large epidemic from a coronavirus occurred 10 years later, in 2012, in Saudi Arabia, now referred to as the Middle East respiratory syndrome coronavirus (MERS-CoV). MERS-CoV is also a zoonotic disease thought to originate in bats and was transmitted to a large reservoir, the dromedary camel. Most recently, a third coronavirus has swept around the globe from 2019 to 2020, now termed the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing hundreds of thousands of deaths.

Epidemiology

The coronavirus-19 disease (COVID-19) caused by SARS-CoV-2 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. The first cases were reported in the city of Wuhan, Hubei Province, in December 2019, after presenting as a cluster of pneumonia cases of unknown etiology. By January 23, 2020, Wuhan declared a state of emergency and implemented a travel ban, with a reported 571 cases of COVID-19 across 25 provinces (districts and cities) in China. By January 30, 2020, China had confirmed 7,734 cases, with 90 other cases reported across a number of countries including Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Cambodia, Japan, Singapore, Republic of Korea, United Arab Emirates, United States, The Philippines, India, Australia, Canada, Finland, France, and Germany. Over the following months, the virus continued to spread rapidly around the world. As of September 1, 2020, there were 25,602,665 confirmed cases and 852,758 deaths worldwide, with every continent affected except Antarctica.

The original cases were traced back to the Huanan seafood market where seafood as well as exotic animals such as snakes, birds, and bats were sold. With genome sequencing finding a 96% match to a known bat coronavirus, it was suspected that bats were the original source of the SARS-CoV-2 virus. By February, a study from China revealed the possibility of person-to-person transmission of the virus. Current data suggest the virus is spread by respiratory droplets, with a range of transmission of 6 feet (or about 2 meters). Droplets, however, have also been noted to spread further and possibly become aerosolized with activities such as coughing and sneezing. Fomites are also a noted source, with transmission from an infected surface to a person's hands and subsequently to mucous membranes. SARS-CoV-2 has been detected in nonrespiratory specimens, including stool, blood, ocular secretions, and semen. However, the role of transmission via these routes is unclear. To date there has been no evidence to support the transmission through contact with non–mucous membrane sites. Few reports suggest the possibility of vertical transmission from mother to baby,

however this is thought to be rare, with a more common cause of neonatal COVID-19 disease from respiratory droplets after birth. SARS-CoV-2 transmission has been well documented from asymptomatic individuals and has played a major role in the spread of the COVID-19 pandemic.

Microbiology

Coronaviruses are members of the Coronaviridae family. They are divided into alphacoronavirus and betacoronavirus that can only infect mammals, and gammacoronavirus and deltacoronavirus, which mostly infect birds. SARS-CoV-2 is a betacoronavirus, an enveloped, positive, single-stranded RNA surrounded by spike glycoproteins that can infect animals and humans (Figure 188.1).

Pathogenesis

SARS-CoV-2 enters the cell through membrane fusion. The first step of the SARS-CoV-2 replicative cycle is attachment of the virus to angiotensin-converting enzyme-2 (ACE-2) glycoprotein, which has a preference for lung epithelial cells. However, ACE-2 is also expressed in the small intestine, kidneys, heart, thyroid, and adipose tissue. The receptor binding domain of the spike protein then latches onto the ACE-2 receptor, followed by cleavage of the spike protein by host transmembrane protease, serine 2 proteases (TMPRSS2), to expose fusion peptides able to fuse the viral and cell membranes.

Once SARS-CoV-2 enters a human cell, the virion releases its RNA in the cytoplasm. Translation and replication occur, and new virions are then released from the cell through exocytosis. In COVID-19, the immune response can be explosive, creating a hyperinflammation syndrome during the second week of the COVID-19 infection.

A cytokine response usually occurs approximately 8 days after symptom onset, and this often requires intensive care support, mechanical ventilation, and is associated with inflammatory factor elevation including interleukin (IL)-6, IL-1B, IL-8; interferon (INF)-y, tumor necrosis factor (TNF)-α; monocyte chemoattractant protein (MCP)-1, and interferon γ-induced protein (IP-10). IL-6 elevation in the serum correlates with acute respiratory distress syndrome and multiple-organ failure.

Clinical manifestations

The incubation period ranges from 2 to 14 days, with an average of 5 days. The mode of transmission is through respiratory droplets (primary mode) or contact with contaminated objects and surfaces. Aerosolized particles (<5 microns) can be generated during certain procedures. The virus can survive <24 hours on cardboard, <72 hours on plastic or steel. Symptoms and risk factors associated with COVID-19 are listed in Table 188.1.

The WHO has stratified COVID-19 disease based on severity. Although approximately 15% of patients are asymptomatic, the spectrum ranges from mild to critical disease (Table 188.2).

Other complications that have been described in COVID-19 patients include acute, life-threatening conditions such as acute pulmonary embolism, acute coronary syndrome, myocarditis, acute stroke, and delirium. Clinical suspicion for these complications should be heightened when caring for COVID-19 patients, and appropriate diagnostic and treatment protocols are available.

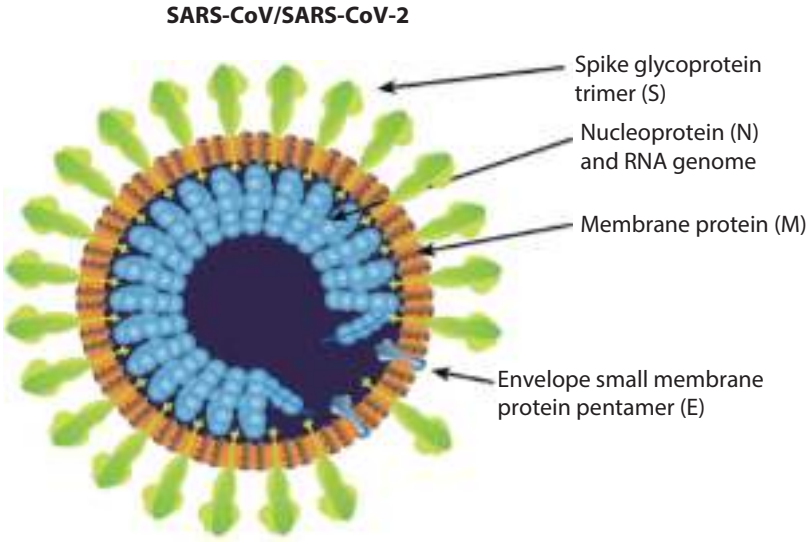

FIGURE 188.1 Molecular image of SARS-CoV-2, which is a Betacoronavirus, enveloped, positive single-stranded RNA surrounded by spike glycoproteins.

TABLE 188.1 **SYMPTOMS AND RISK FACTORS ASSOCIATED WITH COVID-19**

Clinical presentation	Most persons experience fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), myalgias (11–35%). Other nonspecific symptoms, such as sore throat, nasal congestion, headache, diarrhea, nausea, and vomiting, have also been reported. Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported.
Risk factors for severe disease	Age >60 years (increasing with age). Underlying noncommunicable diseases (NCDs): obesity, smoking, diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, chronic kidney disease, immunosuppression, and cancer have been associated with higher mortality.

COVID-19 in special populations

Transplant population

Early reports have suggested poorer outcomes in solid organ transplant recipients with COVID-19 because of chronic immunosuppression and higher rates of comorbidities. In a case control study done at Henry Ford Hospital in Detroit, Michigan, a greater proportion of COVID-19–positive solid organ transplant recipients had coexisting conditions, particularly congestive heart failure, diabetes, chronic kidney disease, and hypertension, compared to non-transplant patients. Interestingly, despite this observation, mortality and other

TABLE 188.2 **SPECTRUM OF COVID-19 DISEASE SEVERITY**

Symptomatic infection	
Mild to moderate disease (80% of patients)	Symptomatic patients (Table 188.1) meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥90% on room air. Child with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia. Increased respiratory rate (in breaths/min): <2 months: ≥60; 2–11 months: ≥50; 1–5 years: ≥40.
Severe disease (14% of patients)	Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO_2 <90% on room air. Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: 1. Central cyanosis or SpO_2 <90%; severe respiratory distress (e.g., fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. 2. Increased respiratory rate (in breaths/min): <2 months: ≥60; 2–11 months: ≥50; 1–5 years: ≥40.
Critical disease (6% of patients) **Sepsis** **Septic shock**	Acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proved infection. Signs of organ dysfunction include altered mental status, dyspnea, tachypnea, hypoxia, anuria, tachycardia, feeble pulse, hypotension, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate levels, or hyperbilirubinemia. Persistent hypotension despite volume resuscitation, requiring vasopressors to maintain a mean arterial pressure (MAP) of ≥65 mm Hg and serum lactate level of >2 mmol/L.
Acute respiratory distress syndrome (ARDS)	**Onset**: Within 1 week of a known clinical insult (i.e., pneumonia) or new or worsening respiratory symptoms. **Chest imaging**: Radiograph, CT scan, or lung ultrasound: Bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates**: Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic cause of infiltrates/edema if no risk factor present. **Oxygenation impairment in adults**: • Mild ARDS: 200 mm Hg < PaO_2/FiO_2a ≤300 mmHg (with PEEP or CPAP ≥5 cm H_2O). • Moderate ARDS: 100 mm Hg < PaO_2/FiO_2 ≤200 mm Hg (with PEEP ≥5 cm H_2O) • Severe ARDS: PaO_2/FiO_2 ≤100 mm Hg (with PEEP ≥5 cm H_2O)

Abbreviations: CPAP = continuous positive airway pressure, PEEP = positive end-expiratory pressure.

adverse outcomes did not occur more frequently among solid organ transplant recipients. The reasons for this are currently unknown but may be related to blunting of inflammatory cascades and cytokine release due to chronic immune suppression in transplant recipients. Mortality in COVID-19–positive solid organ transplant recipients is likely driven by the severity of illness at presentation rather than transplant status. More research is needed to elucidate these theories further.

Patients living with HIV

Current retrospective studies and case and cohort series have suggested that patients living with HIV are not at a greater risk of severe disease or death as compared to patients without HIV. Germany presented 33 virally suppressed people living with HIV and infected with COVID-19; 76% had mild infection, 27% had severe infection, and 3% died. Additionally, an observational prospective study from Madrid, Spain, analyzed 51 patients living with HIV and diagnosed with COVID-19, of whom 69% required hospitalization, 63% had one comorbidity, and 12% were critically ill. Patients living with HIV at Henry Ford Hospital in Detroit, Michigan, had similar comorbidities and hospital admissions compared with non-HIV patients admitted with COVID-19. In a recent publication of 463 patients infected with COVID-19 but without known HIV infection, the investigators from Henry Ford Hospital found that the three most common comorbidities were hypertension (63.7%), obesity (57.6%), and diabetes (38.4%). Patients in this study also had a 16% overall 30-day mortality rate. These comorbidities were also the three most common in the Henry Ford Hospital HIV population (57%, 57%, and 43%, respectively) with a 21% overall 30-day mortality rate. Based on multiple retrospective and cohort and case series, patients living with HIV should not be considered to be protected from COVID-19 or to have a lower risk of severe disease. Therefore, they should receive the same treatment approach applied to the general population.

Pregnancy

There are limited data on the clinical presentation and outcomes of pregnant individuals with COVID-19. Per the WHO, pregnant patients exhibit the same clinical presentation as the general population. As stated earlier, there are a few reports suggesting the possibility of vertical transmission from mother to baby. However, this is thought to be rare, with a more common cause of neonatal COVID-19 disease occurring from respiratory droplets after birth.

Pediatrics

Acute COVID-19 is less severe and results in lower hospitalization rates in children based on limited data. However, on May 14, 2020, the US Centers for Disease Control and Prevention (CDC) issued a national health advisory to report on cases meeting the criteria for multisystemic inflammatory syndrome in children (MIS-C). This syndrome is a rare late complication of COVID-19 that exhibits a clinical presentation that is similar to that of Kawasaki's disease. Symptoms include fever and mucocutaneous manifestations, and children >5 years of age have been found to have an association with cardiovascular involvement.

Radiological findings

The majority of patients show bilateral pneumonia, and only a small percentage of COVID-19 patients show unilateral pneumonia on chest imaging (Figure 188.2). The most frequent CT findings are bilateral patchy shadows and ground-glass opacities. Multilobe involvement and focal lesions (patches, stripes, or nodules) are also very characteristic. Less characteristic CT findings include centrilobular nodules, tree-in-bud sign, cystic change, pleural effusion, interstitial fibrosis, or lymphadenopathy. CT examinations show that lesions are more likely to be localized in the periphery than in the center of the lungs, and the lesions are more likely to be patchy than oval-shaped (Figure 188.3).

Laboratory diagnosis

The information in this section is valid as of September 1, 2020. Accurate molecular diagnostic tests are necessary to confirm a diagnosis of COVID-19 because clinical assessment alone is not accurate in predicting COVID-19 diagnosis due to its nonspecific symptoms. Direct detection of SARS-CoV-2 nucleic acid in respiratory tract specimens assists in patient-, healthcare institution–, and public health-level decision-making.

Nucleic acid amplification test

A SARS-CoV-2 nucleic acid amplification test (NAAT) is recommended in symptomatic individuals in the community

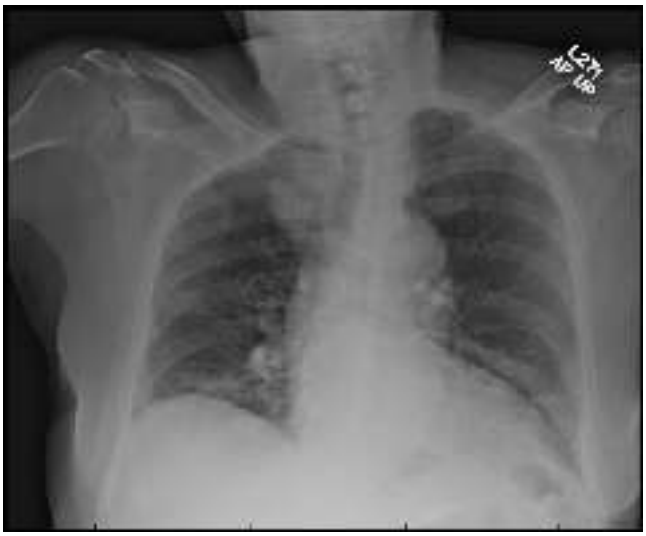

FIGURE 188.2 Chest x-ray revealing bilateral bibasilar infiltrates suggestive of COVID-19.

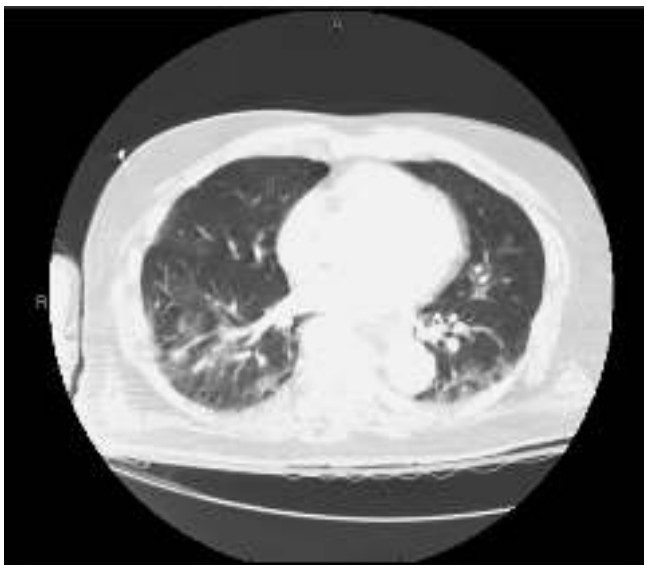

FIGURE 188.3 Peripheral parenchyma changes on CT imaging suggestive of COVID-19.

suspected of having COVID-19 or in individuals with known high-risk exposures to SARS-CoV-2. This test should be collected through nasopharyngeal, mid-turbinate, or nasal swabs rather than oropharyngeal swabs or saliva alone for SARS-CoV-2 RNA testing, with no recommendation of combination testing. Sensitivity and specificity of each test is noted in Table 188.3. The Infectious Disease Society of America (IDSA) panel suggests initially obtaining an upper respiratory tract sample rather than a lower respiratory sample for SARS-CoV-2 RNA testing in hospitalized patients with suspected COVID-19 lower respiratory tract infection. Results within 48 hours of collection are preferable so that they can be used to determine individual care and public health decisions. False negatives may result from improper sampling or handling, low viral load, or viral mutations.

In asymptomatic individuals who are either known or are suspected to have exposure to COVID-19, it is recommended that SARS-CoV-2 RNA testing be performed in the following situations:

1. A *known exposure*, defined as direct contact with a laboratory-confirmed case of COVID-19
2. A *suspected exposure*, defined as working or residing in a congregate setting (i.e., long-term care, correctional facility, cruise ship, factory) experiencing a COVID-19 outbreak
3. The individual exposed was not wearing appropriate personal protective equipment (PPE)
4. Immunocompromised asymptomatic individuals are being admitted to the hospital regardless of exposure of COVID-19
5. Any immunocompromised individuals, defined as receiving procedures such as cytotoxic chemotherapy, solid organ or stem cell transplantation, long-acting biologic therapy, cellular immunotherapy, or high-dose corticosteroids
6. Asymptomatic individuals before immunosuppressive procedures regardless of known exposure to COVID-19
7. Asymptomatic individuals who are undergoing major time-sensitive surgeries, defined as medically necessary surgeries that need to be done within 3 months. This does not include only aerosol-generating procedures (i.e. bronchoscopy) when proper PPE is unavailable

Serology

Serologic testing is not recommended to diagnose SARS-CoV-2 infection during the first 2 weeks (14 days) following symptom onset (Figure 188.4). Immunoglobulin G (IgG) or total antibody testing is only recommended 3 to 4 weeks after symptom onset to detect evidence of past SARS-CoV-2 infection for clinic or epidemiological purposes or if the individual has had repeatedly negative NAAT testing. It should not be used as the sole basis for diagnosing acute SARS-CoV-2 infection or to determine whether an individual is immune to SARS-CoV-2 infection.

Other supporting laboratory findings

Normal or decreased white blood cell counts, lymphopenia, or thrombocytopenia have all been associated with COIVD-19. Higher levels of C-reactive protein (>150 mg/L) and increased D-dimer levels (>1 mg/L) are also strongly associated with an increased risk of COVID-19 pneumonia. Additional laboratory indicators of increased risk include elevated alanine aminotransferase (ALT) (>80 U/L), aspartate aminotransferase (AST) (>80 U/L), α-hydroxybutyrate dehydrogenase (>540 U/L), lactate dehydrogenase activity (>720 U/L), and creatine kinase activity (>600 U/L), and lower total protein level (<60 g/L).

The decrease in the number of lymphocytes is generally observed in the CD4+ subpopulation. No significant changes

TABLE 188.3 **SENSITIVITY AND SPECIFICITY FOR EACH COVID-19 DIAGNOSTIC MODALITY**

	Oral	Nasal	Nasopharyngeal	Saliva	Mid–turbinate
Sensitivity % (95% CI[a])	56 (35–77)	76 (59–94)	97 (92–100)	85 (69–94)	100 (93–100)
Specificity % (95% CI[a])	99 (99–100)	100 (99–100)	100 (99–100)	100 (99–100)	100 (99–100)

[a]Cl, confidence interval.

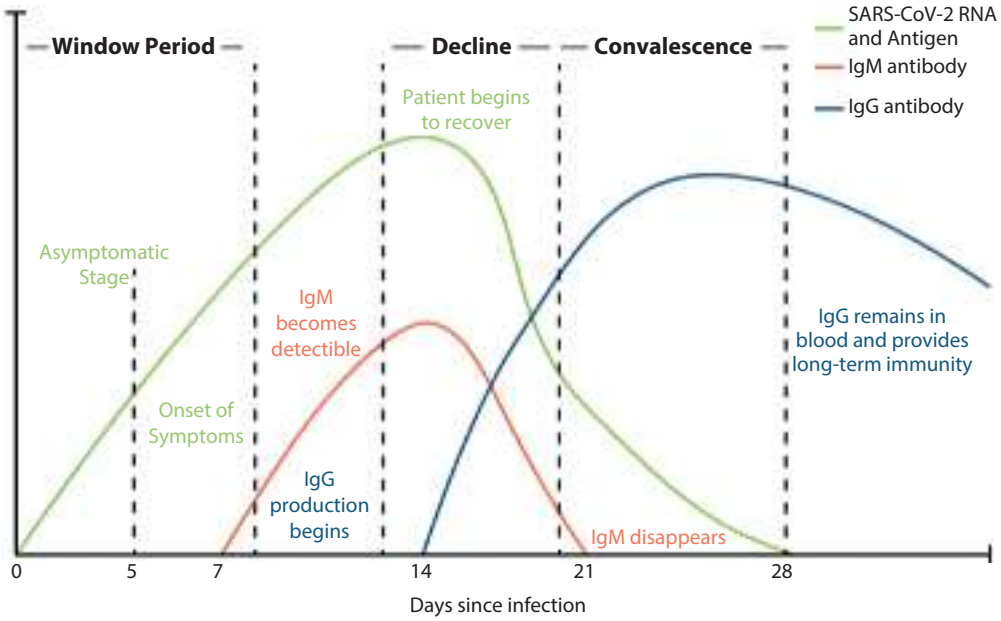

FIGURE 188.4 Serum antibody responses during infection by SARS-CoV-2. For a complete list of FDA approved testing platforms, please visit

https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas

From Kai-Want To K, Tak-Yin Tsang O, Leung W-S, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: An observational cohort study. *Lancet Infect Dis*. 2020 Mar 23. pii: S1473-3099(20)30196-1.

are noted in the CD8+ and B-cell subpopulations. Among many cytokines, IL-6 may exceed the upper limit in severe COVID-19 patients.

Therapy

There are currently no FDA-approved drugs for the treatment of COVID-19. Table 188.4 lists the current classes of agents that are in development for treatment of COVID-19.

Based on the current literature, treatment of COVID-19 as per the NIH guidelines issued by the National Institutes of Health is given here.

Use of antivirals in patients with COVID-19

1. Patients with COVID-19 on supplemental oxygen should receive remdesivir for 5 days or until hospital discharge, whichever is first (evidence level AI).
2. Patients with COVID-19 on high-flow oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), there are no recommendation for or against using remdesivir.
3. The guidelines recommend against use of chloroquine, hydroxychloroquine, or other antivirals except in a clinical trial (evidence level AII–AIII).

Corticosteroid use in patients with COVID-19

1. Patients with COVID-19 on mechanical ventilation should receive dexamethasone, 6 mg/d for up to 10 days (evidence level AI).
2. Patients with COVID-19 on oxygen but not ventilated should receive dexamethasone, 6 mg/d for up to 10 days (evidence level BI).
3. For patients with COVID-19 not requiring oxygen, the guidelines recommend against using dexamethasone (evidence level AI).
4. Alternatives if dexamethasone is not available include prednisone, methylprednisolone, and hydrocortisone (evidence level AIII).

Prevention

As per the CDC, there is currently no vaccine to prevent COVID-19. To prevent illness, avoidance of exposure to the virus by washing hands often with soap and water for at least 20 seconds is essential. If soap and water are not readily available, use of hand sanitizer that contains at least 60% alcohol is recommended. Avoiding touching the eyes, nose, and mouth with unwashed hands is also beneficial, and maintaining a social distance of 6 feet between individuals who do not live in the same household will

TABLE 188.4 **THERAPEUTIC AGENTS IN DEVELOPMENT FOR TREATMENT OF COVID-19**

Class of agents	Agents	Mechanism of action	Comments
Antivirals	Remdesivir	Inhibits RNA synthesis by binding to RNA- dependent RNA polymerase	In Phase 3 trial, reduced length of stay in patients. Mortality data pending. The FDA has authorized EUA of this drug for adult and pediatric patients hospitalized with suspected or confirmed COVID-19.
	Hydroxychloroquine Chloroquine	Inhibits MHC class II expression, antigen presentation, immune activation and various pro-inflammatory cytokines	Open-label RT showed no improvement. Some observational studies showed benefit alone and with azithromycin. FDA withdrew EUA. 180 ongoing studies
	Lopinavir + ritonavir	Inhibits HIV protease enzyme by forming an inhibitor-enzyme complex	No benefit an RCT
	Favipiravir	Inhibits RNA synthesis by binding to RNA- dependent RNA polymerase	Anti-influenza drug, viral clearance, Phase 3 ongoing
	Ivermectin	Interacts with glutamate-gated chloride channels	In vitro and human studies
	MK-4482	Antiviral action through introduction of copying errors during viral RNA replication	Influenza drug, in vitro and animal studies, phase 3 pending
	Recombinant ACE-2	Blocks SARS-CoV-2 from binding to the ACE-2 receptor	In vitro
Immune modulators	Convalescent plasma	Neutralizes spike-driven entry of SARS-CoV-2 into host cells	Phase 3 RCT ongoing, reduced length of stay in patients. Mortality data pending
	Monoclonal antibodies	Inhibitors of receptor binding that prevents viral attachment to target cells	In vitro and animal studies. Human trails phase 2/3
	Interferons	Interfere with viral replication and spread by several mechanisms including secretion of cytokines which promotes adaptive immunity	Open label trials—may prevent infection or reduce progression. RCT in combination with remdesivir
Immune suppressants	Corticosteroids	Attenuate progression to hyperinflammatory phase	Dexamethasone improved mortality in patients on mechanical ventilation and needing supplemental O_2. Methylprednisolone reduced progression, ICU transfer, mortality and length of stay
	Cytokine inhibitors	IL-6 inhibitor	Tocilizumab Phase 3 randomized control trial did not improve clinical status. Other IL-6 blockers alone or in combination ongoing
	Cytokine filtration	Inhibiting cytokine response	Trials ongoing
	Mesenchymal stromal stem cells	Inhibiting cytokine response	Trials ongoing

EUA, emergency use authorization; FDA, US Food and Drug Administration; RTC, randomized control trial; RT, randomized trial.

TABLE 188.5 **PHASE 3 VACCINE TRIALS FOR COVID-19**

	Phase	Type	Trial sites
Moderna	3	mRNA	USA
Biontech—Pfizer—Fosun	3	mRNA	USA, Argentina, Brazil, Germany
CanSinoBIO	3	Ad5	China, Saudi Arabia
Oxford: AstraZeneca	2/3	ChAdOx1	England, India, Brazil, South Africa
Wuhan: Sinopharm	3	Inactivated virus	UAE
Beijing: Sinopharm	3	Inactivated virus	UAE
Sinovac	3	Inactivated virus	Brazil, Indonesia
Murdoch	3	BCG	Repurposed vaccine
Johnson and Johnson-Jansen	3	Adeno associated virus 26	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, USA

help reduce transmission of the virus. Finally, wearing a mask that covers the mouth and nose is crucial to protect individuals when in public settings.

Although there is currently no vaccine available at the time of publications, there are many Phase 3 clinical trials taking place as of September 2020 (Table 188.5).

Suggested reading

Chaudhry ZS, Williams JD, Vahia A, et al. Clinical characteristics and outcomes of COVID-19 in solid organ transplant recipients: A case-control study [published online ahead of print, 2020 Jul 12]. *Am J Transplant*. 2020;10.1111/ajt.16188. doi:10.1111/ajt.16188.

Fadel R, Morrison AR, Vahia A, et al. Early short course corticosteroids in hospitalized patients with COVID-19 [published online ahead of print, 2020 May 19]. *Clin Infect Dis.* 2020;ciaa601. doi:10.1093/cid/ciaa601

Feldstein LR, Rose EB, Horwitz SM, et al.; Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in US children and adolescents. *N Engl J Med*. 2020 Jul 23;383(4):334–346. doi:10.1056/NEJMoa2021680. Epub 2020 Jun 29. PMID: 32598831; PMCID: PMC7346765

Gudipati S, Brar I, Murray S, McKinnon JE, Yared N, Markowitz N. Descriptive analysis of patients living with HIV affected by COVID-19. *J Acquir Immune Defic Syndr.* 2020;85(2):123–126. doi:10.1097/QAI.0000000000002450.

Infectious Disease Society of America. Guidelines on the diagnosis of COVID-19. 2020. https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/

Morrison AR, Johnson JM, Griebe KM, et al. Clinical characteristics and predictors of survival in adults with coronavirus disease 2019 receiving tocilizumab [published online ahead of print, 2020 Jul 3]. *J Autoimmun*. 2020;102512. doi:10.1016/j.jaut.2020.102512.

National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. https://www.covid19treatmentguidelines.nih.gov/

Suleyman G, Fadel RA, Malette KM, et al. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan Detroit. *JAMA Netw Open*. 2020;3(6):e2012270. doi:10.1001/jamanetworkopen.2020.12270

van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med.* 2020;382(16):1564–1567. https://www.nejm.org/doi/full/10.1056/NEJMc2004973. doi:10.1056/NEJMc2004973

World Health Organization (WHO). Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance. March 13, 2020. https://apps.who.int/iris/handle/10665/331446

World Health Organization (WHO). Report of the WHO-CHINA joint mission on coronavirus disease 2019 (COVID-19). 2020. https://www.who.int/publications/i/item/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)

Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-COV-2 in Singapore. *JAMA*. 2020;323(15):1488–1494. doi:10.1001/jama.2020.3204.

189

Papillomavirus in oro-genital infection

Lawrence J. Eron

Human papillomaviruses (HPV) cause >10,000 cases of squamous cell carcinoma (SCC) of the cervix each year in the United States, as well as >4,000 deaths annually. It is the third most common cancer in women worldwide. The virus also causes genital warts (condylomata acuminata) and other subclinical disease, making it the most common sexually transmitted disease (STD) in the United States with an annual incidence of >6 million cases and a prevalence of as many as many as 20 million infections (Figure 189.1). Peak prevalence of infection occurs during the first 10 years following sexual debut. The National Health and Nutrition Examination Survey (NHANES) study reported a 25% prevalence of HPV DNA from vaginal swabs of 20- to 24-year-olds. Because HPV produces persistent infection that in most cases is subclinical and because the virus is easily transmitted via intercourse, 80% of sexually active people become infected during their lifetime.

Rates of transmission differ according to body site: Transmission from penis to cervix is 58.8 cases per 100 patient years; from cervix to penis is 208.8 cases per 100 patient years. Nonpenetrative intercourse may also transmit HPV from the anus to the scrotum and from the hand to the penis.

Genital HPV infection

Of the >100 different DNA types of HPV, distinguished on the basis of relatedness of their genomes, 40 infect the genital area. These 40 genital types fall into two groups distinguished by the type of disease that they produce. The first group, which includes the two most common HPV types, 6 and 11, causes exophytic condylomata acuminata, referred to as *genital warts* (Figure 189.2), as well as low-grade dysplasia of the vulva, vagina, cervix, and penis.

The second group, typified by types 16 and 18, causes SCC as well as high-grade dysplasia of the cervix, vagina, vulva, and penis, which appears as white areas of skin after the application of acetic acid (Figure 189.3). Low-grade dysplasia is referred to as *squamous intraepithelial lesions* (SIL) grade I, moderate dysplasia as SIL grade II, and severe dysplasia as SIL grade III. When the cervix is affected, it is termed *cervical intraepithelial neoplasia* (CIN) with similar grading as SILs. All HPV viruses may produce asymptomatic infection, subclinical disease, or clinically apparent disease (Figure 189.4).

HPV may also infect the perianal region and the distal rectum above the dentate line. In people infected with HIV, HPV may produce small, innocent-appearing ulcers that on biopsy are proved to be SCC. HIV infection, as well as other immunodeficiency states, increases the likelihood that dysplastic lesions of the cervix may evolve into invasive carcinomas. Recurrent or refractory genital warts may be surrogate markers for concomitant infection by HIV, and it is important to test for HIV in patients with HPV infection.

Despite the enormous prevalence, HPV infections in the majority of woman usually resolve in 6 to 12 months. Up to 30% of infections caused by low-grade HPV types 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 73, and 81 may be transient and will not evolve into a malignant state. Women with persistent infection by the oncogenic HPV types 16 and 18 are at risk for developing pre-cancerous and cancerous lesions

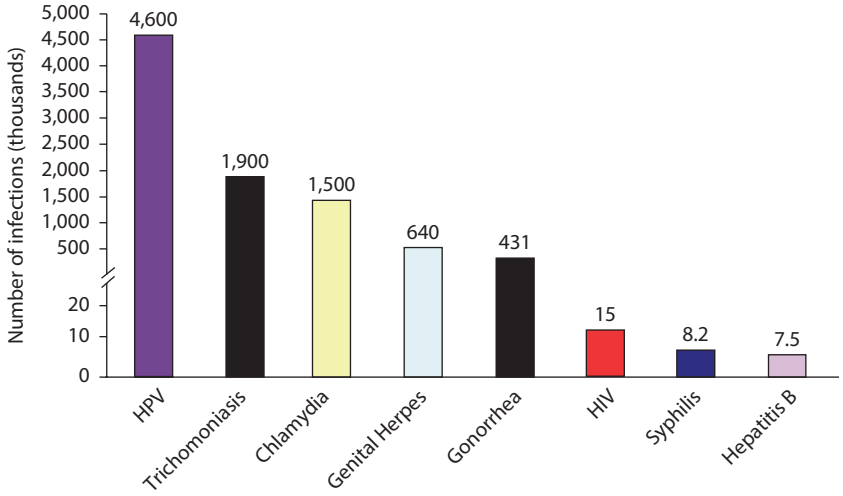

FIGURE 189.1 Human papillomaviruses (HPV) are the cause of the most common sexually transmitted disease, genital warts, with an annual incidence of 6.2 million and a prevalence of 20 million infections. HIV, human immunodeficiency virus.

(Figure 189.5). Although moderate or severe dysplasia may also remit without treatment, women with these lesions should be evaluated by colposcopy to detect the development of carcinoma in situ.

HPV causes most cancers of the oropharynx

SCC of the oropharynx is associated with either tobacco, alcohol, or betel nut use or HPV infection. HPV type 16 and, less commonly, types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 are found in 80% of these tumors. In SCC of the tobacco, alcohol, betel nut type, the host p53 and retinoblastoma oncogenes (pRb) are altered by the virus, while p16, a tumor suppressor, is decreased. In contrast, HPV-associated SCC of the oropharynx contains no mutations of the p53 oncogene, and expression of pRb is downregulated, while p16 is upregulated. HPV+ tumors arise in the base of the tongue and tonsillar region and show a much better response to chemotherapy than the other type.

HPV may be transmitted through open-mouthed kissing as well as oral sex. Among men with no oral sexual contacts, the risk of oral HPV transmission varies with the number of kissing partners. While the overwhelming majority of oral HPV infection clears with no intervention, the increasing prevalence of HPV-positive SCC of the oropharynx suggests a benefit to vaccinating boys as well as girls, and at even earlier ages, to prevent oral as well as sexual transmission of HPV.

Diagnosis of HPV infection

Genital warts are flesh-colored papules with a cauliflower-like appearance. Other papules may be mistaken for genital warts, such as pearly penile papules and skin tags. When doubt exists, healthcare providers should consider other methods to diagnose HPV

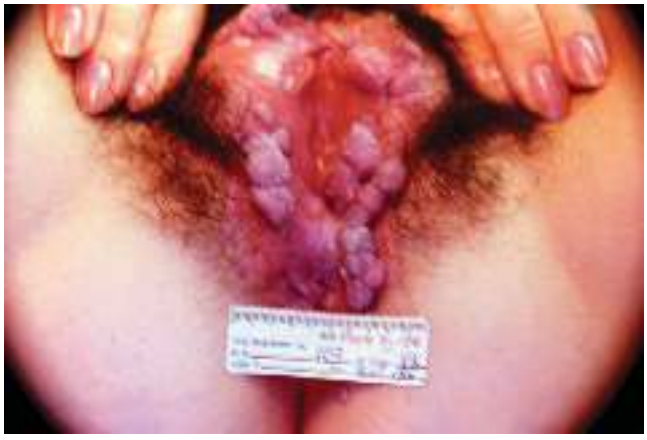

FIGURE 189.2 Exophytic condylomata acuminata, also referred to as genital warts.

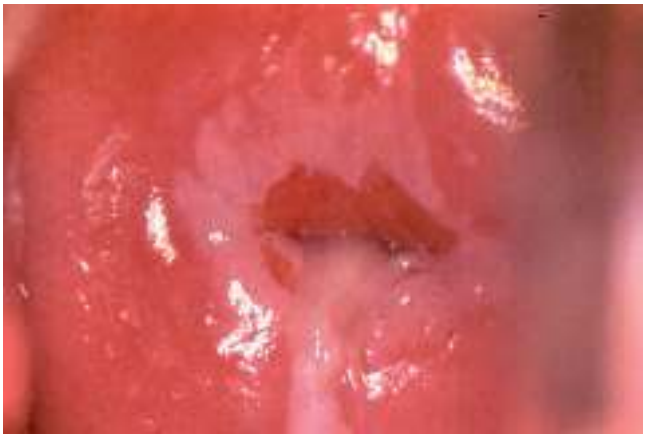

FIGURE 189.3 High-grade dysplasia of the cervix, vagina, and vulva appears as white areas after the application of acetic acid.

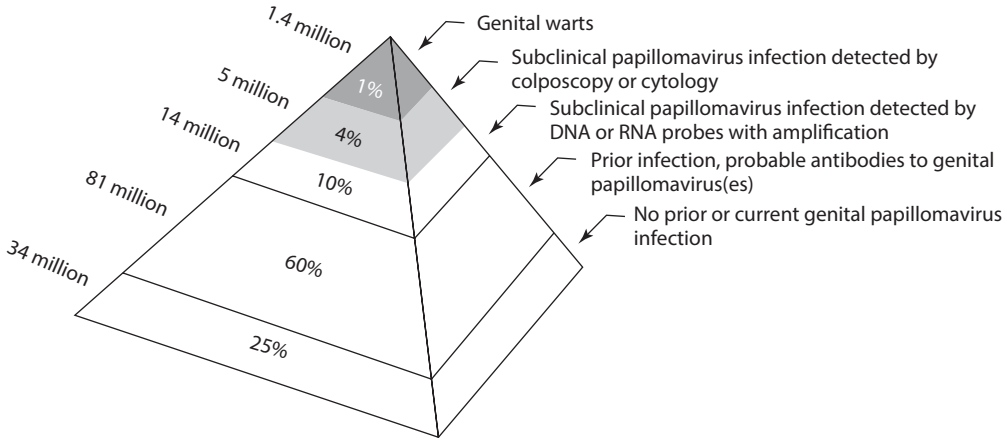

FIGURE 189.4 Human papillomaviruses may produce asymptomatic infection, subclinical disease, or clinically apparent disease.

infection, including cytologic exam via the Pap smear, colposcopy, biopsy, and tests for HPV DNA. Colposcopy of the cervix is useful when there is moderate to severe dysplasia. While HPV DNA testing improves the sensitivity of detecting infection, it lacks specificity, leading to unnecessary colposcopy.

Principles of therapy

While the main goal of treating HPV genital disease is usually to extirpate clinically evident disease, these treatments do not eliminate the underlying HPV infection, which may lead to recurrent disease. The epithelium of healthy-appearing skin surrounding a condyloma may be subclinically infected with HPV up to 1.0 cm from the actual lesion. Therefore. the removal of a wart or dysplastic tissue does not guarantee removal of the adjacent reservoir of virus and therefore does not prevent transmission of HPV infection. Although infections are often asymptomatic and in many cases will resolve spontaneously, nonetheless, patients with genital warts often experience depression, hopelessness, and a sense of social isolation. They should be offered counseling by a healthcare provider and a treatment program. While many patients readily accept treatment, they may need to be educated on the subclinical carriage of HPV and its prolonged incubation period. Given that sexual contact and infection with HPV may have occurred weeks to many months prior to the development of clinically evident lesions, patients with HPV should understand that the presence of condylomata acuminata may not imply infidelity.

Treatment of smaller exophytic condylomata acuminata can be readily accomplished by self-applied imiquimod, podophyllotoxin, trichloroacetic acid, or sinecatechins (an herbal product made from green tea leaves). Larger genital warts may require more intensive treatments that are clinician-administered, such as cryotherapy, surgical excision, electrocautery, and laser treatment. Studies of self-applied treatments of imiquimod report efficacy rates of 35% to 75% and recurrence rates of 6% to 26%. Studies of podophyllotoxin, the least expensive treatment, report efficacy rates of 43% to 70% but recurrence rates of 13% to 100%. Placebo-controlled trials of sinecatechins report complete clearance in 55% compared to 35%

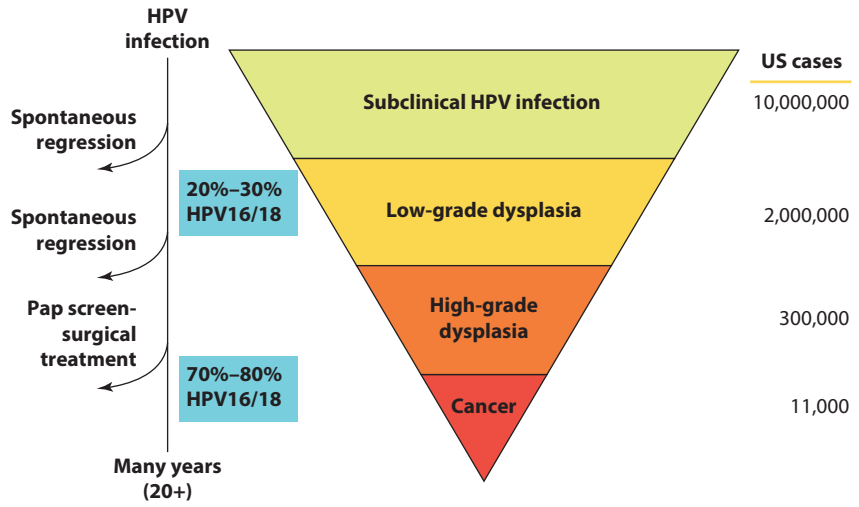

FIGURE 189.5 Infection by low-grade human papillomavirus (HPV) types may be transient.

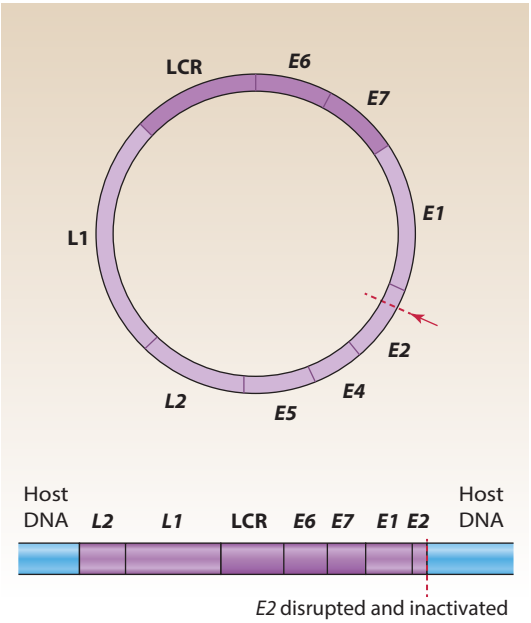

FIGURE 189.6 Human papillomavirus contains a circular, double-stranded DNA genome, consisting of eight structural genes in two distinct regions.

for placebo. Clinician-administered treatments such as cryotherapy report efficacy rates of 44% to 75% and recurrence rates of 5% to 30%. Surgical excision is successful in 89% to 100% of cases, but with recurrences in up to one-third of cases.

For moderate to severe dysplasia of the cervix, vagina, vulva, and the penis, cytodestructive procedures such as surgical excision and cryotherapy using liquid nitrogen may be effective. Both surgical excision and cryotherapy are equally effective and have similar relapse Loop electrical excisional procedure (LEEP) and laser ablation of dysplastic tissue of the cervix may be as effective as surgical excision or cryotherapy. However, recurrences still occur. Modulating the immune response to decrease persistent infection and recurrence rates following treatment is the "holy grail" of HPV treatment.

Immunity to HPV infection

Although the prevalence of HPV infection is high in young women, only a minority (≤5%) of infected women develop persistent infection and progress to SIL. In most cases, infection may be transient if the individual develops a sufficient immune response to the virus. When infection of the cervix by HPV 16 or 18 becomes persistent, SILs and CIN may evolve to SCC, usually several decades later.

Seroconversion following HPV infection occurs in only 60% of infected females and far less frequently in males. HPV may evade the immune system since its replication does not induce cytolysis, necrosis, or viremia. Viral proteins are released only in terminally differentiated epithelial cells, which are programmed for apoptosis and thus evade immune surveillance. Furthermore, HPV inhibits the synthesis of interferon and other cytokines.

Viral, environmental, and host factors play a role in the evolution of infection to the development of SIL/CIN and thence to SCC. Polymorphisms among HPV type 16 variants are associated with longer persistence, more aggressive infection, and higher frequency of SCC. Environmental factors that are associated with progression of SIL to SCC include smoking, long-term oral contraceptive use, high parity, and coinfection with other STDs. Host factors associated with increased susceptibility to SCC include genetic polymorphisms in the major histocompatibility complex (MHC) genes which decrease class I MHC cell surface expression and in TAP proteins associated with antigen processing, thereby interfering with host immune response.

The HPV genome and carcinogenesis

HPV contains a circular, double-stranded DNA genome consisting of eight structural genes in two distinct regions (Figure 189.6). The early region is composed of six genes (E1–E2 and E4–E7) that control viral replication, transcription, and cell transformation. The late region is composed of two genes (L1 and L2) that encode the viral coat proteins. The "long control region" regulates the expression of these eight genes. In productive infection, as is the case for types 6 and 11, both early and late regions of the virus are transcribed into messenger RNA (mRNA), which codes for proteins essential for viral DNA replication and for coat proteins. Many copies of HPV DNA are produced in each infected cell as circular, extrachromosomal plasmids. The net result is mature infectious virions.

In contrast to productive infection, when type 16 or 18 infects a cell, late genes are not transcribed, viral coat proteins are not synthesized, and no mature virions are produced. Instead the circular HPV genome inserts itself into the host chromosome, disrupting its E2 gene, resulting in the loss of E1 and E2 gene functions (Figure 189.6). Normally E1 and E2 downregulate E6 and E7 expression, but, with the loss of E1 and E2 control, E6 and E7 functions are upregulated. The E6 and E7 gene products then alter host oncogenes (p53 and pRb, respectively) that normally control cell growth and differentiation by arresting host cell division in the G1 phase. This normally allows the cell time to repair damaged DNA before progressing to the S (DNA replication) phase. The loss of this repair mechanism results in cell transformation, which renders the host genome susceptible to other carcinogens, such as smoking. The time between initial HPV infection and the development of SCC is between 10 and >20 years.

HPV prevention

Because the viral genome is highly conserved and because HPV uses cellular enzymes to replicate (and thus cannot easily develop resistance, in contrast to HIV, for example), effective vaccines (Gardasil and Cervarix) have been developed that produce neutralizing

antibodies that protect against viral infection. In addition the vaccines also produce cytotoxic CD8 lymphocytes that eliminate nascent HPV-infected cells. The vaccines are approximately 95% effective in the prevention of infection by HPV types 16 and 18 (which represent 70% of oncogenic HPV types). The Gardasil vaccine is also highly effective (close to 100%) against HPV types 6 and 11 that produce condylomata.

Vaccine administration is recommended for females aged 11 to 26 years to induce immunity prior to the female sexual debut, which in 77% occurs by age 19. Following the sexual debut, the incidence of HPV infection rises to 40% within 2 years and to >50% within 4 years, at which point the vaccine may be less effective. Widespread vaccination of males prevents oropharyngeal cancers caused by HPV 16 and 18. The vaccines offer durable protection against HPV types contained in the vaccines for at least 5 years but are woefully underutilized in the United States as compared to Australia, where an 80% vaccination rate of young girls has very nearly eliminated condylomata from not only females but also males <21 years of age, due to the development of herd immunity. Furthermore, high-grade lesions have also decreased in girls <18 years old. Between 2005 and 2015, the percentage of Australian women 18 to 24 years old with HPV decreased from 22.7% to 1.1%. Already Australia has noted a decrease in HPV-associated oral cancers in men. In the United States, only 50% of girls 13 to 17 years old and 38% of boys have been vaccinated, with far less reduction in HPV prevalence. It is anticipated that Australia will become the first country to eliminate HPV-associated cancer.

In addition to vaccines, the most cost-effective strategy for reducing HPV infection is the consistent use of condoms. In a well-designed and executed study, condoms reduced the incidence of genital HPV infection from 89.3 per 100 patient-years to 37.8. In those women whose partners used condoms 100% of the time, there were no cervical SILs observed in 32.1 patient-years, whereas 14 SILs were detected in 96.8 patient-years among women whose partners used condoms less than 100% of the time.

Because the HPV genome contains two oncogenes, E6 and E7, that are involved in the production of SCC, vaccines against the products of these genes could be used theoretically to prevent or treat cervical cancer. While in animals such a vaccine can protect against challenge with tumors expressing E6 and E7 antigens, no such results have been reported in humans.

Suggested reading

Chaturvedi AK, Angels EA, Pfeirffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29:4294–4301.

Cox JT, Palefsky JM. Human papillomavirus vaccination. In Hirsch MS. ed. *UpToDate*. Waltham, MA: UpToDate; 2019.

Palefsky JM, Cranston RD. Virology of human papillomavirus infections and the link to cancer. In Dizon DS, Aboulafia DM, ed. *UpToDate*. Waltham, MA: UpToDate; 2019.

Read TR, Hocking JS, Chen MY, et al. The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme. *Sex Transm Infect*. 2011;87:544–547.

Scheinfeld N. Condylomata acuminata (anogenital warts): Management of external condylomata acuminata in men. In Rosen T, ed. *UpToDate*. Waltham, MA: UpToDate; 2018.

Acute and chronic parvovirus infection

Neal S. Young

Parvoviruses are small viruses with unenveloped icosahedral capsids that contain a single-stranded DNA genome. These physical properties contribute to viral resistance to heat, solvents, and extreme chemical conditions. Because of their limited genome, parvoviral propagation depends on infection of mitotically active cells. B19 parvovirus is the only member of the Parvoviridae family known to cause diseases in humans (although other parvoviruses recently have been isolated from human blood and tissue, their pathogenicity remains uncertain). In the taxonomy of the parvovirus family, B19 and closely related simian parvoviruses constitute the *Erythrovirus* genus, separated from autonomous animal parvoviruses, dependoviruses (which require coinfection with a second virus for efficient propagation in cell culture), and insect parvoviruses called densoviruses.

B19 parvovirus has a peculiar and extreme tropism for human erythroid progenitor cells, which are responsible for the generation of circulating erythrocytes. In tissue culture, B19 has been propagated in hematopoietic cells: bone marrow, fetal liver, peripheral blood, and (rather inefficiently) in a few leukemic cell lines. B19 viral DNA replication in patients has been detected in blood and marrow. Specificity for erythroid cells follows from the cellular receptor for the virus, globoside or P antigen, a tetrahexose ceramide present on erythroid cells, megakaryocytes, endothelial cells, and some placental cell types, as well as fetal liver and heart. Parvovirus infection is terminated by host production of neutralizing antibodies. Failure to produce neutralizing antibodies can result in persistent infection. Cellular immune responses to parvoviruses have been measured and some CD4 and CD8 T-cell epitopes defined.

B19 diseases

Serologic studies have shown that more than half of the adult population has antibodies to B19 parvovirus; although most infection occurs during childhood, the seropositivity rate continues to rise with age. Probably the majority of infections are asymptomatic. Reliable diagnostic assays are now widely available. The presence of immunoglobulin G (IgG) to virus only signifies past infection. Immunoglobulin M (IgM) or virus DNA detected by direct hybridization testing indicates recent infection. The interpretation of a positive DNA study obtained by gene amplification (polymerase chain reaction) is more problematic, as individuals may not clear small amounts of virus for many months after an acute infection, and laboratory contamination can produce false positives.

Fifth disease

This common childhood exanthem is caused by acute parvovirus infection. The slapped-cheek rash and the evanescent maculopapular eruption over the trunk and proximal extremities are typical

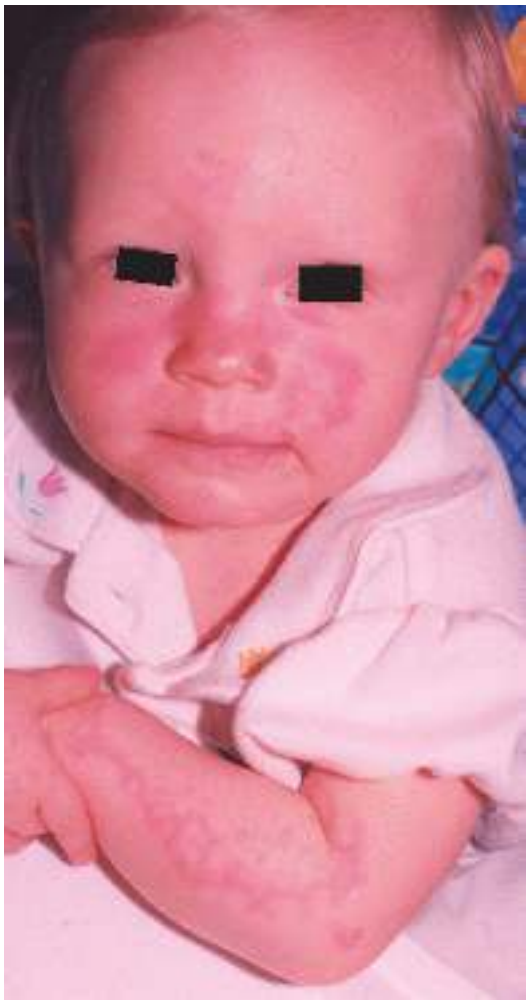

FIGURE 190.1 Fifth disease; note characteristic maculopapular rash with "slapped cheek" appearance.

(Figure 190.1). Children may be febrile but usually have few symptoms. Meningitis and encephalitis have been reported as very rare complications. The blood of children with fifth disease contains IgM antibody to B19 but little if any virus; because the syndrome is due to immune-complex formation between virus and antibodies, affected individuals are not considered infectious. Reassurance and antipyretics as needed are sufficient for this self-limited illness.

In adults, acute parvovirus infection may be more serious. Adults have more rheumatic complaints than do children, and there may be frank joint inflammation and a pattern of distribution and chronicity mimicking rheumatoid arthritis; occasionally rheumatoid factor will be present. In most cases, symptoms resolve within a few days or weeks, but in some individuals the arthropathy and systemic symptoms become chronic and debilitating, although there is no joint destruction. The pathophysiology of the rheumatic manifestations after B19 infections is not well understood, but symptoms usually can be addressed with conventional anti-inflammatory drug therapy. Parvovirus is not a cause of rheumatoid arthritis.

Transient aplastic crisis and other hematologic syndromes

Transient aplastic crisis is caused by parvovirus infection in patients who have hemolytic anemia, compensated hemolysis (as in many cases of hereditary spherocytosis), or an increased demand for red cell production (iron deficiency, acute hemorrhage). B19 briefly interrupts erythropoiesis in most persons infected but without consequence because of the long survival of circulating red blood cells. Transient aplastic crisis is manifested by anemia, reticulocytopenia, and red cell aplasia in the marrow. There may be moderate thrombocytopenia and neutropenia in addition to the severe anemia, especially in patients with functioning spleens. The syndrome may be accompanied by marrow necrosis and has been fatal, especially in young children. As the anemia is self-limited, transfusion is adequate therapy. Specific antibody production terminates the episode and likely prevents recurrence.

Hydrops fetalis and congenital infection

Parvovirus infection of the pregnant woman may be transmitted to the fetus. Midtrimester events have been best characterized; first trimester infection may result in abortion, and third trimester infection has not been associated with adverse outcomes. Infection of the fetus is predominantly in the liver, the site of red cell production; the heart may also be affected (fetal myocardial cells express P antigen). Untreated, the fetus develops severe anemia and heart failure leading to the massive edema of hydrops and death at birth or shortly afterward (Figure 190.2). In utero blood transfusions have apparently been successful in a few instances; however, untreated fetal infection need not result in mortality or morbidity. As ultrasound diagnosis may not be definitive, a conservative recommendation is to document progressive hydrops on serial testing before intervention.

Congenital parvovirus infection after transfusion treatment of hydrops can produce chronic anemia from birth. Only a few infants have been described: In all, virus was localized to the marrow and did not circulate, and gene amplification was required to detect the low levels of B19 DNA. The pathology of the marrow was erythroid hypoplasia (Diamond–Blackfan anemia) or erythroid dysplasia resembling congenital dyserythropoietic states. Immunoglobulin therapy has not been effective.

Persistent infection

In the absence of an appropriate immune response, B19 infection can become chronic. Persistent infection has been observed in congenital immunodeficiency (Nezelof syndrome), acquired immunodeficiency syndrome (AIDS) secondary to human immunodeficiency virus (HIV) 1 infection, and during therapy with cytotoxic

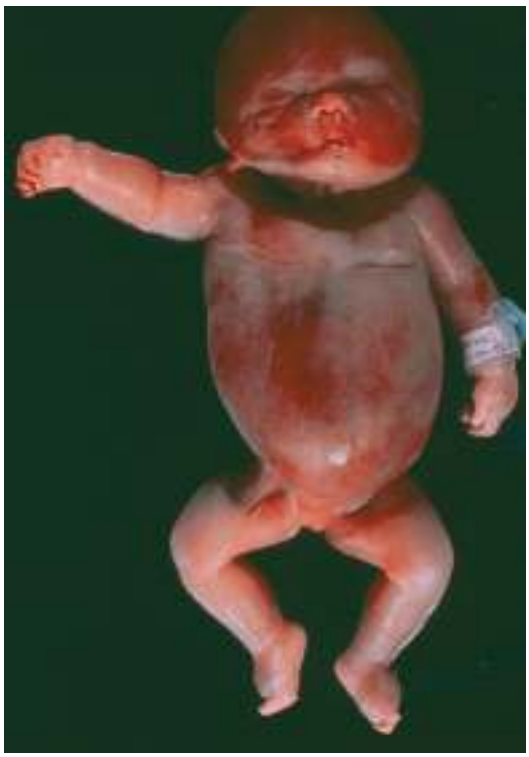

FIGURE 190.2 Hydrops fetalis (see text).

or immunosuppressive drugs. The deficit in the immune response may be subtle; B19 infection may be the only evidence of constitutional immunodeficiency and the first sign of AIDS. Clinically, the patients have typical pure red cell aplasia with severe anemia, absent reticulocytes in the blood, and a paucity of red cell precursors in the marrow. Scattered giant pronormoblasts, a morphologic feature of B19 infection, may signal the diagnosis, which is established by DNA hybridization studies of serum.

Persistent infection results from inability to mount an effective humoral immune response, measured either as neutralizing antibodies in functional tissue culture experiments or by immunoblot binding of viral capsid proteins. Most AIDS patients lack any antibodies to B19; some congenital cases may have circulating IgM to B19 suggestive of a class-switch abnormality. Fortunately, commercial immunoglobulin preparations are a good source of effective antibodies to parvovirus. Administration of IgG 0.4 g/kg/day intravenously for 5 to 10 days terminates infection. The reticulocyte count dramatically increases after the first week, the marrow shows healthy normoblastic erythroid proliferation, and the hemoglobin rises to a level appropriate for the patient. Treatment can be curative, and the virus may no longer be detectable in some patients who have congenital immunodeficiency or whose immunosuppressive therapy is discontinued. AIDS patients have intense chronic parvoviremia, and IgG treatment appears to reduce but not eliminate the virus (Figure 190.3). Although relapse after some months is common, recurrent anemia responds to a second course of IgG. Monthly maintenance injections of IgG have been used in a few patients.

Other possible associations

Accumulated case reports are suggestive of a link between B19 and neonatal and childhood myocarditis (P antigen is present on fetal heart cells), a variety of pediatric neurologic syndromes, and some cases of acute, self-limited hepatitis. The association of B19 parvovirus with other clinical syndromes is less secure. Apparent links to childhood neutropenia, idiopathic thrombocytopenic purpura, vasculitis, and juvenile rheumatoid arthritis have not been reproducible.

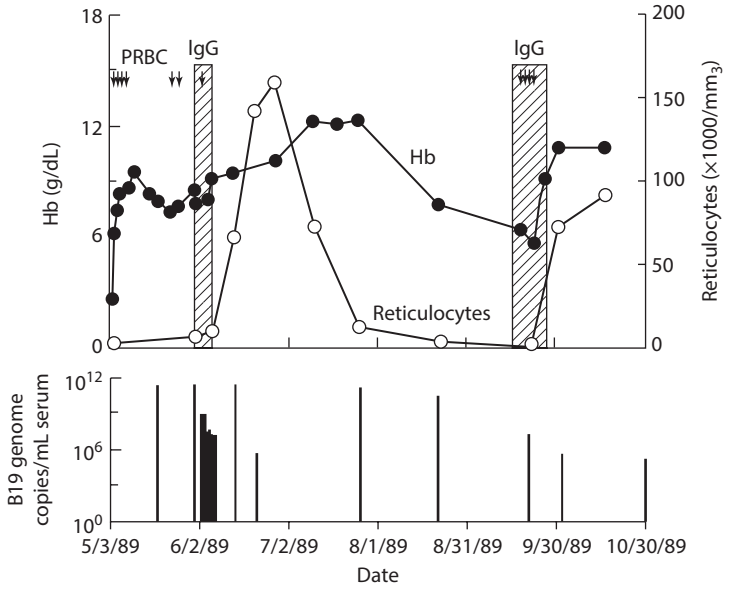

FIGURE 190.3 Immunoglobulin G (IgG) treatment of B19 persistence in acquired immunodeficiency syndrome (AIDS), illustrating recurrence predicted by molecular studies and the effectiveness of repeated treatment. PRBC = packed red blood cells.

A major technical problem has been the use of gene amplification methods, which not only are susceptible to false-positive results but also are positive in a high proportion of normal individuals: Viral DNA has been found in almost half of knee joints biopsied for trauma and in 20% of normal bone marrows using this sensitive method. Polymerase chain reaction-derived data that are reported without other clinical or serologic evidence of recent infection should be especially suspect. In addition, paroxysmal cold hemoglobinuria, a severe childhood hemolytic anemia that usually follows a viral illness, is a good candidate as a B19 parvovirus syndrome because of the presence of the pathogenic Donath–Landsteiner antibody, directed against erythrocyte P antigen, the virus's cellular receptor.

Vaccine development

Effective vaccines to prevent parvovirus infection in animals have been produced by tissue culture modification of virus. For B19, which resists conventional cell culture, recombinant empty capsids have been produced in a baculovirus system by expression of a portion of the parvovirus genome; they contain no viral DNA. Capsids enriched for the highly immunogenic VP1 protein elicit strong neutralizing antibody responses in test animals and, with the appropriate adjuvant, in normal volunteers. The limitation to development of a vaccine is commercial—the perceived market—rather than scientific.

Suggested reading

De Jong EP, de Haan TR, Kroes AC, *et al*. Parvovirus B19 infection in pregnancy. *J Clin Virol*. 2006;36:1–7.

Ergaz Z, Ornoy A. Parvovirus B19 in pregnancy. *Reprod Toxicol*. 2006;21:421–435.

Kurtzman G, Cohen BJ, Field AM, *et al*. The immune response to B19 parvovirus infection and an antibody defect in persistent viral infection. *J Clin Invest*. 1989;84:1114–1123.

Lindner J, Barabas S, Saar K. CD4+ T-cell responses against the VP1-unique region in individuals with recent and persistent parvovirus B19 infection. *J Vet Med*. 2005;52:351–361.

Molina KM, Garcia X, Denfield SW, *et al*. Parvovirus B19 myocarditis causes significant morbidity and mortality in children. *Pediatr Cardiol*. 2013;34:390–397.

Mouthon L, Guillevin L, Tellier Z. Intravenous immunoglobulins in autoimmune- or parvovirus B19-mediated pure red cell aplasia. *Autoimmun Rev*. 2005;4:264–269.

Rahiala J, Koskenvuo M, Meriluoto M, *et al*. Human parvoviruses B19, PARV4 and bocavirus in pediatric patients with allogeneic hematopoietic SCT. *Bone Marrow Transplant*. 2013;48:1308–1312.

Sokal EM, Melchior M, Cornu C, *et al*. Acute parvovirus B19 infection associated with fulminant hepatitis of favourable prognosis in young children. *Lancet*. 1998;352:1739–1741.

Terhes G, Jenei M, Bereg E, Turi S, Deak J. Neurologic consequence of a parvovirus B19 infection. *J Clin Virol*. 2013;56:156–158.

Young NS, Brown KE. Parvovirus B19. *N Engl J Med*. 2004;350:586–597.

Rabies

Anita Mahadevan, Susarla K. Shankar, and Avindra Nath

History

The first clear reference to rabies was from writings by Aristotle in c. 380 BC in which he described the symptoms and transmission of rabies in dogs. Despite centuries of observations on the transmission, symptoms, and a myriad of unsuccessful remedies, the disease remained invariably fatal until approximately 1885, when Louis Pasteur developed the first rabies vaccine in Paris. Unable to identify the organism—indeed unaware of even the difference between bacteria and viruses—he serially passaged the virus 90 times by intracerebral inoculation in rabbits and then air-dried the spinal cord samples from infected rabbits. This process made the virus less virulent—or attenuated—and it could be used to protect dogs from the infection. He ultimately injected an emulsion of the infected rabbit spinal cord into Joseph Meister, a young boy attacked by a rabid dog on his way home from school. Given the severity of his wounds on his face, hands, and legs he undoubtedly would have died; however, he received a series of 13 injections, survived, and subsequently spent his life working as a guard at the Pasteur Institute. Although this vaccine protected many patients, it also caused an immune-mediated encephalomyelitis and neuritis in some.

Epidemiology

In 2010, the US Centers for Disease Control and Prevention (CDC) reported 6,153 cases of rabies in animals and 2 human cases in the United States. A total of 25 human cases were reported in the years 2009–2018. The number of animal cases have also been decreasing with 5,508 cases in 2015, 4,910 cases in 2016, and 4,454 cases in 2017. However, in 2018, there were 4,951 cases reported, suggesting an increase in cases. Hawaii has been the only state free of rabies infection in humans and animals. Ninety-two percent of animal cases were in wild animals. In Europe, the World Health Organization (WHO) reported 6,065 cases of animal rabies and 9 human cases in 2012. Most of these occurred in Eastern Europe. In Latin America, there were 111 cases of human rabies reported between 2010 and 2012. The highest prevalence of rabies worldwide is still in developing countries, with India being in the lead followed by China, Nepal, and Myanmar. A rising incidence has also been seen in some African countries such as Malawi. Children between the ages of 5 and 14 years are the most common victims. About 60,000 cases of human rabies are reported to the WHO each year but the WHO estimates that the true incidence is much higher in these countries and that cases are grossly underreported. In the United States, while bats are the most common mode of transmission of rabies to humans, the largest reservoirs remain in raccoons followed by skunks, bats, foxes, and coyotes. Raccoon and fox reservoirs are mainly from the eastern states; bat and skunk cases were also found in parts of the south, Pacific Northwest, and California. Domestic animals only accounted for about 6.8% of rabies. Interestingly, cats are found to be infected with rabies at almost double the infection rate of dogs. The cases of rabid cats continue to rise, whereas cases in other animals are declining yearly. This paradox may be due to administration of vaccines in certain animals, especially dogs. In Europe, the rabies reservoir is mainly the fox,

whereas the bat is the main reservoir in Australia, Mexico, and parts of South America. Worldwide, death from rabies is usually from a rabid dog. In countries where dogs are commonly infected with rabies virus, nearly 99% of transmission occurs through dog bites.

Pathogenesis and pathology

Rabies is caused by a number of different species of neurotropic viruses in the *Rhabdoviridae* family, genus *Lyssavirus* named after Lyssa, the Greek goddess of madness, rage, and frenzy. The virus is typically transmitted by saliva of the infected animal through a bite or scratch. Mucosal exposure to the virus such as through the eyes, nose, or mouth could also transmit the virus. Drinking raw milk from infected animals can also transmit the infection. For bat-acquired rabies, the site of exposure is most commonly the face. The virus replicates at the wound site for a period of days and then, via retrograde axoplasmic flow, moves up the peripheral nerves to the anterior horn cells in the spinal cord and then transsynaptically to the brain. Both sensory and motor nerves can propagate the infection. Once the central nervous system (CNS) is seeded with the virus, it then centrifugally spreads back to the periphery. This process involves infection of non-neural tissues, especially the salivary glands, whereby the viral transmission occurs. This extraneuronal spread can also occur in the heart, autonomic plexus causing dysautonomia, skin, and serous glands of the tongue. For this reason, skin from the nape of the neck and hair follicles can serve as diagnostic tools, and the virus can be transmitted by organ transplantation.

Histologic examination of the brain shows perivascular inflammation of the gray matter, neuronal degeneration, and the characteristic cytoplasmic inclusions called Negri bodies (Figure 191.1A). Negri bodies are membraneless compartments within the cell where viral replication takes place. These compartments arise from a liquid–liquid phase separation and represent a new class of liquid organelle in which viral replication takes place. Renal tubular necrosis has also been demonstrated at autopsy. In 2005 and in 2012, cases of rabies were also reported in organ transplant recipients. Neuropathologic features in the latter showed Duret hemorrhages, widespread neuronal loss, perivascular lymphocytic infiltration, and extensive spinal cord pathology. The case in 2012 was unusual in that rabies occurred 18 months after the kidney transplant, and

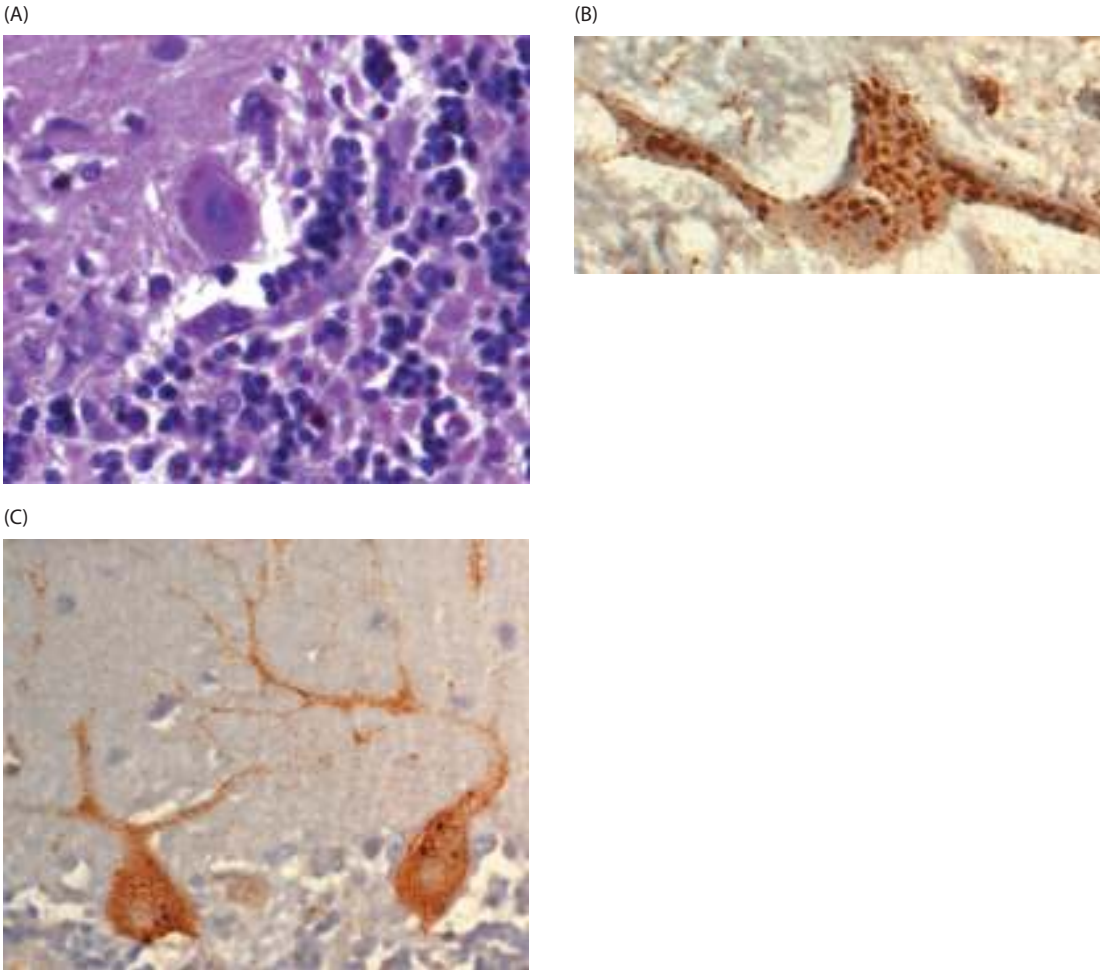

FIGURE 191.1 Histopathology of human rabies encephalitis. (A) Eosinophilic Negri bodies in a Purkinje cell. (B) Anterior horn cell immunostaining for rabies virus. (C) Purkinje cells immunostaining for rabies virus antigen.

three others who received organs from the same donor remained asymptomatic, likely due to a low dose of the inoculum.

Clinical symptoms

The clinical course in humans is acute, usually progressing from initial symptoms to death within 2 to 3 weeks, even with intensive supportive care. The incubation period of rabies can vary from a few days to several years with an average of 1 to 2 months. The length of the incubation period varies with the infecting strain and is thought to be inversely related to the size of the inoculum and the proximity of the bite to the CNS. Approximately half of the patients develop pain or paresthesias at the wound site. A diagnosis of rabies should not always depend on a history of an animal bite. Exposure may not be obvious in bat-acquired rabies, which is often misdiagnosed. The prodrome includes low-grade fevers, loss of appetite, and anxiety. Most patients have "furious rabies," which resembles an intense anxiety reaction or acute psychosis that can be aggravated by sensory stimuli such as touch, light, and sound. Three categories of symptoms are pathognomonic of furious rabies. (1) *Altered mental status that fluctuates between severe agitation and normality and depression*. The acute psychosis with hallucinations can result in an initial psychiatric evaluation. Seizures are more common in children. (2) *Inspiratory spasms caused by sensitivity of movement of air through the respiratory tract* resulting in spasm of the accessory respiratory muscles and diaphragm causing dyspnea. Hydrophobia (spasm of the pharynx and larynx provoked by drinking or the sight of water) and aerophobia (similar effect produced by blowing air on the face of the patient) are considered hallmarks of the disease. The inability to swallow from paralysis of bulbar muscles may also result in hypersalivation. (3) *Autonomic dysfunction* that manifests as hypersalivation, pupillary abnormalities, piloerection, sweating, priapism, and repeated ejaculation as well as neurogenic pulmonary edema. Rarely, there may be respiratory distress with medullary involvement. A few patients die during this stage, but most go on to develop progressive paralysis and eventually coma. Abnormal cranial nerve, motor, and sensory examinations; tremor; myoclonus; and local sensory symptoms at the exposure site are more common in bat-acquired rabies. In some patients, the paralytic state dominates the entire clinical picture; hence, it is termed "paralytic rabies." Paralysis or paresis involves the proximal muscles and can be accompanied by constipation, urinary retention, and respiratory failure. Alternatively, inflammation with demyelination and axonal dysfunction of the peripheral nerve causes an ascending lower motor neuron weakness without anterior horn cell involvement. Physical exam shows a motor weakness involving the respiratory muscles and loss of deep tendon reflexes with maintained consciousness which may mimic an acute axonal Guillain–Barré syndrome. This lack of involvement of spinal cord motor neurons and brainstem is called an "escape phenomenon." Most patients may eventually develop CNS symptoms. In some patients, however, the clinical manifestations can be nonspecific; hence, in all patients with an unknown cause of progressive encephalitis, the possibility of rabies should be considered. Hydrophobia, aerophobia, and encephalopathy are more common in dog-acquired rabies, whereas bat-acquired rabies more frequently has symptoms at the exposure site, tremor, myoclonus, and abnormal cranial nerve, motor, and sensory examinations. In patients receiving intensive supportive care, the average duration of illness between onset of paralysis and death is 7 days. Once neurologic symptoms have developed, survival is rare. Cardiopulmonary complications and multiorgan failure are common in the terminal stages of the illness in patients aggressively managed in intensive care units.

Diagnosis

Prior to available accurate laboratory tests, a potentially infected animal was placed in isolation for observation. If it died a characteristic rabies death, the diagnosis was established. With the advent of the microscope in 1903, intracytoplasmic inclusion bodies were discovered in infected brain tissue by Aldelchi Negri, who at the time was an assistant of Camillo Golgi. These structures were subsequently called *Negri bodies*. In the 1980s, the direct fluorescent antibody (DFA) test was developed, which remains to this day the diagnostic gold standard (Figure 191.1). For postmortem diagnosis in animals, fresh unfixed brain tissue is necessary for DFA testing because fixed tissue with agents such as formalin may yield inaccurate results. Brain tissue is the only sample tissue type for diagnosis because saliva and salivary gland excretion of the virus can be intermittent. The predictive value of a negative brain DFA test is 100%.

Routine laboratory tests and diagnostic studies are of little value in the diagnosis of rabies. Examination of the cerebrospinal fluid (CSF) may show leukocytosis, but protein and glucose assays are often normal. Antibodies to the virus in an unvaccinated patient with encephalitis confirms the diagnosis. In addition, saliva samples can be cultured and then tested for viral nucleic acid. A tissue diagnosis can be made in premortem humans using the DFA test on a skin sample from the back of the neck. Polymerase chain reaction (PCR) can also be used in diagnosis, but DFA is still considered the gold standard because PCR is hampered by obtaining universal *Lyssavirus* primers. Due to the ability to detect low copy numbers of viral nucleic acid, rapid turnaround time, and falling costs, it is likely that PCR-based techniques may become a viable diagnostic test in the near future.

In 2006, the CDC reported a case of encephalitis in a 15-year-old girl from Wisconsin who was bitten by a bat. Antibody titers to rabies virus were found in CSF and serum. She survived the infection. Another young boy developed encephalitis of undetermined etiology that progressed rapidly. He developed rabies-specific immunoglobulin G (IgG) antibodies in increasing titers. Rabies virus could not be detected in the CSF by PCR; however, antibodies to the rabies virus were present.

MRI changes most likely occur in the early stages of the infection. More extensive involvement of various regions of the brain has been shown in advanced stages on serial imaging. There are no specific features attributable to the rabies virus. Patients with acute rabies encephalitis have T2 hyperintense lesions in the brainstem, thalami, temporal cortex, hippocampus, and subcortical white matter. Some patients may develop signs of hypoxic damage and

cerebral hemorrhagic infarcts. Mild signal changes can also be seen in the spinal cord and nerve roots corresponding to the site of injury of some patients. This may involve only the anterior horns or both gray and white matter. Enhancement with gadolinium contrast is not present until the patient is comatose.

Treatment

Treatment efforts are concentrated on preventing and treating complications of established infection and protecting those who come in contact with the patient from virus exposure. Neither vaccine nor rabies immunoglobulin increases survival in symptomatic patients and should be avoided. Attempts to treat symptomatic patients infected with dog rabies with therapeutics and intensive care support are usually unsuccessful. A few patients who survived infection with good functional recovery had evidence of an early immune response to rabies virus in blood and CSF, with absence of virus in biologic fluids or hair follicles. Thus, a good outcome likely depends on a prompt host response in eradication of virus. Steroids should also be avoided in the treatment of cerebral edema if it develops. Universal precautions should be followed by hospital staff, and respiratory precautions are recommended for suctioning. Postexposure prophylaxis is recommended for contacts who were bitten or had clear contamination of mucous membranes to the patient's saliva, urine, or other body tissue.

Symptomatic treatment

Benzodiazepines, barbiturates, ketamine, or intravenous morphine may be used for treatment of the pharyngeal spasms. However, impairment of consciousness to the extent that ventilatory support is needed should be avoided. Autonomic symptoms should be monitored and treated.

Postexposure prophylaxis

Once an individual is bitten by an animal presumed to have rabies, it is vital to immediately begin the immunization. Raccoons, skunks, foxes, and coyotes are most often infected with the rabies virus. Patients exposed to these animals should receive postexposure prophylaxis as soon as possible. Transmission of rabies virus can occur from minor, even unrecognized, bites from bats. Therefore, rabies postexposure prophylaxis is recommended for all persons with bite, scratch, or mucous membrane exposure to a bat and should be considered if the history indicates that a bat was physically present, even if the person is unable to reliably report contact that could have resulted in a bite. An unprovoked attack by a domestic animal is more likely than a provoked attack to indicate that the animal is rabid. If the animal has been vaccinated, it is unlikely to be infected; if not vaccinated but otherwise healthy, the animal should be confined and observed for 10 days. Any illness during this time should be evaluated by a veterinarian and the public health department. Vaccination can be withheld if the animal remains healthy during this time. Small rodents (e.g., squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice) and lagomorphs (including rabbits and hares) are almost never infected with the virus and have not been known to transmit rabies to humans. Large rodents such as woodchucks are sometimes infected. Therefore, in cases involving rodent exposure, the state or local health department should be consulted before initiating prophylaxis. Postexposure therapy for rabies is highly effective, and no failures have been recorded in patients who have received all three arms of treatment. Failures have occurred only on deviation from the recommended protocol.

Local wound care

The abraded skin after a bite must be cleaned immediately and thoroughly by soap and water or povidone-iodine solution for a minimum of 15 minutes. Even scratches or contaminated skin from saliva should be cleaned the same way. It has been found that cleaning the wound would help reduce the chances of developing rabies. There are no areas that are deemed more susceptible after a bite. All bites in any area should be treated with the same level of care. Tetanus prophylaxis and antibiotics may be necessary to prevent secondary infection.

Vaccination

Postexposure therapy includes both passive immunization with rabies immune globulin (RIG) and active immunization with the vaccine in those who have not been vaccinated previously. RIG is administered as a one-time dose and should be given within the first 7 days of the vaccine because after this time period the vaccine production of antibody is thought to have occurred. The recommended dose of RIG is 20 IU/kg body weight for any age group. It is typically administered around the bite wound. The RIG and vaccine should not be given at the same site. Vaccine alone is indicated in persons who have had pre-exposure prophylaxis with a cell culture vaccine series or who had been vaccinated with other types of rabies vaccine with a documented neutralizing antibody response.

In the United States, there are currently two Food and Drug Administration (FDA)-approved vaccines. The human diploid cell vaccine (HDCV), trade name Imovax, and the purified chick embryo cell vaccine (PCEC), trade name RabAvert, which are both administered intramuscularly (IM). Outside the United States, there are a purified vero cell rabies vaccine (PVRV) and a purified duck embryo vaccine available in addition to the HDCV and PCEC vaccines.

The vaccine should be given as a 1.0 mL IM injection in the deltoid area (the outer thigh may be used in younger children, but vaccine should not be given in the gluteal area) on days 0, 3, 7, and 14 according to CDC guidelines. All of these vaccines are used for both pre- and postexposure prophylaxis. The WHO still recommends a five-dose immunization (with an additional dose on day 28) in cases of higher exposure, and both the WHO and CDC recommend five doses in immunocompromised individuals.

HDCV is the most expensive rabies vaccine, but PCEC and PVRV are just as efficacious and safe and can be administered at lower doses intradermally in resource-limited settings. Older vaccines that are produced in sheep, goat, or mouse nervous tissue have unreliable potency and a high incidence of neurologic complications but are still used in some developing countries because they are cheaper.

Pre-exposure vaccination

Pre-exposure prophylaxis should be offered to persons at high risk for exposure to rabies. Persons who work with rabies virus in research laboratories or vaccine-production facilities are at highest risk for exposure and should have rabies antibody titers checked every 6 months. Other laboratory workers (e.g., those performing rabies diagnostic testing), spelunkers, veterinarians and staff, and animal-control and wildlife officers in areas where animal rabies is enzootic should also have antibody measurements done every 2 years. Outdoor travelers to and expatriates living in remote areas with a high rabies exposure risk should be vaccinated. This should include children since they are at risk for more severe bites and they often play with animals and may not report bites.

Booster doses (IM or ID) of vaccine should be administered to maintain an adequate serum titer. The Immunization Practices Advisory Committee (ACIP) recommends three pre-exposure doses of the HDCV given IM at 0, 7, and 21 or 28 days. This ensures both seroconversion and adequate duration of protective antibody. Routine serologic testing after vaccination is not needed as seroconversion has been uniform. Patients who are immunosuppressed or taking medications such as chloroquine, which may interfere with antibody response to the vaccine, should postpone pre-exposure vaccinations and consider avoiding activities for which rabies pre-exposure prophylaxis is indicated. When this is not possible, they should be vaccinated and their antibody titers checked.

Education

Prevention is the best cure. Knowledge is extremely vital in this disease. People should be informed of preventative measures if they are considered to be a high-risk group. The CDC has immensely resourceful web-based information for individuals who have concerns or common questions related to a dog bite. They have recommendations for people who would like to have a dog or cat as a household pet. Casual handshaking or standing next to someone who may be infected are not considered to be risks for acquiring the infection. Changing bed linen from an infected individual does not pose a threat, either. Certain risks seen in the domestic setting, barring animal bites, would also be from sexual activity, sharing utensils or cigarettes, and saliva contact from an infected source (CDC). A healthy person undergoing postexposure prophylaxis (PEP) does not constitute a potential threat for infecting others. If a person is found to be infected, the local health department should be notified once the infection is documented. In an unknown case of encephalitis, especially in children, a history must be ascertained about recent animal bites. Patients may not recognize that certain animals can be a threat for a rabies virus infection.

Because there is currently no cure for rabies infection once it has reached the CNS, determining a definitive, positive diagnosis does not aid the patient directly. However, it is an important part of the workup and differential for acute encephalitis in that a negative result points toward a different cause for the encephalitis. Alternatively, a positive result is important from a public health perspective and makes patient isolation a necessity. It also aids in establishing a more detailed history for possible exposure in other family members.

Suggested reading

Hemachuda T, Laothamatas J, Wilde H. Rabies and other lyssaviruses. In Nath A and Berger JR, eds. *Clinical neurobiology*, 2nd ed. Boca Raton, FL: CRC Press; 2021: 187–224.

Centers for Disease Control and Prevention. www.cdc.gov/rabies

Fisher DJ. Resurgence of rabies: a historical perspective on rabies in children. *Arch Pediatr Adolesc Med*. 1995;149:306–312.

Hemachudha T, Ugolini G, Wacharapluesadee S, et al. Human rabies: Neuropathogenesis, diagnosis, and management. *Lancet Neurol*. 2013;12:498–513.

Laothamatas J, Hemachudha T, Mitrabhakdi E, Wannakrairot P, Tulayadaechanont S. MR imaging in human rabies. *Am J Neuroradiol*. 2003;24:1102–1109.

Mitrabhakdi E, Shuangshoti S, Wannakrairot P, et al. Difference in neuropathogenetic mechanisms in human furious and paralytic rabies. *J Neurol Sci*. 2005;238:3–10.

Nevers Q, Albertini AA, Lagaudrieri-Gesbert C, et al. Negri bodies and other virus membrane-less replication compartments. *Biochim Biophys Acta Mol Cell Res*. 2020;1867:118831.

Vora NM, Basavaraju SV, Feldman KA, et al. Raccoon rabies virus variant transmission through solid organ transplantation. *JAMA*. 2013;310:398–407.

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Varicella-zoster virus

Jeffrey M. Weinberg

Varicella-zoster virus (VZV) is a member of the herpesviruses family and is the etiologic agent of varicella and varicella zoster. Varicella, the exanthem caused by primary infection with VZV, generally occurs in childhood. Shingles, the clinical syndrome of segmental, unilateral exanthem and neuralgic pain due to reactivation of latent VZV infection, usually occurs many years after the primary infection. In the immunodeficient person, both primary and reactivated VZV infection can lead to severe generalized virus dissemination, the life-threatening form of VZV infection. The availability of antiviral agents for management of VZV infection has raised the importance of recognizing this infection in high-risk groups. Prior to the introduction of the VZV vaccine in the United States in 1995, approximately 4 million cases of chickenpox occurred each year, 83% in children >9 years. The association between aging and VZV vulnerability is apparent in the epidemiology of the disease: of the estimated 1 million cases of herpes zoster in the United States each year, approximately 50% occur in individuals aged 50 years or older. A VZV vaccine was approved in 2006 for the prevention of shingles. A newer, more effective vaccine was approved in 2017.

Clinical presentation

Varicella (chickenpox)

In healthy unvaccinated children, VZV infection manifests as a vesicular exanthem often associated with prodromal malaise, pharyngitis, rhinitis, and abdominal pain. The rash generally appears 15 days after VZV exposure; the range is 10 to 21 days. The vesicular eruption emerges in successive crops over the first 3 to 4 days of illness, usually with concomitant enanthem. Each skin vesicle appears on an erythematous base, resulting in the descriptive image of a dewdrop on a rose petal.

The eruption most commonly originates on the head and quickly progresses to the trunk, arms, and, finally, the legs. It is common to observe all cutaneous stages, including macules, vesicles, papules, and crusts, in the same area of the skin (Figure 192.1). Varicella often is associated with fever, headache, sore throat, or stomachache. These symptoms may last for a few days, with fever in the 38.3°C/101°F to 38.8°C/102°F range. Primary VZV infection may involve the mucosal surfaces of respiratory, alimentary, and genitourinary systems; therefore those with varicella can have severe laryngitis, laryngotracheobronchitis, vaginitis, urethritis, pancreatitis, and enteritis. In immunocompromised individuals, severe abdominal pain or back pain can be an indicator of progressive VZV infection.

Varicella vaccine was licensed in the United States in 1995 for individuals ≥12 months of age. A second dose was recommended in the United States in June 2006. Since the introduction of the vaccine, the age-unadjusted incidence of chickenpox has been approximately 3 cases per 1,000 population, and the hospitalization rate for complications of varicella has decreased dramatically. Complications of varicella occur most frequently in those younger than 1 year and older than 15 years. These complications include bacterial superinfection of skin, dehydration, pneumonia, encephalitis, and hepatitis. With the availability of the

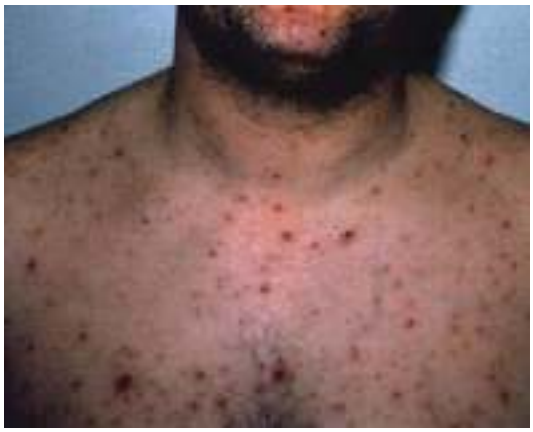

FIGURE 192.1 Varicella. Note various stages of lesions in each area of eruption.

Courtesy of David Schlossberg, MD.

vaccine, hospitalizations for chickenpox have significantly decreased and VZV-associated mortality is at an all-time low of <0.1 per million population.

Varicella zoster (shingles)

Although 10% to 20% of Americans overall will develop zoster in their lifetimes, 50% of persons reaching age 85 can be expected to do so; the incidence of herpes zoster rises dramatically, from a low of between 1.1 and 2.9 per 1,000 person-years in people <50 to 4.6 and 6.9 per 1,000 person-years, respectively, in the age groups 50–59 and 60–69. The age groups 70–79 and ≥80 years old have the highest incidence, with 9.5 and 10.9 per 1,000 person-years, respectively.

The principal risk factor for herpes zoster is prior history of VZV exposure. Any person who has had chickenpox or received the varicella vaccine as a child, which includes >90% of the US adult population, is at risk for herpes zoster. The association with advancing years, as previously described, is due to the age-related decline in VZV-specific cell-mediated immunity. Childhood zoster is rare but not unheard of, with cases reported in children as young as 4 months. The incidence of zoster in children younger than 10, however, is only 0.74 per 1,000 person-years.

Immunocompromised people or those receiving immunosuppressive drugs are also at increased risk for zoster. Thus, HIV patients have a higher incidence of zoster disease than do individuals with a healthy immune system, reported in one longitudinal study as 29.4 cases per 1,000 patient-years. Patients undergoing bone marrow or organ transplant and treated with immunosuppressives are known to develop zoster with increased frequency.

Genetics may play a role in the development of herpes zoster, as suggested by the finding that elderly white men are four times more likely to develop zoster than elderly black men. Some reports have suggested that systemic steroid therapy can incite VZV reactivation as well, placing persons with conditions such as rheumatoid arthritis or lupus at increased risk. Finally, both trauma and stressful life circumstances have been suggested to play a role in development of herpes zoster, further increasing the population at risk.

The characteristic feature of herpes zoster is a vesicular rash of unilateral distribution limited to one to three adjacent dermatomes. The onset of the rash, however, often is preceded by a prodromal phase. Beginning 4 days to 2 weeks before lesions appear, patients often note pain and paresthesia in what will become the zoster-affected dermatome. The pain can be intermittent or continuous, and has been described by patients variously as throbbing, sharp, stabbing, burning, or shooting pain. Malaise, dysesthesia, and itching are frequent elements of the prodrome, as well.

The most common site of infection is the trigeminal nerve. Most patients exhibit thoracic distribution of zoster rash, with >50% of cases presenting with cutaneous lesions of the trunk. The rash generally appears proximally, then spreads distally along the affected dermatome. The initial lesions appear as erythematous maculopapules, which turn into vesicles within 12 to 24 hours. The vesicles become pustules in about 3 days, and form scabs 7 to 10 days later. New lesions generally appear over no more than 3 to 7 days, but the duration of the rash has been correlated with patient age (advancing age associated with longer duration) and site of infection (face healing more rapidly than other loci).

Zoster affecting the first division of the trigeminal nerve, as occurs in 10% to 15% of cases, can lead to herpes zoster ophthalmicus (HZO), which produces the characteristic zoster rash on the forehead, periocular area, and nose and can be accompanied by local pain. Ocular complications of HZO are among the most dangerous morbidity of zoster disease, placing patients at risk for sight impairment or vision loss due to nerve damage or ocular pathology.

Approximately 60% to 90% of zoster patients experience local neuritic pain and hypersensitivity in association with the acute herpetic rash. This pain is likely due to an immediate nociceptive response: local inflammation and tissue damage stimulate the primary afferent neurons of the skin and subcutaneous tissue, which neurologically manifests as pain. In addition, allodynia and hyperalgesia may be present, adding to patient discomfort during acute herpes zoster.

Pain associated with zoster disease resolves within several days for many patients, although the degree of pain can be variable; one report has suggested that more extensive pain during the acute phase might predict the prolonged pain of postherpetic neuralgia (PHN), and another indicates that early pain therapy might limit the central development of chronic PHN pain following herpes zoster.

Diagnosis

The features of varicella and varicella zoster are so characteristic that a diagnosis is generally made clinically. In chickenpox, lesions in all stages of development (macules, vesicles, pustules, and crusted lesions) may be a suggestive finding. The differential diagnosis of varicella includes herpes simplex virus, Coxsackie and other enteroviruses, mycoplasma, streptococcal impetigo, rickettsialpox, insect bites, and allergic contact dermatitis.

For herpes zoster, the diagnosis can be made based on the presence of prodromal pain and/or itching and the defining zoster rash. For patients presenting in the prodromal period, the pain and

dysesthesia may require differentiation from other pain sources, such as trauma, myocardial ischemia, renal colic, gallbladder disease, or dental pain. Atypical lesions, furthermore, may require laboratory confirmation, which sometimes is obtained from viral culture (often difficult to recover from swabs) or more readily from direct immunofluorescence assay. Recently, nested and real-time polymerase chain reaction (PCR) testing of samples from skin lesions have proved valuable for identifying VZV, with more rapid amplification than other methods and high sensitivity. These laboratory techniques are most valuable for differentiating VZV from zosteriform herpes simplex, a herpes simplex viral infection that mimics zoster disease.

Prevention and therapy

Varicella vaccine

The live, attenuated varicella vaccine (Varivax) was approved in the United States in 1995 and is recommended for persons >12 months. Every person in the United States who does not have indicators for VZV immunity should have two doses of varicella vaccine. The first dose should be administered at the age of 12 to 15 months. The second dose should be given between the ages of 4 and 6 years. People 13 years of age and older who have never had chickenpox or received chickenpox vaccine should get two doses, at least 28 days apart.

Each dose, for infants and adults, is 0.5 mL administered subcutaneously.

Other populations may benefit from varicella vaccine, including eligible healthcare and daycare workers, college students, prisoners, military recruits, nonpregnant women of childbearing age, and international travelers.

Prior to the introduction of the vaccine, about 11,000 people were hospitalized for chickenpox each year in the United States, and about 100 people died each year as a result of chickenpox in the United States. As noted previously, since the introduction of the vaccine, the incidence of chickenpox and the hospitalization rate for complications of varicella has decreased dramatically.

The vaccine is not recommended for infants <1 year old, for those on salicylate therapy, for pregnant women, or those allergic to components of the vaccine, including neomycin, gelatin, and monosodium glutamate. Immunosuppressed individuals should confer with their physician about the risks and benefits of vaccination.

Zoster live vaccine

The herpes zoster vaccine is a live attenuated preparation of the Oka/Merck strain of VZV that boosts the recipient's immunity to VZV, thus increasing the chance that their latent VZV will remain dormant and that they will not develop herpes zoster. Its efficacy and safety in reducing the risk of herpes zoster disease in adults >60 were established in a pivotal trial, on the basis of which the US Food and Drug Administration (FDA) approved the vaccine in May 2006 for clinical use. On March 24, 2011, the FDA approved Zostavax for individuals 50 to 59 years of age.

Recombinant zoster vaccine

In October 2017, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention issued a recommendation for use of a new shingles vaccine, known as the recombinant zoster vaccine (Shingrix). This vaccine is recommended for adults ≥50. Based on published data, the recombinant zoster vaccine appears to be more effective than the live vaccine. The newer vaccine reduces the risk of both shingles and postherpetic neuralgia by about 90% in adults ≥50. In contrast to the older vaccine, the newer product is not a live vaccine. The recombinant zoster vaccine involves a series of two shots given 2 to 6 months apart.

Chickenpox

Overall assessment

The goal in management is to treat the symptoms of primary VZV infection and prevent complications if possible. The three stages of management are (1) establishing the likelihood of the diagnosis, (2) determining whether antiviral therapy is indicated, and (3) ruling out secondary bacterial infection, other complications, and failure of previous antiviral treatment.

Symptomatic therapy

Itching is the major symptom of chickenpox, and antipyretic management is important. Warm baths containing baking soda (1/3 cup per bathtub) or emulsified oatmeal (Aveeno) can temporarily relieve pruritus. This can be combined with the oral administration of either diphenhydramine (Benadryl), 1.25 mg/kg every 6 hours, or hydroxyzine (Atarax, Vistaril), 0.5 mg/kg every 6 hours. In older children, cold pramoxine HCl 1% lotion with calamine 8% (Caladryl) can be used, but this should be avoided in infants because of the risk of excessive surface exposure and absorption of drug or vehicle (alcohol 2.2%). Fever should be controlled with acetaminophen, but salicylates should not be used because administration of certain salicylates to children with chickenpox increases the risk of subsequent Reye's syndrome. For severe dysuria, a cold compress on the genital area during urination will ease the pain and minimize the likelihood of a functional bladder obstruction.

Antiviral therapy

Acyclovir (Zovirax) is the only agent licensed in the United States for the treatment of chickenpox. It is indicated for treatment of chickenpox in certain normal persons, for disseminated VZV infection in immunosuppressed persons, and for treatment of shingles. Oral acyclovir should be used in otherwise healthy persons with chickenpox who are at risk for moderate to severe disease, such as those >12 years, those with chronic cutaneous or pulmonary disorders, those receiving chronic salicylate therapy, and those receiving short, intermittent, or aerosolized courses of corticosteroids or aerosolized corticosteroids (Table 192.1). The American Academy of Pediatrics

TABLE 192.1 **ANTIVIRAL TREATMENT OF VARICELLA-ZOSTER VIRUS (VZV) INFECTION**[a]

Agent	Indication	Creatinine clearance (mL/min/1.73 M^2)	Dose	Dosing interval	Duration (days)
Oral acyclovir	Chickenpox >age 12 yr	>25	20 mg/kg up to 800 mg	4 times/d	5
		10–25	Same	q8h	5
		0–10[b]	Same	q12h	5
	Shingles	>25	20 mg/kg up to 800 mg	5 times/d	5–7
		10–25	Same	q8h	5–7
		0–10[b]	Same	q12h	5–7
IV acyclovir	Life-threatening VZV infection	>50	500 mg/M^2 or 10 mg/kg[c,d]	q8h	7
		25–50	Same	q12h	7
		10–25	Same	q24h	7
		0–10[b]	250 mg/M^2	q24h	7
Famciclovir	Shingles >age 18 yr	>60	500 mg	q8h	7
		40–59	500 mg	q12h	7
		20–39	500 mg	q24h	7
		≤20	250 mg	q24h	7
Valacyclovir	Shingles >age 18 yr	>50	1000 mg	q8h	7
		30–49	1000 mg	q12h	7
		10–29	1000 mg	q24h	7
		≤10	500 mg	q24h	7
Foscarnet	Acyclovir-resistant VZV[e]	>100[f]	60 mg/kg	q8h	7–10

[a] See package insert for recommended dose adjustment of all drugs.
[b] An additional dose is recommended after each hemodialysis treatment.
[c] To minimize renal toxicity an adequate urine output is required. This can be assured if the acyclovir is infused at a concentration of approximately 4 mg/mL over 1 hour and the same volume of fluid is given over the next hour.
[d] Use ideal body weight for height to calculate dose in obese person: M^2, square meter of body surface area.
[e] Foscarnet is recommended by experts for treatment of life-threatening acyclovir-resistant VZV infection, but this is not a US Food and Drug Administration (FDA)-approved indication for foscarnet use. Appropriate informed consent should be obtained before such use.
[f] Foscarnet is nephrotoxic, and dosage should be based on creatinine clearance. Guidelines for dosage adjustment are listed in the package information.

(AAP) does not recommend that otherwise normal children <12 years receive oral acyclovir for chickenpox.

All adults with chickenpox should receive oral acyclovir, and those with rapidly progressive infection should be treated with intravenous (IV) acyclovir. Valacyclovir (Valtrex) and famciclovir (Famvir), both of which are approved for treatment of shingles, are not approved in the United States for treatment of chickenpox. All immunosuppressed persons with chickenpox should be treated with IV acyclovir until the course of infection is defined. However, as noted by the AAP, some experts have used oral acyclovir in highly selected immunocompromised persons who are at relatively low risk for developing complications and in whom follow-up is assured. Case-by-case evaluation of risks versus benefits is necessary, but for many groups the risk of disseminating infection is sufficiently high and so unpredictable that IV treatment should be recommended in nearly all cases. IV acyclovir should be used for the pregnant patient with serious complications of varicella, but, if acyclovir is used routinely for the pregnant woman with uncomplicated chickenpox, it should be recognized that the risk and benefits to the fetus and mother are mostly unknown. Varicella-zoster immune globulin (VZIG) is licensed for use in high-risk individuals at the time of exposure to VZV infection but is not recommended for treatment of chickenpox.

Complications

Pyoderma is the most frequently observed bacterial complication of varicella. It can be minimized by attention to good hygiene, including daily bathing with bacteriostatic soap or dilute bleach baths. Streptococcal and staphylococcal bacterial infections can be associated with bacteremia and subsequent osteomyelitis, with scarlet fever, and with bacterial synergetic gangrene.

Bacterial superinfection can affect the lower respiratory tract, producing pneumonia and bronchitis. Viral pneumonia is more likely to be a problem in older persons with chickenpox. Therefore, it is important to monitor pulmonary status during treatment.

It is important to monitor for gastrointestinal tract involvement, including bleeding and vomiting. Mild asymptomatic hepatitis is observed in a majority of children with varicella, usually asymptomatic elevation of hepatic enzymes for which no treatment is necessary. However, elevation of serum or urinary amylase may indicate pancreatitis, which may require supportive treatment. Although rare today, Reye's syndrome and other metabolic diseases must be considered in any child with varicella in whom there is vomiting and changes in mental status.

Neurologic complications include cerebral or cerebellar abnormalities; the latter is a more benign disease. Cerebellar ataxia, the most common syndrome associated with varicella encephalitis, is most often a benign entity due to postinfectious demyelination. There is no evidence that acyclovir treatment is necessary in postchickenpox cerebellitis, but it is prudent to include antiviral therapy in any cerebral presentation of VZV infection, especially if it may be associated with continued viral replication, as in AIDS or other immunosuppressive states.

Bleeding disorders associated with varicella include disseminated intravascular coagulation, vasculitis, and idiopathic thrombocytopenic purpura (ITP). These should be managed according to conventional treatment, and there is no VZV-specific management regimen.

Immunosuppressed patients

As noted, acyclovir is the only indicated drug for the treatment of VZV infections in the immunosuppressed patient. These infections include disseminated chickenpox, disseminated shingles, or localized shingles. Three other antiviral medications, valacyclovir, famciclovir, and foscarnet (Foscavir), have activity against VZV. Valacyclovir and famciclovir are indicated for the treatment of shingles as described later (see Table 192.1). Foscarnet is recommended for the treatment of acyclovir-resistant VZV.

Shingles

Overall assessment

The development of shingles in and of itself does not produce substantial morbidity; rather, it is the potential for neurologic and inflammatory complications of zoster disease that cause patients—and physicians—the greatest difficulty. The relationship between zoster infection and destruction of neurons and satellite cells has been well established, with neurologic damage beginning even before the characteristic zoster rash appears. PHN (Box 192.1), the most frequent complication of VZV, can cause debilitating pain and impaired quality of life among the otherwise healthy elderly. The associated pain, furthermore, can continue long after the rash resolves, despite aggressive antiviral and/or pain therapy.

Symptomatic therapy

Individuals with zoster should be instructed to keep the cutaneous lesions clean and dry to reduce the risk of bacterial superinfection. A sterile, nonocclusive, nonadherent dressing placed over the involved dermatome will protect the lesions from contact with clothing. Acute pain can be very severe and refractory to therapy. Sympathetic nerve blockade can provide rapid, temporary relief of severe pain. Scheduled short-acting narcotic analgesics can be prescribed. For persistent pain, long-acting, controlled-release formulations are preferred. If the eye is involved, an ophthalmologist should be consulted for use of topical anti-inflammatory or antiviral medication and for long-term evaluation.

BOX 192.1

Postherpetic neuralgia (PHN) can present with a range of neurologic features

Pain can be intermittent or continuous, deep or superficial
Pain described as throbbing or stabbing
Spontaneous aching or burning
Paroxysmal shooting pain
Allodynia
Hyperalgesia
Intense itching

Adapted from Johnson and Whitton. *Expert Opin Pharmacother*. 2004;5:551–558.

Treatment with corticosteroids may in the short term reduce herpes-related pain intensity, but it is associated with a risk of serious adverse effects. Longer term studies have demonstrated that corticosteroids, administered orally or intrathecally, offer acute benefits but fail to prevent PHN. Corticosteroids may reduce pain intensity, but the high prevalence of diabetes, hypertension, and glaucoma among adults ≥50 years, those most likely to develop herpes zoster, severely limits the number of patients for whom corticosteroids would be helpful.

Antiviral therapy

Antiviral drugs have been consistently found to effectively reduce the severity and duration of herpes zoster and are safe and well-tolerated, with minimal adverse effects. They do not, however, reliably prevent the development of PHN. Nearly all study protocols require initiation of antiviral therapy within 72 hours of rash onset. Although 72 hours is frequently mentioned as a cutoff for therapy, there are no data showing that antiviral therapy initiated >72 hours after rash onset is not helpful, and there are observational data to suggest that it is quite helpful.

Acyclovir, valacyclovir, and famciclovir are licensed in the United States for the treatment of shingles in otherwise normal persons (see Table 192.1). Acyclovir is the agent of choice for immunocompromised persons and is the only IV agent available for treatment of shingles. Valacyclovir is the prodrug of acyclovir and, because of better bioavailability, is preferred over acyclovir for oral therapy of shingles. Famciclovir is an oral prodrug of the antiviral agent penciclovir, which has potent activity against VZV, and famciclovir undergoes rapid biotransformation to the active antiviral compound. Safety and efficacy in children has not been established for either valacyclovir or famciclovir. Also, because of the potential for

tumorigenicity in rats, famciclovir should not be given to pregnant or nursing mothers unless nursing is discontinued.

Management of exposure to VZV

The spread of infectious VZV from a person with chickenpox is by air droplets from nasopharyngeal secretions, which usually requires face-to-face exposure indoors for an hour but can also be via air currents to susceptible individuals without direct contact. The period of respiratory infectivity is generally considered to begin 48 hours prior to the onset of exanthem and to continue for 4 days after onset. In addition, the vesicular fluid can spread the virus by direct contact, so infectivity by contact with skin lesions is possible until they are crusted. Shingles can also spread by direct contact or by exposure to airborne infectious material. The incubation period for chickenpox following exposure to shingles is the same as for exposure to chickenpox: 15 days with a range of 10 to 21 days. The varicella attack rate in susceptible children on household exposure to chickenpox is approximately 90% and is 25% on exposure to household shingles.

Immunocompromised host exposed to VZV

Prior to the introduction of the varicella vaccine, the only protection from VZV infection was passive immunization at the time of exposure. Families and school personnel must continue to be aware of exposure to VZV in high-risk persons so that VZIG can be administered within 96 hours. Any susceptible person at risk for complications of VZV (Box 192.2) should receive passive immunization if exposure was adequate to communicate disease and occurred within approximately 4 days.

BOX 192.2

Groups at risk for complications of varicella-zoster virus (VZV) infection[a]

Susceptible persons on immunosuppressive therapy[b]
Persons with congenital cellular immunodeficiency
Person with an acquired immunodeficiency, including AIDS
Persons >20 years
Newborn infants exposed to onset of maternal varicella <5 days before or 2 to 7 days after birth
Premature infants weighing <1 kg[c]

[a] Susceptible (antibody negative) persons exposed to VZV by indoor face-to-face contact with an infected person <2 days before or anytime during vesiculopustular stage of chickenpox are at highest risk and should receive VZIG.

[b] All cytoreductive chemotherapy and radiotherapy is considered immunosuppressive. The immunosuppressive dose of prednisone equivalent can vary in individual cases but is in the range of 1 to 2 mg/kg/d.

[c] The risk of complications of VZV infection in this group, which is poorly defined, is based on the likelihood of protective maternal antibody versus gestational age at birth.

AIDS, acquired immunodeficiency syndrome; VZIG, varicella-zoster immune globulin; VZV, varicella-zoster virus.

Individuals receiving immunosuppressive therapy should have this discontinued during the incubation period, although this precaution is waived if the underlying disease requires continued treatment. Although not approved for such use, especially in children ≤12 years, valacyclovir, given at a dose of 1,000 mg orally three times daily or 500 mg in those weighing <40 kg, can be effective in settings of acute exposure to VZV to prevent the development of chickenpox.

Normal adults exposed to VZV

More than 90% of adults have had VZV. Susceptible adults are at risk for life-threatening chickenpox, and they are the source of unexpected epidemics. The decision to use VZIG in susceptible healthy adults following close exposure to VZV should be made on an individual basis, taking into consideration the person's health, the type of exposure, and the likelihood of previous chickenpox.

Nosocomial VZV

Control of nosocomial infections requires three actions: (1) routine, continuous surveillance of VZV susceptibility among hospital staff, with VZV vaccination as indicated; (2) adequate isolation of contagious VZV infections; and (3) rapid evaluation of and response to exposure. Hospitals that care for immunodeficient children should screen staff at the time of employment for susceptibility. This can be done efficiently by performing antibody tests on those who have a negative or unknown history of chickenpox. Susceptible employees should be vaccinated and excluded from care of patients with VZV infection until approximately 1 month after the second dose of vaccine. Exposed susceptible healthcare workers should be furloughed from the eighth day after initial exposure until 21 days after the last exposure.

If the VZV exposure is from a patient, he or she should be discharged if possible. If not possible, the patient should be placed in isolation designed to prevent spread of infection by both air and direct contact. Isolation should remain in effect until skin lesions are crusted.

After control of the source of infection comes quick assessment of three types of information: (1) the nature of the exposure and whether it is likely to result in secondary infections, (2) the susceptibility to VZV of the exposed patients or staff, and (3) the risk for complications in these exposed patients. Thus, the initial step is to define the hospital areas in which a definitive VZV exposure has occurred and then to focus on which patients in these areas are at risk for infection. Those patients remaining in the hospital should be placed in respiratory isolation between days 8 and 21 postexposure or for 8 to 28 days for those receiving VZIG.

Management of the pregnant woman

A syndrome of congenital varicella consisting of low birth weight, cutaneous scarring, limb hypoplasia, microcephaly, and other brain and eye abnormalities can occur in the baby of a pregnant woman who has chickenpox. Teratogenic damage results only from first- and second-trimester infection, and clinically apparent disease

occurs only in approximately 2% of infants born after maternal varicella in early pregnancy. For this reason, experts advise that maternal chickenpox is not a medical indication for abortion. There is no reliable diagnostic method, including amniocentesis and ultrasound, for determining teratogenic intrauterine infection. VZIG should be offered to pregnant, varicella-seronegative women with significant exposure to VZV infection. Oral antiviral prophylaxis should be considered for susceptible pregnant women exposed to VZV who did not receive VZIG or have risk factors for severe disease. IV acyclovir should be given to pregnant women who develop complicated varicella at any stage of pregnancy. However, it is generally recommended that these agents be used only if the benefit to the pregnant woman clearly exceeds the potential risk to the fetus.

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Suggested reading

Centers for Disease Control and Prevention (CDC). Evolution of varicella surveillance–selected states, 2000–2010. *MMWR Morb Mortal Wkly Rep*. 2012;61(32):609–612.

Enders G, Miller E, Cradock-Watson J, et al. Consequences of varicella and herpes zoster in pregnancy: Prospective study of 1739 cases. *Lancet*. 1994;343:1548–1551.

Gnann JW Jr, Whitley RJ. Clinical practice: Herpes zoster. *N Engl J Med*. 2002;347(5):340–346.

Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57(RR-5):1–30; quiz CE2–4.

Johnson RW, Whitton TL. Management of herpes zoster (shingles) and postherpetic neuralgia. *Expert Opin Pharmacother*. 2004;5(3):551–559.

Lopez AS, Zhang J, Brown C, Bialek S. Varicella-related hospitalizations in the United States, 2000–2006: The 1-dose varicella vaccination era. *Pediatrics*. 2011;127(2):238–245. doi:10.1542/peds.2010–0962.

Nguyen HQ, Jumaan AO, Seward JF. Decline in mortality due to varicella after implementation of varicella vaccination in the United States. *N Engl J Med*. 2005;352(5):450–458.

Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352(22):2271–2284.

Preblud SR. Age-specific risks of varicella complications. *Pediatrics*. 1981;68:14–17.

Tricco AC, Zarin W, Cardoso R, et al. Efficacy, effectiveness, and safety of **herpes zoster** vaccines in adults aged 50 and older: Systematic review and network meta-analysis. *BMJ*. 2018 Oct 25;363:k4029.

Weinberg JM. Herpes zoster: Epidemiology, natural history, and common complications. *J Am Acad Dermatol*. 2007;57(6 Suppl):S130–S135.

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Viral hemorrhagic fevers

Daniel G. Bausch

Introduction

The term *viral hemorrhagic fever* (VHF) refers to an acute systemic illness classically involving fever, a constellation of initially nonspecific signs and symptoms, and a propensity for bleeding and shock. VHFs are caused by small, single-stranded, lipid-enveloped RNA viruses from four families (Table 193.1).

Epidemiology

Natural maintenance and transmission to humans

With the exception of dengue virus (see Chapter 183, Dengue), for which humans can now be considered to be the reservoir, hemorrhagic fever viruses are zoonotic and maintained in nature in mammals (Table 193.1). The endemic area of any given VHF is thus restricted by the distribution of its natural reservoir and/or arthropod vector, although the distribution of the virus and disease are often less vast than that of the reservoir. Infection is presumed to most often result from inadvertent inoculation of virus-contaminated reservoir excreta into mucous membranes or broken skin or, in the case of the arbovirus VHFs, mosquito or tick bite. Aerosol transmission has been suggested but there are few data to confirm or refute this route of exposure and empiric field observations suggest that aerosol transmission is not a predominant mode of spread, if it occurs at all. Nevertheless, artificially produced aerosols can infect laboratory animals, with obvious implications for potential use as bioweapons.

Human-to-human transmission

Secondary human-to-human transmission occurs in many VHFs, usually through direct contact with contaminated blood or body fluids (Table 193.1), although secondary attack rates are generally low (15%–20%). Infection probably occurs most often through oral or mucous membrane exposure. Again, there are few data on aerosol spread. Large outbreaks are almost always the result of amplification in healthcare settings in which basic infection control measures have broken down, usually in areas of extreme poverty or civil strife. The risk of transmission during the incubation period or from asymptomatic persons is negligible, although a case of Argentine hemorrhagic fever was reported due to blood transfusion from a donor who was asymptomatic. Although rare, sexual transmission during early convalescence has been suspected, best documented for Ebola, Marburg, Lassa, and Junín viruses. Despite the ease of modern-day travel, imported VHF cases remain extremely rare.

TABLE 193.1 **PRINCIPAL VIRUSES CAUSING HEMORRHAGIC FEVER**

Virus	Disease	Geographic distribution of disease	Principal reservoir/vector	Annual cases	Case: infection ratio	Human-to-human transmissibility
Filoviridae						
Ebolavirus[a]	Ebola HF	Sub-Saharan Africa	Fruit bat?	_[b]	1:1	High
Marburgvirus	Marburg HF	Sub-Saharan Africa	Fruit bat: Egyptian fruit bat *(Rousettus aegyptiacus)*	_[b]	1:1	High
Arenaviridae[c, d]						
Old World Group						
Lassa	Lassa fever	West Africa	Rodent: natal mastomys or multimammate rat *(Mastomys natalensis)*	50 000-100 000	1:5-10	Moderate
Lujo[c]	Lujo HF	Zambia	Unknown, presumed rodent	Unknown	Unknown	Moderate-to-high
New World Group						
Junin	Argentine HF	Argentine pampas	Rodent: corn mouse *(Calomys musculinus)*	~100	1:1.5	Low
Machupo	Bolivian HF	Beni department, Bolivia	Rodent: large vesper mouse *(Calomys callosus)*	≤50	1:1.5	Low
Guanarito	Venezuelan HF	Portuguesa state, Venezuela	Rodent: cane mouse *(Zygodontomys brevicauda)*	≤50	1:1.5	Low
Sabiá[f]	Proposed name: Brazilian HF	Rural area near Sao Paulo, Brazil?	Unknown, presumed rodent	Unknown	1:1.5	Low?
Chapare[g]	Chapare HF	Cochabamba,Bolivia BoliviaBoliviaBolivia	Unknown, presumed rodent	Unknown	Unknown	Unknown
Bunyaviridae[c]						
Old World Group						
Hantaan, Seoul, Puumala, Dobrava-Belgrade, others	HF with renal syndrome	Hantaan: northeast Asia; Seoul: urban areas worldwide; Puumala and Dobrava-Belgrade: Europe	Rodent: Hantaan—striped field mouse *(Apodemus agrarius);* Seoul—Brown or Norway rat *(Rattus non/egicus);* Puumala -bank vole *(Clettirionomys glareolus);* Dobrava-Belgrade - yellow-necked field mouse (*Apodemus flavicollis*) mouse *(Apodemus flavicollis)*	50 000-150 000	Hantaan: 1:1.5 Others: 1:20	None
New World Group						
Sin Nombre, Andes, Laguna Negra, others (see also Chapter 186, Hantavirus cardiopulmonary syndrome in the Americas)	Hantavirus cardiopulmonary syndrome	Americas	Rodent: Sin Nombre—deer mouse *(Peromyscus maniculatus);* Andes—long-tailed colilargo *(Oligoryzomys longicaudatus);* Laguna Negra—little laucha or small vesper mouse *(Calomys laucha)*	50 000-150 000	Sin Nombre: 1:1; others up to 1:20	None, except for Andes virus
Rift Valley fever	Rift Valley fever	Sub-Saharan Africa, Madagascar, Saudi Arabia, Yemen	Domestic livestock/mosquitoes (sylvatic *Aedes* and others)	100-100 000[bh]	1:100	None

(*continued*)

TABLE 193.1 **CONTINUED**

Virus	Disease	Geographic distribution of disease	Principal reservoir/vector	Annual cases	Case: infection ratio	Human-to-human transmissibility
Crimean-Congo HF	Crimean-Congo HF	Africa, Balkans, southern Russia, Middle East, India, Pakistan, Afghanistan, western China	Wild and domestic vertebrates/tick (primarily *Hyalomma* species)	-500	1:1-2	High
Flaviviridae						
Yellow fever	Yellow fever	Sub-Saharan Africa, South America up to Panama	Monkey/mosquito *(Aedes aegypti,* other *Aedes* and *Hemagogus* species)	5000-200 000[1]	**1**:2-20	None
Dengue	Dengue HF	Tropics and subtropics worldwide	Human/mosquito *(Ae. aegypti and As. albopictus)*	100 000-200 000[1]	1:10-100 depending on age, previous infection, genetic background, and infecting serotype	None
Omsk HF	Omsk HF	Western Siberia	Rodent/tick (primarily *Dermacentor* and *Ixodes* species)	100-200	Unknown	Not reported
Kyasanur Forest disease	Kyasanur Forest disease	Karnataka state, India; Yunnan Province, China; Saudi Arabia	Vertebrate (rodents, bats, birds, monkeys, others)/tick *(Haemophysalis* species and others)	-500	Unknown	Not reported, but laboratory infections have occurred
Alkhumra HF	Proposed name: Alkhumra HF	Saudi Arabia, Egypt	Ticks?	<50	Unknown	Not reported

Abbreviation: HF = hemorrhagic fever.
[a] Six species or subtypes of Ebolavirus are recognized with varying associated case-fatality ratios (see Table 193.2). All are endemic to sub-Saharan Africa, with the exceptions of Reston ebolavirus that is found in the Philippines and
Lloviu ebolavirus which was detected in bats in Spain.
[b] Although some endemic transmission of the filoviruses (Ebolavirus >Marburgvirus) and Rift Valley fever virus occurs, these viruses have most often been associated with outbreaks. Filovirus outbreaks are typically less than
100 cases and have never been greater than 500.
[c] The virus families Arenaviridae and Bunyaviridae are serologically, phylogenetically, and geographically divided into Old World (i.e., Africa) and New World (i.e., the Americas) complexes.
[d] In addition to the arenaviruses listed in the table, Flexal and Tacaribe viruses have caused human disease as a result of laboratory accidents. Another arenavirus, Whitewater Arroyo, has been noted in sick persons in California but its
role as a pathogen has not been clearly established.
[e] Discovered in 2008. Only 5 cases (4 of them fatal) from one outbreak have been noted. The index case came to South Africa from Zambia.
[f] Discovered in 1990. Only 3 cases (1 fatal) have been noted, 2 of them from laboratory accidents.
[g] Discovered in 2003 from a small outbreak from which blood was obtained from one fatal case and Chapare virus isolated. Few other details have been reported.
[h] Although Rift Valley fever virus can be found throughout sub-Saharan Africa, large outbreaks usually occur in East Africa's Rift Valley region.
[i] Based on estimates from the World Health Organization. Significant underreporting occurs. Incidence may fluctuate widely in place and time.
[j] Alkhumra is considered by some to be a variant of Kyasanur Forest disease virus. Disagreement exists over the proper spelling of the virus, written as "Alkhurma" in some publications.

Pathology and pathogenesis

Microvascular instability, increased vascular permeability, and impaired hemostasis are the pathophysiologic hallmarks of VHF, although the mechanisms vary with each virus. Mortality usually results not from exsanguination but from a process akin to septic shock, with insufficient effective circulating intravascular volume leading to cellular dysfunction and multiorgan system failure. In fact, external bleeding is seen in a minority of cases of some VHFs (Table 193.2).

After inoculation, virus typically replicates in dendritic cells before disseminating to regional lymph nodes and then through the

TABLE 193.2 **CLINICAL ASPECTS OF THE VIRAL HEMORRHAGIC FEVERS**

Disease	Incubation period (days)	Onset	Bleeding	Rash	Jaundice	Heart	Lung	Kidney	Central nervous System	Eye	Case fatality ratio	Clinical management
Filoviridae												
Ebola HF	3-21	Variable	++	+++	+	++?	+	+	+	+	40%-85%[a]	Supportive
Marburg HF	3-21	Abrupt	++	+++	+	++?	+	+	+	+	22%-85%[b]	Supportive
Arenaviridae												
Lassa fever	5-16	Graduai	+	+[c]	0	++	+	0		0	20%	Ribavirin
Lujo HF	9-13	Abrupt	++	+	0	?	+	+		0	80%	Ribavirin
South American HFs[d]	4-14	Graduai	+++	+	0	++	+	0		0	15%—40%	Ribavirin, convalescent plasma
Bunyaviridae												
Hemorrhagic fever with rénal syndrome	9-35	Abrupt	+++	0	0	++	+	+++	+	0	< 1 -50% depending on spécifie virus	Ribavirin
Hantavirus pulmonary syndrome	7-35	Graduai	0 (except for Andes virus infection)	0	0	+++	+++	+	+	0	< 1 —50% depending on spécifie virus	Supportive, ECMO?
Rift Valley fever[e]	2-5	Abrupt	++	+	++	+?	0	+	+ +	++	Up to 50% in severe forms	Ribavirin?
Crimean-Congo HF	1-12*	Abrupt	+++	0	++	+?	+	0	+	0	15%-30%	Ribavirin
Flaviviridae	3-6	Abrupt	++	0	+++ +	++	+ +	0	++	0	20%-50%	Supportive
Yellow fever	3-15	Abrupt		+++		++			+	0	Untreated: 10-15%	Supportive
Dengue HF											Treated: <1%	
Omsk HF	3-8	Abrupt	++	0	0	+	++	0	+++	+	1%-3%	Supportive
Kyasanur Forest disease	3-8	Abrupt	++	0	0	+	++	0	+++	+	3%-5%	Supportive
Alkhumra HF[g]	3-8	Abrupt	++	+	+		+	0		+	20%-25%	Supportive

Abbreviations: ECMO = extracorporeal membrane oxygénation; HF = hemorrhagic fever.

[a] Six species or subtypes of Eboiavirus are recognized with varying associated case-fatality ratios: Zaire – 85%, Sudan – 55%, Bundibugyo – 40%, Tai Forest (also called Cote d'Ivoire) – 0 (only one recognized case, who survived),
Reston – 0 (not pathogenic to humans), Lloviu – no human infections recognized.

[b] The case fatality ratio was 22% in the first recognized outbreak of Marburg HF in Germany and Yugoslavia in 1967 but has been consistently over 80% in outbreaks in central Africa where the virus is endemic. Possible reasons for
this discrepancy include differences in quality of care, strain pathogenicity, route and dose of infection, underlying prevalence of immunodeficiency and comorbid illnesses, and genetic susceptibility.

[0] A morbilliform or maculopapular skin rash almost always occurs in persons with lighter skin, who are usually expatriates, but, for unclear reasons, is rarely present in darker-skinned Africans from the endemic area.

[d] Data are insufficient to distinguish between the syndromes produced by the various arenavimses found in the Americas. They are thus frequently grouped as the "South American hemorrhagic fevers."

[e] HF, encephalitis, and retinitis may be seen in Rift Valley fever independently of each other.

[f] The incubation period of Crimean-Congo HF varies with the mode of transmission: typically 1–3 days after tick bite and 5–6 days after contact with infected animal blood or tissues.

[g] Based on preliminary observations. Fewer than 100 cases have been reported.

Key: 0 = sign not typically noted/organ not typically affected, + = sign occasionally noted/organ occasionally affected, ++ = sign commonly noted/organ commonly affected, +++ = sign characteristic/organ involvement severe.

lymph and blood monocytes to a broad array of organs, including liver, spleen, lymph node, adrenal gland, lung, and endothelium. The particular organs most affected vary with the VHF (Table 193.2). Virus interaction with immune cells, especially macrophages and endothelial cells, results in cell activation and the unleashing of an inflammatory vasoactive process consistent with the systemic inflammatory response syndrome. Impaired hemostasis may entail endothelial cell, platelet, and/or coagulation factor dysfunction. Disseminated intravascular coagulation (DIC) is frequent in some VHFs (Table 193.2). The degree of tissue damage varies with the VHF and may be mediated either through necrosis or apoptosis. Cardiac inotropy may be inhibited in some VHFs, further impairing organ perfusion. Adrenal or pituitary gland necrosis with consequent vascular collapse has been postulated but not specifically demonstrated. Virus is cleared rapidly from the blood in survivors but may remain for weeks or months in a few immunologically protected sites, such as the chambers of the eye, central nervous system, and gonads, the latter resulting in the aforementioned sexual transmission during convalescence.

The pathogenesis of most VHFs appears to be related to unchecked viremia, with most fatal cases failing to mount a significant antibody response, in some cases due to virus-induced suppression of the host adaptive immune response. Virus can be found in a wide variety of body fluids during the acute illness, including blood, saliva, stool, and breast milk. Inflammatory cell infiltration is usually mild, consisting of a mix of mononuclear cells and neutrophils. However, in dengue, yellow fever, and hantavirus infections (see Chapter 186, Hantavirus cardiopulmonary syndrome in the Americas), in which viremia is usually cleared prior to the most severe phase of the disease, the host immune response may play a detrimental role. The unique process of antibody-mediated enhancement may facilitate the development of dengue hemorrhagic fever (see Chapter 183, Dengue).

Clinical presentation

VHF is seen in both genders and all ages. Although the clinical manifestations of each VHF may differ as disease progresses, distinction in the early phases is rarely possible. Most patients present with nonspecific signs and symptoms difficult to distinguish from other common febrile illnesses, including fever, general malaise, anorexia, headache, chest or retrosternal pain, sore throat, myalgia, arthralgia, and lumbosacral pain (Table 193.2). The pharynx may be erythematous or even exudative, especially in Lassa fever, resulting in misdiagnosis of streptococcal pharyngitis or mononucleosis (Figure 193.1A). Conjunctival injection or hemorrhage is frequent but not typically accompanied by itching, discharge, or rhinitis (Figures 193.1B and C). Hiccups may be seen early in Ebola hemorrhagic fever. Gastrointestinal signs and symptoms ensue in the first few days, including nausea and vomiting, epigastric and abdominal pain and tenderness (especially in the right upper quadrant in Ebola hemorrhagic fever), and non-bloody diarrhea. Appendicitis or other acute abdominal emergencies are sometimes suspected, prompting potentially hazardous (in terms of risk of bleeding and nosocomial spread) surgical interventions. Morbilliform, maculopapular, petechial, or ecchymotic skin rashes may be seen, depending on the specific VHF (Table 193.2 and Figure 193.1D). Hepatosplenomegaly is frequently noted but may simply represent high underlying prevalence in populations in sub-Saharan Africa where most clinical observations have been made. Relative bradycardia (Faget's sign) and orthostatic hypotension may be noted, especially in yellow fever and dengue virus infections. Biphasic illnesses are described with a quiescent period of days (yellow fever, dengue hemorrhagic fever, and Rift Valley fever) to weeks (Kyasanur Forest disease and Omsk hemorrhagic fever) after which the most severe manifestations may set in, but not uniformly noted. Distinct progressive phases of prodrome, hypotension, oliguria/renal failure, diuresis, and convalescence are classically described for hemorrhagic fever with renal syndrome (HFRS), but again not uniformly seen. Neck pain and stiffness, retro-orbital pain, and photophobia and other meningeal signs are common in Rift Valley fever, Kyasanur Forest disease, and Omsk hemorrhagic fever.

In severe cases, patients progress towards the end of the first week of illness to vascular instability that may be manifested by facial flushing, edema, bleeding, hypotension, shock, and proteinuria (Figures 193.1E–H). The likelihood of hemorrhage varies with the VHF (Table 193.2) and may be manifested as hematemesis, melena, hematochezia, menometrorrhagia, petechiae, purpura, epistaxis, and bleeding from the gums and venipuncture sites (Figures 193.1E–G). Hemoptysis and hematuria are infrequent. Hemorrhage is almost never present in the first 48 hours of illness. Facial and neck swelling are classic signs of severe Lassa and Lujo virus infection. Central nervous system manifestations, including delirium, tremor, gait anomalies, convulsions, and hiccups may be noted in end-stage disease. Renal insufficiency or failure may occur, especially in HFRS. Pregnant women often present with spontaneous abortion and vaginal bleeding. A dry cough, sometimes with a few scattered rales on auscultation, is frequently noted, but prominent pulmonary symptoms early in the course of disease are uncommon, with the exception of with hantavirus pulmonary syndrome. With the exception of yellow fever, jaundice is not typical in the absence of underlying Gilbert's syndrome, drug reaction, or coinfection. Radiographic and electrocardiographic findings are generally nonspecific.

Disease usually progresses rapidly, with death 7 to 14 days after symptom onset in fatal cases. Common indicators of a poor prognosis include shock, bleeding, neurologic manifestations, high viremia (or surrogate measurements of antigen or genome copies), and elevated levels of aspartate aminotransferase (>150 IU/L). Maternal and fetal mortality are elevated in pregnancy, especially during the third trimester, where they approach 100%. However, mild and even asymptomatic cases have been reported even for what are considered the most virulent VHFs, possibly related to differences in route and dose of infection, underlying comorbid illness, and host genetic predisposition. Specific human genotypes or histocompatibility markers have been associated with risk of Lassa fever and hantavirus infection.

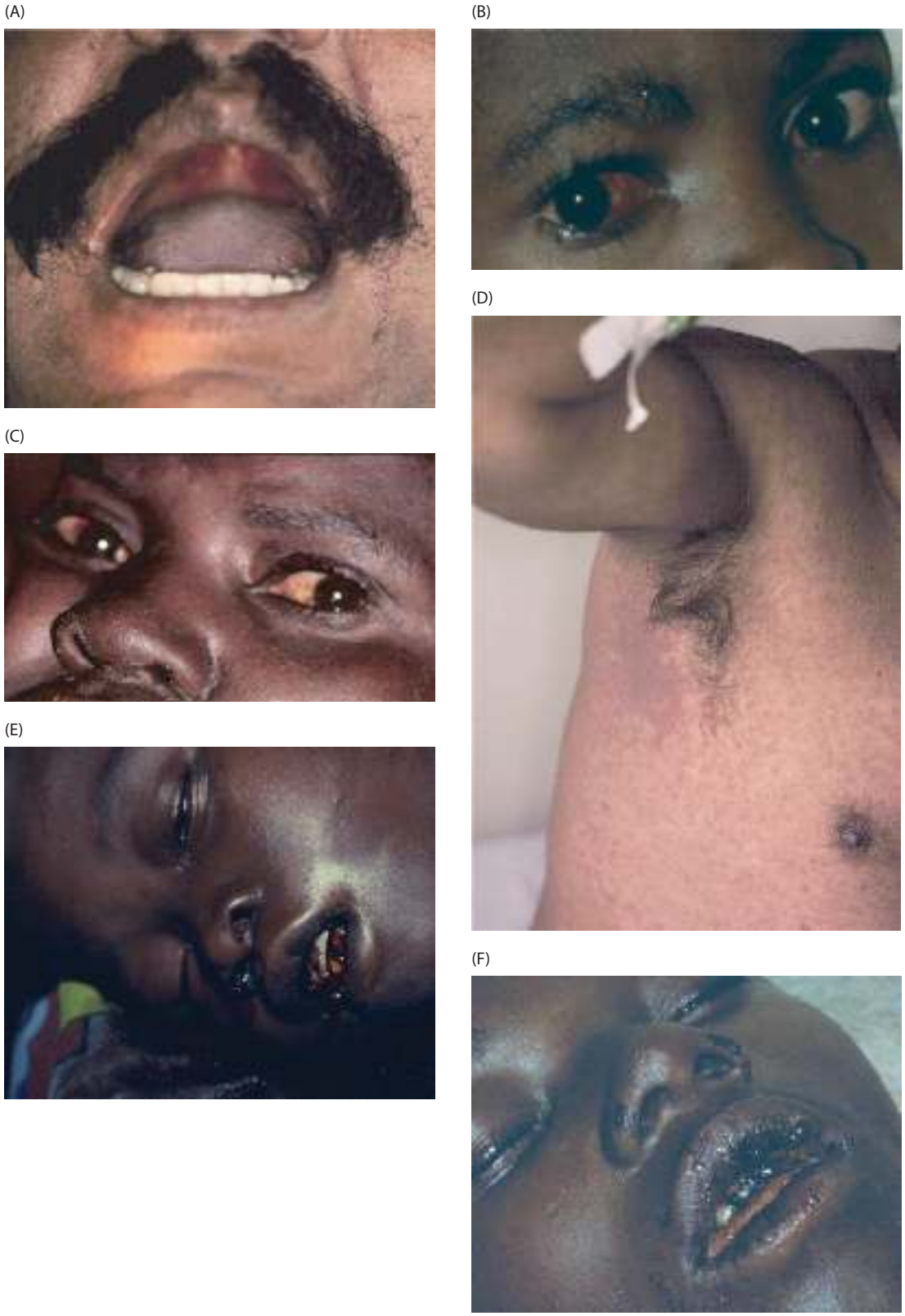
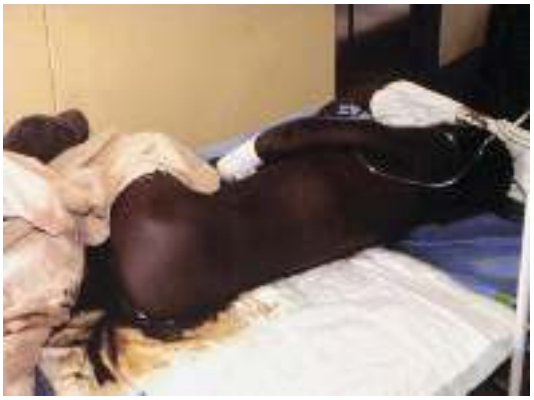


FIGURE 193.1 Clinical manifestations of viral hemorrhagic fever. (A) Soft and hard palate erythema in Lassa fever. (B) Subconjunctival hemorrhage in Lassa fever. (C) Subconjunctival hemorrhage in Ebola hemorrhagic fever. (D) Maculopapular skin rash in Lassa fever. (E) Severe oral and nasal mucosal bleeding in Ebola hemorrhagic fever. (F) Mild oral and nasal mucosal bleeding in Lassa fever. (G) Rectal bleeding in Ebola hemorrhagic fever. (H) Facial edema in Lassa fever.

(G)



(H)

FIGURE 193.1 Continued

Differential diagnosis

The nonspecific early clinical presentation makes clinical diagnosis difficult, with a long differential diagnosis (Table 193.3). Recognition of case clusters, often involving healthcare workers, is a common first clue. A detailed epidemiologic history and physical exam and preliminary laboratory results (Table 193.4) are critical, including details of travel, exposures, occupational risks, and disease progression (for example, timing of hemorrhage relative to onset of illness). VHF should be considered in patients who (1) reside in or traveled to an endemic area (Table 193.1); (2) had potential direct contact with blood or body fluids of someone with a VHF during their acute illness (this group most often is composed of healthcare workers, persons caring for family members at home or preparing bodies for burial, and laboratory personnel); (3) had contact with live or recently killed wild animals (especially nonhuman primates) in or recently arriving from an endemic area, including veterinarians, hunters, farm and abattoir workers, and taxidermists. Food potentially recently contaminated by these animals could also be a source of infection, although this remains to be clearly documented; (4) worked in a VHF research laboratory or animal facility; or (5) had sexual relations with someone recovering from a VHF in the last 3 months. Most VHFs are rare even in persons meeting the above criteria so alternative diagnoses, especially malaria and typhoid fever, should always be aggressively sought. Acts of bioterrorism must be considered if VHF is strongly suspected in a patient without any of the above criteria, especially if clusters of cases occur.

Laboratory diagnosis

Prompt laboratory confirmation of VHF is imperative but testing is unfortunately only available in a few specialized laboratories since no commercial assays exist, with the exception of various kits for dengue fever and hantavirus pulmonary syndrome. In the United States, testing can be arranged through the Centers for Disease Control and Prevention (phone 404–639–1115, after hours 770–488–7100; e-mail dvd1spath@cdc.gov). Commonly used diagnostic assays include enzyme-linked immunosorbent assay (ELISA) for viral antigen and IgM antibody, polymerase chain reaction, virus culture, immunofluorescent antibody assay, and immunohistochemistry on postmortem tissues. Research is underway on a variety of new diagnostic approaches.

Clinical management

Patients should generally be treated in an intensive care unit. For most VHFs, only supportive therapy is available. Treatment guidelines generally follow those recommended for septic shock, given the overlap in the pathogenesis of that condition and severe VHF, and considering that results from controlled trials on VHF are rare. Consultation with infectious disease specialists with experience treating VHF should be sought as soon as the diagnosis is considered. The process of performing a workup for non-VHF etiologies while assuring staff and patient safety and avoiding undue panic is a delicate one. Knowledge that most VHFs are rare and that routinely practiced universal and contact precautions are protective in the vast majority of cases should offer reassurance. Confirmed cases of VHF should be reported immediately to government health authorities.

Fluid management

Fluid management in VHF poses a particular challenge. Severe microvascular instability, often complicated by vomiting, diarrhea, decreased fluid intake, and third-spacing, often dictates aggressive fluid replacement, which may prevent shock and DIC. However, overaggressive and unmonitored rehydration may lead to pulmonary edema, especially given the impaired cardiac function

TABLE 193.3 **DIFFERENTIAL DIAGNOSIS OF THE VIRAL HEMORRHAGIC FEVERS**

Disease	Distinguishing characteristics and comments
Parasites	
Malaria	Classically shows paroxysms of fever and chills; hemorrhagic manifestations less common; malaria smears or rapid test usually positive; coinfection (or baseline asymptomatic parasitemia) common; responds to antimalarials
Amebiasis	Hemorrhagic manifestations other than bloody diarrhea generally not seen; amebic trophozoites identified in the stool by microscopy and/or antigen assays; responds to antiparasitics
Giardiasis	Positive stool antigen test and/or identification of trophozoites or cysts in stool; responds to antiparasitics
African trypanosomiasis (acute stages)	Especially the east African form. Examination of peripheral blood smear/buffy coat may show trypanosomes
Bacteria (including Spirochetes, *Rickettsia, Ehrlichia, and Coxiella*)	
Typhoid fever	Hemorrhagic manifestations other than bloody diarrhea generally not seen; responds to antibiotics
Bacillary dysentery (including shigellosis, campylobacteriosis, salmonellosis, and enterohemorrhagic *Escherichia coli* and others)	Hemorrhagic manifestations other than bloody diarrhea generally not seen; respond to antibiotics
Capnocytophaga canimorsus	Associated with dog and cat bites, typically in persons with underlying immunodeficiency, notably asplenic patients; responds to antibiotics
Meningococcemia	Bacterial-induced DIC may mimic the bleeding diathesis of VHF; bleeding within the first 24–48 hours after onset of illness and rapidly progressive illness typical; large ecchymoses typical of meningococcemia are unusual in the VHFs except for Crimean-Congo HF; rapid serum latex agglutination tests can be used to detect bacterial antigen in meningococcal septicemia; may respond to antibiotics (critical to administer early)
Staphylococcemia	Bacterial-induced DIC may mimic the bleeding diathesis of VHF; may respond to antibiotics
Septic abortion	History of pregnancy and positive pregnancy test
Septicemic or pneumonic plague	Bacterial-induced DIC may mimic the bleeding diathesis of VHF; large ecchymoses typical of plague are unusual in the VHFs except for Crimean-Congo HF; pneumonic plague may mimic hantavirus pulmonary syndrome; may respond to antibiotics
Streptococcal or Epstein–Barr virus pharyngitis	May mimic the exudative pharyngitis sometimes seen in Lassa fever
Tuberculosis	Hemoptysis of advanced pulmonary tuberculosis may suggest VHF, but tuberculosis generally has a much slower disease evolution
Tularemia	Ulceroglandular and pneumonic forms more common; responds to antibiotics
Acute abdominal emergencies	Appendicitis, peritonitis, and bleeding upper gastrointestinal ulcer
Pyelonephritis and poststreptococcal glomerulonephritis	May mimic HF with renal syndrome
Anthrax (inhalation or gastrointestinal)	Prominent pulmonary manifestations and widened mediastinum on chest x-ray in inhalation form; responds to antibiotics
Atypical bacterial pneumonia (*Legionella*, *Mycoplasma*, *Chlamydia pneumoniae* and *Chlamydia psittaci*, others)	May mimic hantavirus pulmonary syndrome; exposure to birds; symptoms often not present until late in the illness in psittacosis; respond to antibiotics
Relapsing fever	Recurrent fevers and flu-like symptoms, with direct neurologic involvement and splenomegaly; spirochetes visible in blood while febrile; responds to antibiotics

(continued)

TABLE 193.3 CONTINUED

Disease	Distinguishing characteristics and comments
Leptospirosis	Jaundice, renal failure, and myocarditis in severe cases; responds to antibiotics
Spotted fever group rickettsia (including African tick-bite fever, Boutonneuse fever, Rocky Mountain spotted fever)	Incubation period of 7–10 days after tick bite, compared with 1–3 days in Crimean-Congo HF; necrotic lesions (eschar) typically seen at site of tick bite in some rickettsial diseases while there may only be slight bruising at the bite site in Crimean-Congo HF; rash (if present) of rickettsial infection classically involves palms and soles
Q fever *(Coxiella burnetii)*	Broad spectrum of illness, including hepatitis, pneumonitis, encephalitis, and multisystem disease with bleeding; responds to antibiotics
Ehrlichiosis	Diagnosis by serology and PCR; blood film may be useful; responds to antibiotics
Viruses	
Influenza	Prominent respiratory component to clinical presentation; no hemorrhagic manifestations; influenza rapid test may be positive; may respond to anti-influenza drugs
Arbovirus infection (including dengue and West Nile fever)	Encephalitis unusual, but when present may mimic the VHFs with significant neurologic involvement (Kyasanur Forest disease, Omsk HF); usually less severe than VHF; hemorrhage not reported
Viral hepatitis (including hepatitis A, B, and E, Epstein–Barr, and cytomegalovirus)	Jaundice atypical in HF except yellow fever; tests for hepatitis antigens positive; fulminant infection resembling VHF may be seen in persons with underlying immune deficiencies
Herpes simplex or varicella-zoster	Fulminant infection with hepatitis (with/without vesicular rash); elevated transaminases and leukopenia typical; disseminated disease may be noted in otherwise healthy persons; poor response to acyclovir drugs unless recognized early
HIV/AIDS	Seroconversion syndrome or HIV/AIDS with secondary infections, especially septicemia
Measles	Rash may mimic that seen in early stages of some VHFs and may sometimes be hemorrhagic; prominence of coryza and upper respiratory symptoms in measles should help differentiate; vaccine preventable
Rubella	Rash may mimic that seen in early stages of some VHFs; usually a mild disease; vaccine preventable
Hemorrhagic or flat smallpox	Diffuse hemorrhagic or macular lesions; in contrast to the VHFs, the rash may involve the oral mucosa, palms, and soles; smallpox in the wild has been eradicated
Alphavirus infection (including chikungunya and o'nyong-nyong)	Joint pain typically a predominant feature
Fungi	
Histoplasmosis	Pulmonary disease may mimic hantavirus pulmonary syndrome; recent entry into mines or caves
Noninfectious etiologies	
Heat stroke	History for extreme heat exposure; absence of sweating; bleeding not typical but DIC may occur
Idiopathic and thrombotic thrombocytopenic purpura (ITP/TTP)	Presentation usually less acute than VHF; may have prominent neurologic symptoms in TTP; coagulation factors normal and DIC absent; often respond to corticosteroids (ITP) or plasma exchange (TTP)
Acute glaucoma	May mimic the acute ocular manifestations of Rift Valley fever
Hematologic malignancies (leukemia, lymphoma)	May resemble leukemoid reaction occasionally seen in HF with renal syndrome
Drug sensitivity or overdose	Stevens–Johnson syndrome and anticoagulant (warfarin) overdose
Industrial and agricultural chemical poisoning	Especially anticoagulants, although other symptoms of VHF absent
Hematoxic snake bite envenomation	History of snake bite

Abbreviations: AIDS = acquired immunodeficiency syndrome; DIC = disseminated intravascular coagulopathy; HF = hemorrhagic fever; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; VHF = viral hemorrhagic fever.

TABLE 193.4 **INDICATED LABORATORY TESTS AND CHARACTERISTIC FINDINGS IN THE VIRAL HEMORRHAGIC FEVERS**

Test	Characteristic findings and comments
Leukocyte count	Early: moderate leukopenia (except for hantavirus infection, in which early leukocytosis with immunoblasts are classically noted); later: leukocytosis with left shift; granulocytosis more suggestive of bacterial infection
Hemoglobin and hematocrit	Hemoconcentration (especially noted in hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome)
Platelet count	Mild-to-moderate thrombocytopenia
Electrolytes	Sodium, potassium, and acid–base perturbations, depending upon fluid balance and stage of disease Often increased
BUN/creatinine	Renal failure may occur late in disease
Serum chemistries (AST, ALT, amylase, gamma-glutamyl transferase, alkaline phosphatase, creatinine kinase, lactate dehydrogenase, lactic acid)	Usually increased, especially in severe disease; AST > ALT; a lactate level greater than 4 mmol/L (36 mg/dL) may indicate persistent hypoperfusion and sepsis. Lactate dehydrogenase is typically markedly increased in hantavirus pulmonary syndrome
Sedimentation rate	Normal or decreased
Blood gas	Metabolic acidosis may be indicative of shock and hypoperfusion
Coagulation studies (PT, PTT, fibrinogen, fibrin split products, platelets, D-dimer)	DIC common in Ebola, Marburg, Lujo virus, Crimean-Congo HF, and New World arenavirus infections. D-dimers appear to be an especially early and sensitive indicator
Urinalysis	Proteinuria common; hematuria may be occasionally noted; sediment may show hyaline-granular casts, and round cells with cytoplasmic inclusions
Blood culture	Useful early to exclude VHF and later to evaluate for secondary bacterial infection; blood should be drawn before antibiotic therapy is instituted
Stool culture	Useful to exclude VHF (in favor of hemorrhagic bacillary dysentery)
Thick and thin blood smears	May aid in the diagnosis of blood parasites (malaria and trypanosomes), bacterial sepsis (meningococcus, capnocytophaga, and anthrax) and ehrlichiosis; all negative in VHF unless coinfection
Rapid test, PCR, or other assay for malaria	Negative in VHF unless coinfection with malaria

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DIC = disseminated intravascular coagulation; VHF = viral hemorrhagic fever; BUN = blood urea nitrogen; PT = prothrombin time; PTT = partial thromboplastin time; PCR = polymerase chain reaction.

present in some VHFs, particularly hantavirus pulmonary syndrome. Although invasive hemodynamic monitoring would seem to be in order, with the exception of peripheral intravenous lines, indwelling vascular devices are contraindicated due to the risk of bleeding at the site, although they have been occasionally placed without reported complications. Intramuscular and subcutaneous injections should be avoided due to the risk of hematoma. It is probably best to rely on frequent sphygmomanometer readings and fluid balance assessment from capillary refill and urine output.

Early goal-directed therapies have been shown to mitigate both mortality and organ dysfunction in shock. Crystalloids (normal saline or Ringer's lactate), blood products (see below), and, if necessary, vasopressors (norepinephrine, adding epinephrine when warranted) should be infused to maintain mean arterial blood pressure above 65 mm Hg in adults. Vasopressin (0.03 U/min) can be added to decrease the norepinephrine dose but should not be used as the initial vasopressor. Dobutamine should be considered if there is evidence of myocardial dysfunction but dopamine is not recommended. Peritoneal and hemodialysis have been employed extensively in patients with HFRS without frequent complications, but there is little published experience with the other VHFs. Specific World Health Organization (WHO) guidelines exist for the fluid management of dengue shock syndrome (see Chapter 183).

Blood products and management of DIC

Despite profuse bleeding in some VHFs (Table 193.2), blood products should not be given empirically but rather only to meet defined clinical and laboratory parameters in the face of clinically significant hemorrhage. Transfusions, preferably with packed red blood cells, should be used to maintain a hemoglobin over 7.0 g/dL while avoiding volume overload, taking into account that chronic anemia due to malaria and malnutrition may be frequent in patients in certain geographic areas. Whole blood may be substituted if

packed cells are not available. Transfusion of platelet concentrate (1–2 U/10 kg) and/or fresh frozen plasma (FFP) (15–20 mL/kg) may be required if DIC is present (Table 193.2). Treatment should not be based on laboratory results alone except in preparation for an invasive procedure or when platelet levels fall to dangerously low levels (<50 000/mm^3 in a bleeding patient or 20 000/mm^3 without bleeding). The platelet count should generally rise by at least 2000/mm^3 per unit of platelets transfused, although the response will be less if there is ongoing DIC and platelet consumption. Impaired platelet aggregation may promote hemorrhage in some VHFs, especially Lassa fever, even when platelet counts are not drastically low. Fibrinogen concentrate (total dose 2–3 g) or cryoprecipitate (1 U/10 kg) may be administered instead of FFP, although FFP has the theoretical advantage of containing all coagulation factors and inhibitors deficient in DIC but no activated coagulation factors. Vitamin K (10 mg intravenous or orally for 3 days) and folic acid may be given, especially if underlying malnutrition or liver disease is suspected, although their efficacy is unknown.

Oxygenation and ventilation

With the exception of hantavirus pulmonary syndrome, for which early mechanical ventilation is often lifesaving, impaired gas exchange is not typically a prominent feature of VHF, especially in the early phases of disease and in the absence of iatrogenic pulmonary edema. Most patients can be supported with oxygen administered via a nasal cannula or face mask. In neurologically intact patients, noninvasive positive pressure ventilation may be a useful adjunct to forestall intubation. When mechanical ventilation is required, lung-protective tidal volumes (6–8 mL/kg of ideal body weight) should be employed to avoid ventilator-induced lung injury (i.e., barotrauma) and pulmonary hemorrhage. Extracorporeal membrane oxygenation has been used with apparent benefit in hantavirus pulmonary syndrome. Due to the risk of bleeding, arterial puncture for blood gas determination should be minimized, relying on respiratory rate and pulse oximetry if possible.

Antiviral drugs

The guanosine analog ribavirin is the only currently available antiviral therapy for any VHF (Table 193.2). Early treatment is imperative for maximum benefit. The best data are for the arenaviruses, especially Lassa fever, and HFRS (Table 193.2). Ribavirin also appears to be efficacious in Crimean-Congo HF, although few randomized controlled clinical trials have been performed. A prospective trial of ribavirin in Rift Valley fever in Saudi Arabia in 2000 was stopped after an increase in encephalitis was noted in the treatment group, but significant baseline discrepancies between the treatment and control groups make definitive conclusions difficult. In vitro data generally show activity of ribavirin against dengue, yellow fever, and Omsk hemorrhagic fever viruses, but clinical studies have not been performed. Ribavirin is not efficacious against Ebola or Marburg viruses. The main side effects of intravenous ribavirin are a mild-to-moderate hemolytic anemia, which infrequently necessitates transfusion and disappears with cessation of treatment, and rigors when the drug is infused too rapidly. A number of experimental therapies have shown in vitro activity and therapeutic benefit in animal studies and have been used on a compassionate-use basis in humans, but are not yet approved or widely available.

Convalescent plasma and antibody therapy

Although cellular immunity is thought to be the primary arm of protection in most VHFs, treatment with convalescent immune plasma has often been tried, especially for arenavirus infections. Transfusion of appropriately titered convalescent plasma within the first 8 days of illness reduces the case fatality of Argentine hemorrhagic fever to less than 1%. However, this therapy has been associated with a convalescent-phase neurologic syndrome characterized by fever, cerebellar signs, and cranial nerve palsies in 10% of those treated 7 to 80 days (mean 20 days) after initial symptom resolution. Animal studies show convalescent plasma to be efficacious in Lassa fever as well, but only if it contains a high titer of neutralizing antibody (which is not automatically the case) and there is a close antigenic match between the infecting viruses of the donor and recipient. Convalescent plasma or blood has been given to numerous patients with Ebola hemorrhagic fever, but their efficacy is still unknown. Risk of concomitant transmission of other bloodborne pathogens and lack of an existing bank of immune plasma for VHF treatment are significant impediments to this approach in most countries. With the exception of for Argentine hemorrhagic fever, this therapy should be reserved for severe and refractory cases when ribavirin is not an option. Numerous mono- and polyclonal antibody preparations show promise in VHF animal models.

Coagulation modulators

A growing body of literature suggests that disturbances in the procoagulant–anticoagulant balance play an important role in the mediation of septic shock. Coagulation-modifying drugs that have been explored anecdotally in humans or in animal models of sepsis and/or VHF, with varying degrees of efficacy, included rNAPc2 (a potent experimental recombinant inhibitor of the tissue factor/factor VIIa coagulation pathway), recombinant factor VIIa itself (paradoxically, since it would have the opposite effect of rNAPc2), heparin sulfate, and antithrombin III. Lower mortality was recently noted in heparin-treated patients with severe sepsis in a phase III clinical trial. Nevertheless, use of coagulation modulators for VHF should still be considered experimental. Despite early promise, recombinant activated protein C is no longer recommended for septic shock or VHF.

Immune modulators

Trials of various immune modulators in septic shock or VHF, including ibuprofen, corticosteroids, anti-tumor necrosis factor-α (TNF-α), nitric oxide inhibitors, statins (HMG-CoA reductase inhibitors), and interleukins, have not shown conclusive benefit. Ribavirin combined with interferon (IFN) alfacon-1, a consensus IFN, diminished mortality in a hamster arenavirus model. Although approved for clinical use in humans, IFN alfacon-1 has not been tested in human VHF. In a small study, recombinant interleukin-2 reduced renal insufficiency in HFRS, but confirmation is needed before this can be considered the standard of care. There has been renewed interest in the use of corticosteroids for possible adrenal insufficiency in septic shock. Interestingly, viral infection of the adrenal cortex and adrenal gland necrosis have been reported in various VHFs. Results of a few clinical trials of corticosteroids in shock as well as in HFRS have been mixed. Furthermore, their use might exacerbate the immunosuppression common in some VHFs. Until more conclusive studies are conducted, corticosteroids should probably not be administered unless adrenal insufficiency is strongly suspected, the target blood pressure is not maintained despite adequate fluid repletion and vasopressors, or if cerebral edema is suspected. If necessary, a dose of 200 mg intravenous hydrocortisone per day in adults should be used, divided into two to four daily doses or administer by continuous infusion.

Antibiotics and secondary infection

Patients should be immediately covered with appropriate antibacterial and/or antiparasitic therapy, with specific consideration of malaria and rickettsial disease, until VHF can be confirmed (Table 193.3). These drugs should then be stopped unless there is evidence of coinfection. Secondary bacterial infection should be suspected when patients have persistent or new fever after about 2 weeks of illness, when most VHFs have either resulted in death or are resolving.

Pain control, gastrointestinal stress ulcer prophylaxis, and management of seizures and other central nervous system manifestations

Oral or parenteral acetaminophen, tramadol, opiates, or other analgesics should be used as needed for pain control, adjusting as necessary for hepatic insufficiency. Avoid salicylates and nonsteroidal anti-inflammatory drugs because of the risk of bleeding. Prophylactic therapy for gastrointestinal stress ulcers with proton pump inhibitors or histamine-2 receptor antagonists is recommended. Antiemetics, such as the phenothiazines, are frequently warranted. Seizures can usually be managed with standard use of benzodiazepines, phenytoins, or levetiracetam, with careful attention to possible respiratory depression and hypotension. These drugs should not be given prophylactically.

Clinical laboratory testing

A broad range of clinical laboratory parameters should be monitored in patients with VHF (Table 193.4). Laboratory tests for DIC should be performed. Third-spacing, vomiting, diarrhea, decreased fluid intake, and the administration of intravenous fluids may result in significant electrolyte imbalance, especially hypokalemia, so regular potassium supplementation may be needed, keeping a close eye on renal function, which is often compromised in late disease. Although hyperglycemia has not been reported frequently in VHF, glucose should be monitored and levels kept <180 mg/dL via the use of intravenous insulin.

Nutrition

Gut feeding is preferable to parenteral alimentation when possible. Nasogastric tubes may be theoretically indicated for patients unable to eat, but there is little practical experience with their use in the VHFs. Exacerbation of gastrointestinal bleeding and heightened risk of transmission to healthcare workers during tube placement are concerns.

Management of pregnancy

Uterine evacuation in pregnant patients appears to lower maternal mortality and should be considered given the extremely high maternal and fetal mortality associated with VHF. However, this procedure must be performed with extreme caution, since it can be considered high risk with regard to nosocomial transmission. Although technically contraindicated in pregnancy (US Food and Drug Administration [FDA] Category X), ribavirin should nevertheless be considered, in consultation with the patient, as a lifesaving measure for the mother in VHFs for which the drug is efficacious (Table 193.2).

Convalescence and sequelae

Since patient clinical status and infectivity generally correlate with the level of viremia, patients who have recovered from their acute illness can safely be assumed to have cleared their viremia and discharged without concern of subsequent transmission at home. RT-PCR testing of blood and other body fluids has sometimes revealed residual nucleic acids, but the significance of this is unclear without cell culture confirming the presence of infectious virus.

Sexual abstinence or condom use is recommended for 3 months because of the delayed virus clearance in the urine and semen, as well as simple precautions to avoid contact with excretions, including separate toilet facilities and regular hand washing, although transmission through toilet facilities has not been noted. Breastfeeding should be avoided unless there is no other way to support the baby.

Survivors usually suffer no obvious long-term sequelae, with the exceptions of deafness in Lassa fever and optic retinopathy with vision loss in Rift Valley fever, both of which appear during early convalescence and may persist for life to varying degrees. Nevertheless, convalescence may be prolonged, with persistent myalgia, arthralgia, anorexia, weight loss, alopecia, pancreatitis, uveitis, and orchitis up to a year after infection. The psychological effects may also be significant, with some patients experiencing irritability, depression, post-traumatic stress disorder, or social stigmatization. Clinical management during convalescence is supportive.

Infection control

Patient isolation, personal protective equipment, and nursing precautions Although normal barrier nursing and precautions to prevent parenteral and droplet exposure to blood and body fluids suffice in most instances, for added safety these should be upgraded to "VHF precautions" once the diagnosis is suspected, which includes patient isolation and the use of surgical masks, face shields, double gloves, gowns, head and shoe covers, and protective aprons. It is prudent to place the patient in a negative airflow room if available. Hermetically sealed isolation chambers are not required and may have profound negative psychological effects. Patient access should be limited to essential designated trained staff and family members. Use of sharps should be minimized. Small particle aerosol precautions, such as the use of high-efficiency particulate air filter masks, should be employed when performing procedures which may generate aerosols, including endotracheal intubation. The hospital laboratory should be alerted before sending specimens so that appropriate precautions can be implemented. Blood samples can be inactivated by the addition of detergents, such as Triton X-100, although their effect on the various laboratory parameters to be measured has not been firmly established. Use of point-of-care diagnostic assays at the bedside can further limit exposure to laboratory personnel. Disinfection of items coming into direct contact with the patient is advised, including chemical or heat inactivation of human waste.

Contact tracing

Given the generally low secondary attack rates, widespread contact tracing, laboratory testing, or postexposure prophylaxis are not indicated for casual contacts. Contacts should be defined as persons with unprotected direct contact with someone during the symptomatic phase of a human-to-human communicable VHF. Contacts should be monitored daily for the duration of the longest possible incubation period starting after their last contact (Table 193.2), checking and recording their temperature daily. It is usually recommended that exposed persons avoid intimate contact and sharing of utensils with household members for the duration of the incubation. Confinement of asymptomatic persons is not warranted. Persons who develop signs and symptoms suggestive of VHF should be immediately isolated and tested.

Postexposure prophylaxis

Postexposure prophylaxis should be considered in persons with distinct high-risk exposure defined as one of the following: (1) penetration of skin by a contaminated sharp instrument (e.g., needlestick injury), (2) exposure of mucous membranes or broken skin to blood or body secretions (e.g., blood splashing in the eyes or mouth), (3) participation in emergency procedures without appropriate personal protective equipment (e.g., resuscitation after cardiac arrest, intubation, or suctioning), and (4) prolonged (i.e., hours) and continuous contact in an enclosed space without appropriate personal protective equipment (e.g., a healthcare worker accompanying a patient during medical evacuation in a small airplane). Most infections come from contact with severely ill patients late in the course of illness.

Postexposure prophylaxis with oral ribavirin has been recommended for Lassa fever and other arenavirus infections and Crimean-Congo HF, although no systematically collected data on its efficacy are available. Because of the high first-pass metabolism of oral ribavirin, relatively high doses are needed to provide serum levels in the range of the minimum inhibitory concentration of most hemorrhagic fever viruses (Table 193.5). Persons taking prophylaxis who develop manifestations of VHF should also be immediately laboratory tested and converted to intravenous ribavirin unless the syndrome can be readily excluded. Convalescent plasma is also routinely given as postexposure prophylaxis for Argentine hemorrhagic fever. Numerous experimental approaches have shown efficacy as postexposure prophylaxis in VHF animal models but are not yet approved for use in humans.

Vaccines

The 17D live attenuated yellow fever vaccine has an excellent protection and safety profile, despite recent recognition of rare serious adverse events in elderly persons. Confirmed previous vaccination should essentially rule out yellow fever. Candid 1, a highly efficacious live attenuated vaccine for Argentine hemorrhagic fever (only licensed in Argentina) may also be effective in Bolivian hemorrhagic fever but does not protect against other arenaviruses. Vaccines for HFRS, Rift Valley fever, and Kyasanur Forest disease exist but most are not widely tested, approved, or available. A number of experimental vaccines are efficacious in animal models of VHF. Clinical trials of various Ebola vaccines are underway.

TABLE 193.5 **RIBAVIRIN THERAPY FOR VIRAL HEMORRHAGIC FEVER**

Indication	Route	Dose[a]	Interval
Treatment	IV[b]	30 mg/kg (maximum 2 g)[c]	Loading dose, followed by:
	IV[b]	15 mg/kg (maximum 1 g)[c]	Every 6 h for 4 days, followed by:
	IV[b]	7.5 mg/kg (maximum 500 mg)[c]	Every 8 h for 6 days
Prophylaxis	PO	35 mg/kg (maximum 2.5 g)[c]	Loading dose, followed by:
	PO	15 mg/kg (maximum 1 g)[c]	Every 8 h for 10 days

Abbreviations: IV = intravenous; PO = oral administration.
[a] Pharmacokinetic and sensitivity testing for ribavirin has not been extensively performed for each VHF. The intravenous dose used is derived from that found efficacious in Lassa fever. Oral ribavirin has also been reported to be efficacious in many VHFs, especially for Crimean-Congo HF, but few controlled data are available. IV administration is strongly suggested whenever possible.
[b] The drug should be diluted in 150 mL of 0.9% saline and infused slowly.
[c] Reduce the dose in persons know to have significant renal insufficiency (creatinine clearance of less than 50 mL/min).

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Suggested reading

Bausch DG, Hadi CM, Khan SH, Lertora JJ. Review of the literature and proposed guidelines for the use of oral ribavirin as postexposure prophylaxis for Lassa fever. *Clin Infect Dis*. 2010;51(12):1435–1441.

Bond NG, Moses LM, Peterson AT, Mills JN, Bausch DG. Environmental aspects of the viral hemorrhagic fevers. In: Friis R, ed. *Praeger Handbook of Environmental Health*. Santa Barbara, CA: Praeger Publishing Company; 2012:133–161.

Centers for Disease Control and Prevention and World Health Organization. *Infection Control for Viral Hemorrhagic Fevers in the African Health Care Setting*. Atlanta, GA: CDC/WHO; 1998.

Kortepeter MG, Bausch DG, Bray M. Basic clinical and laboratory features of filoviral hemorrhagic fever. *J Infect Dis*. 2011;204 (Suppl 3): S810–S816.

World Health Organization. *Interim Infection Control Guidelines for Care of Patients with Suspected or Confirmed Filovirus (Ebola, Marburg) Haemorrhagic Fever*. Geneva: WHO; 2008.

Section 24

Specific organisms: Parasites

Intestinal roundworms

Kathryn N. Suh, Anne E. McCarthy, and Jay S. Keystone*

Nematodes (roundworms) are the most common parasites infecting humans worldwide. Of almost half a million species of roundworms, approximately 60 are known to be pathogenic to humans. Among the most prevalent human infections are those due to the intestinal (lumen-dwelling) nematodes.

Ascaris lumbricoides, Trichuris trichiura, and hookworms (*Ancylostoma duodenale* and *Necator americanus*), collectively referred to as *geohelminths* (soil-transmitted helminths), infect approximately 1.5 billion people—one-quarter of the world's population. Coinfection, in particular with *A. lumbricoides* and *T. trichiura*, is common. Geohelminths share the requirement for eggs or larvae to mature in soil in order to be infective to humans. Due to this obligate soil stage of maturation, these parasites cannot be transmitted from person to person. Geohelminths are unaffected by host immune responses, leading to chronic infection if untreated, although the natural history of such infections is usually one of decreasing worm burden over time; even with treatment, however, reinfection is common.

Other important nematodes of humans include *Strongyloides stercoralis* and *Enterobius vermicularis*. *S. stercoralis* is able to complete its entire life cycle within the human host, and like *E. vermicularis*, both person-to-person transmission and autoinfection can occur.

The prevalence and intensity of helminthic infections, and in particular geohelminthic infections, are primarily related to poverty, educational and agricultural standards, population density, and sanitary (public health) conditions, all of which have a far greater impact on the burden of disease than do ecologic factors. Most infections occur in Africa, the Americas, China, and southeast Asia. The majority of geohelminthic infections is asymptomatic and associated with low worm burdens, whereas the minority (10–35%) of infected individuals harbors most of the worm burden and suffers from more intense symptoms. Geohelminthic infections are important contributors to growth and cognitive delay in children; >800 million children live in endemic regions. Mass anthelminthic therapy for populations living in endemic areas is recommended by the World Health Organization; in 2015, an estimated 60% of children received preventive therapy. With improved disease control efforts, geohelminthic infections have decreased significantly over the past 25 years. Conclusively proving the benefit of large-scale anthelminthic therapy in endemic areas is challenging for a number of reasons, however.

Ascariasis

Ascariasis is among the earliest recorded and most prevalent helminthic infections of humans. King Richard III's remains, discovered in 2012 in the United Kingdom, contained *Ascaris* eggs. Disease is caused by *A. lumbricoides*; infection due to the closely related porcine ascarid *A. suum* has been reported following accidental ingestion of ova. Ascariasis is widely distributed throughout the world, with the highest prevalence in Asia and in young children. In 2013, an estimated 800 million people were infected. Complications of

*Dr. Jay S. Keystone is deceased.

infection are generally related to a high worm burden and thus only a minority of infected individuals is at risk of serious morbidity. The prevalence of ascariasis is attributable in part to the prodigious output of eggs by each adult female and the ability of these eggs to survive in a diverse range of environmental conditions.

The life cycle of *Ascaris* is shown in Figure 194.1. Fertilized eggs are excreted in stool, embryonate, and become infective after a period of weeks to months in soil, depending on environmental conditions. One to two days after infective eggs are ingested, larvae are released in the small bowel, penetrate the intestinal wall, travel to the pulmonary circulation, and enter the lungs, where they ascend the trachea and are swallowed. Approximately 10 weeks after ingestion of eggs, larvae mature into adults in the small intestine, where they live for up to 18 months. Egg production occurs 3 to 4 months after initial ingestion; females can produce >200,000 eggs per day.

Most *Ascaris* infections are asymptomatic. Adult worms may be seen in emesis or stool and are occasionally coughed up or extruded through the nose. *Loeffler's syndrome*, characterized by migratory pulmonary infiltrates and peripheral eosinophilia, results from larval migration through the pulmonary parenchyma and may develop within 2 weeks of ingestion. Clinical manifestations include fever, dyspnea, wheezing, and dry cough. Gastrointestinal complications are generally due to a heavy adult worm burden (e.g., intestinal obstruction from worm masses) or to migration of a single adult worm into the bile or pancreatic duct or the appendix. Complications from worms in other organs are rare.

Ascariasis is diagnosed by the demonstration of ova, larvae, or adult worms. Eggs are generally readily demonstrated in stool, although the interval between ingestion and egg production, and the variability in the distribution of eggs in stool, may be limiting factors. Molecular testing (specifically polymerase chain reaction [PCR]) for diagnosis of *Ascaris* (and other roundworm) infections can be highly sensitive and specific but is limited by the lack of an appropriate gold standard, cost, and practical limitations for use in endemic areas. Adult worms can be visualized with imaging studies

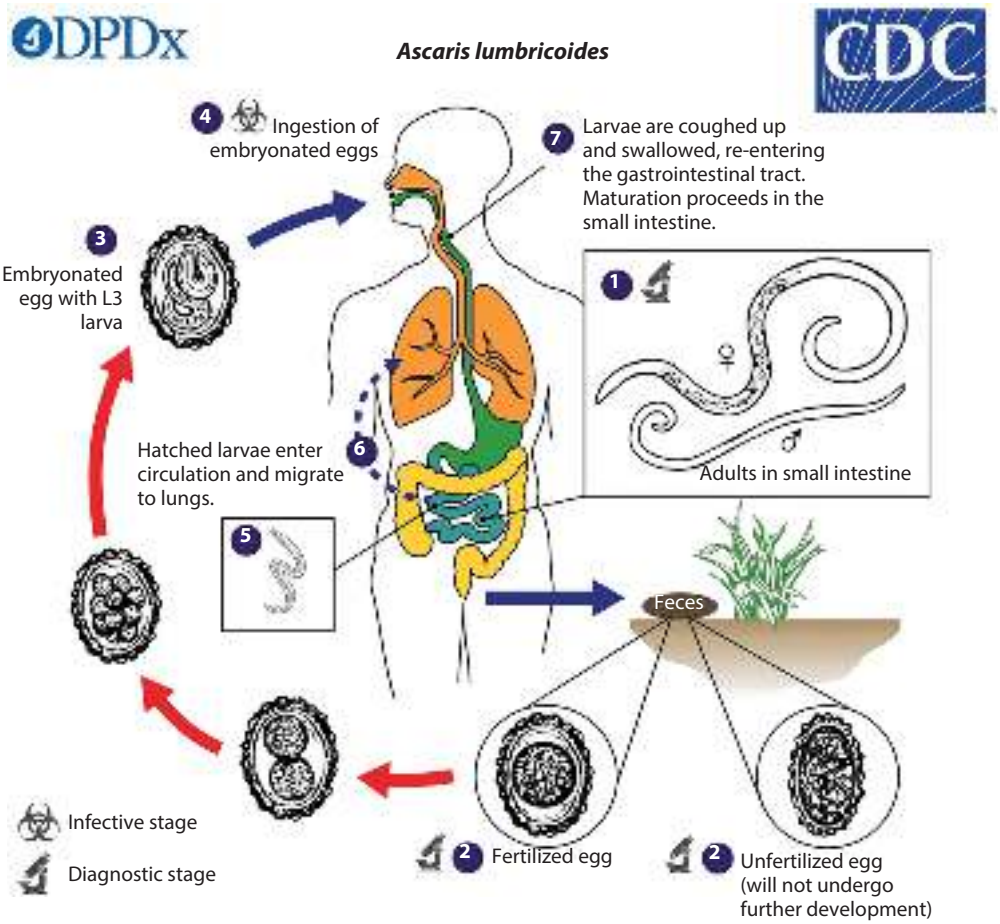

FIGURE 194.1 Life cycle of *Ascaris lumbricoides*. Adult worms (1) live in the lumen of the small intestine. A female may produce approximately 200,000 eggs per day, which are passed with the feces (2). Unfertilized eggs may be ingested but are not infective. Fertile eggs embryonate and become infective after 18 days to several weeks (3), depending on the environmental conditions (optimum: moist, warm, shaded soil). After infective eggs are swallowed (4), the larvae hatch (5), invade the intestinal mucosa, and are carried via the portal then systemic circulation to the lungs (6). The larvae mature further in the lungs (10–14 days), penetrate the alveolar walls, ascend the bronchial tree to the throat, and are swallowed (7). Upon reaching the small intestine, they develop into adult worms (1). Between 2 and 3 months are required from ingestion of the infective eggs to oviposition by the adult female. Adult worms can live 1 to 2 years.

From Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia. https://www.cdc.gov/dpdx/ascariasis/index.html

(e.g., ultrasound, barium studies) or during endoscopy or surgery. Eosinophilia is not a feature of adult ascariasis but is a common finding during the migration phase.

Because of the potential for worm migration, all infections, whether symptomatic or not, should be treated. When mixed helminthic infections are being treated, *Ascaris* should always be treated first because medications may stimulate worms to migrate. Mebendazole or albendazole is appropriate first-line therapy (Table 194.1). Single-dose therapy with either achieves high cure rates.

Trichuriasis

Like ascariasis, trichuriasis is a widely distributed disease, affecting almost 500 million individuals. Humans are the only hosts of *T. trichiura* (whipworm, so named for the characteristic morphology of adult worms). It is most common in tropical climates, with the highest prevalence in children. Human disease may rarely be caused by related species of porcine (*T. suis*) and canine (*T. vulpis*) whipworm.

Eggs passed in stool embryonate after 2 to 4 weeks of maturation in soil. There is no tissue (pulmonary) phase; eggs are deposited directly in the cecum, where larvae hatch and mature into adults over several days. Adult worms survive for up to 8 years in the cecum, where they remain attached to the intestinal mucosa. Egg production begins 2 to 3 months after initial infection, with females releasing up to 20,000 eggs per day.

Most infected individuals are asymptomatic. Moderate worm burdens may cause nonspecific gastrointestinal symptoms, including abdominal pain or distension or diarrhea. Heavy worm burdens more often affect children and may lead to failure to thrive, growth delay, profuse bloody diarrhea, or rectal prolapse, the hallmark of trichuriasis in endemic areas. Iron deficiency anemia may also be present, but peripheral eosinophilia is uncommon.

The diagnosis of *T. trichiura* infection rests on demonstration of eggs or adult worms, with similar limitations as for ascariasis. Endoscopy may reveal colitis and the presence of visible worms hanging within the intestinal lumen. Treatment with a 3-day course of mebendazole or albendazole is recommended (Table 194.1); single-dose therapy leads to suboptimal cure rates.

Hookworm infection

Hookworm infection affects approximately 500 million individuals, with most cases in sub-Saharan Africa, Asia, and the Americas. Disease due to *Necator americanus* is most common and is found predominantly in tropical climates in the Americas, China and southeast Asia, and Africa. *Ancylostoma duodenale* infection is more geographically restricted, mainly occurring in the Mediterranean, northern India, North Africa and the Middle East, and parts of Asia. Prevalence increases throughout early childhood and then peaks and plateaus in adulthood, with worm burden remaining essentially constant (or declining modestly) throughout the life of the infected host. Other hookworm species, including *Ancylostoma ceylanicum* and *A. caninum*, rarely cause enteritis, although *A. ceylanicum* is known to be prevalent in India and southeast Asia. *A. braziliense* infection typically causes cutaneous larva migrans.

TABLE 194.1 **TREATMENT OF INTESTINAL ROUNDWORM INFECTIONS**

Disease	Drug	Adult and pediatric dose
Ascariasis	Albendazole	400 mg 1×
	or	
	Mebendazole	500 mg 1× or 100 mg BID × 3 d
	or	
	Pyrantel pamoate	11 mg/kg (max 1 g) daily × 3 d
	or	
	Ivermectin	150–200 μg/kg 1×
Trichuriasis	Albendazole	400 mg/d × 3 d
	or	
	Mebendazole	100 mg BID × 3 d
	or	
	Ivermectin	200 μg/kg/d × 3 d
Hookworm	Albendazole	400 mg 1×
	or	
	Mebendazole	100 mg BID × 3 d
	or	
	Pyrantel pamoate	11 mg/kg (max 1 g) daily × 3 d
Strongyloidiasis: Immunocompetent	Ivermectin or Albendazole	200 μg/kg/d × 2 d 400 mg BID × 7 d
Strongyloidiasis: Hyperinfection	Ivermectin	200 μg/kg/d, until stools negative × 2 wk
Pinworm[a]	Albendazole	400 mg 1×
	or	
	Mebendazole	100 mg 1×
	or	
	Pyrantel pamoate	11 mg/kg (max 1 g) 1×
Trichostrongyliasis	Ivermectin	200 μg/kg 1×
	or	
	Pyrantel pamoate	11 mg/kg (max 1 g) 1×
	or	
	Albendazole	400 mg × 3 d
	or	
	Mebendazole	100 mg BID × 3 d
Anisakiasis	Albendazole	400 mg BID × 3–21 d

[a] Regardless of the agent used, therapy must be repeated 2 to 4 weeks after the first course.

Hookworm eggs are excreted in stool and hatch in soil; within 7 days larvae become infective. Following penetration of intact skin, larvae migrate through lymphatics to enter the bloodstream and travel to the lungs, ascend the trachea, and are swallowed. *A. duodenale* larvae may also cause infection by the oral route. Within the small intestine, larvae mature into adults and attach themselves to the intestinal mucosa. *A. duodenale* adults survive for up to 1 year, and *N. americanus* for up to 9 years. Egg production begins 1.5 to 2 months after infection. Females release 5 to 30,000 eggs per day, depending on the infecting species.

Infection is often asymptomatic. An intensely pruritic erythematous maculopapular eruption, "ground itch," may develop at entry points of filariform larvae, typically on the hands or feet. Dermatitis is more likely with repeated exposure and can be complicated by secondary infection. Loeffler's syndrome may occur 10 to 14 days after infection and may be accompanied by an urticarial eruption. Nausea, epigastric pain, or abdominal tenderness may be present early in the course of disease and with heavy worm burdens. Infection by the oral route may lead to pharyngeal irritation, hoarseness, cough, and nausea (Wakana disease). The hallmark of hookworm infection is chronic iron deficiency anemia, which results from local blood loss at the site of attachment of the adult worms as well as from their ingestion of blood. The occurrence and severity of anemia depend on the infecting species of hookworm (*A. duodenale* causes more blood loss than *N. americanus*), the intensity of infection, the iron reserves of the host, and the availability of iron in the diet; therefore, hookworm anemia is mostly seen in developing countries. Complications of severe anemia, including weakness, fatigue, and high-output cardiac failure, are common. Infection and resultant anemia during pregnancy are associated with low birth weight and increased neonatal mortality.

In addition to laboratory findings of iron deficiency anemia, eosinophilia is common. Hypoalbuminemia may result from protein-losing enteropathy. The diagnosis is made by identification of hookworm ova in the stool; fecal concentration techniques are not usually required. Occasionally, rhabditiform larvae may be present in stool and must be differentiated morphologically from those of *Strongyloides*. Mebendazole and albendazole are drugs of choice for treatment (Table 194.1); single-dose mebendazole has poor cure rates and should not be used. Efforts to develop an effective hookworm vaccine are ongoing.

Strongyloidiasis

Human strongyloidiasis is caused primarily by *S. stercoralis*, which is endemic to Africa, Asia, Southeast Asia, and Central and South America, where 20% or more of the population may be infected. Disease is also found in the Caribbean and, to a much lesser extent, in Europe, Japan, Australia, and parts of the southern United States. Infection caused by *S. fuelleborni*, found sporadically in Africa and Papua New Guinea, is relatively rare. Strongyloidiasis may affect up to 600 million individuals worldwide; the true prevalence is unclear given the challenges associated with diagnosing this infection.

The life cycle of *S. stercoralis* is complex (Figure 194.2). Rhabditiform larvae released in the stool of infected hosts mature into infective (filariform) stages in soil. Infection usually results from the penetration of intact skin by filariform larvae. These travel via the circulatory system to the lungs where they penetrate the alveoli, ascend the trachea, are swallowed, and then mature into adult worms in the small intestine. Although sexual reproduction does take place within the intestine, adult females are also parthenogenetic (capable of reproduction without males). Eggs are deposited in the intestinal mucosa, hatch, and release rhabditiform larvae, which are excreted in the stool to begin another cycle. Rhabditiform larvae in the bowel may also transform directly into filariform larvae that enter the circulation and begin another cycle of infection (autoinfection) or, in the appropriate clinical setting (i.e., immunosuppression), may lead to disseminated disease (hyperinfection syndrome). Rhabditiform larvae have the capacity to develop into adults in soil, where they reproduce sexually (heterogonic development) and give rise to infective filariform larvae (Figure 194.2).

Infection is common in childhood, and prevalence continues to increase with age. Most infected persons have low worm burdens and are persistently infected for life, often with minimal or no symptoms. If symptoms are present they are generally intermittent, with long asymptomatic periods between episodes. Acute infection may be apparent with very rapid (1–2 cm/h) migratory serpiginous skin lesions (larva currens) or urticaria at the sites of larval penetration; cutaneous larva migrans from dog or cat hookworms may produce a similar picture, but with much slower migration in skin (1–2 cm/d). Larva currens in the perianal area is pathognomonic of chronic strongyloidiasis. Urticarial rashes may occur over many years during chronic infection. Pulmonary manifestations of disease are unusual due to the small numbers of larvae passing through the lungs, except at the onset of a heavy infection or, more commonly, when hyperinfection syndrome is present (see later discussion). Epigastric pain mimicking peptic ulcer disease, persistent abdominal pain, diarrhea, and anorexia are common manifestations of symptomatic chronic infection. Abdominal bloating, distension, and intestinal malabsorption can also occur.

Hyperinfection syndrome, in which unregulated parasitic proliferation occurs, results in disseminated infection and most often occurs in the presence of impaired cellular immunity, typically due to the use of systemic steroids. Other chemotherapeutic agents, hematologic malignancies (notably lymphoma), organ transplants, malnutrition, chronic alcoholism, and coinfection with human T-lymphotropic virus 1 (HTLV-1) are also predisposing factors. Interestingly, HIV infection is not associated with an increased risk of disseminated disease. Insidious gastrointestinal symptoms may be present. Pulmonary disease is the most common extraintestinal manifestation of hyperinfection syndrome and is characterized by diffuse pulmonary infiltrates with dyspnea, cough, wheezing, or hemoptysis. In uncontrolled hyperinfection, filariform larvae also penetrate organs not normally involved in the *Strongyloides* life cycle, including the urinary tract, liver, and brain. Gram-negative and occasionally gram-positive bacterial infections, including bacteremia, peritonitis, meningitis, and sepsis, may result from the concurrent migration of bacteria and larvae across the bowel wall. The triad of hemorrhagic pneumonitis, enteritis, and gram-negative bacteremia

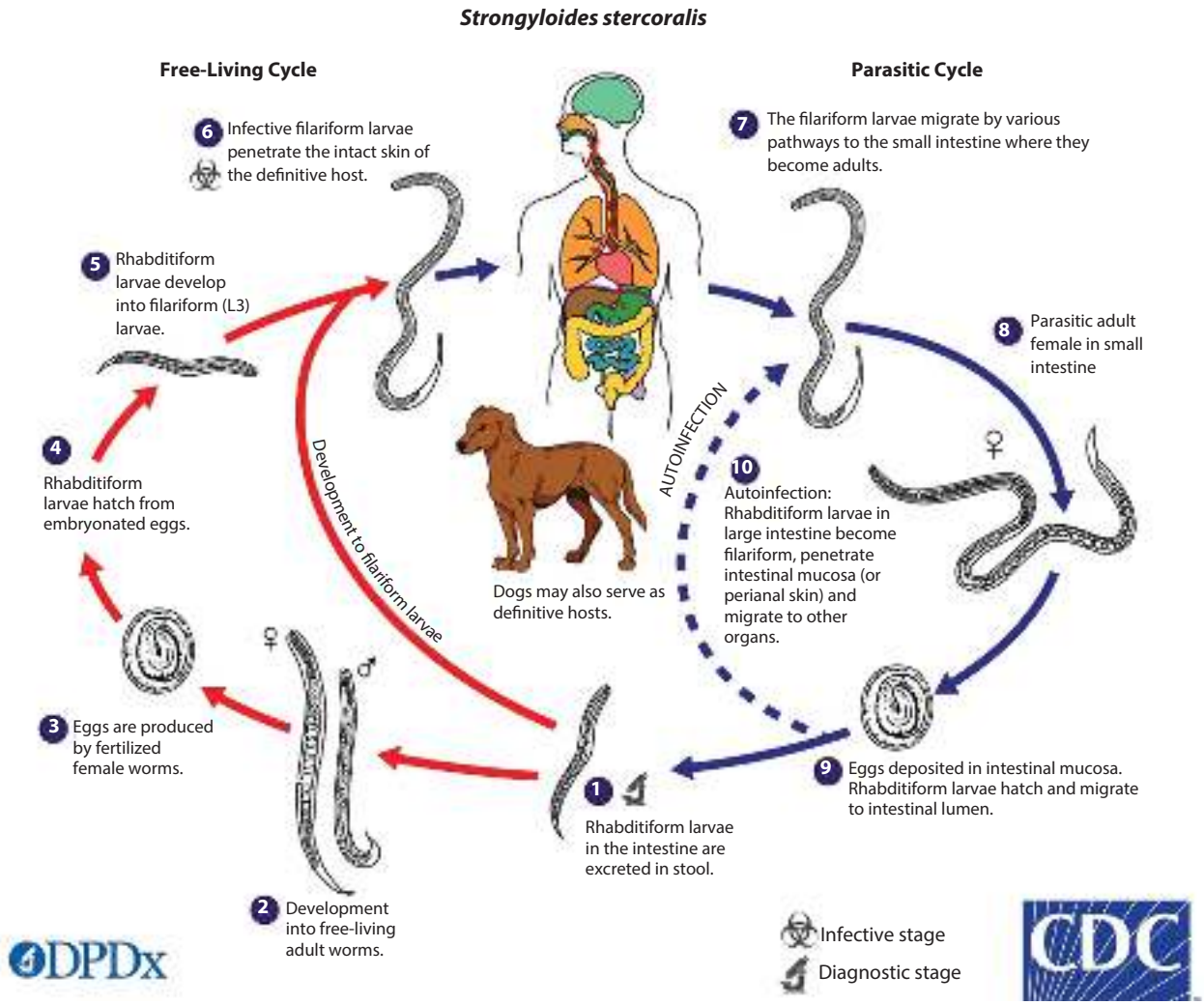

FIGURE 194.2 Life cycle of *Strongyloides stercoralis*. The *Strongyloides stercoralis* life cycle is complex, alternating between free-living and parasitic cycles and involving autoinfection. In the *free-living cycle*: Rhabditiform larvae are passed in the stool of an infected definitive host (1), develop into either infective filariform larvae (direct development) (6) or free-living adult males and females (2) that mate and produce eggs (3), from which rhabditiform larvae hatch (4) and eventually become infective filariform (L3) larvae (5). The filariform larvae penetrate the human host skin to initiate the parasitic cycle (see later discussion) (6). This second generation of filariform larvae cannot mature into free-living adults and must find a new host to continue the life cycle.

Parasitic cycle: Filariform larvae in contaminated soil penetrate human skin when skin contacts soil (6) and migrate to the small intestine (7). It has been thought that the L3 larvae migrate via the bloodstream and lymphatics to the lungs, where they are eventually coughed up and swallowed. However, L3 larvae appear capable of migrating to the intestine via alternate routes (e.g., through abdominal viscera or connective tissue). In the small intestine, the larvae molt twice and become adult female worms (8). The females live embedded in the submucosa of the small intestine and produce eggs via parthenogenesis (parasitic males do not exist) (9), which yield rhabditiform larvae. The rhabditiform larvae can either be passed in the stool (1; see *Free-living cycle*" above), or can cause autoinfection (10).

Rhabditiform larvae in the gut become infective filariform larvae that can penetrate either the intestinal mucosa or the skin of the perianal area, resulting in autoinfection. Once the filariform larvae reinfect the host, they are carried to the lungs, pharynx, and small intestine as described above, or disseminate throughout the body. The significance of autoinfection in *Strongyloides* is that untreated cases can result in persistent infection even after many decades of residence in a non-endemic area, and may contribute to the development of hyperinfection syndrome.

From Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia. https://www.cdc.gov/dpdx/strongyloidiasis/index.html

in an immunocompromised individual from an endemic area should raise suspicion of disseminated strongyloidiasis. The mortality rate for disseminated disease is approximately 50%.

The diagnosis of chronic strongyloidiasis is difficult due to the nonspecific symptoms of the disease and the minimal, irregular larval output in stool. Peripheral eosinophilia is present in up to 80% of patients with intestinal disease and can be a clue to diagnosis, but it is rarely a feature of disseminated infection (although pulmonary eosinophilia may be noted in the latter). Demonstration of larvae in clinical specimens (e.g., stool, bronchial washings in disseminated infection) is diagnostic but insensitive. In gastrointestinal infection, a single stool specimen may fail to detect larvae in up to 70% of cases, although sensitivity approaches 100% with seven consecutive stool samples. Specialized laboratory techniques

(e.g., Baermann concentration, Harada–Mori filter paper test) and duodenal aspirates are more sensitive than single stool examinations but are impractical to perform. The agar plate method, in which stool is plated on solid medium and incubated for up to 72 hours, is highly sensitive (90%) but has a slow turnaround time. Agar plate specimens containing *S. stercoralis* larvae will, after incubation, reveal linear tracks formed by bacteria that have been carried by motile larvae. While PCR is highly specific, the reported the sensitivity is around 70%, in part reflecting the variable larval output in stool but also the absence of a clear gold standard for diagnosis.

Strongyloides serology has a reported sensitivity of 70% to 95% and specificity of 39% to 99%. Its use is limited by cross-reactivity with other helminthic infections (in particular filariasis, ascariasis, and acute schistosomiasis), and the inability of a positive result to distinguish between treated or ongoing infection because antibodies may persist for years following effective treatment. However, serologic tests are invaluable in diagnosing chronic infection. In addition, antibody levels drop significantly over the first year following successful therapy, making serology useful as a test of cure. Newer methods, such as luciferase immunoprecipitation assays, are promising approaches to improved serodiagnosis but are currently not widely available.

Treatment of strongyloidiasis in asymptomatic individuals is often successful, whereas those with disseminated disease may require prolonged or repeated courses of therapy. Currently, ivermectin is considered the treatment of choice. If possible, immunosuppressant therapy should be discontinued in those with hyperinfection. Recommended regimens are summarized in Table 194.1.

Prevention of disseminated disease in at-risk individuals is strongly recommended. Serology is the most reliable test for screening in this population, with treatment offered to those with positive results. Presumptive treatment can be considered if immune-suppressing therapy cannot be delayed while awaiting serologic results.

Enterobiasis

In contrast to other gastrointestinal helminthic infections, *E. vermicularis* infection (pinworm, threadworm) does not respect socioeconomic or geographic boundaries. *E. vermicularis* is ubiquitous, found in both urban and rural settings worldwide. Enterobiasis is the most common helminthic infection in North America and is among the most prevalent throughout the world. Humans are the only hosts, with infection occurring most commonly in young children.

Eggs are ingested, either by the fecal–oral route or by exposure to contaminated fomites. There is no tissue phase of infection. Larvae hatch in the upper gastrointestinal tract and mature into adults. Adult worms mate in the small intestine before migrating to the appendix and cecum, where they survive for up to 13 weeks. Gravid females migrate to the perianal area, where they release >10,000 eggs daily, beginning 3 to 7 weeks after infection.

Symptoms are rarely serious but may be problematic. Nocturnal pruritus ani is the most common symptom and can lead to insomnia and irritability. Local bacterial infection as a result of scratching can occur. Gastrointestinal and other attributable symptoms appear to be infrequent. Abdominal pain or diarrhea should prompt a search for *Dientamoeba fragilis*, because the coinfection rate with *E. vermicularis* may be as high as 50%; recent studies suggest that *D. fragilis* is transmitted in or on pinworm eggs. There is no evidence of an association between pinworm infection and behaviors such as tooth grinding, nail biting, or enuresis.

Eosinophilia is not a feature of enterobiasis. The diagnosis is established by identifying adult worms or eggs. The most reliable approach is the cellulose tape test using transparent adhesive tape to demonstrate eggs on perianal skin. A wooden tongue depressor draped with tape (sticky side out) is firmly pressed against the perianal skin immediately on waking in the morning, before defecation or bathing. The tape is removed, placed sticky side down on a slide, and examined under a microscope. Ninety percent of infections can be detected with three slides obtained on consecutive mornings, and seven tests detect 100% of infections. In contrast, routine stool examination for ova and parasites is positive in only 10% to 15% of infected persons. Presumptive treatment of suspected infection may be a more practical approach than using cellulose tape (or pinworm paddles).

The treatment of enterobiasis is summarized in Table 194.1. In the absence of reinfection or autoinfection, a primary infection will clear without treatment in 30 to 45 days. Because intrafamilial transmission is common, treatment of the entire family is recommended. A second course of therapy should be administered 2 to 4 weeks after the first to treat possible autoinfection or reinfection as medications are relatively ineffective against developing larvae and newly ingested eggs. Specific personal hygiene measures such as good hand hygiene, daily bathing in the morning, the use of underwear and pyjamas for sleeping at night, daily change of underwear, and regular laundering of bedclothes are also important for eradication of infection. Recurring infections should be treated at least 4 times at 2-week intervals.

Trichostrongyliasis

Trichostrongylus spp. are parasites of herbivores such as sheep, cattle, and goats, primarily in the Middle East and Asia; humans are accidental hosts, with infection most commonly due to *T. colubriformis* or *T. orientalis*. Ova released in the feces of infected animals hatch in soil within 1 to 2 days and pass through three free-living stages before becoming infective. Human infection typically results from ingestion of larvae in contaminated food or water, although larvae can also penetrate skin. There is no tissue phase, and adults reside embedded in the duodenal or upper jejunal mucosa. Little is known about the pathology of human trichostrongyliasis.

Most human infections are mild or asymptomatic, but anorexia, diarrhea, flatulence, and epigastric pain may occur. Peripheral eosinophilia may be marked but is more commonly absent. Diagnosis depends on identification in stool of ova, which are often difficult to differentiate from hookworm ova. Treatment is outlined in Table 194.1.

Anisakiasis

Anisakiasis (anasakidosis; herring worm or cod-worm disease), caused by infection with the third-stage larvae of *Anisakis simplex* or *Pseudoterranova decipiens*, is most prevalent in Japan and less frequent in Hawaii and the coastal areas of North America and northern Europe (in particular, Spain). It is acquired by consumption of raw or inadequately cooked marine fish or squid, as found in sushi or ceviche, for example. The primary hosts of anisakids are sea mammals, including dolphins, porpoises, whales, seals, sea lions, and walruses. Eggs released in feces mature in seawater. Free-swimming second-stage larvae are ingested by small marine crustacea and develop into third-stage (infective) larvae in squid and predatory fish. Herring, salmon, mackerel, halibut, cod, and squid are important sources of infection for humans. Larvae ingested by consumption of raw or inadequately cooked fish invade the submucosa of the stomach or intestine but cannot mature into adult worms in the human host. The larvae cause local inflammation and hemorrhage that generally last about 10 days.

Anisakiasis is categorized into gastric, intestinal, or extraintestinal disease. The presentation varies depending on both geography and the infecting species. Gastric anisakiasis usually presents acutely after ingestion of infected food with severe epigastric pain, nausea, and vomiting. Acute symptoms subside in a few days, but intermittent nausea, vomiting, and vague abdominal pain may persist for weeks to months. Symptoms of intestinal anisakiasis develop 1 to 5 days after the infecting meal and are due to invasion of the distal ileum. Abdominal pain, nausea, vomiting, and mild leukocytosis occur. Extraintestinal complications include peritonitis and pleurisy caused by larval perforation of the intestinal wall. Hypersensitivity reactions, including anaphylaxis, have also been associated with anisakiasis.

With the appropriate history and presenting symptoms, the diagnosis of gastric anisakiasis can be most easily confirmed by endoscopy. An ulcerated lesion and the protruding larva may be visualized. Intestinal and extraintestinal anisakiasis are difficult to differentiate from other causes of acute abdomen, and patients often undergo laparotomy. Serologic diagnosis may be helpful but is not readily available. Peripheral eosinophilia is common. Treatment includes removal of the parasite and supportive care, although even untreated infection subsides in a few days. Anthelmintic therapy for human anisakiasis is not well established, although albendazole has been reported to be effective (Table 194.1).

Suggested reading

Balachandra D, Ahmad H, Arifin N, Noordin R. Direct detection of *Strongyloides* infection via molecular and antigen detection methods. *Eur J Clin Microbiol Infect Dis.* 2020 Jul 29. E-pub ahead of print. doi:10.1007/s10096-020-03949-x.

Else KJ, Keiser J, Holland CV et al. Whipworm and roundworm infections. *Nat Rev Dis Primers.*2020;6:44. doi:10.1039/s41572-020-0171-3.

Hochberg NS, Hamer DH. Anisakidosis: Perils of the deep. *Clin Infect Dis*. 2010;51:806–812.

Ghanbarzadeh L, Saraei M, Kia EB, Amini F, Sharifdini M. Clinical and haematological characteristics of human trichostrongyliasis. *J Helminthol.* 2019;93:149–153. doi:10.1017/ S0022149X17001225.

Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;386:743–800. doi.org/10–1016/ S0140-6736(15)60692-4.

Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. *Lancet.* 2018;391:252–265. doi:10.1016/ S0140-6736(17)31930-X.

Kalantari N, Chehrazi M, Ghaffair S, Gorgani-Firouzjaee T. Serologic assays for the diagnosis of *Strongyloides stercoralis* infection: A systematic review and meta-analysis of diagnostic test accuracy. *Trans R Soc Trop Med Hyg.* 2020;114:459–469. doi:10.1093/trstmh/trz135.

Khurana S, Sethi S. Laboratory diagnosis of soil transmitted helminthiasis. *Trop Parasitol*. 2017;7:86–91. doi:10.4103/tp.TP_29_17.

Krolewiecki A, Nutman TB. Strongyloidiasis: a neglected Neglected Tropical Disease (NTD). *Infect Dis Clin North Am.* 2019;33:135–151. doi:10.1016/j.idc.2018.10.006.

Loukas A, Hotez PJ, Diemert D, et al. Hookworm infection. *Nat Rev Dis Primers.* 2016;2:16088. doi:10.1038/nrdp.2016.88.

Moser W, Schindler C, Keiser J. Efficacy of recommended drugs against soil-transmitted helminths: Systematic review and network meta-analysis. *BMJ.* 2017;358:j4307. doi:10.1136/bmj.j4307.

World Health Organization. Guideline: Preventive chemotherapy to control soil-transmitted helminth infections in at-risk population groups. Geneva: World Health Organization; 2017. https://www.who.int/nutrition/publications/guidelines/deworming/en/

Tissue nematodes

Ian C. Michelow and Daniel B. Blatt

Tissue-dwelling nematodes are considered neglected tropical diseases that frequently cause debilitating illness in the most marginalized communities of the world. Infected travelers, immigrants, and refugees from endemic regions may present in the United States with a wide variety of clinical manifestations. Invasive nematode infections tend to result in eosinophilia and elevated serum immunoglobulin E (IgE), but normal blood tests do not rule out parasitic diseases. The diagnostic considerations can be focused through an understanding of the invading parasite's geographic distribution and its prevalence in endemic areas, incubation periods, and clinical manifestations. Treatment strategies must be tailored to the individual parasitic infection. Additional information about the availability of diagnostic tests and treatment is available from the US Centers for Disease Control and Prevention (CDC; dpdx@cdc.gov) and the Laboratory of Parasitic Diseases, National Institutes of Health (301-496-5398).

Trichinellosis

Trichinellosis develops when raw or inadequately cooked meat containing the encysted larvae of one of nine *Trichinella* spp. is consumed. Larvae are released from the ingested cysts by digestive enzymes in the stomach of the host; they migrate to the small intestine villi, where they penetrate the intestinal mucosa and develop into male and female adult worms in 1 to 2 days (enteral phase). Within 1 to 8 weeks, infective larval progeny are released and invade striated muscle via the circulation. There, they encyst within individual muscle fibers (parenteral phase) and can persist for months to years. In invasive infections, humans serve as both the definitive and intermediate host for this parasite.

Epidemiology

Trichinellosis has a worldwide distribution, occurring in temperate and tropical climates. Internationally, it is considered an emerging zoonosis, with increased rates of infection attributed to changing human dietary habits and the breakdown in some developing countries of veterinary management practices. In the United States, the principal mode of transmission historically has been consumption of undercooked *Trichinella*-infected pork, most frequently *T. spiralis*. The incidence has decreased from a median of 360 cases per year in the decade from 1947 to 1956 to a median of 14.5 cases annually from 2006 to 2015. Factors contributing to these favorable trends include improved observance of standards and regulations in the US commercial pork industry, increased usage of home freezers, and improved knowledge about safe cooking practices. The number of reported cases from eating wild boar, bear, and, rarely, walrus and deer meat currently far exceeds the number of reported cases related to eating commercial or farm-raised pork products. In the United States, the accuracy of surveillance was enhanced after the disease became notifiable in 1966.

Among US travelers, most cases of trichinellosis have been associated with consumption of wild pigs, especially the bush pig and warthog. Most reported travel-related infections have been associated with visits to Mexico, Southeast Asia, and sub-Saharan Africa.

Clinical presentation

The severity of symptoms depends on the number of ingested larvae, host immune status, and history of a previous infection that may have induced immunological priming. Because most infections result from ingestion of a small number of larvae, most infected persons are asymptomatic. The adult worm in the small intestine may cause gastrointestinal symptoms within a week of infection. Early symptoms may include abdominal discomfort, nausea, vomiting, and diarrhea, which may evolve into fulminant enteritis in unusually heavy infections. However, most clinical manifestations are related to systemic invasion by larvae, and they usually begin in the second week after infection, peak over a week's time, then slowly subside over weeks to months if the infection is not treated early in its course. Classical features of trichinellosis include myalgia (90% of cases), progressive eosinophilia (75%), fever (70%), and periorbital edema (45%). Myositis usually begins in the extraocular muscles and progresses to involve the masseters, neck muscles, and limb flexors. Other symptoms and signs include cough, headache, rash, pruritus, subungual splinter hemorrhages, thromboembolic events, and weakness. In fulminant infection encephalitis, myocarditis, and pneumonia may be fatal.

Diagnosis

Eosinophils may increase to a maximum of 20% to 90% of the total white blood cell count, although this is not pathognomonic for trichinellosis. Elevated creatine phosphokinase and lactate dehydrogenase levels reflect extensive muscle involvement. A diagnosis is usually made on the basis of clinical characteristics and a positive result for one of several types of *Trichinella*-specific serologic assays. A definitive diagnosis may be established by identifying larvae in a muscle biopsy, but this is usually unnecessary. Antibodies are not detectable until at least 3 weeks after infection and can persist for years. Infection with other helminths can cause false-positive test results.

Therapy

The goal of treatment in the enteral phase of infection is to prevent muscle invasion by larvae; the goal during the parenteral phase is to reduce muscle inflammation. However, the effectiveness of delayed initiation of antiparasitic therapy once parasites are encysted in muscle is markedly reduced. For mild *Trichinella* infections, only symptomatic therapy may be required because the clinical course is usually uncomplicated and self-limited. Specific treatment includes albendazole (400 mg with fatty food BID for 10–14 days) or mebendazole (200–400 mg TID for 3 days, followed by 400–500 mg TID for 10 days; available only at compounding pharmacies in the United States). Prednisone (30–60 mg/d for 10 to 14 days including a taper) is effective for severe symptoms. Postexposure prophylaxis with mebendazole (5 mg/kg BID for 5 days) may be effective to prevent trichinellosis in individuals who consumed contaminated meat within the past 6 days.

Filariasis

Of the eight filarial species capable of infecting humans, the four that cause the most disease worldwide are *Wuchereria bancrofti* (lymphatic filariasis), *Brugia malayi* (lymphatic filariasis), *Onchocerca volvulus* (onchocerciasis), and *Loa loa* (loiasis). Because only a small proportion of insect bites is infective, the risk of transmission is proportionate to the duration of exposure in an endemic area. The clinical manifestations of filariasis depend in part on the immune response of the host. The response to the parasite in endemic populations is downregulated because of immunosuppression and immunological tolerance, and a large parasite burden is common. In contrast, individuals who have grown up outside of endemic regions and become infected manifest prominent signs and symptoms and usually have a low parasite burden.

Lymphatic filariasis

Lymphatic filariasis is caused by infection with one of the lymph-dwelling filariae, *W. bancrofti, B. malayi*, or *Brugia timori*. An infected female mosquito of several species deposits larvae in subcutaneous tissue during a blood meal. Over a period of at least 6 months, the larvae mature into adult worms (macrofilariae) that live for 5 to 7 years. These threadlike adults reside in afferent lymphatic channels or sinuses of lymph nodes. All lymph-dwelling filariae contain *Wolbachia*, an intracellular bacterial endosymbiont that is essential for their growth, development, fertility, and survival, and can be targeted with antimicrobial agents for therapy of lymphatic filariasis. The filariae reproduce sexually in the lymphatics and their progeny (larvae or microfilariae) circulate in the bloodstream.

Epidemiology

W. bancrofti, found in tropical and subtropical regions throughout the world, is the most widely distributed human filaria and is responsible for 90% of cases of lymphatic filariasis. In most of the world, the parasite is nocturnally periodic, with the microfilariae scarce in peripheral blood during the day but increased at night. In the Pacific Islands, however, the microfilariae are subperiodic; microfilaremia is seen throughout the day, reaching maximal levels in the afternoon. Brugian filariasis occurs throughout Asia, including India and the Philippines. This form of filariasis is nocturnally periodic, except in forested areas, where it is subperiodic. Short-term tourists to endemic areas have a very low risk of acquiring infection.

Clinical presentation

Among endemic populations, most people infected with lymphatic filariasis are asymptomatic. Presence of microfilariae in the bloodstream and death of adult worms in lymph vessels are responsible for the common early manifestations, which include acute

filarial fevers, lymphadenopathy, and lymphangitis with transient lymphedema. More than half of these patients have hematuria, proteinuria, or both. The episodes abate after 7 to 10 days but can recur. A hallmark of lymphatic filariasis is lymphangitis that develops in a retrograde fashion, spreading distally, which is opposite to that seen in cellulitis. Genital involvement, which may manifest as tender epididymitis, funiculitis, or orchitis, is found exclusively with *W. bancrofti*.

Inflammation of lymphatic tissues caused by adult worms leads to long-term damage and lymphatic obstruction years after the infection has cleared in up to 30% of infected people. Pitting edema is an early manifestation of obstruction that heralds chronic lymphedema, most commonly affecting the legs, but it can also occur in arms, genitals, and breasts. Scrotal edema can be severe (Figure 195.1). The edema eventually causes characteristic features of elephantiasis, with thickening of subcutaneous tissues, hyperkeratosis, and fissuring of skin. Chyluria can develop in *W. bancrofti* infections if retroperitoneal lymphatics are obstructed. Lymphedema renders patients susceptible to recurrent bacterial and fungal infections, which cause pain and fever and exacerbate the lymphatic damage.

Persons new to endemic areas who acquire lymphatic filariasis usually develop acute lymphatic inflammation with lymphangitis, lymphadenitis, and, in the case of *W. bancrofti*, genital pain, but they may also develop allergic phenomena such as hives, urticaria, and eosinophilia.

FIGURE 195.1 Massive scrotal swelling in lymphatic filariasis.

Diagnosis

A diagnosis of lymphatic filariasis is supported by compatible epidemiologic risk factors, clinical features, and laboratory tests. However, a definitive diagnosis requires visualization of the parasite. Microfilariae can be detected in blood by microscopic examination of thick and thin blood smears stained with Giemsa or hematoxylin-and-eosin. Concentration techniques such as blood filtration (e.g., Nuclepore membranes) or centrifugation of blood lysed with 2% formalin (Knott's technique) may improve the diagnostic yield. The timing of blood collection is critical and should be based on the periodicity of the microfilariae in the endemic region in question. For nocturnally periodic microfilariae, blood should be collected between 10 PM and 2 AM. A 10- to 14-day period is required for microfilarial periodicity to adjust to the local time zone if the patient has left the endemic area.

A sensitive but nonspecific serologic screening test (filarial IgG4) is available to rule out filarial infections (including *Wuchereria*, *Brugia*, *Onchocerca*, and *Loa loa*). Assays to detect circulating parasite antigens of *W. bancrofti* are not approved in the United States. Polymerase chain reaction (PCR)-based assays that detect DNA of *W. bancrofti* and *B. malayi* have been developed but are not commercially available in the United States.

In general, laboratory data supporting a diagnosis of filarial infections include eosinophilia, elevated serum IgE levels, and antifilarial IgG4 antibodies in the serum. However, serology tests may be falsely positive because of cross-reactivity of antibodies with other helminths. False-negative test results may occur because lymphedema may develop many years after infection, by which time antibody levels have declined.

Adult worms in lymphatics are generally inaccessible and excisional biopsies are unhelpful. Ultrasonographic examination of the scrotum or breast in females using a high-frequency transducer with Doppler may demonstrate motile adult worms within dilated lymphatics (the so-called *filarial dance sign*).

Therapy

To select an appropriate and safe therapy, it is important to be aware of possible coinfections with other filariae. The geographic distributions of lymphatic filariasis, loiasis, and onchocerciasis overlap in West Africa and coinfection can occur. Diethylcarbamazine (DEC) is contraindicated in regions where onchocerciasis is endemic because DEC can exacerbate onchocercal skin and eye disease (Mazzotti reaction). Since treatment of loiasis with DEC or ivermectin can result in severe adverse effects, it is imperative to diagnose *Loa loa* before initiating therapy for patients with lymphatic filariasis.

The main goal of therapy is to kill adult worms that are responsible for lymphedema. For individuals not coinfected with onchocerciasis, the CDC recommends DEC, which is both microfilaricidal and active against adult worms, at a dose of 6 mg/kg in a single dose or 6 mg/kg/d in three divided doses for 12 days. For single-dose DEC therapy, the WHO recommends adding a single dose of albendazole (400 mg). For individuals coinfected with onchocerciasis, singles dose of albendazole (400 mg) and ivermectin

(200–400 μg/kg) are recommended. DEC is not commercially available in the United States but can be obtained through the CDC Drug Service under an Investigational New Drug protocol (telephone 404–639–3670). Doxycycline (100 mg PO BID × 4 weeks) targets the intracellular *Wolbachia* and also demonstrates macrofilaricidal activity.

The severity of adverse reactions correlates with the pretreatment level of microfilaremia, but the etiology is unclear and may represent either an acute hypersensitivity reaction to massive antigen release or an inflammatory reaction induced by the release of *Wolbachia*. Usually, the reactions, which include fevers, headache, lethargy, arthralgia, and myalgia, can be managed with antipyretics and analgesics.

Antiparasitic treatment of chronic lymphatic obstruction is ineffective. If the infection is recognized early, some signs of lymphatic obstruction can be reversed. Severe chronic lymphedema (elephantiasis), however, requires supportive measures. Therapies include elevation of the affected limb, use of elastic stockings, skin hygiene, and skin and wound care with antifungal ointment and antibacterial antiseptics in consultation with a lymphedema therapist. There is no proven role for prophylactic antibiotics to prevent recurrent bacteremia and cellulitis. Hydroceles can be managed surgically, and surgical decompression with a nodo-venous shunt may provide relief for patients with severely affected limbs.

Infection can be prevented by using insect repellants that contain N,N-Diethyl-meta-toluamide (DEET), covering exposed body parts to prevent mosquito bites, and treating clothes with permethrin.

Tropical pulmonary eosinophilia

Tropical pulmonary eosinophilia (TPE) is a rare but serious variant of lymphatic filariasis caused by immunologic hyperresponsiveness to *W. bancrofti* or *B. malayi*. The syndrome affects men four times as commonly as women, most commonly from the ages of 15 to 40 years. Most cases have been reported from Pakistan, India, Sri Lanka, Southeast Asia, and Brazil.

The signs and symptoms of TPE are attributed to trapping of microfilariae in pulmonary vasculature, with resultant eosinophilic alveolitis; patients develop paroxysmal cough, dyspnea, and wheezing that is often misdiagnosed and treated as asthma. The characteristic nocturnal worsening of symptoms is due to the nocturnal periodicity of the microfilariae. Other symptoms include fever, malaise, and weight loss. The majority of cases have reticulonodular or interstitial infiltrates on chest radiographs. Typical symptoms in combination with extreme eosinophilia (>3,000/mm^3), high polyclonal IgE levels, elevations of antifilarial antibodies, and a prompt response to DEC establish the diagnosis. Untreated, TPE can lead to lung fibrosis and progressive respiratory compromise.

Therapy

The CDC recommends DEC at a dose of 6 mg/kg/d in three divided doses for 14 to 21 days. Symptoms usually resolve within 1 week. However, adjunctive treatment with corticosteroids may improve outcomes if the disease persists or relapses. As many as 20% to 40% of treated patients relapse, requiring retreatment.

Loiasis

Also known as *African eye worm*, loiasis results from infection with *Loa loa* acquired in the rainforests of West and Central Africa. After the bite of daytime-active infected female deer or mango flies, the filarial larvae are inoculated into the subcutaneous tissue, where they mature over several months and migrate throughout the body, including the CNS. The adult parasites reproduce sexually, and their progeny reside mostly in humans' lungs. The microfilariae then enter the bloodstream intermittently with a diurnal periodicity. Adult worms can survive longer than a decade.

Epidemiology

The countries with reported transmission include Angola, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo, Equatorial Guinea, Ethiopia, Gabon, Nigeria, and Sudan. In some regions, individual histories of eye worm exceed 40%.

Clinical presentation

Clinical manifestations differ between indigenous people and nonimmune travelers. In the native population, microfilaremia is generally asymptomatic, remaining subclinical until the adult worm visibly migrates through the subconjunctival tissues of the eye (over hours to days) or causes Calabar swellings, which are localized, nontender angioedematous lesions in the extremities (Figure 195.2) that are reactions to migrating worms. Nephropathy, encephalopathy, and cardiomyopathy are rare. In travelers, hypersensitivity responses predominate (e.g., pruritus, hives, myalgia, arthralgia), microfilaremia is rare, and Calabar swellings occur more frequently and can be debilitating. Eye worm can cause eye congestion, itching, pain, and sensitivity to light.

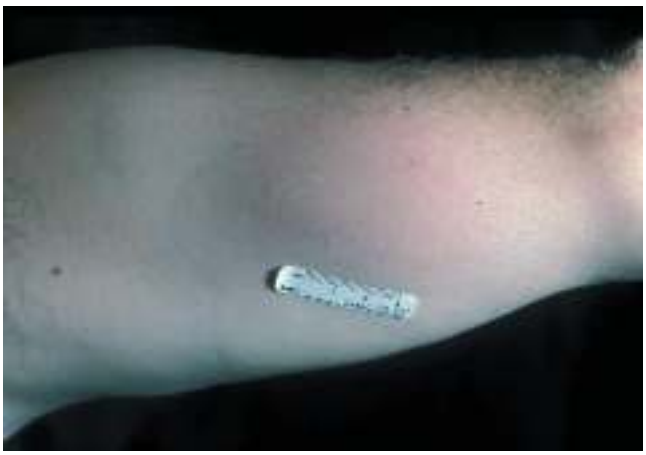

FIGURE 195.2 Calabar swelling of loiasis.

Diagnosis

A presumptive diagnosis is supported by characteristic clinical features associated with elevated filarial IgG4 antibodies and blood eosinophilia. *Loa*-specific antibody and antigen tests, and PCR assays are available in research laboratories. A definitive diagnosis can be made by (1) identifying microfilariae in peripheral blood with microscopy, as for lymphatic filariasis; (2) a healthcare professional visualizing an adult worm migrating across the eye; or (3) confirming the identity after extraction from the subcutaneous tissue or eye. Because the microfilariae of *Loa loa* exhibit diurnal periodicity, blood must be drawn from the patient between 10 AM and 2 PM in the time zone of the endemic region or 10 to 14 days after leaving that time zone. Quantification of the parasite load (microfilariae/mL) in the blood smear is required to guide therapy. The worm is not found in Calabar swellings, and biopsy of these lesions is not indicated.

Therapy

Surgery to remove worms from the eye is not curative. The drug of choice to treat loiasis is DEC, which is effective against both the adult worm and microfilariae. The recommended dose is 8 to 10 mg/kg/d in three divided doses for 21 days. A single course of therapy is curative in the majority of patients, although multiple courses may be required. In refractory cases, albendazole 400 mg twice per day for 21 days may be effective.

Extreme caution is warranted in patients who have microfilaremia of >8,000/mL because treatment with standard dosages of DEC has resulted in life-threatening complications including encephalopathy and renal failure due to rapid killing of microfilariae. Asymptomatic individuals with high parasitic loads should not receive DEC until the blood parasite density has been reduced to <2,500/mL by means of apheresis of blood or albendazole 200 mg twice per day for 21 days. In patients without microfilaremia, the DEC dose should be escalated gradually: day 1, 50 mg; day 2, 50 mg three times a day; day 3, 100 mg three times a day; day 4 to 21, 9 mg/kg/d in three divided doses. Pretreatment with steroids has not been proved to reduce the risk of serious complications. Doxycycline is not effective for loiasis because these filarial worms do not contain endosymbiotic *Wolbachia*, unlike lymphatic filariae and *Onchocerca*.

It is not unusual for treated patients to develop transient pruritus, fever, anorexia, or localized inflammatory reactions such as subcutaneous papules or hives. These reactions, which are distinct from Calabar swellings, are a response to dying adult worms.

It is important to consider the possibility of *Loa loa* coinfection in anyone who will be treated for lymphatic filariasis or onchocerciasis because of the risk of fatal encephalopathy during treatment with DEC or ivermectin for the other filarial infections, particularly if there is a high density of *Loa loa* in the bloodstream.

Prophylaxis should be considered for travelers and nonresident workers with longer term exposures. Once-weekly treatment with DEC 300 mg is effective prophylaxis.

Infection can be prevented by avoiding habitats of deerflies, using insect repellants that contain DEET, covering exposed body parts during the day, and treating clothes with permethrin.

Onchocerciasis

Infection with *O. volvulus* is second only to trachoma as a leading infectious cause of blindness worldwide. Areas of transmission are focal because the *Simulium* blackfly vector has a limited range near the fast-flowing streams and rivers where it breeds; hence the name "river blindness." After the bite of daytime-active infected female blackflies, larvae penetrate the skin and migrate into the subcutaneous tissue, where they mature into adults over 3 to 12 months. Aggregates of adults live in visible subcutaneous fibrous nodules for up to 15 years. For approximately 9 years, gravid females produce millions of microfilariae that migrate throughout the dermis, lymphatics of subcutaneous tissue, and eyes where they have a life span as long as 2 years.

Epidemiology

Onchocerciasis occurs predominantly in sub-Saharan Africa in the savannah of rural agricultural areas. It is also found in Yemen and in limited regions of Venezuela and Brazil. Because risk of transmission is proportionate to the number of bites, short-term travelers (generally <3 months) are at low risk.

Clinical presentation

Most infected individuals experience symptoms caused by the hosts' response to dead or dying larvae in the skin, lymph nodes, and eyes. Pruritus is the most frequent manifestation of onchocerciasis, and it can be debilitating. An itchy, erythematous, papular rash prominent early in the infection is also seen (Figure 195.3). With chronic infection, pigmentary skin changes can have a "leopard skin" appearance; epidermal atrophy with loss of elasticity and exaggerated wrinkling can lead to a "cigarette paper" appearance. Loose, redundant skin with inguinal and femoral lymphadenopathy may lead to a "hanging groin" effect in people from endemic regions. Nonmigratory subcutaneous fibrous nodules containing aggregates of adult worms are typical of onchocerciasis.

Infection of the eye may involve several structures. A common early finding is conjunctivitis with photophobia. Inflammation of

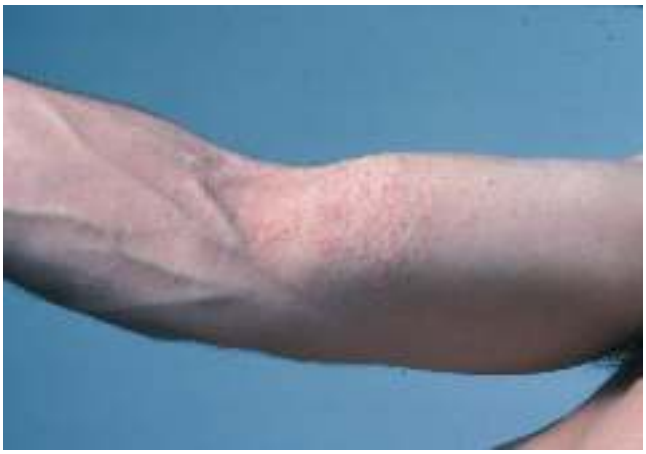

FIGURE 195.3 Papular eruption in onchocerciasis.

the cornea leads to painful punctate keratitis (snowflake opacities) that are reversible, but sclerosing keratitis, which develops later if treatment is not initiated early, is the most common cause of blindness in onchocerciasis. Other manifestations include anterior uveitis, iridocyclitis, secondary glaucoma, chorioretinal lesions, and optic atrophy.

Diagnosis

Compatible clinical features associated with eosinophilia and elevated IgE and nonspecific filarial IgG4 antibodies are suggestive of onchocerciasis. Definitive diagnosis rests most commonly on the detection of microfilariae that emerge from skin snips during incubation in saline. Typically 6 skin snips are obtained by sampling superficial skin layers either using a corneoscleral punch or a scalpel while tenting the skin with a needle. The sensitivity of skin snips is limited in the pre-patent period, which can last up to 1.5 years or in travelers who may have low-density infections. Alternative methods of diagnosis include identification of adult worms in an excised nodule or visualization of microfilariae with slit-lamp examination of the anterior chamber of the eye. Specific serological tests and PCR assays have been developed but are not commercially available.

Therapy

Ivermectin is the drug of choice for onchocerciasis control programs. Ivermectin kills microfilariae, and, although it doesn't kill adult worms, it sterilizes the females. The treatment dosage is 150 μg/kg every 3 to 6 months until there is no evidence of pruritus or ongoing infection. In endemic countries, ivermectin is administered annually to affected people for 15 years or longer to interrupt transmission. Reactions to ivermectin (Mazzotti reaction) are associated with death of the microfilariae and are usually mild, including transient pruritus, dizziness, headache, arthralgia, rash, or edema. Antihistamines and/or analgesics have been used for mild to moderate Mazzotti reactions. More serious reactions are rare and have only been reported in patients who were coinfected with *Loa loa*. Therefore, *Loa loa* should be ruled out before initiating therapy for onchocerciasis. Some strains of *O. volvulus* have been reported to have relative resistance to ivermectin.

Moxidectin, widely used in veterinary medicine, was approved by the FDA in 2018 as the first new treatment for onchocerciasis in 20 years. Approval was based on two randomized controlled trials conducted in endemic African countries that clearly demonstrated superiority of a single 8 mg dose of moxidectin over a single dose of ivermectin to rapidly reduce or eradicate microfilariae. Like ivermectin, it does not kill adult worms and is contraindicated in *Loa loa* coinfected patients. However, moxidectin has a more sustained reduction in microfilarial levels because it has a longer half-life (23 days vs. 18 hours for ivermectin). In addition to adverse reactions (Mazzotti reactions) similar to those for ivermectin, it may cause transient symptomatic orthostatic hypotension in the first 2 days after treatment.

Doxycycline at a dose of 100 to 200 mg/d for 6 weeks exhibits macrofilaricidal activity and induces cessation of embryogenesis by eliminating *Wolbachia*, a bacterial endosymbiont. Doxycycline does not kill the microfilariae and therefore needs to be used in conjunction with ivermectin for symptomatic relief. The safety of concurrent treatment is unknown, but it is suggested that ivermectin be given 1 week before initiation of doxycycline and 6 months after treatment.

DEC is contraindicated because it can exacerbate onchocercal eye disease. Historically, nodulectomy was performed to reduce parasitic load. However, this approach is impractical and ineffective because multiple or inaccessible nodules result in persistence of worms.

Other filarial infections

Humans can harbor infections with other filariae, most notably *Mansonella* spp.: *M. streptocerca*, *M. perstans*, and *M. ozzardi*. The majority of infected individuals are asymptomatic and these organisms are discovered incidentally. However, clinical disease may be associated with a variety of nonspecific manifestations frequently including pruritus. As with other filariases, eosinophilia, elevated IgE, and nonspecific antifilarial antibodies are commonly found even in the absence of symptoms. Infection of travelers occurs infrequently.

M. streptocerca, found in western and central Africa, is transmitted by biting midges. Clinical manifestations resemble onchocerciasis with papular rashes, pigmentation changes, pruritus, and inguinal adenopathy, but adult worms do not aggregate in subcutaneous nodules. Diagnostic PCR assays are not commercially available. Diagnosis is made by finding the characteristic unsheathed microfilariae in skin snips, as for onchocerciasis. Treatment with DEC (6 mg/kg/d in divided doses for 21 days) kills adult worms and microfilariae. Ivermectin (150 μg/kg) is effective against the microfilariae only. Both drugs can produce Mazzotti reactions. It is not known if *Wolbachia* is an endosymbiont of *M. streptocerca*.

M. perstans, also transmitted by biting midges, is found in western and central Africa as well as South America. Clinical manifestations resemble loiasis, with transient angioedema, arthralgias, Calabar swellings, fatigue, fever, headache, and pruritus. Occasionally pericarditis, pleuritis, meningoencephalitis, hepatitis, and eye lesions occur. A PCR assay to detect microfilaremia is available at the Laboratory of Parasitic Diseases at the US National Institutes of Health (NIH). The diagnosis is established by the demonstration in the blood of the microfilariae, which do not exhibit periodicity. Treatment options include DEC combined with mebendazole or doxycycline to target *Wolbachia* that can be found in some strains of *M. perstans*.

M. ozzardi is found in Central and South America and the Caribbean. This parasite is transmitted by biting midges and blackflies. Attributable symptoms and signs are nonspecific and include arthralgias, fever, headache, hepatomegaly, pruritus, and urticaria. Diagnostic PCR assays are not commercially available. Diagnosis relies on finding the microfilariae in the peripheral blood, which circulate without periodicity, or in skin snips. A single dose of ivermectin (200 μg/kg) is effective. Although *M. ozzardi* does harbor *Wolbachia*, there are no data to support treatment with doxycycline.

Dirofilaria spp. are filarial nematodes that primarily infect dogs, wild canids, and raccoons. *D. immitis* causes heartworm disease in

dogs throughout the United States, with the highest incidence in the southeast. Humans are incompetent hosts because infecting parasites cannot grow to maturity and the worms are usually found incidentally. In humans, the bite of an infected mosquito deposits parasites in the subcutaneous tissues where they commonly form subcutaneous nodules. *D. immitis* worms migrate to the pulmonary vasculature, where they are trapped and die, resulting in a solitary lung granuloma, often asymptomatic, that appears as a nonspecific coin lesion on chest film. Eosinophilia is seen in fewer than 15% of infected persons at an early stage of infection. Often no treatment is required. If needed, surgical removal of lung granulomas and subcutaneous nodules is curative.

Brugia of small mammals can cause isolated lymph node enlargement in humans, but eosinophilia and antifilarial antibodies are uncommon. These zoonotic infections are diagnosed and cured by excisional biopsy.

Dracunculiasis

Dracunculiasis or Guinea worm disease is a neglected tropical disease caused by *Dracunculus medinensis*, which occurs only in remote, poor parts of Africa. This parasite is on the verge of global eradication through the coordinated efforts of the highly effective Guinea Worm Eradication Program under the auspices of the WHO, UNICEF, and the Carter Center.

Epidemiology

During the mid-1980s, 20 countries worldwide reported Guinea worm disease. Currently, residual pockets of disease (30 cases in 2017) affects poor communities in Chad and Ethiopia where people bathe or wade in stagnant surface water sources used for drinking. The infection develops after consumption of water contaminated with water fleas (copepods) infested with *D. medinensis* larvae. The larvae are released in the stomach, pass into the small intestine, and penetrate the mucosa, ultimately reaching retroperitoneal tissues, where they mature and sexually reproduce.

Clinical presentation

The infection remains asymptomatic until 10 to 14 months after infection, when the adult female worm migrates to the subcutaneous tissues of the legs in 90% of cases. A painful papule forms and is occasionally associated with low-grade fever, pruritic rash, dizziness, nausea, and vomiting. The lesion develops into a vesicle that ruptures and ulcerates, exposing a portion of the gravid worm. Affected people often immerse the infected extremity in water to soothe the burning sensation. On contact with water, hundreds of thousands of larvae are discharged and ingested by water fleas to complete the life cycle.

Diagnosis

Once the worm protrudes from the skin, a clinical diagnosis is sufficient to confirm the disease.

Therapy

There are no specific antiparasitic drugs or vaccines available. Treatment of dracunculiasis has remained unchanged for thousands of years. It consists of slow extraction of the emerging worm by securing the end to a small stick or gauze and gradually winding it a few centimeters daily until it is removed over a period days to weeks. If the worm ruptures during removal, the remaining part of the dead worm can exacerbate local inflammation. Proper wound care and topical antibiotics are essential to prevent secondary bacterial infections, which can cause greater debilitation.

Interruption of transmission is achieved through surveillance, case containment, provision of safe drinking water, vector control with chemical larvicides, and health education.

Unusual tissue helminth infections

Visceral and ocular larva migrans

Visceral larva migrans (VLM) or toxocariasis is 1 of 5 neglected parasitic diseases in the United States prioritized by the CDC for public health action. The others include Chagas disease, cysticercosis, toxoplasmosis, and trichomoniasis. VLM is a syndrome caused by nematodes that typically parasitize dogs or cats. Humans are incompetent incidental hosts and therefore cannot sustain the maturation of larvae, which elicit eosinophilic inflammation as they migrate through human tissues. Most human infections are caused by *Toxocara canis* from dogs or less commonly by *T. cati* from cats.

Epidemiology

Worldwide, people of all ages, especially children, acquire toxocariasis by accidentally ingesting infective *Toxocara* eggs, or soil, food, or water contaminated with eggs that are shed in the stool of host animals (e.g., sandboxes). It takes 2 to 4 weeks for *Toxocara* eggs in the environment to become infective. Rarely, humans can be infected by eating undercooked meat from intermediate hosts such as a rabbit or lamb. *Toxocara* is more prevalent in people who own pet dogs and in hot, humid regions where eggs remain viable longer.

Clinical presentation

VLM is usually asymptomatic and is referred to as *covert toxocariasis*. Clinical manifestations of visceral toxocariasis may include abdominal pain, anorexia, cough, fever, malaise, rash, and wheezing. Hepatomegaly is commonly seen. Less common severe complications include eosinophilic meningoencephalitis (neurotoxocariasis), myocarditis, and pneumonitis.

Ocular larva migrans (OLM) or ocular toxocariasis may be associated with symptomatic VLM, but it often occurs in isolation. Typically, OLM presents with unilateral visual deficits, ocular pain,

leukocoria, photophobia or strabismus caused by chorioretinitis, uveitis, and/or retinal scarring. The features may be confused with retinoblastoma.

Diagnosis

Marked eosinophilia and elevated IgE levels are nonspecific features of VLM, but they may be absent in OLM. An enzyme-linked immunosorbent assay (ELISA) that detects antibodies to *Toxocara* excretory/secretory (TES) larval antigens and that minimizes cross-reactivity with antigens of *Ascaris* and other parasites is commercially available. Nevertheless, results must be interpreted with caution as broad variations in antibody responses occur and levels may remain elevated for years after infection. Detection of rising antibodies with acute and convalescent serologic testing confirms acute infection but the assay cannot distinguish between *T. canis* and *T. cati*. Serum antibodies may be absent in OLM, but finding antibodies in vitreous or aqueous humor may help confirm the diagnosis. The symptoms and signs of VLM may be caused by migrating larvae of other helminths, including *Baylisascaris procyonis*, *Paragonimus* spp., *Strongyloides* spp., and certain filariae.

Therapy

The majority of patients with toxocariasis do not require treatment because they have no or mild symptoms. Treatment with albendazole (400 mg BID for 5 days; preferred) or mebendazole (100–200 mg BID for 5 days) is generally reserved for patients with severe VLM. The optimal duration of therapy is unknown. Use of adjunctive prednisone (0.5—1.0 mg/kg/d) may reduce inflammation during treatment of severe VLM with neurological, cardiac, or pulmonary manifestations.

Treatment of OLM with the same medications as for VLM is recommended, although longer therapy may be needed. The administration of topical and systemic steroids may improve visual outcomes. Surgical intervention in quiescent disease may be indicated.

Cutaneous larva migrans ("creeping eruption")

Cutaneous larva migrans (CLM), also known as "creeping eruption," is a zoonosis caused by larval stages of animal hookworms, most often those of the dog (*Ancylostoma caninum*) or cat (*A. braziliense*). As with human hookworms, the infection starts when the worm enters the skin from contaminated soil or sand, as found on beaches or in sandboxes where domestic animals may roam. The incubation period is 1 to 5 days but can be longer than 1 month.

Epidemiology

The infection is seen in short- and long-term travelers to Africa, Asia, the Caribbean, and South America.

Clinical presentation

As in visceral larva migrans caused by *Toxocara* spp., the worm cannot complete the infective cycle in humans, who are incidental hosts, so it continues to burrow through the subcutaneous tissues, resulting in the characteristic serpiginous, erythematous, mildly swollen, and intensely pruritic skin lesion (Figure 195.4). The worms may create tracks several centimeters in length each day, typically on the feet and buttocks. Systemic symptoms are rare.

Diagnosis

Diagnosis is based on characteristic clinical findings. Eosinophilia is not a usual feature. Skin biopsy is not recommended.

Therapy

CLM is a self-limiting disease because the larvae usually die spontaneously after 5 to 6 weeks. Treatment with a 3-day course of albendazole (400 mg/d) or a single dose of ivermectin (200 μg/kg) is highly effective. Symptomatic treatment of severe pruritus is indicated.

Eosinophilic meningitis due to helminths

Eosinophilic meningitis due to infection with helminths is most often caused by the rat lungworm *Angiostrongylus cantonensis*, followed by the nematode *Gnathostoma spinigerum* and the raccoon ascarid *Baylisascaris procyonis*. However, the condition has been reported to be a consequence of infection with other helminths, specifically *Schistosoma japonicum*, *Paragonimus* spp., and *Taenia solium* cysticerci.

Angiostrongyliasis, caused by *Angiostrongylus cantonensis*, is naturally transmitted between rats and mollusks (e.g., snails and slugs). Humans acquire the nematode incidentally by eating raw

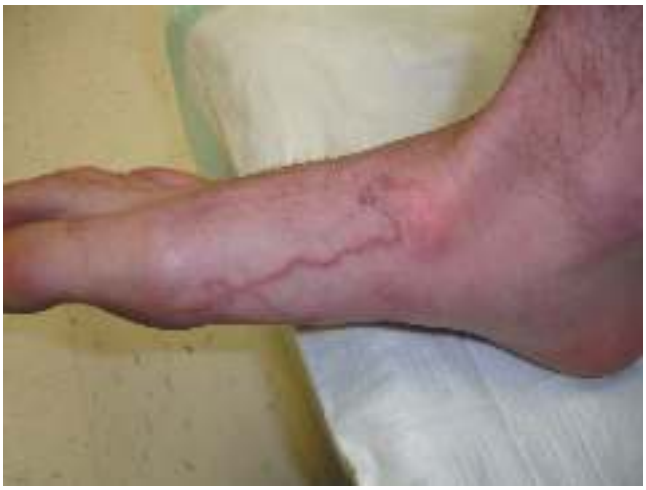

FIGURE 195.4 Cutaneous larva migrans.

or undercooked infected mollusks, vegetables contaminated with mollusks or their slime, or possibly raw or undercooked freshwater shrimps, crabs, or frogs that eat infected mollusks.

The disease is prevalent mostly in Southeast Asia and Pacific islands, but it has also been identified in Africa, Australia, the Caribbean, Hawaii and the US (Louisiana). *A. costaricensis* is found in Latin America.

The average incubation period is 1 to 3 weeks. Individuals present with symptoms and signs of meningitis such as headache, meningism, nausea, and vomiting. The clinical illness lasts typically for 2 to 8 weeks.

Peripheral blood eosinophilia (>5%) is prominent and lasts for about 3 months, although it may be absent in the early stages of infection. Typical cerebrospinal fluid (CSF) findings consist of an elevated opening pressure, pleocytosis with at least 10% eosinophilia, and elevated protein content with low or normal glucose levels. Visualization of the larvae from CSF is diagnostic but rare. Serological tests and PCR assays have been developed but are not commercially available. Findings from neuroimaging studies are nonspecific but may be helpful to rule out focal lesions caused by other parasites associated with eosinophilic meningitis such as neurocysticercosis and gnathostomiasis.

Antihelminthic agents have not been proved to be safe and effective. There is a theoretical concern that antiparasitics may lead to an exacerbation of the neurological symptoms caused by an immunological response to dying worms. Treatment is symptomatic with analgesics and corticosteroids (60 mg/d for 2 weeks with a taper). Intermittent removal of CSF affords symptomatic relief.

B. procyonis, a raccoon nematode, rarely causes human disease that can be severe if the parasite invades organs (visceral larva migrans), the eye (ocular larva migrans or diffuse unilateral subacute neuroretinitis), or the brain and spinal cord (neural larva migrans). Humans are infected by accidentally ingesting *B. procyonis* eggs in contaminated soil, sand, or water. Eggs in the environment take 2 to 4 weeks to become infective and can remain viable for years.

Infected humans have been identified in the United States (<25 cases), Europe, and Japan. Children are at greatest risk. Worms may also infect some dogs that ingest infected small mammals, and eggs shed in their feces may become infective.

The incubation period is 1 to 4 weeks. Infections may be asymptomatic. Symptoms and signs depend on parasitic load and location, and include cough, fatigue, nausea, hepatomegaly, visual defects, and a variety of neurological deficits including signs of meningoencephalitis that may cause death or permanent disability in a substantial proportion of patients.

Laboratory tests demonstrate peripheral eosinophilia, CSF eosinophilic pleocytosis, nonspecific abnormalities of white matter on brain neuroimaging, and positive *B. procyonis* serologic testing of serum and CSF, which can be performed at the CDC. Ophthalmologic examination may reveal evidence of larvae.

Prompt therapy with albendazole (25–50 mg/kg/d for 10–20 days) after exposure to infected material or early in the disease process in conjunction with corticosteroids may be effective. Mebendazole and ivermectin are less effective. Laser therapy may be indicated for retinal infections.

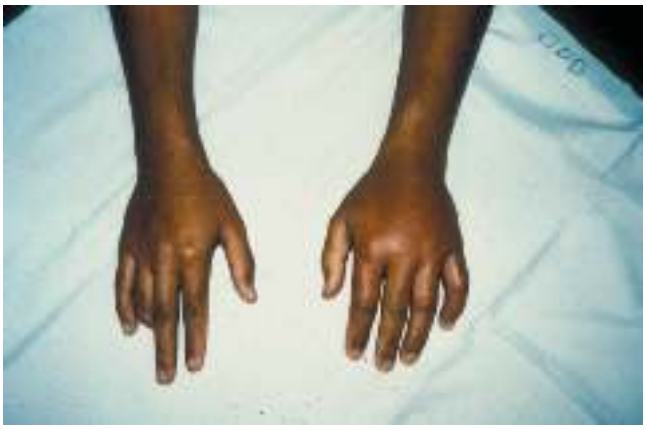

FIGURE 195.5 Angioedema of left hand in gnathostomiasis.

Gnathostomiasis, is caused by *Gnathostoma spinigerum*, an intestinal nematode of domestic and wild dogs and cats. These and other animals become parasitized when they feed on infected copepods (water fleas), which are intermediate hosts. Humans are incidental hosts in the life cycle. Other *Gnathostoma* species infect a variety of other mammals.

Gnathostoma spp. cause human infections predominantly in Southeast Asia, but also elsewhere in Asia, Central and South America, and southern and eastern Africa. Humans accidentally acquire the infection by eating raw or undercooked freshwater fish, eels, frogs, birds, and reptiles that harbor encysted larvae.

The most common manifestation is intermittent subcutaneous swelling associated with pruritus that lasts for 1 to 2 weeks (Figure 195.5), mimicking the Calabar swelling of loiasis. Severe complications of gnathostomiasis include vision loss, hepatitis, and eosinophilic encephalomyelitis. CNS disease manifests as severe headache or radicular pain that may be followed by paralysis of the legs, urinary retention, coma, and death.

Gnathostomiasis is commonly associated with hypereosinophilia. The diagnosis is usually established clinically. Serologic testing is not available in the United States; the CDC can coordinate testing of serum at specialty laboratories in Thailand and Japan.

Both albendazole (400 mg BID for 21 days) and ivermectin (200 μg/kg/d for 2 days) are effective for cutaneous manifestations. Because albendazole may cause larvae to migrate and ivermectin may cause a disease flare, the safety and effectiveness of these agents for CNS or ocular disease have not been proved. There is concern that antihelminthics may exacerbate neurological disease and cause permanent sequelae. Adjunctive treatment with steroids has not been proved to be beneficial.

Suggested reading

Baylisascaris

Liu EW, Schwartz BS, Hysmith ND, et al. Rat lungworm infection associated with central nervous system disease—Eight US states,

January 2011–January 2017. *MMWR Morb Mortal Wkly Rep. 2018;67*:825–828.

Cutaneous larva migrans

Vasievich MP, Villarreal JD, Tomecki KJ. Got the travel bug? A review of common infections, infestations, bites, and stings among returning travelers. *Am J Clin Dermatol*. 2016;17:451–462.

Dracunculiasis

Tayeh A, Cairncross S, Cox FEG. Guinea worm: From Robert Leiper to eradication. *Parasitology*. 2017;144:1643–1648.

Filariasis

King CL, Suamani J, Sanuku N, et al. A trial of a triple-drug treatment for lymphatic filariasis. *N Engl J Med*. 2018;379:1801–1810.

Loa loa

Whittaker C, Walker M, Pion SDS, Chesnais CB, Boussinesq M, Basanez MG. The population biology and transmission dynamics of Loa loa. *Trends Parasitol*. 2018;34:335–350.

O'Connell EM, Nutman TB. Reduction of Loa loa microfilaremia with imatinib: A case report. *N Engl J Med*. 2017;377:2095–2096.

Onchocerciasis

Opoku NO, Bakajika DK, Kanza EM, et al. Single dose moxidectin versus ivermectin for Onchocerca volvulus infection in Ghana, Liberia, and the Democratic Republic of the Congo: A randomised, controlled, double-blind phase 3 trial. *Lancet*. 2018;392:1207–1216.

Kamgno J, Pion SD, Chesnais CB, et al. A test-and-not-treat strategy for onchocerciasis in Loa loa-endemic areas. *N Engl J Med*. 2017;377:2044–2052.

Toxocariasis

Ma G, Holland CV, Wang T, et al. Human toxocariasis. *Lancet Infect Dis*. 2018;18:e14–e24.

Trichinellosis

Centers for Disease Control and Prevention (CDC). *Surveillance for trichinellosis—United States, 2015. Annual summary*. Atlanta, GA: US Department of Health and Human Services; 2017. https://www.cdc.gov/parasites/trichinellosis/resources/trichinellosis_surveillance_summary_2015.pdf

196

Schistosomes and other trematodes

James H. Maguire

The trematode flatworms that infect human beings include the schistosomes, which live in venules of the gastrointestinal or genitourinary tract, and other flukes that inhabit the bile ducts, intestines, or bronchi. The geographic distribution of each species of trematode parallels the distribution of the specific freshwater snail that serves as its intermediate host (Table 196.1). Schistosomes infect approximately 235 million persons worldwide; infections caused by the other flukes are more limited in distribution and number. Trematode infections last for years; most are subclinical, and in general only the small proportion of persons who have heavy worm burdens develops severe disease.

Schistosomiasis

Clinical presentation

A history of contact with possibly infested freshwater in an endemic area should prompt an evaluation for schistosomiasis, even in the absence of symptoms (Figure 196.1). Clinical manifestations that suggest the diagnosis vary according to the stage of infection. Some persons complain of intense pruritus or rash shortly after the infective cercariae penetrate the skin. Previously uninfected visitors to endemic areas may develop acute schistosomiasis, or Katayama fever, 2 to 12 weeks after exposure, as the immune system responds to maturing worms and eggs. Symptoms range from mild malaise to a serum sickness-like syndrome that lasts for weeks and may be life-threatening. Common features include fever, headache, abdominal pain, myalgia, dry cough, diarrhea, hepatosplenomegaly, lymphadenopathy, urticaria, and marked eosinophilia.

Chronic infections with schistosomes usually are asymptomatic; slight or moderate eosinophilia occurs frequently. Long-term residents of endemic areas may harbor heavy infections for long periods and thus are more likely than transient visitors to have symptoms. Disease results from egg deposition in tissues and the ensuing inflammatory and fibrotic response (Figure 196.2). In infections due to *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma mekongi*, *Schistosoma intercalatum*, and *Schistosoma guineensis*, involvement of the bowel leads to mucosal inflammation and microulcerations, diarrhea, bleeding, polyps, and strictures. Embolization of eggs to the liver results in hepatosplenomegaly, periportal fibrosis, portal hypertension, and esophageal varices. Hematuria and dysuria are early symptoms of chronic infection by *Schistosoma haematobium;* later, fibrosis and calcification of the bladder and lower ureters results in hydroureter and hydronephrosis (Figure 196.3), and squamous cell carcinoma of the bladder may develop. Ectopic deposition of eggs in the skin, genitalia, and other organs occurs during both the acute and chronic stages of infection. Transverse myelitis, seizures, and other serious sequelae result from egg deposition in the central nervous system. In endemic areas, chronic infections of even moderate intensity have been associated with anemia, poor nutritional status, and cognitive impairment.

TABLE 196.1 **GEOGRAPHIC DISTRIBUTION OF IMPORTANT TREMATODES**[a,b]

Schistostomes	
Schistosoma mansoni	South America, Caribbean, Middle East, Africa
Schistosoma japonicum	China, Philippines, Indonesia, Thailand
Schistosoma mekongi	Cambodia, Laos
Schistosoma intercalatum, Schistosoma guineensis	West and Central Africa
Schistosoma haematobium	Africa, Middle East
Biliary and liver flukes	
Clonorchis sinensis	China, Taiwan, Korea, Japan, Vietnam
Opisthorchis viverrini	Thailand, Laos, Cambodia
Opisthorchis felineus	Eastern Europe, former Soviet Union
Fasciola hepatica	Europe, North Africa, Asia, western Pacific, Latin America
Lung flukes	
Paragonimus westermani and other species	Far East, South Asia, Philippines, Central and South America, West Africa, Mississippi River Basin (USA)
Intestinal flukes	
Fasciolopsis buski	Far East
Heterophyes heterophyes	Far East, Egypt, Middle East
Metagonimus yokogawai	Far East
Nanophyetus salmincola	Pacific Northwest

[a] Parasites may be limited to certain countries in the regions listed and certain foci within these countries.
[b] Many less common trematodes that infect human beings are not listed here.

Diagnosis

The most direct method of diagnosis is microscopic examination of stool or urine for schistosome eggs (Figure 196.4). Because egg output is low in light infections, concentration techniques and examination of several specimens obtained on different days should be routine. Eggs should be counted to estimate the intensity of infection and to monitor the response to therapy. Counts above 400 eggs per gram of feces or 10 mL of urine are considered heavy and

FIGURE 196.1 Shallow pond infested with *Biomphalaria*, the snail host of *Schistosoma mansoni* in Brazil.

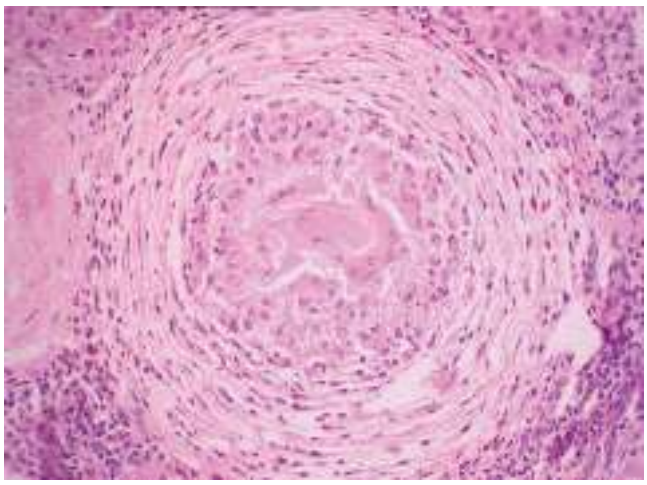

FIGURE 196.2 Granuloma around egg of *Schistosoma mansoni* that embolized to the liver and was trapped in a small branch of the portal vein.

are associated with higher rates of complications. Microscopic examination of snips of rectal mucosa obtained at proctoscopy may reveal eggs when stool examination is negative.

Serologic tests for antibodies to schistosomes are available at commercial laboratories in the United States and at the Centers for Disease Control and Prevention (CDC) in Atlanta. The CDC uses a sensitive and specific Falcon assay screening test/enzyme-linked immunosorbent assay (FAST-ELISA) for screening and a highly specific immunoblot for confirmation and species determination. These tests cannot distinguish active from past infections but are useful for the diagnosis of acute schistosomiasis before eggs are shed in the stool. Serologic tests should be used to screen previously unexposed travelers and expatriates; a positive serologic test is presumptive evidence of infection even if subsequent microscopy is negative.

Persons with confirmed infections due to the intestinal schistosomes should be evaluated with measurement of liver function tests and tests for chronic hepatitis B and C to rule out concomitant hepatocellular disease. Heavy infection or evidence of liver disease should prompt an ultrasound to document periportal fibrosis and signs of portal hypertension (Figure 196.5). Esophageal varices are visualized by barium swallow or endoscopy. Urinalysis, urine culture, and serum creatinine determination are indicated for persons with *S. haematobium* infection. Ultrasonography or other imaging studies detect complications such as hydronephrosis, polyps, stones, and carcinoma of the bladder.

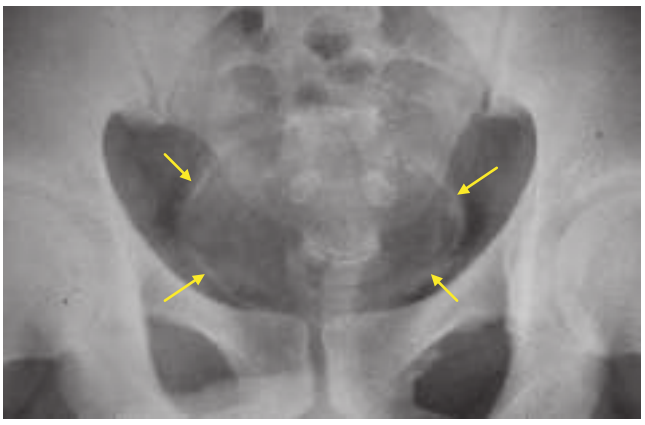

FIGURE 196.3 Plain radiograph of the pelvis showing calcification of the wall of the bladder and lower ureters (*arrows*).

Therapy

All persons with schistosomiasis should receive treatment. Eradication of infection is desirable because even a single pair of worms may deposit eggs in the central nervous system. In endemic areas where reinfection is inevitable, the goal is to reduce worm burdens to levels that are unlikely to produce disease. Successful treatment not only prevents complications but also may cause regression of polyps and fibrotic lesions. Fortunately, the treatment of choice, praziquantel, is safe and highly effective after one or a few oral doses (Table 196.2).

Praziquantel causes an influx of calcium ions across the tegument of the adult worm, leading to a tetanic contraction and vacuolization of the tegument that makes the parasite susceptible to immune destruction. Cure rates range from 65% to 95%, and in persons not cured, egg excretion is reduced by >90%. A few reports suggest that resistance to praziquantel may be developing. Adverse effects, which are usually mild and last less than 24 hours, may be caused by reactions to dying worms rather than drug toxicity. Patients occasionally report malaise, headache, dizziness, or abdominal discomfort. Nausea, vomiting, diarrhea, bloody stools, fever, and urticaria are uncommon. The World Health Organization has judged praziquantel safe for pregnant or lactating women. Persons with known or suspected cysticercosis should remain under observation during therapy because of the risk of seizures or other neurologic consequences of dying cysticerci. Praziquantel is metabolized in the liver, and the dosage need not be reduced because of renal insufficiency.

Severely ill persons with acute schistosomiasis should receive corticosteroids as well as praziquantel, although there is controversy about timing of anthelmintic therapy. Some experts recommend delaying praziquantel treatment because maturing schistosomes are less susceptible to praziquantel than are adult worms, corticosteroids lower serum levels of praziquantel, and acute illness may be exacerbated by reactions to killing of parasites. Because of the risk of ectopic infection, we favor administration of praziquantel shortly after administration of steroids. All patients should receive a second course of treatment 4 to 6 weeks after the first. Artemisinin derivatives have activity against immature parasites, but although they can be effective in preventing infection, their utility in the management of acute schistosomiasis is uncertain.

Because antischistosomal drugs may temporarily inhibit egg laying by adult worms, stool and urine should be examined 3 and 6 months after completion of therapy. Eosinophilia, hematuria, and other symptoms that persist beyond this time should prompt repeat parasitologic studies and evaluation for causes other than schistosomiasis. Serologic tests may remain positive for years after successful treatment and are of limited utility for the assessment of cure.

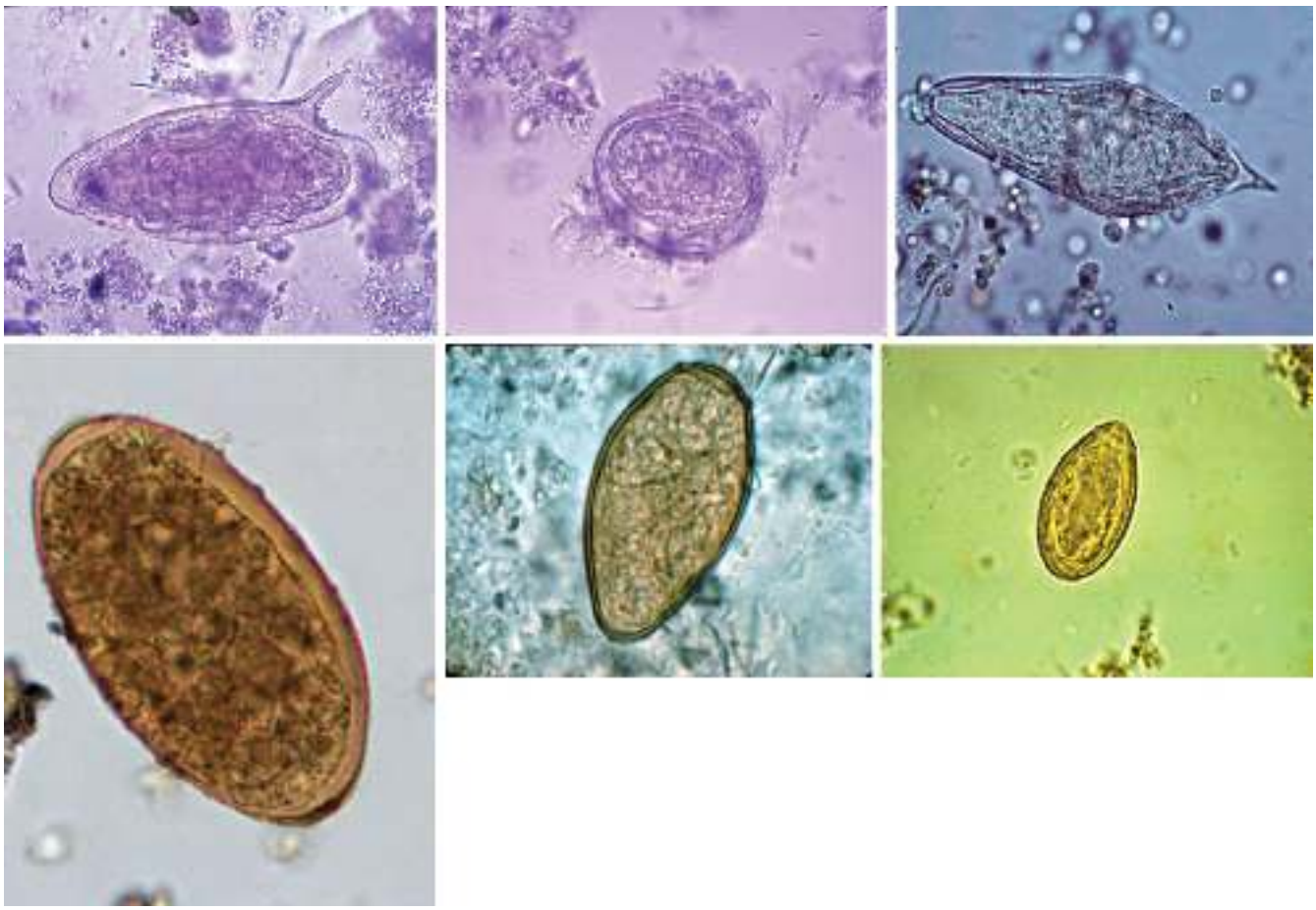

FIGURE 196.4 Trematode eggs. **Top row, left to right**: *Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium*. **Bottom row, left to right**: *Fasciola hepatica, Paragonimus westermani, Clonorchis sinensis*.

Other trematode infections

More than 70 species of trematodes other than schistosomes infect 65 million or more persons worldwide. Most are parasites of wild and domestic animals. Human beings become infected by ingestion of metacercariae encysted in freshwater fish, crustacea, and plants, the second intermediate hosts.

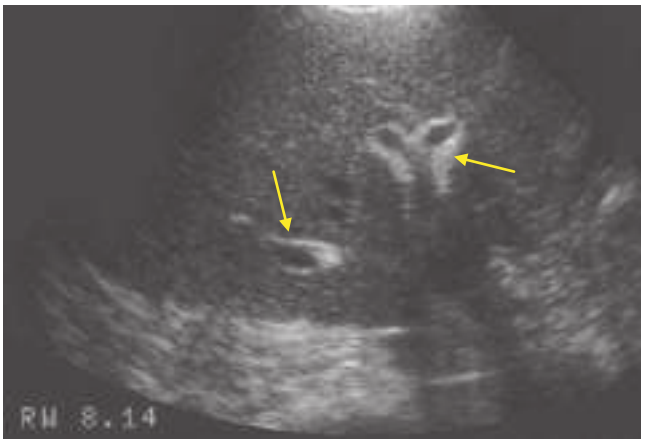

FIGURE 196.5 Ultrasound of the liver showing periportal fibrosis. Two portal tracts (one of the tracks is bifurcated) are surrounded with an area of increased echo (*arrows*).

Clonorchiasis and opisthorchiasis

The oriental liver flukes *Clonorchis sinensis*, *Opisthorchis viverrini*, and *Opisthorchis felineus* inhabit the biliary tree of persons who ingest infected carp and other freshwater fish without proper cooking. Most patients are asymptomatic, but eosinophilia is common. An acute illness resembling Katayama fever occasionally occurs 2 to 3 weeks after initial exposure. Persons with heavy infections for many years develop symptoms due to irritation and inflammation of biliary epithelium. Patients complain of right upper quadrant discomfort, anorexia, and weight loss. On physical examination the liver is palpable and firm. Cholangitis, pancreatitis, and cholangiocarcinoma are infrequent complications.

Diagnosis is made by finding eggs in the stool (Figure 196.4) or identifying adult worms during endoscopic retrograde cholangiopancreatography (ERCP) or surgery for complications. In symptomatic cases, ultrasonography or computed tomography (CT) demonstrates dilation and stricture of bile ducts, thickening

TABLE 196.2 **TREATMENT OF TREMATODE INFECTIONS**

Parasite	Drug of choice	Dosage
Schistosoma mansoni, S. haematobium, *S. intercalatum*, S. *guineensis*[a]	Praziquantel	40 mg/kg/d in 2 doses ×1 d
Schistosoma japonicum, S. mekongi	Praziquantel	60 mg/kg/d in 2 or 3 doses ×1 d
Clonorchis sinensis, Opisthorchis spp.	Praziquantel	75 mg/kg/d in 3 doses ×1 d
Fasciola hepatica, F. gigantica	Triclabendazole	10 mg/kg ×1 or 10 mg/kg × 2 doses 6 h apart
Paragonimus spp.	Praziquantel	75 mg/kg/d in 3 doses ×2 d
Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai	Praziquantel	75 mg/kg/d in 3 doses ×1 d
Nanophyetus salmincola	Praziquantel	60 mg/kg/d in 3 doses ×1 d

[a] To increase the likelihood of a complete cure, praziquantel 60 mg/kg/day in 2 or 3 split doses can be given to persons with schistosomiasis who have left an endemic area. Many experts suggest that persons who acquired *S. mansoni* infection in Africa should also receive 60 mg/kg/day in 2 or 3 split doses.

of the gallbladder wall, and stones. A single course of praziquantel eradicates infection in more than 85% of cases (Table 196.2). An alternative is albendazole for 7 days.

Fascioliasis

Infection with the sheep liver fluke *Fasciola hepatica* and the closely related *Fasciola gigantica* results from ingestion of uncooked watercress or other aquatic vegetation from sheep- and cattle-raising parts of the world. After excysting in the duodenum, immature worms pass through the bowel wall and peritoneal cavity, invade the liver, and burrow through the parenchyma to the bile ducts. This migration provokes an acute syndrome of fever, nausea, tender hepatomegaly, eosinophilia, and urticaria lasting weeks to months. Aberrant migration causes nodules in the skin, painful inflammation of the intestinal wall, pleural effusion, or lesions in the lungs, brain, or elsewhere. Chronic fascioliasis is usually subclinical, but some persons have symptoms due to inflammation and obstruction of bile ducts.

Diagnosis is confirmed by demonstrating eggs in samples of stool, bile, or duodenal aspirates (Figure 196.4) or by recovering worms at surgery. Serologic tests are useful during acute infection because symptoms develop 1 to 2 months before eggs appear in the stool. Ultrasonography and ERCP may demonstrate adult worms and biliary pathology, and CT or magnetic resonance (MR) shows migratory hypodense lesions in the liver corresponding to necrosis along the path of larval migration.

Treatment of fascioliasis is with one or two doses of the veterinary drug triclabendazole which is available from Victoria Pharmacy in Zurich, Switzerland (Table 196.2). Given with food, treatment is successful in approximately 80% of cases, and a repeat course cures most of the remaining cases. The alternative, nitazoxanide, is less effective, and fascioliasis responds poorly to praziquantel.

Paragonimiasis

Infection with *Paragonimus westermani*, the oriental lung fluke, and, less commonly, other species of *Paragonimus*, follows ingestion of raw or poorly cooked freshwater crabs or crayfish. An acute phase with fever, abdominal and chest pain, cough, and eosinophilia corresponds to migration of immature parasites through the bowel wall, diaphragm, and pleura en route to the lungs. The inflammatory reaction to adults encapsulated in the lungs and the shedding of eggs into the bronchial tree are responsible for chronic symptoms. Patients complain of cough, rusty or golden sputum, hemoptysis, vague chest pains, and dyspnea on exertion. Radiographs of the chest show poorly defined infiltrates, cysts, nodules, cavities, calcified lesions, and pleural effusions that on aspiration are seen to contain eosinophils. The findings may suggest tuberculosis. Bronchiectasis, bacterial pneumonia, or empyema complicates heavy infections. Extrapulmonary migration of flukes causes migratory subcutaneous nodules, involvement of abdominal viscera, or focal lesions of the central nervous system. Cerebral paragonimiasis is characterized by headache, seizures, focal neurologic deficits, cerebrospinal fluid eosinophilia, and cystic lesions on radiographs and scans.

Paragonimiasis is diagnosed by identifying expectorated eggs in the sputum, swallowed eggs in the feces, or worms and eggs in biopsy specimens (Figure 196.4). Several examinations of stool and sputum may be necessary. Serologic tests, such as the immunoblot offered by the CDC, are useful for diagnosis of early, light, and extrapulmonary infections.

The treatment of choice for paragonimiasis is praziquantel or alternatively, triclabendazole (Table 196.2). Because the inflammatory reaction to dying worms may precipitate seizures or other neurologic complications, corticosteroids should be used simultaneously with praziquantel for cerebral paragonimiasis.

Intestinal fluke infections

Adult intestinal flukes live attached to the mucosa of the duodenum and jejunum, where they cause local inflammation and ulceration. Of the dozens of species that infect human beings, *Fasciolopsis buski*, the giant intestinal fluke, is the best known. Infection is acquired by eating uncooked aquatic plants, such as water caltrop, water chestnut, and watercress. Heavily infected persons develop hunger pains that suggest peptic ulcer, diarrhea with mucus, and in extreme cases, malabsorption, ascites, anasarca, and intestinal obstruction. Eosinophilia is common.

Other important intestinal flukes include *Heterophyes heterophyes* and *Metagonimus yokogawai*, both of which are acquired by ingestion of raw or undercooked freshwater fish. Symptoms caused by these parasites resemble those produced by *Fasciolopsis*,

but embolization of eggs that enter the circulation may cause severe myocarditis or cerebral hemorrhage. *Nanophyetus salmincola* is transmitted in the Northwest United States by ingestion of raw or undercooked salmon or trout. Manifestations include abdominal pain, watery diarrhea, and eosinophilia.

The diagnosis of all intestinal fluke infections is made by demonstrating eggs in the feces. Because the number of eggs excreted may be low, concentration techniques and repeated examinations are recommended. Praziquantel is the drug of choice (Table 196.2). Alternatives include triclabendazole and, for *Fasciolopsis* and *Heterophyes* infections, niclosamide.

Suggested reading

Clerinx J, Van Gompel A. Schistosomiasis in travellers and migrants. *Travel Med Infect Dis*. 2011;9:6–24.

Esteban JG, Fried B. Current status of food-borne trematode infections. *Eur J Clin Microbiol Infect Dis*. 2012;31:1705–1718.

Ferrari TSA, Moreira PR. Neuroschistosomiasis: clinical symptoms and pathogenesis. *Lancet Neurol*. 2011;10:853–864.

Fürst T, Duthaler U, Sripa B, et al. Trematode infections. Liver and lung flukes. *Infect Dis Clin North Am*. 2012;26:399–419.

Gray DJ, Ross AG, Li Y-S, et al. Diagnosis and management of schistosomiasis. *BMJ*. 2011;342:d2651.

Gryssels B. Schistosomiasis. *Infect Dis Clin North Am*. 2012;26:383–397.

Jauréguiberry S, Paris L, Caumes E. Acute schistosomiasis, a diagnostic and therapeutic challenge. *Clin Microbiol Infect*. 2010;16:226–231.

Lane MA, Marcos LA, Onen NF, *et al. Paragonimus kellicotti* fluke infections in Missouri, USA. Emerg Infect Dis. 2012;18:1263–1267.

Procop GW. North American paragonimiasis (caused by *Paragonimus kellicotti*) in the context of global paragonimiasis. *Clin Microbiol Rev*. 2009;22:415–446.

World Health Organization. *Report of the WHO Expert Consultation on Foodborne Trematode Infections and Taeniasis/Cysticercosis*. Geneva: World Health Organization; 2011.

Tapeworms (cestodes)

Zbigniew S. Pawlowski

Cestodes cause intestinal (e.g., taeniasis, hymenolepiasis) and/or tissue parasitoses (e.g., cysticercosis, echinococcosis). Most of intestinal tapeworm infections are meat-borne zoonoses, whereas tissue infections with larval cestodes are fecal-borne, acquired mainly through ingestion of the tapeworm eggs from human, dog, or fox feces.

Taenia saginata and *taenia asiatica* taeniasis

Taenia saginata, the beef tapeworm, sometimes >5m long, may live up to 30 years in the small intestine of humans, who are its only natural host. Humans are infected by ingestion of the cysticercus, a bladder worm <1 cm in diameter, present in raw or undercooked beef.

Taenia saginata infections can spread easily because of a high fecundity of the tapeworm (>500 000 eggs produced daily for years), wide and long-term contamination of the environment with eggs, bovine cysticercosis that may escape routine meat inspection when of a low intensity, and, finally, common consumption of raw beef. More than 10% of nomads are infected in East Africa; in Europe the annual incidence in urban populations is <0.1%; in the United States and Canada, *T. saginata* taeniasis is uncommon and observed mainly among migrants from Latin America.

Taenia saginata infection occurs mainly in well-nourished middle-aged individuals who are raw beef eaters. Complaints include vague abdominal pains, nausea, weight loss or gain, and some perianal discomfort caused by gravid proglottids (about six per day) crawling actively out of the anus. Sometimes, the patient passes a longer part of tapeworm strobila; in that case the expulsion of proglottids may stop for some weeks. The diagnosis is set up by questioning and macroscopic examination of expulsed tapeworm proglottids. *Taenia* eggs are found more often on anal swabs than in feces. Tests detecting parasite antigen in feces are highly sensitive and specific and may detect the infections even when proglottids or eggs are not expelled.

Treatment of *T. saginata* taeniasis with praziquantel or niclosamide is safe and effective in 95% and 80% of cases, respectively. Praziquantel is given orally in a single dose of 5 to 10 mg/kg an hour after a light breakfast. Niclosamide is preferred for children younger than 4 years and for pregnant women. Niclosamide (use only the original products, recently manufactured) should be chewed thoroughly on an empty stomach in a single dose of 2 g for adults, 1 g for children who weigh 10 to 35 kg, and 0.5 g for smaller children. For both drugs adverse effects, such as abdominal discomfort, headache, and dizziness, are rare and transient. Tapeworm is usually expelled in fragments within a few hours; the scolex, indicating elimination of the entire worm, is often difficult to find. Therefore, successful therapy can be confirmed only when no proglottids reappear within 4 months after treatment.

Taenia asiatica, described recently in several Asian countries, is a sister species of *T. saginata*, similar morphologically but a distinct species when examined by molecular techniques. Its life cycle is different; small cysticerci develop in liver and viscera of pigs and a range of wild animals. Humans become infected by eating raw viscera, especially liver, of the infected animals. The diagnosis and treatment are similar to *T. saginata*. *Taenia asiatica* and *T. saginata* do not produce cysticercosis in humans.

Taenia solium taeniasis and cysticercosis

Taenia solium (pork tapeworm) infection is common in Latin American countries, Central and South Africa, India, Indonesia, and China. Intestinal infection is acquired by eating undercooked pork containing cysticerci. Cysticercosis, a cystic larval form developing in the tissues, is acquired by ingesting *T. solium* eggs present in contaminated food or water or on hands spoiled with feces (autoinfections or family infections are not uncommon). Human cysticercosis may be common in endemic countries; sporadic cases of cysticercosis are diagnosed in humans in the United States and in Europe, having been acquired abroad or from immigrants infected with *T. solium* tapeworm.

The pork tapeworm is smaller than *T. saginata*, and its proglottids are usually expelled with feces, starting 2 months after ingestion of infected pork. Clinical symptoms and signs of taeniasis are not characteristic and are similar to *T. saginata* infection. The diagnosis is made by examination of the expelled proglottids or detecting the specific coproantigens. Finding *Taenia* eggs in feces can only confirm the diagnosis of taeniasis (*T. solium* eggs are morphologically indistinguishable from those of *T. saginata*). Proglottids and feces should be handled with care because *T. solium* eggs are infective for humans.

Treatment of *T. solium* taeniasis is mandatory as soon as possible, in both confirmed and suspected cases, due to a danger of spreading eggs causing cysticercosis in humans or pigs. Treatment of intestinal infection is the same as for *T. saginata* taeniasis; rarely, praziquantel may provoke symptoms in concomitant asymptomatic cysticercosis. Evaluation of treatment is by frequent fecal examination for *Taenia* eggs or coproantigens during the second and third months after anthelmintic therapy.

In cysticercosis, *T. solium* cysticerci may be localized in muscle and subcutaneous tissues (Figure 197.1A) without much symptomatology; the clinically important are mainly the cases of neurocysticercosis, ocular cysticercosis, and heart cysticercosis. Neurocysticercosis is suspected when epileptiform seizures (70% to 90% of cases), intracranial hypertension, or psychiatric disturbances occur, especially in adolescents or adults in endemic areas or having contact with a *T. solium* carrier (household infection is common). The most malignant forms of cysticercosis are at ventricular and basal cisternal parasite localizations. If subcutaneous nodules are present (which is uncommon, except in India), the final diagnosis

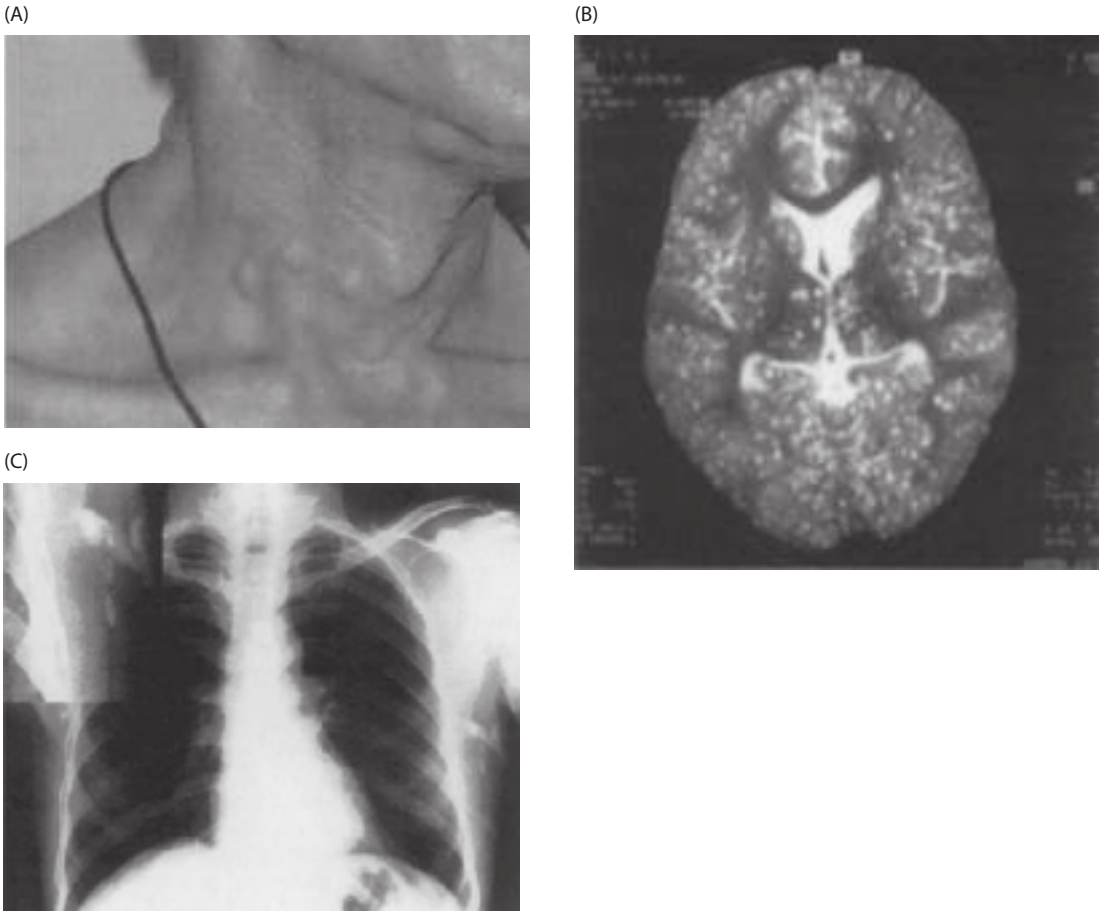

FIGURE 197.1 Cysticerci in subcutaneous location (A), on brain computed tomography (CT) showing innumerable cysticerci (starry-night appearance) (B), and calcifications in soft tissues (C). (Courtesy of Dr. S. K. Gaekwed.)

Bradley's *Neurology in Clinical Practice*, 4th edn. Butterworth-Heinemann; 2004.

can be made by biopsy demonstrating a scolex or typical structures of cysticercus wall. Most often, cysticerci are diagnosed by finding cysticercus-like structure(s) in the brain, spine, eye, or heart by computed axial tomography (CAT) or magnetic resonance imaging (MRI) scans (Figure 197.1B). In some cases the inflammatory reaction or edema and ventricular dilatation are present. In ocular cysticercosis the diagnosis can be made by ophthalmoscopy. Less often cysticercosis is suspected on the basis of ultrasound scanning and/or x-ray examination, particularly if calcifications are present (Figure 197.1C). Positive serologic tests, especially enzyme immunoassay (EIA) and enzyme-linked immunoelectrontransfer blot (EITB) assays, support the clinical diagnosis but cannot differentiate between active and past infections.

Neurocysticercosis is often asymptomatic; in such cases, indications for treatment must be considered carefully. Symptomatic cases can be active or inactive (calcified). Therapy can be via specific anthelmintic treatment, surgery, corticosteroids, or symptomatic treatment. The choice of treatment has to be individually tailored. Anthelmintic therapy with praziquantel or albendazole is indicated in active cysticercosis with several parenchymal cysts or with clinical signs of vasculitis, encephalitis, and arachnoiditis. Traditionally, praziquantel is given orally in a daily dose of 50 mg/kg for 14 days, but a shorter regimen with a higher dose has been proposed. Albendazole is given orally in a daily dose of 15 mg/kg for 8 days. For parenchymal brain cysticerci, the efficacy is about 60% for praziquantel and 85% for albendazole. Damage to cysticerci, caused by both drugs, may result in a local inflammatory reaction and edema, which necessitates a concomitant additional corticosteroid or antihistamine drug therapy.

Surgical extirpation is indicated for single parenchymal, intraventricular, spinal, and ocular cysticerci and with focal symptoms (e.g., cranial nerve dysfunction). A ventricular shunt is indicated in hydrocephalus. Corticosteroids and immunosuppressants may control vasculitis and encephalitis. Antiepileptic drugs are used mainly in inactive cysticercosis with granulomatous or calcified lesions. The global disability and mortality from neurocysticercosis are still considerable but its control measures are introduced only locally.

Hymenolepis nana infections

Hymenolepis nana, the dwarf tapeworm, 15 to 40 mm long, lives only up to 3 months in human small intestine. Some of the tapeworm eggs are expelled with feces and constitute a source of autoinfection or infection for other people. The other eggs hatch in the human intestine and develop within a month into cysticercoids in intestinal villi and later into the next generation of adult tapeworms in the same host.

Such a cycle facilitates spread of infection in close communities (day-care centers, schools, psychiatric institutions) as well as permits intensive infections of thousands of tapeworms, especially in malnourished or immunodeficient individuals. Usually a specific immunity develops and regulates the intensity and duration of infection, which occurs mainly in children and often clears spontaneously in adolescence. Hymenolepiasis is very common in regions with a hot, dry climate; it is rare in countries with appropriate sanitation.

Intensive infections may cause diarrhea, abdominal pains, and general symptoms such as weight loss, pallor, and weakness. Diagnosis is made by finding characteristic *H. nana* eggs in feces. Treatment with a single dose of praziquantel, 15 to 25 mg/kg, is highly effective; in intensive infections treatment must be repeated after 3 weeks. Niclosamide is much less effective and requires repeated courses of 7 days with the daily dose of 2 g for adult patients. Successful treatment has to be confirmed by negative fecal examination every 2 weeks for 2 months after therapy.

Other intestinal cestodes

Diphyllobothriasis, caused by *Diphyllobothrium latum*, *Diphyllobothrium dendriticum*, and *Diphyllobothrium pacificum*, still occurs around unpolluted large lakes in moderate climates (the Great Lakes in the United States and Canada and lakes in Finland and Switzerland) and along the Pacific Coast in South America. An uncommon clinical complication of diphyllobothriasis is vitamin B_{12} deficiency. Diagnosis is made by finding characteristic eggs during fecal examination. Treatment is a single dose of praziquantel, 15 to 25 mg/kg. Evaluation of successful therapy is by repeated fecal examination some months after.

Hymenolepis diminuta (rat tapeworm) and *Dipylidium caninum* (dog tapeworm) infections occur accidentally in humans and are usually nonintensive and asymptomatic. They are diagnosed by fecal examination and can be easily treated by a single dose of praziquantel, 15 mg/kg.

Spirometra spp., a tapeworm parasitizing a broad spectrum of amphibian hosts, reptiles, birds, and mammals, occur sporadically but worldwide. It causes sparganosis, larval worm infection, mainly in the subcutaneous tissue or in an orbit.

Cystic echinococcosis (hydatid disease)

Echinococcus granulosus is a tiny tapeworm living in the small intestine of some carnivores, mainly dogs. *Echinococcus granulosus* eggs, which are excreted in dog feces and contaminate an environment, are the source of cystic echinococcosis in various animals, mainly sheep or pigs, and sporadically in humans. Echinococcosis is still common in sheep-breeding regions in South America, Mediterranean countries, Middle East, Central Asia, and China. Small enzoonotic foci are found in Alaska, California, southern Utah, northern Arizona, and New Mexico. In Europe, sporadic cases of cystic echinococcosis are frequently caused by an *E. granulosus* strain, originating from pigs.

Echinococcus cysts develop mainly in the liver (about 65%) or lungs (25%), but they can invade any tissue, including the brain, kidney, spleen, heart, and bone. Clinical manifestations are diverse, depending on location, size, and number of the cysts as well as the complications resulting from cyst rupture and communication with biliary or bronchial systems or with adjacent body cavities. Bacterial

infection of the cysts and secondary peritoneal echinococcosis are not uncommon. Clinical diagnosis is confirmed mainly by imaging techniques (sonography, CT, MRI, positron emission tomography [PET], and/or x-ray examination. Classification of cystic echinococcosis in sonography is based on cyst morphology, considering also fertility and the content of the cyst; one can differentiate a cystic lesion (CL) stage, similarly to nonparasitic cysts, and C1 to C5 stages from young active cysts to old inactive cysts. Diagnosis can be confirmed by the serologic tests (sensitive enzyme-linked immunosorbent assay [ELISA], followed by more specific immunodiffusion or immunoblot tests). In some cases the clinical picture, imaging, and serology are not conclusive, and the final diagnosis is made by finding parasite hooks, protoscolices, or cyst wall fragments in sputum or in biopsy, surgical, or necropsy samples. In some specialized centers, cyst puncture with a fine needle guided by sonography and performed under the cover of albendazole is becoming widely used. Most commonly the differential diagnosis considers liver simple nonparasitic cysts.

The echinococcus cysts may be sterile or fertile (with protoscolices), simple or multiple, small or large (up to 20 cm in diameter), asymptomatic or symptomatic, active or inactive, complicated or noncomplicated. The choices of management are surgery, chemotherapy, PAIR (puncture, aspiration, injection of a cysticidal substance, and reaspiration), or observation without any intervention. Major indications for surgery are large, active, superficially located, and easy-to-rupture liver cysts and most of the brain, spinal, heart, and bone cysts. Surgery can be radical (removal of the whole intact cyst) or conservative (cystectomy and removal of the parasite but not the host pericyst). Surgery brings a risk of complications, such as anaphylactic shock or secondary echinococcosis and death (0.5% to 4%).

Chemotherapy is used more widely, mainly but not exclusively in inoperable cases. An important indication for chemotherapy before surgery or a puncture is prevention of secondary echinococcosis due to unintentional spillage of a cyst's contents. The drugs used are mebendazole, 40 to 50 mg/kg daily for at least 3 months, or albendazole, 10 to 15 mg/kg daily for at least 1 month. Sometimes repeated courses of treatment are necessary. Chemotherapy with both drugs brings a risk of embryotoxicity in early pregnancy. Careful clinical monitoring can prevent hepatotoxicity, neutropenia, and thrombocytopenia but not alopecia, which may occur.

PAIR is used in endemic regions with poor healthcare facilities. Unfortunately, no protoscolicide is both effective and safe; widely used now are 75% to 95% ethanol, 20% hypertonic sodium chloride solution, and 0.5% cetrimide. Formalin solution should no longer be used, as it can provoke sclerotic cholangitis.

Alveolar and polycystic echinococcosis

Echinococcus multilocularis tapeworms develop in the intestine of some carnivores, mainly foxes, but also dogs; the intermediate hosts are rodents such as voles, lemurs, and mice. Large natural enzoonotic foci of alveolar echinococcosis are in the Northern Hemisphere, especially the region of the Alps (France, Switzerland, Germany, Austria), Siberia, northern Japan, and Alaska. Humans are infected accidentally by *E. multilocularis* eggs present in fecally polluted natural environments (water, soil, berries) or on fox's skin or dog's hair.

Incidence of human alveolar echinococcosis varies between 0.02 and 0.18 per 100 000 inhabitants. However, a spread of *E. multilocularis* is observed in Europe westward (France), eastwards (Poland and Lithuania), northwards (Norway and Sweden), and southwards (northern Italy). In addition to its natural foci it spreads, together with foxes, in some urbanized areas.

Echinococcus multilocularis lesions, composed of clusters of tiny vesicles, usually begin in the liver, grow slowly over the years in a tumorlike pattern, and may metastasize to lungs and brain. Modern (PNM) classification of alveolar echinococcosis lesions in liver is based on the size of parasitic mass, involvement of the neighboring tissues, and distant metastases. The early clinical manifestations are usually vague; the advanced disease is invariably symptomatic due to liver lesions or lung or brain metastases. Diagnosis is based on imaging techniques and molecular and immunologic tests; the latter (e.g., Em2G11) are highly specific. The differential diagnosis is mainly with neoplasma conditions. Treatment is by radical surgical resection of liver lesions followed by at least 2 years of chemotherapy. Recurrent or nonresectable lesions require lifelong chemotherapy with mebendazole or albendazole, which are parasitostatic rather than parasitocidal. Nitrazoxanide and amphotericin B are now suggested as potential alternative additional or combined drugs. The treatment has to be performed in specialized centers because of various and frequently severe complications, which may need another surgery or in rare cases a liver transplantation.

Polycystic echinococcosis occurs in humans in Central and South America and is caused by *Echinococcus vogeli* and *Echinococcus oligartrus*, the parasites of wild mammals. The numerous small cystic lesions can be found in the liver, lungs, abdominal cavity, stomach, heart, and orbit. The clinical course is similar to alveolar echinococcosis. Polycystic echinococcosis frequently requires surgery and responds well to albendazole.

Suggested reading

Brunetti E, Kern K, Vuitton DA; Writing Panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. *Acta Trop*. 2010;114:1–16.

Combes B, Comte S, Raton V, et al. Westward spread of *Echinococcus multilocularis* in foxes, France, 2005–2010. *Emerg Infect Dis*. 2012;18:2059–2062.

Ito A, Craig PS, Schantz PM, eds. Taeniasis/cysticercosis and echinococcosis with focus on Asia and the Pacific. *Parasitol Int*. 2006; 55(Suppl):S1–S308.

Marval de F, Gottstein B, Weber W, et al. Imported diphyllobothriasis in Switzerland: molecular methods to define a clinical case of *Diphyllobothrium* infection as *Diphyllobothrium dendriticum*, August 2010. *Euro Surveill*. 2013;18(3). pii: 20355.

Murrell KD, ed. *Guidelines on Taeniasis/Cysticercosis*. Geneva: WHO/OIF/FAO; 2005.

Singh G, Prabhakar S, eds. *Taenia solium Cysticercosis: From Basic to Clinical Science*. Wallingford, Oxon, UK: CABI Publishing; 2002.

Toxoplasma

Roderick Go and Benjamin J. Luft

Toxoplasmosis, caused by the obligate intracellular parasite *Toxoplasma gondii,* is responsible for significant morbidity and mortality throughout the world. Although it has long been recognized as a serious congenital disease, it is only with the advent of acquired immunodeficiency syndrome (AIDS) and the increased use of immunosuppressive therapy that toxoplasmosis has reached epidemic proportions.

Humans are incidental hosts in the life cycle of *T. gondii*. Acute infection occurs via ingestion of meats or water contaminated with tissue cysts or tachyzoites or by handling cats, the definitive host. Once the human host develops an adequate immune response, tissue cysts are formed and a chronic or latent infection ensues. Antibodies against *T. gondii* will be present in serum for life. When a chronically infected person becomes immunocompromised, particularly with defects in cell-mediated immunity, devastating reactivation of the latent infection may occur.

Clinical manifestations and diagnosis

In the immunocompetent host, primary infection is often asymptomatic. Acute infection can mimic the symptoms of mononucleosis with a common manifestation of cervical or occipital lymphadenopathy. The lymph nodes usually are nontender, are nonsuppurative, and persist for less than 4 to 6 weeks. Infrequently, toxoplasmosis can lead to myocarditis, hepatitis, polymyositis, pneumonitis, and encephalitis.

Toxoplasmosis in the immunocompromised patient is most commonly manifested by toxoplasmic encephalitis (TE), usually alone but sometimes as part of a multiorgan infection. Isolated organ involvement without central nervous system (CNS) disease is uncommon. In the AIDS patient, TE usually develops when the CD4 lymphocyte count falls below 100/mm^3, although the risk of developing overt infection begins when CD4 counts fall below 200/mm^3. The clinical manifestations of TE are protean, including signs and symptoms of focal or generalized neurologic dysfunction or more commonly both, depending on the number, size, and location of the lesions. Cerebral edema, vasculitis, and hemorrhage, which can accompany active infection, also contribute to the disease process. Toxoplasmic encephalitis most commonly presents with a subacute onset of focal neurologic deficits with or without evidence of generalized cerebral dysfunction. Less often, seizures are the initial manifestation. Occasionally, signs and symptoms of generalized cerebral dysfunction dominate the presentation, and patients develop focal deficits as the infection progresses. The clinical presentation varies from an insidious process evolving over several weeks to a more acute or even fulminant course. Headaches may be focal or generalized and unremitting.

Serologic tests for diagnosis of toxoplasmosis in AIDS patients are useful only to identify human immunodeficiency virus (HIV)-infected individuals at risk for development of TE and as support for the diagnosis in AIDS patients with focal brain lesions. The Sabin–Feldman dye test is the accepted standard for measurement of immunoglobulin G (IgG) antibodies, which have been shown to be higher in AIDS patients with TE than in those without TE. The immunofluorescence assay (IFA), which is more commonly used, measures the same IgG antibodies as the dye test. Almost all AIDS patients with TE have detectable IgG. The absence of these antibodies strongly suggests another cause of the neurologic signs and symptoms.

The standard of care allows for the treatment of TE to be initiated on presumptive diagnosis when a typical neuroradiographic abnormality is noted on computed tomography (CT) or magnetic resonance imaging (MRI). MRI is more sensitive than CT in the demonstration of focal CNS lesions. The clinical diagnosis is a result of clinical and radiographic response to specific therapy because patients may have similar symptoms resulting from lesions of other causes, such as CNS lymphoma, progressive multifocal leukoencephalopathy, brain abscess, and focal lesions caused by other organisms, including *Cryptococcus neoformans, Aspergillus* spp., *Mycobacterium tuberculosis,* and *Nocardia* spp. The practice of presumptive therapy for patients who have not been receiving effective prophylaxis for *Toxoplasma* with a characteristic finding on CT or MRI and positive serology for *Toxoplasma* is widely accepted. With the use of these criteria, the predictive value has been estimated at 80%. However, for patients such as intravenous drug abusers in whom other CNS processes are more prevalent, the predictive value of a positive serology for *Toxoplasma* is reduced, and the widespread use of prophylaxis may further reduce it. Toxoplasmic encephalitis is predominantly intra-axial, so significant meningeal involvement is uncommon. Examination of cerebrospinal fluid (CSF) is used to exclude other diseases. Detection of *T. gondii* DNA by polymerase chain reaction (PCR) in CSF has demonstrated high specificity but variable sensitivity in establishing the diagnosis of TE in AIDS patients with focal lesions.

The lungs are the second most common site of infection in AIDS patients and in recipients of bone marrow transplants. The clinical manifestations of toxoplasma pneumonia are nonspecific, similar to those seen with *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP). Most patients have fever, a nonproductive cough, dyspnea, and occasionally hemoptysis. However, the onset of disease tends to be faster than with PCP. The chest roentgenogram typically reveals bilateral interstitial infiltrates, although multiple nodular infiltrates, single nodules, isolated cavitary disease, lobar infiltrates, pleural effusions, and hilar adenopathy may occur. Pneumothorax complicating toxoplasmic pneumonia has been reported, as well as acute respiratory distress syndrome (ARDS). The diagnosis relies on a high index of suspicion and the demonstration of *T. gondii* from bronchoalveolar lavage (BAL) fluid or biopsy specimens, given the nonspecific nature of both clinical and radiologic manifestations in most cases.

Ocular toxoplasmosis is the most common retinal infection in the United States and is the second most common retinal infection in patients with AIDS after cytomegalovirus (CMV) retinitis. Patients usually present with decreased visual acuity and, less often, eye pain. Ocular toxoplasmosis may be the sole manifestation of infection or may accompany TE or disseminated disease. At times, in the immunocompromised host, ocular toxoplasmosis is a harbinger of TE. A CT scan of the head should be obtained to assess presence of concomitant TE. Fundoscopic findings are consistent with a necrotizing chorioretinitis. The lesions, which may be single or multiple and bilateral and are usually nonhemorrhagic, are yellow-white areas of retinal necrosis with ill-defined fluffy borders. They occur at the posterior pole and may be associated with a moderate to severe inflammatory response in the vitreous and anterior chamber. These characteristics help in the differential diagnosis with CMV retinitis. Fluorescein angiography may also be helpful. Dye leakage tends to occur along the edge of the lesions in toxoplasmosis and to be more prominent in the center of lesions in CMV retinitis. Ocular toxoplasmosis should be suspected in the AIDS patient who is seropositive for *T. gondii* and has changes in visual acuity with accompanying fundoscopic changes. A prompt response to specific therapy should also be expected. Definitive diagnosis has been made by demonstrating the organism in retinal biopsy specimens or isolation of *T. gondii* from vitreal fluid or PCR.

Therapy

Immunocompetent host

Most infections in immunocompetent hosts are asymptomatic and do not require therapy. Lymphadenopathy, the most common manifestation, is self-limited and usually resolves within 1 to 3 weeks. Treatment should be considered only if systemic symptoms are severe or long lasting or in the rare event of visceral involvement (encephalitis, myocarditis, pneumonitis). Acute infection as a result of laboratory accidents or transfusions may be severe and should be treated. The treatment regimen of choice consists of a combination of pyrimethamine (Daraprim) and sulfadiazine given for 2 to 4 weeks with folinic acid (leucovorin) (Table 198.1). In the event of pyrimethamine-induced hematologic toxicity, the dosage of folinic acid can be increased to 20 to 50 mg/day. For patients allergic to sulfa, clindamycin in combination with pyrimethamine and folinic acid has been used successfully (see Table 198.1).

For ocular toxoplasmosis, the drugs of choice are pyrimethamine and sulfadiazine or trisulfapyrimidine with folinic acid in the same dosages as described earlier. Therapy is given for 4 weeks and repeated as needed. Treatment is required to prevent relapse with the risk of progressive vision loss and other complications such as glaucoma. Adjunctive therapy with systemic corticosteroids (prednisone, 80 to 120 mg/day, or an equivalent) is indicated if the macula, optic nerve, or papillomacular bundle is involved.

Immunocompromised host

For TE, the combination of pyrimethamine, 200 mg loading dose in two divided doses followed by 50 to 75 mg/day orally, plus sulfadiazine, 4 to 6 g/day orally in four doses, remains the mainstay of treatment (see Table 198.1). Oral folinic acid is added to preclude the hematologic toxicities associated with antifolate agents. Acute therapy is recommended for at least 6 weeks. Longer treatment durations may be needed if there is extensive clinical and radiographic disease or the response is incomplete at 6 weeks. Patients who cannot tolerate sulfas can be given clindamycin in combination with pyrimethamine as described. Prophylactic use of anticonvulsants is not recommended. Corticosteroids should not be used routinely but are indicated if there is evidence of increased intracranial pressure. In one study, 70% of AIDS patients treated for TE had a quantifiable

TABLE 198.1 **DRUGS FOR TREATMENT OF TOXOPLASMIC ENCEPHALITIS AND EXTRANEURAL TOXOPLASMOSIS**

Antimicrobial	Mode of action	Metabolism	Adverse effects	Recommended dosage (immunocompromised)	Recommended dosage (immunocompetent)
Pyrimethamine (Daraprim) oral	Inhibits folic acid synthesis	Readily absorbed by gut; hepatic metabolism, lipid soluble	Cytopenias, rash, GI intolerance	Acute: loading dose 200 mg then 50–75 mg daily; with oral folinic acid (leucovorin) 10–20 mg/d Maintenance: 25–50 mg/day with oral folinic acid 10–25 mg/d	Loading dose 200 mg daily for 2 d, then 50–75 mg daily for 2–4 wk; with oral folinic acid 10–20 mg/d
plus					
Sulfadiazine[a] oral	Inhibits folic acid synthesis; acts synergistically and sequentially with pyrimethamine	Readily absorbed by the gut; penetrates blood–brain barrier; some hepatic metabolism	GI intolerance, rash (Stevens–Johnson syndrome), cytopenias, nephrolithiasis, crystalluria, interstitial nephritis, encephalopathy	Acute: 1–1.5 g q6h Maintenance: 500–1000 mg/day QID	1–1.5 g q6h, 2–4 wk
or					
Clindamycin[a] oral and IV	Unknown; possibly inhibition of plastid and/or mitochondrial protein synthesis	Readily absorbed by gut; excellent tissue penetration	GI intolerance, rash, pseudomembranous colitis	Acute: 600 mg q6h (up to IV 1200 mg q6h) Maintenance: 300–450 mg PO q6–8h	300 mg q6h, 4 wk, repeat as needed

Abbreviation: GI = gastrointestinal.
[a] Used in combination with pyrimethamine.
Adapted from Mofenson et al. *MMWR Recomm Rep*. 2004;53(RR–14):1.

clinical improvement by day 7 of therapy. Conversely, patients not responding to empiric therapy had evidence of progressive disease within the first 10 days. Ninety percent of patients had improvement on neuroradiographic studies within 6 weeks of starting therapy.

In immunocompromised hosts, maintenance therapy (secondary prophylaxis) should be initiated. The regimen is usually the same as that used for primary treatment but at half dose. Maintenance therapy should be continued for the life of the patient or until the underlying immunosuppression has resolved. In patients with AIDS, secondary prophylaxis can be discontinued if they have sustained CD4 counts greater than 200 cells/mm^3 for longer than 6 months.

The same chemotherapeutic regimens are used for extraneural toxoplasmosis; however, there are limited data available on the optimal length and outcome of treatment. As a rule, ocular toxoplasmosis responds favorably to therapy, and treatment of pulmonary infection has been reported to be successful in 50% to 77% of patients.

Intravenous trimethoprim–sulfamethoxazole (TMP–SMX, Bactrim, Septra), at 5 mg/kg/day trimethoprim component, has been used when oral therapy is contraindicated. Although TMP–SMX is available for oral use, response rates have been lower than standard regimens. Recently, trials have shown higher initial response rates when the dose was increased (trimethoprim, 6.6 to 10 mg/kg body weight per day).

The drugs described thus far are active only against the tachyzoite form of *T. gondii*. Surviving tissue cysts can reinitiate TE and other manifestations of reactivated latent disease if treatment is discontinued. Therefore it is necessary to give long-term suppressive therapy. Pyrimethamine, 25 to 50 mg/day, and sulfadiazine, 2 to 4 g/day orally in four doses, with 10 mg/day of oral folinic acid is recommended because of the low relapse rate associated with this combination. Clindamycin is used in cases of sulfa allergy. Atovaquone monotherapy at 750 mg two to four times a day may be considered in patients who are unable to tolerate pyrimethamine; however, this regimen has a 1-year relapse rate of 26%.

Primary chemoprophylaxis is a very attractive therapeutic option for patients known to be at risk for toxoplasmosis (i.e., those with CD4 counts less than 100 cells/mm^3 and seropositive for anti-*T. gondii* antibodies). Retrospective data suggest that TMP–SMX, one double-strength tablet per day orally, is efficacious. Neither dapsone nor pyrimethamine, when used as a single agent, is consistently effective. However, the combination of pyrimethamine, 50 mg/week, plus dapsone, 50 mg/day, plus folinic acid has been a useful alternative. In patients with a sulfa allergy, desensitization is also an option. Primary prophylaxis can be safely discontinued when the patient has sustained immune reconstitution with a CD4 count greater than 200 cells/mm^3 for 3 months.

Other drug regimens that have proven useful as initial and maintenance therapy (Table 198.2) include atovaquone (Mepron). An AIDS Clinical Trials Group (ACTG) trial evaluating the efficacy of atovaquone-containing regimens (either in combination with pyrimethamine or sulfadiazine) showed encouraging results, with 77% response to therapy. As salvage therapy, atovaquone alone induced initial clinical response in 50% of study patients. The response to

TABLE 198.2 **ALTERNATIVE TREATMENTS OF TOXOPLASMOSIS IN IMMUNOCOMPROMISED PATIENTS**

Antimicrobial	Mode of action	Metabolism	Adverse effects	Recommended dosages
Atovaquone (Mepron)[a] oral	Uncoupling electron biosynthesis; inhibition of de novo pyrimidine biosynthesis	Suspension has better bioavailability than old tablet formulation; improved absorption if taken with food, particularly fatty foods	Rash, elevated liver function tests	Acute: suspension 1500 mg q12h Maintenance: suspension 750 mg q6–12h
Azithromycin (Zithromax)[a] oral	Unknown; possibly inhibition of plastid and/or mitochondrial protein synthesis	Readily absorbed by gut; high intracellular levels	GI intolerance	Acute: 900–1200 mg/d Maintenance: same
Trimethoprim–sulfamethoxazole (TMP–SMX)[b] (Bactrim, Septra) oral or IV	Inhibits folic acid synthesis	Renal metabolism	Rash, Stevens–Johnson syndrome, bone marrow suppression, hepatotoxicity, increased serum creatinine	Acute: 5 mg/kg TMP and 25 mg/kg SMX IV or oral BID

Abbreviations: GI = gastrointestinal.
[a] Used in combination with pyrimethamine or sulfadiazine.
[b] Used in combination with pyrimethamine.

therapy with atovaquone has been directly correlated with serum drug levels achieved. The macrolide antibiotics azithromycin (Zithromax) and clarithromycin (Biaxin) in combination with pyrimethamine have limited utility as alternative agents.

Pregnancy

Women who acquire toxoplasmosis (primary infection) during pregnancy expose their fetuses to risk of infection. Infection of the fetus may result in stillbirth, spontaneous abortion, or birth of a symptomatic or an asymptomatic infant. Rarely, transmission has been reported in cases where the mother contracts acute toxoplasmosis 6 to 8 weeks before conception. Fetal infection is less common when the mother is treated during pregnancy. Early diagnosis, through serology, amniotic sampling for PCR, and fetal ultrasonography, is important in further management (antibiotics or therapeutic abortion).

Pyrimethamine plus a sulfonamide or spiramycin, a macrolide antibiotic available in western Europe, Mexico, and Canada and through the Food and Drug Administration of the United States, appears to decrease the incidence of congenital toxoplasmic infection when given to women who acquire *T. gondii* during pregnancy (Table 198.3). Pyrimethamine is teratogenic and should

TABLE 198.3 **DRUGS USED IN TREATMENT OF TOXOPLASMOSIS IN PREGNANT WOMEN**

In pregnant women infected during gestation	Medication	Dosage	Duration of therapy
First 18 wk of gestation or until term if fetus found not to be infected by amniocentesis at 18 wk	Spiramycin[a]	1 g every 8 h without food	Until fetal infection is documented or until it is excluded at 18 wk of gestation
If fetal infection confirmed, after wk 18 of gestation and in all women infected after wk 18	Pyrimethamine[b] plus	Loading dose: 50 mg each 12 h for 2 d; then beginning on day 3, 50 mg/d	Until term
	Sulfadiazine plus	Loading dose: 75 mg/kg; then beginning 50 mg/kg each 12 h (maximum 4 g/d) 10–20 mg daily	Until term
	Leucovorin (folinic acid)		During and for 1 wk after pyrimethamine therapy

[a] Spiramycin is not commercially available. Available only on request from the US Food and Drug Administration (telephone number: 301–443–5680), and then with approval by physician's request to Sanofi–Aventis (908–231–3365).
[b] Adjusted for megaloblastic anemia, granulocytopenia, or thrombocytopenia.
From Remington JS, McLeod R, Thulliez P, Desmonts G. Toxoplasmosis. In: Remington JS, Klein JO, Wilson CB, Baker CJ, eds. *Infectious Diseases of the Fetus and Newborn Infant*, 6th edn. Philadelphia, PA: Elsevier; 2006.

not be used until after the first trimester. There is no optimal medical therapy in the United States for treatment of women who become infected during the first trimester. However, sulfadiazine or trisulfapyrimidines should be used during the first trimester because sulfonamides alone have been shown to be effective in acute toxoplasmosis in animal models. If spiramycin can be obtained, pregnant women acutely infected in the first trimester may be treated until term with 30 to 50 mg/kg/day in three doses until fetal infection is confirmed or excluded. Treatment with spiramycin alone decreases the incidence of transmission but not the severity of established congenital infection. As spiramycin does not readily cross the placenta, treatment should be switched to pyrimethamine, sulfadiazine, and folinic acid in pregnant women with confirmed or a high possibility of fetal infection after the 18th week of gestation. If maternal or fetal infection is suspected or confirmed after the first trimester, pyrimethamine and sulfadiazine plus folinic acid should be used for treatment.

Pregnant women or women who are trying to become pregnant should be advised about risk factors for primary infection with toxoplasmosis. Education has been shown to be effective in decreasing the seroconversion rate during pregnancy. Women with cats should have someone else changing the litter box daily. They should avoid consuming undercooked meats, raw eggs, unpasteurized milk, or unfiltered water. All uncooked fruits and vegetables should be washed. Gloves should be used if they are working with soil, if they are preparing raw meat, or if they must change the cat litter box themselves. Proper hand hygiene should be practiced after working with soil, after handling the cat or the litter box, or after touching raw or undercooked meat.

Suggested reading

Coster LO. Parasitic infections in solid organ transplant recipients. *Infect Dis Clin North Am*. 2013;27(2):395–427.

Kravetz JD, Federman DG. Toxoplasmosis in pregnancy. *Am J Med*. 2005;118:212–216.

Luft BJ, Hafner R, Korzun AH, *et al*. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1993;324:995–1000.

Mariuz P, Bosler EM, Luft BJ. Toxoplamosis in individuals with AIDS. *Infect Dis Clin North Am*. 1994;8:365–381.

Montoya JG, Liesenfeld O. Toxoplasmosis. *Lancet*. 2004;363: 1965–1976.

Montoya JG, Remington JS. Mangement of *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis*. 2008;47: 554–566.

Novati R, Castagna A, Morsica G, *et al*. Polymerase chain reaction for *Toxoplasma gondii* DNA in the cerebrospinal fluid of AIDS patients with focal brain lesions. *AIDS*. 1994;8:1691–1694.

Porter SB, Sande MA. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *N Engl J Med*. 1992;327:1643–1648.

Torre D, Casari S, Speranza F, *et al*. Randomized trial of trimethoprim-sulfamethoxazole vs. pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. *Antimicrob Agents Chemother*. 1998;42:1346–1349.

Torres RA, Weinberg W, Stansell J, *et al*. Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. Atovaquone/Toxoplasmic Encephalitis Study Group. *Clin Infect Dis*. 1997;24:422–429.

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Malaria

Jessica K. Fairley and Henry M. Wu

Malaria remains a life-threatening parasitic infection endemic throughout much of the world. It is estimated that in 2018 there were 228 million infections worldwide and 405,000 deaths due to malaria, with the majority of deaths among African children. In nonendemic countries, it is one of the most common causes of fever in returned travelers and recent immigrants, and several thousand people with malaria arrive in nonendemic countries yearly.

Malaria is a mosquito-borne protozoal infection caused by one of four human *Plasmodium* species (*P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*) or by the monkey parasite, *P. knowlesi*, which has been increasingly described in parts of Southeast Asia. Malaria-endemic countries are shown in Figure 199.1. Given the risk of rapid progression to severe disease in nonimmune individuals, a high index of suspicion is critical when evaluating patients with febrile illness following travel to malarious areas, especially those endemic for *P. falciparum*. Proper treatment of malaria requires knowledge of the infecting species and where it was acquired since drug resistance patterns vary geographically. Widespread chloroquine-resistant *P. falciparum* (CRPF) malaria and emergence of resistance to other drugs have complicated treatment and prophylaxis.

Clinical aspects

Fever in a patient who has recently traveled to an area endemic for malaria should be considered a medical emergency. The minimum incubation period is generally considered to be 7 days after inoculation, and of greatest concern is the patient who has traveled to a *P. falciparum* endemic area within 2 months of presentation since an incubation period of 2 to 4 weeks is typical for falciparum malaria. Presentation several months to 1 year after departing an endemic region is also possible, particularly when infected with *P. vivax* or *P. ovale,* since infection with these species can result in a dormant liver stage. Patients with falciparum malaria can also present months after exposure because the use of prophylaxis or presence of semi-immunity can modify or delay the onset. For these reasons, febrile patients who have traveled to a malarious region in the preceding year should be ruled out for malaria regardless of prophylaxis history.

Malaria transmission occurs when a malaria-infected female *Anopheles* mosquito inoculates sporozoites into a human host. Initially, infected persons are asymptomatic as the sporozoites enter the bloodstream and travel to the liver where maturation occurs in hepatocytes. Malaria symptoms begin when merozoite forms are released into the bloodstream and the erythrocytic stage begins. In this stage, merozoites infect erythrocytes and replicate within them, resulting in rupture and further merozoite release. Symptom severity typically depends on the percentage of erythrocytes infected and the presence or absence of partial immunity due to previous infection.

Initial symptoms are nonspecific and include fever, chills, malaise, anorexia, headaches, and myalgias. Cough, abdominal pain, and diarrhea may also be present. The illness may resemble numerous other febrile syndromes including enteric fever, dengue fever, influenza, meningitis, and septicemia, so a high index of suspicion for malaria is critical even when an alternate diagnosis appears more likely. Although regular

periodicity of fever is classically described, this is unlikely early in the disease course and may not be seen at all, particularly with falciparum malaria.

Severe falciparum malaria is a multi–organ system disease. Infected erythrocytes adhere to vascular endothelium cells, resulting in sequestration, circulatory obstruction, and inflammation in the affected organ. Complications include severe anemia, jaundice, thrombocytopenia, hypoglycemia, pulmonary edema, acute respiratory distress syndrome (ARDS), renal failure, and disseminated intravascular coagulation (DIC). Seizures, impaired consciousness, and coma may result from hypoglycemia or suggest the presence of cerebral malaria. Even with treatment, the case fatality rate of severe malaria is 15% to 20%. Lactic acidosis suggests a worse prognosis. Nonimmune pregnant woman are at higher risk for severe disease, as well as preterm birth and fetal loss. Among travel-associated cases in nonendemic countries, patients >65 years have the worst outcomes. Though *P. vivax* typically causes uncomplicated malaria, severe *P. vivax* malaria can occur. However, since severe disease is most associated with falciparum malaria and mixed infection with multiple species is possible, severe disease in a patient diagnosed with nonfalciparum malaria should raise the possibility of coexisting falciparum malaria.

P. vivax and *P. ovale* infections can also result in a dormant hypnozoite liver stage which requires special consideration for treatment and prophylaxis. Patients carrying hypnozoites are asymptomatic until the infection reactivates and results in a relapsed infection.

Diagnosis

Prompt and accurate diagnosis is critical in malaria management. The diagnostic gold standard is examination of Giemsa-stained thick and thin blood smears. Thick smears are highly sensitive and can detect parasites in patients with low parasitemia levels that might be missed in thin smears. However, thin smears are best for speciation, quantification of parasites (i.e., percent of erythrocytes parasitized), and assessment of treatment response. If the initial blood smears are negative, they should be repeated at 12- to 24-hour intervals for a total of three sets before considering the disease ruled out. When expertise to prepare or examine thick smears is not immediately available, thin blood smears alone are better than none at all since a negative thin smear suggests a high parasitemia infection is unlikely. Wright's stain, which is typically used in clinical laboratories for peripheral blood smears, is not optimal for blood parasites; however, it can be helpful when Giemsa staining is unavailable.

A number of rapid diagnostic tests (RDTs) are available for malaria diagnosis when blood smears are not readily available. These tests rely on the detection of *Plasmodium* spp. antigens, including histidine-rich protein 2 (HRP2) and parasite lactate dehydrogenase. These tests can be highly sensitive and specific for falciparum malaria. However, test performance can vary widely among different kits, and false results can occur if instructions on use and storage are not strictly followed. Nonetheless, RDTs can be important in situations where microscopy is not feasible or timely.

Therapy

The increasing prevalence of drug-resistant plasmodia has complicated malaria treatment. In addition to widespread CRPF, mefloquine-resistant *P. falciparum* is endemic in several Southeast Asian countries, and strains of *P. vivax* resistant to drugs including chloroquine and primaquine have emerged. In contrast, drug resistance has not been described in *P. ovale* or *P. malariae*. When species identification is uncertain in a patient with malaria, clinicians should treat for the worst-case scenario (i.e., infection caused by CRPF). Malaria acquired while taking prophylaxis should not be treated with the same medication used for prophylaxis. Recommended drug regimens for treatment in the United States are listed in Table 199.1. Since effective malaria therapy requires consideration of the infecting species and local resistance patterns, clinicians are strongly advised to review current recommendations and seek diagnostic assistance when needed. Suspected or confirmed malaria should always be treated with the assistance of an infectious diseases or tropical medicine specialist when available. Updated country guides and detailed US treatment

(A)

FIGURE 199.1 (A and B) Malaria-endemic countries of the Western and Eastern Hemispheres.

Courtesy of Centers for Disease Control and Prevention, *Yellow book 2020: Health information for the international traveler.* New York: Oxford University Press; 2019: Chapter 4.

(B)

FIGURE 199.1 Continued

recommendations are available from the US Centers for Disease Control and Prevention (CDC), either online (www.cdc.gov/malaria/index.html) or by phone through the CDC Malaria Hotline (1-770-488-7788 or 1-855-856-4713 toll free, weekdays 9 AM–5 PM; or 1-770-488-7100 for emergency consultation after hours).

Plasmodium malariae, Plasmodium knowlesi, and uncomplicated chloroquine-sensitive *P. falciparum* malaria

Chloroquine-sensitive *P. falciparum* malaria is confined to Central America north of the Panama Canal, Haiti, and the Dominican Republic. Chloroquine or hydroxychloroquine should be used to treat *P. falciparum* from these areas, as well as *P. malariae* and *P. knowlesi* infections from any part of the world.

Uncomplicated chloroquine-resistant *P. falciparum* malaria

With the exception of the regions just mentioned, CRPF is widespread. Artemisinin-based combination therapies (ACTs) are rapidly becoming the treatment of choice for CRPF. Artemisinin and its derivatives are well tolerated and lead to a rapid reduction in parasitemia and fever. Since monotherapy is associated with a high rate of recrudescence, the addition of a second agent is necessary. ACTs currently recommended by the World Health Organization (WHO) include artemether-lumefantrine, artesunate-amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, and dihydroartemisinin-piperaquine. Artemether-lumefantrine is approved in the United States for the oral treatment of uncomplicated falciparum malaria. Atovaquone-proguanil is another recommended and well-tolerated oral regimen for uncomplicated falciparum malaria. These regimens are effective against multidrug-resistant falciparum malaria acquired in Southeast Asia.

When artemether-lumefantrine and atovaquone-proguanil are not available or are contraindicated, oral quinine sulfate in combination with tetracycline, doxycycline, or clindamycin is an effective regimen, though longer and less well tolerated. Clindamycin is usually reserved for pregnant women and for young children (those <8 years old) in whom tetracycline derivatives are generally avoided. Patients taking quinine typically experience cinchonism,

TABLE 199.1 **TREATMENT OF MALARIA (UNITED STATES GUIDELINES)**

Clinical severity/species	Resistance	Recommended treatments for adults[1]	Recommended pediatric treatments[1]
Uncomplicated *P. falciparum* or species not identified NOTE: If an unidentified species is subsequently determined to be *P. vivax* or *P. ovale,* addition of primaquine therapy is indicated to prevent relapse, see below	Chloroquine-resistant or unknown	**Atovaquone-proguanil: Adult tablet = 250 mg atovaquone/100 mg proguanil** 4 adult tablets daily × 3 d	**Atovaquone-proguanil: Pediatric tablet = 62.5 mg atovaquone/25 mg proguanil** **Adult tablet = 250 mg atovaquone/100 mg proguanil** 5- <8 kg: 2 ped tabs daily × 3 d 8– <10 kg: 3 ped tabs daily × 3 d 10–<20 kg: 1 adult tab daily × 3 d 20–<30 kg: 2 adult tabs daily × 3 d 30–<40 kg: 3 adult tabs daily × 3 d ≥40 kg: 4 adult tabs daily × 3 d
		Artemether–lumefantrine: One tablet = 20 mg artemether/120 mg lumafantrine Three-day treatment with total of 6 oral doses based on weight. Initial dose is followed by second dose 8 h later, then 1 dose BID for the following 2 days.	
		4 tabs per dose	5–<15 kg:1 tab/dose 15–<25 kg: 2 tab/dose 25–<35 kg: 3 tabs/dose ≥35 kg: 4 tabs/dose
		Quinine sulfate: 542 mg base (= 650 mg salt) PO TID × 3 or 7 days[2]	**Quinine sulfate:** 8.3 mg base/kg (= 10 mg salt/kg) PO TID × 3 or 7 days[2]
		PLUS one of the following:	**PLUS one of the following:**
		Doxycycline: 100 mg PO BID × 7 d **OR** **Tetracycline:** 250 mg PO QID × 7 d **OR** **Clindamycin:** 20 mg base/kg/d PO divided tid × 7 d	**Doxycycline**[3]: 2.2 mg/kg PO BID × 7 d **OR** **Tetracycline**[3]: 25 mg/kg/d PO divided QID × 7 d **OR** **Clindamycin:** 20 mg base/kg/d PO divided tid × 7 d
		Mefloquine[4]: 684 mg base (= 750 mg salt) PO as initial dose, followed by 456 mg base (= 500 mg salt) PO given 6–12 h after initial dose	**Mefloquine**[4]: 13.7 mg base/kg (= 15 mg salt/kg) PO as initial dose, followed by 9.1 mg base/kg (= 10 mg salt/kg) PO given 6–12 h after initial dose
Uncomplicated *P. falciparum* or species not identified acquired in area with no chloroquine resistance *P. malariae* (all regions) *P. knowlesi* (all regions) NOTE: If an unidentified species is subsequently determined to be *P. vivax* or *P. ovale*, addition of primaquine therapy is indicated to prevent relapse, see below	Chloroquine-sensitive	**Chloroquine phosphate:** 600 mg base (= 1000 mg salt) PO immediately, followed by 300 mg base (= 500 mg salt) in 6, 24, and 48 h **Hydroxychloroquine:** 620 mg base (= 800 mg salt) PO immediately, followed by 310 mg base (= 400 mg salt) in 6, 24, and 48 h	**Chloroquine phosphate:** 10 mg base/kg (= 16.7 mg salt/kg) PO immediately, followed by 5 mg base/kg (= 8.3 mg salt/kg) PO at 6, 24, and 48 h **Hydroxychloroquine:** 10 mg base/kg (= 12.9 mg salt/kg) PO immediately, followed by 5 mg base/kg (= 6.5 mg salt/kg) at 6, 24, and 48 h
Uncomplicated *P. vivax or P. ovale*[6]	Chloroquine-sensitive[6]	**Chloroquine phosphate or hydroxychloroquine (doses as above)**	**Chloroquine phosphate or hydroxychloroquine (doses as above)**
		PLUS	**PLUS**
		Primaquine phosphate[5]: 30 mg base (= 52.6 mg salt) PO qd × 14 d OR Tafenoquine 300 mg PO once	**Primaquine phosphate**[5]: 0.5 mg base/kg (= 0.8 mg salt/kg) PO qd × 14 d OR Tafenoquine 300 mg PO once

TABLE 199.1 CONTINUED

Clinical severity/species	Resistance	Recommended treatments for adults[1]	Recommended pediatric treatments[1]
Severe malaria (usually *P. falciparum*)	All resistance profiles	**Artesunate IV,** 1 dose = 2.4 mg/kg 3 doses at 0, 12, and 24 hours If parasitemia >1%, continue for up to 6 more days qday When parasitemia, ≤1%, give a complete oral regimen as described in oral therapy	

Readers are strongly recommended to visit www.cdc.gov/malaria/diagnosis_treatment/index.html for further details, updated recommendations, and recommendations for pregnant women.
[1] Malaria acquired while taking prophylaxis should not be treated with the same medication used for prophylaxis.
[2] Infection acquired in Southeast Asia should be treated for 7 days with quinine/quinidine, and infections acquired in Africa and South America should be treated with 3 days of quinine/quinidine.
[3] Doxycycline and tetracycline are not indicated for children <8 years old.
[4] Treatment with mefloquine is not recommended for infections acquired in Southeast Asia due to *P. falciparum* resistance in this region. Due to high rates of neuropsychiatric side effects at treatment doses, mefloquine is only recommended when other options (i.e., atovaquone/progruanil, artemether-lumefantrine, quinine-based regimens) cannot be used.
[5] G6PD deficiency and pregnancy must be ruled out prior to primaquine use to eradicate hypnozoites in *P. vivax* and *P. ovale* infections. Expert consultation is recommended in patients with G6PD deficiency or in pregnant patients.
[6] *P. vivax* acquired in Papua New Guinea or Indonesia should be considered as potentially chloroquine-resistant and treated with alternative regimens. See www.cdc.gov/malaria/diagnosis_treatment/index.html for recommendations.
Adapted from: Centers for Disease Control and Prevention, 2020.

the reversible symptom complex that includes tinnitus, dizziness, headache, nausea, visual disturbances, and hearing loss. These side effects usually do not necessitate drug change. If oral medication is not tolerated, parenteral treatment is necessary (see parenteral regimens discussed later for severe malaria).

Mefloquine is also effective therapy for uncomplicated CRPF malaria, but it is not recommended for patients who might have multidrug-resistant infections acquired in Southeast Asia, particularly along the Thai–Myanmar (Burma) or Thai–Cambodian borders. Furthermore, concern for significant side effects generally restrict its use and make it an alternative regimen for uncomplicated malaria. Severe neuropsychiatric adverse reactions (psychosis, convulsions) are more likely to occur when the drug is used at treatment doses compared to prophylaxis dosing. Due to the QTc prolonging effects of mefloquine, an alternative regimen should be used in patients with a history of arrhythmia or other risk factors for prolonged QTc including medications.

The use of pyrimethamine-sulfadoxine (Fansidar) is no longer recommended due to widespread resistance to this regimen. Although halofantrine is widely used in malaria endemic areas, the CDC recommends against its use due to the risk of potentially fatal cardiac adverse events.

Plasmodium vivax malaria

The erythrocytic stage of *P. vivax* malaria is effectively treated with chloroquine or hydroxychloroquine. Eradication of hepatic hypnozoites requires treatment with primaquine or the newer tafenoquine. Primaquine is a potent oxidizing agent; therefore, glucose-6-phosphate dehydrogenase (G6PD) deficiency must be ruled out before primaquine therapy is initiated to avoid severe hemolysis.

Chloroquine-resistant *P. vivax* malaria was first described on the island of New Guinea in 1989, with subsequent spread across Indonesia. Since then, there are sporadic reports of declining chloroquine efficacy elsewhere in Southeast Asia, Africa, and the Amazon Basin of South America. Malaria caused by chloroquine-resistant *P. vivax* should be suspected when the illness recurs within 28 days after a patient has received standard therapy with chloroquine and primaquine. Due to the risk of chloroquine resistance, *P. vivax* malaria originating from Indonesia or Papua New Guinea should be treated with alternative regimens (Table 199.1). Notably, a recent Cochrane review concluded that some ACTs are as effective as chloroquine in treating the blood stage *P. vivax* infection, suggesting a potential strategy for simplifying empiric treatment for all forms of uncomplicated malaria where *P. falciparum* and *P. vivax* coexist. Though somewhat controversial, primaquine-resistant *P. vivax* malaria has been reported from the island of New Guinea, other parts of Southeast Asia, Somalia, and Colombia. When a relapse of *P. vivax* occurs more than 28 days after treatment with chloroquine and primaquine, primaquine resistance should be considered.

A newer agent, tafenoquine, can also be used for prevention of relapse in place of primaquine. However, it should only be given following chloroquine or hydroxychloroquine treatment (as opposed to other blood-stage treatments) and to those aged ≥16. Like primaquine, tafenoquine should not be given to those with G6PD deficiency or pregnant women.

Plasmodium ovale malaria

Malaria caused by *P. ovale,* found mostly in Africa, is managed in the same way as chloroquine-sensitive *P. vivax*. No drug-resistant strains of *P. ovale* have been documented.

Severe *P. falciparum* malaria

Even with appropriate treatment, the mortality rate of severe falciparum malaria ranges from 15% to 20%. Management comprises four main areas: clinical assessment, specific antimalarial treatment, adjunctive therapy, and supportive care. Severe falciparum malaria is typically defined by the presence of parasitemia of ≥5% or signs of major organ failure. Signs of major organ failure may include

impaired consciousness/coma, severe anemia, renal failure, ARDS, hypotension, DIC, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, and repeated seizures.

Patients with severe malaria require parenteral therapy with artesunate, which was Food and Drug Administration (FDA) approved for the treatment of severe malaria in the United States in 2020. Quinidine is no longer recommended or available in the United States. Intravenous artesunate is safe and effective treatment, and it is a WHO-preferred treatment for severe falciparum malaria. If artesunate is not available commercially at their hospital, clinicians should contact the CDC Malaria Hotline to obtain artesunate dispensed through the CDC within 24 hours. Artesunate regimens require the addition of a second drug, as outlined in Table 199.1. The CDC recommends bridging with oral therapy while waiting for artesunate.

Supportive care is critical for the effective management of severe malaria. Blood glucose must be monitored closely as hypoglycemia is a common complication, especially in pregnant women and children, and it can contribute to impaired consciousness and seizure activity. Fluid balance should be corrected judiciously with the aim of avoiding fluid overload that increases the risk of ARDS. Exchange transfusion has historically been used as an adjunctive treatment for severe malaria, but a 2013 CDC analysis did not show a survival benefit and it is no longer recommended. Other important supportive measures include mechanical ventilation for ARDS and hemodialysis for renal failure. Ruling out coexisting infections such as meningitis and septicemia is important, and empiric antimicrobials might be indicated.

Prevention

Malaria prevention in travelers involves both prophylaxis and protective measures against mosquito bites. The primary goal of prophylaxis is to prevent *P. falciparum* infection in nonimmune travelers because almost all fatal cases are associated with illness caused by this species. Careful review of itineraries is important when advising travelers to assess whether they will enter malaria-endemic areas and the presence of any drug resistance. Risk can vary widely within a country. For example, when travel to Thailand is limited to the malaria-free cities of Bangkok and Phuket, prophylaxis is not needed, whereas travel to many rural areas in Thailand warrants prophylaxis against multidrug-resistant *P. falciparum*. Travel timing should also be considered, as some regimens require starting 1 to 2 weeks prior to departure, and the number of tablets prescribed will be determined by the duration of travel. Other considerations include medical contraindications to specific regimens, drug–drug interactions between prophylaxis drugs and the traveler's usual medications, and client preference. Client preference is often based on side-effect profile, convenience of the regimen, and cost. A general algorithm for determining an appropriate prophylactic regimen is shown in Figure 199.2. Since malaria distribution and resistance patterns can change, clinicians are strongly advised to review current country-specific recommendations, such as those provided by the CDC (www.cdc.gov/malaria/travelers), when advising travelers.

The various malaria prophylactic agents have different schedules, though all require starting prior to arrival in the malarious area and continuation after departure for a specified period (Table 199.2). Weekly chloroquine remains an excellent option for travel to the limited endemic areas without CRPF, although atovaquone-proguanil, doxycycline, and mefloquine are also options. For most areas with CRPF, prophylaxis with atovaquone-proguanil, doxycycline, and mefloquine are recommended. An exception exists for travel to areas in Southeast Asia with multidrug-resistant strains where atovaquone-proguanil and doxycycline are the only options.

Mefloquine prophylaxis has a weekly schedule and should be started 2 weeks prior to entering malaria risk areas. It is generally well tolerated by most travelers, though it can cause sleep disturbance, dizziness, and abnormal dreams. Mefloquine has been associated with rare but severe neurologic or neuropsychiatric side effects, including permanent vestibular toxicity, seizures, psychosis, anxiety, and depression. Its use is contraindicated in travelers with a history of active or recent major psychiatric or seizure disorder, and travelers prescribed mefloquine should be informed of potential adverse effects. Because the majority of adverse reactions to mefloquine occur with the first three doses, if possible it is prudent to commence the drug 4 weeks prior to departure to ascertain drug tolerance. Atovaquone-proguanil and doxycycline have daily schedules and can be started 1 to 2 days prior to arriving to the malaria risk area. Both drugs are usually well tolerated, but doxycycline can cause photosensitivity and gastrointestinal side effects such as nausea and esophagitis. Travelers taking doxycycline should be advised to take it with food and sufficient fluids, and it should not be taken at bedtime. Mefloquine and doxycycline need to be continued for 4 weeks after departing from the malaria risk area, while atovaquone-proguanil needs only to be continued for 7 days.

Prolonged exposure to malaria in areas intensely endemic for *P. vivax* or *P. ovale* (e.g., Central America, northwest Africa, South Asia, Oceania) warrants terminal prophylaxis or presumptive antirelapse therapy with primaquine to eradicate hypnozoites. As previously noted, G6PD deficiency should be ruled out before prescribing this drug, and it is contraindicated during pregnancy. Primaquine and tafenoquine are also recommended as an alternative for primary prophylaxis for short-term travelers to areas with primarily *P. vivax* malaria.

Prophylaxis options for pregnant women are limited to mefloquine in areas with CRPF and chloroquine in areas without CRPF. Unfortunately, there are no recommended prophylactic regimens at this time for pregnant women traveling to areas with multidrug-resistant *P. falciparum* in Southeast Asia. Long-term travelers (such as missionaries or overseas workers) and immigrants visiting their countries of origin pose additional challenges. These travelers often have itineraries and accommodations that are at higher risk

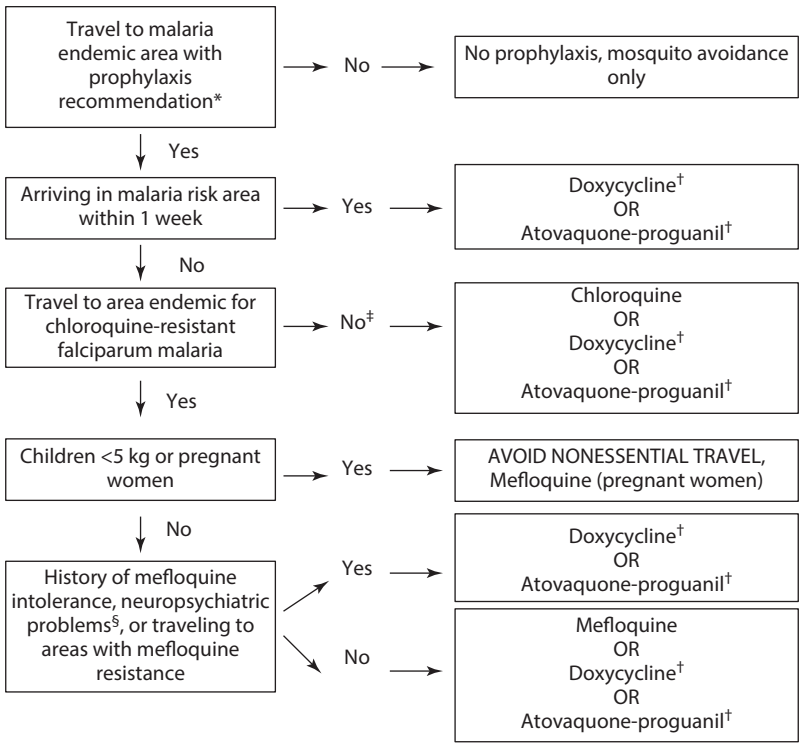

FIGURE 199.2 Algorithm for the prophylaxis of malaria. See Table 199.2 for dosages.

*Country-specific recommendations available at www.cdc.gov/malaria/travelers

† Contraindicated or not recommended in pregnancy.

‡ If traveling for short durations to an area with primary *P. vivax* malaria, primaquine primary prophylaxis is an option if glucose-6-phosphate deficiency and pregnancy are ruled out.

§ Seizures, psychosis, schizophrenia, generalized anxiety disorder, active or recent depression, other major psychiatric disorders.

for malaria than those of typical short-term travelers. Long-term travelers often adhere poorly to prophylaxis and mosquito-bite avoidance recommendations. Immigrants visiting friends and relatives in their country of origin often do not seek pre-travel advice and are often unaware that any malaria semi-immunity wanes quickly. Substandard or counterfeit drugs are also a common problem in developing countries, so travelers should be strongly cautioned against obtaining prophylaxis medications locally.

Because no prophylaxis regimen is 100% effective, all travelers to malarious regions need to be meticulous about personal protection measures. Furthermore, malarious areas are often endemic for other mosquito-transmitted infections, such as dengue fever. Insect repellents containing 30% to 50% of diethyltoluamide (DEET) are very effective. The CDC, American Academy of Pediatrics, and US Environmental Protection Agency have indicated that 30% DEET is safe for infants as young as 2 months of age. Other effective compounds used in repellents include picaridin, oil of lemon eucalyptus (OLE), PMD, and IR3535. Permethrin-impregnated protective clothing (long sleeves, pants) add further protection. Travelers should always follow product instructions carefully so these products are used safely and are reapplied at appropriate intervals. Since *Anopheles* mosquitoes typically bite between dusk and dawn, sleeping under permethrin-impregnated bed netting or in screened-in or air-conditioned rooms is important.

Because malaria prophylaxis recommendations often vary according to different authorities, travelers should be cautioned about potentially conflicting advice from fellow travelers and overseas healthcare providers. Also, travelers should be advised to seek medical attention immediately in the event of high fever during travel, as well as fevers that occur up to a year after travel. Acutely ill travelers should seek the best medical care available and follow local treatment recommendations. However, since malaria is often overdiagnosed in developing countries, travelers should be strongly cautioned against discontinuing their prophylaxis regimen if they are diagnosed with malaria.

Acknowledgments

We would like to acknowledge the contributions of Phyllis Kozarsky and Jay Keystone to prior editions of this chapter.

TABLE 199.2 **MALARIA CHEMOPROPHYLAXIS REGIMENS**

Drug	Adult dose	Pediatric dose	Adverse effects
Chloroquine phosphate	300 mg base (= 500 mg salt) PO weekly, starting 1 wk before entering malarious area and continue for 4 wk after departing risk area	5 mg base/kg (= 8.3 mg salt/kg) PO weekly, starting 1 wk before entering malarious area and continue for 4 wk after departing risk area	Bitter taste, headache, pruritus, rash, blurry vision, reversible corneal opacity, partial alopecia. Rare: retinopathy, blood dyscrasias, nail discoloration, nerve deafness, myopathy. May exacerbate psoriasis
Hydroxychloroquine	310 mg base (= 400 mg salt) PO weekly, starting 1 wk before entering malarious area and continue for 4 wk after departing risk area	5 mg base/kg (= 6.5 mg salt/kg), maximum 310 mg base, PO weekly, starting 1 wk before entering malarious area and continue for 4 wk after departing risk area	As for chloroquine
Atovaquone–proguanil	250 mg atovaquone and 100 mg proguanil (1 adult tablet) PO daily, starting 1–2 d before entering malarious area and continue for 7 d after departing risk area	Weight-based daily dose starting 1–2 d before entering malarious area and continue for 7 d after departing risk area. Pediatric tablet contains 62.5 atovaquone and 25 mg proguanil: 5–8 kg: ½ ped tab PO daily >8–10 kg: 3/4 ped tab PO daily >10–20 kg: 1 ped tab PO daily >20–30 kg: 2 ped tab PO daily >30–40 kg: 3 ped tab PO daily >40 kg: see adult dosing	Nausea, abdominal pain, headache. May transiently increase transaminases. Rare: rash. Take with food. Do not use if creatinine clearance ≤30 mL/min. Not recommended for pregnant women, breastfeeding women, or children <5 kg
Doxycycline	100 mg PO daily, starting 1–2 d before entering malarious area and continue for 4 wk after departing risk area	≥8 years old: 2.2 mg/kg PO daily (maximum dose 100 mg/d), starting 1–2 d before entering malarious area and continue for 4 wk after departing risk area	Esophageal irritation, gastrointestinal upset, photosensitivity, candida vaginitis. Stains teeth of children aged ≤8 yr and fetuses. Contraindicated in pregnancy
Mefloquine	One 228 mg base tablet (= 250 mg salt) PO weekly, starting ≥2 wk before entering malarious area and continue for 4 wk after departing risk area	Weight-based daily dose starting ≥2 wk before entering malarious area and continue for 4 wk after departing risk area: ≤9 kg: 4.6 mg base/kg (= 5 mg salt/kg) PO weekly >9–19 kg: ¼ tablet PO weekly >19–30 kg: ½ tablet PO weekly >30–45 kg: 3/4 tablet PO weekly >45 kg: 1 tablet PO weekly One tablet contains 228 mg base (= 250 mg salt)	Dizziness, nausea, diarrhea, headache, nightmares, altered dreams, insomnia, mood changes. Rare: seizure, psychosis, permanent vestibular toxicity. Do not use if history of seizures, psychosis, schizophrenia, generalized anxiety disorder, active or recent depression, other major psychiatric disorders, or cardiac conduction abnormality present
Primaquine			
Terminal prophylaxis	30 mg base (52.6 mg salt) PO daily for 14 d	0.5 mg base/kg (0.8 mg salt/kg) PO daily for 14 d	G6PD deficiency should be ruled out prior to use to prevent hemolysis.
Primary prophylaxis (for short-duration travel to areas with primarily *P. vivax*)	30 mg base daily, starting 1–2 d before entering malarious area and continue for 7 d after departing risk area	0.5 mg base/kg (0.8 mg salt/kg) PO daily, starting 1–2 d before entering malarious area and continue for 7 d after departing risk area	Contraindicated in pregnancy and breastfeeding women (unless the breastfed infant has documented normal G6PD levels). Should be taken with food to prevent gastrointestinal upset
Tafenoquine			
Primary prophylaxis (for short-duration travel to areas with primarily *P. vivax*)	200 mg PO daily × 3 days 3 days prior to travel, then weekly while there and for 1 week after leaving malarious area	Not indicated in children <16 years old	Contraindicated in pregnancy, children under 16 years old and breastfeeding women (unless the breastfed infant has documented normal G6PD levels). Should be taken with food to prevent gastrointestinal upset

Suggested reading

Baird JK. Resistance to therapies for infection by *Plasmodium vivax*. *Clin Microbiol Rev*. 2009;22:508–534.

Centers for Disease Control and Prevention. *Malaria diagnosis & treatment in the United States*. 2012. www.cdc.gov/malaria/diagnosis_treatment/index.html

Centers for Disease Control and Prevention. *Health information for international travel 2020.* Philadelphia: Oxford University Press; 2020.

Chen LE, Wilson ME, Schlagenhauf P. Prevention of malaria in long-term travelers. *JAMA*. 2006;296:2234–2244.

Hill DR, Ericsson CD, Pearson RD, et al. The practice of travel medicine: Guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43:1499–1539.

Maltha J, Gillet P, Heutmekers M, et al. Self-diagnosis of malaria by travelers and expatriates: Assessment of malaria rapid diagnostic tests available on the internet. *PLoS One*. 2013;8:e53102.

Schwartz E, Parise M, Kozarsky P, Cetron M. Delayed onset of malaria: Implications for chemoprophylaxis in travelers. *N Engl J Med*. 2003;349:1510–1516.

Steinhardt LC, Magill AJ, Arguin PM. Review: Malaria chemoprophylaxis for travelers to Latin America. *Am J Trop Med Hyg*. 2011;85:1015–1024.

Whitty CJM, Chiodini PL, Lalloo DG. Investigation and treatment of imported malaria in non-endemic countries. *BMJ*. 2013;346:f2900.

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Babesiosis

Tempe K. Chen, Choukri Ben Mamoun, and Peter J. Krause

Babesiosis is an emerging zoonotic disease caused by intraerythrocytic protozoa of the Apicomplexa phylum and transmitted by hard-bodied ticks. The first well-documented case of human *Babesia* infection was reported in 1957, in a splenectomized resident of Yugoslavia. The patient died after an acute illness marked by anemia, fever, hemoglobinuria, and renal failure. Intraerythrocytic parasites were noted in his blood and tentatively identified as *Babesia divergens*. Since then, other *Babesia* spp. have been found to cause disease in humans, including *B. microti, B. duncani*, and *B. divergens*-like parasite in North America; *B. divergens, B. microti*, and *B. venatorum* in Europe; and *B. crassa*-like agent, *B. venatorum*, *B. microti,* KO-1, and XXB/HangZhou in Asia. *B. microti* is endemic in the United States and is responsible for most babesiosis cases worldwide, while *B. crassa*-like agent and *B. venatorum* are endemic in China. All other species cause sporadic disease. Although most babesiosis cases are vector-borne, transmission through blood transfusion, organ transplantation, and transplacentally also have been reported.

Epidemiology

More than 100 species in the genus *Babesia* infect a wide variety of wild and domestic animals. Humans are an uncommon and terminal host for *Babesia* spp., which depend on other species for their development and transmission. The most common cause for human babesiosis is *B. microti,* a *Babesia* of rodents. The primary reservoir for *B. microti* in North America is the white-footed mouse (*Peromyscus leucopus*). As many as two-thirds of *P. leucopus* have been found to be parasitemic in endemic areas. *Babesia* spp. are transmitted by hard-bodied ticks. The primary vector in eastern North America is *Ixodes scapularis* (also known as *Ixodes dammini*), which is the same tick that transmits *Anaplasma phagocytophilum,* the agent of human granulocytic anaplasmosis; *Borrelia burgdorferi* and *Borrelia miyonii,* etiologic agents of Lyme disease; *Borrelia miyamotoi* that causes relapsing fever; Powassan virus that causes Powassan encephalitis; and the *Ehrlichiosis muris euclairensis* agent that causes ehrlichiosis. Simultaneous human infection with two or more of these pathogens may occur due to transmission by coinfected ticks.

Each of the three active stages in the life cycle of *I. scapularis* (larva, nymph, and adult) requires a blood meal from a vertebrate host to mature to the next stage (Figure 200.1). The *Babesia* spp. ingested by one tick stage are transmitted to the next stage. The tick transmission cycle begins in late summer when newly hatched larvae ingest the parasite during a blood meal from an infected rodent and maintain the parasite to the nymphal stage. Nymphs transmit *Babesia* spp. to rodents in late spring and summer of the following year. Larvae, nymphs, and adults can feed on humans, but the nymph is the primary vector (Figure 200.2). All active tick stages also feed on the white-tailed deer (*Odocoileus virginianus*), which is an important host for the tick but is not a reservoir for *B. microti*. An increase in the deer population over the past few decades is thought to be a major factor in the emergence of *I. scapularis* and the resulting increase in human babesiosis cases.

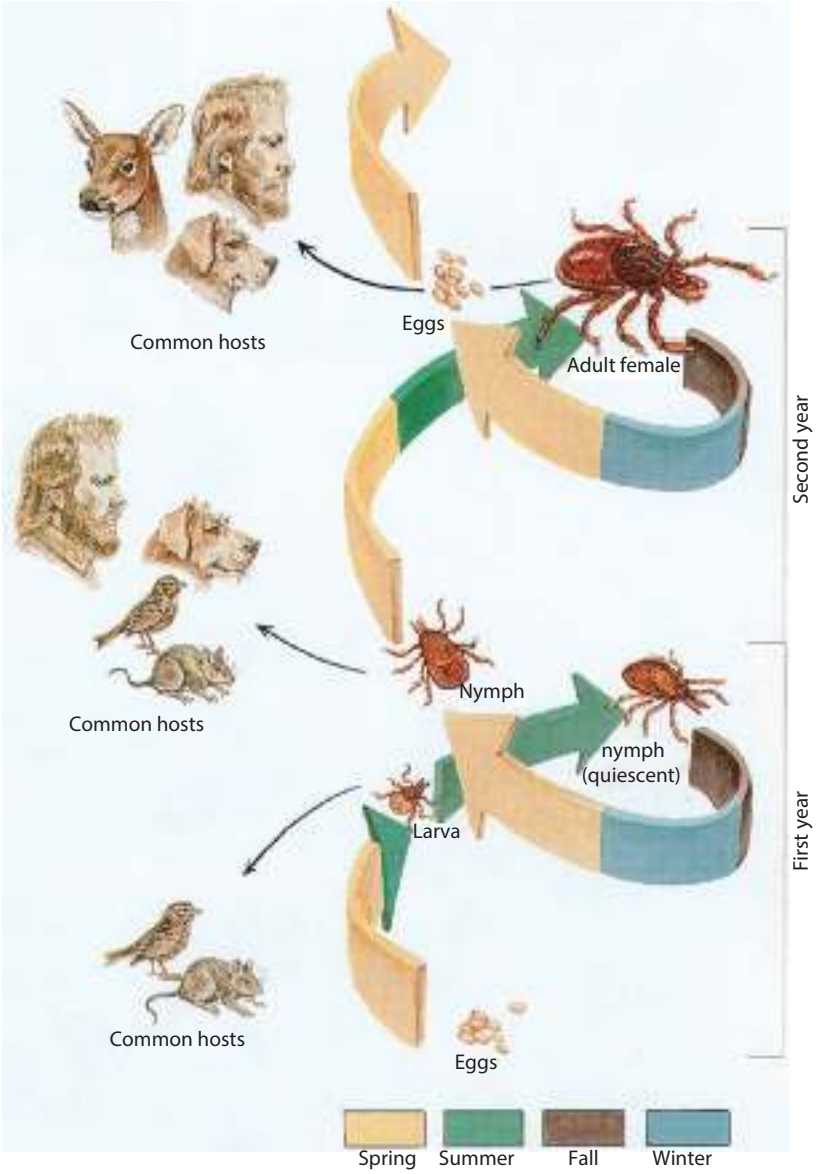

FIGURE 200.1 Life cycle of *Babesia microti*.
Reproduced with permission from DW Miller.

FIGURE 200.2 *Ixodes scapularis* (also known as *Ixodes dammini*) ticks showing larval, nymphal, and adult stages.

Beginning in the 1990s, human babesiosis has been described with increasing frequency at sites in the northeastern and north-midwestern United States. Recent studies suggest that the endemic range continues to expand. In certain sites during years of high transmission, babesiosis may constitute a significant public health burden. For example, in one study of a highly endemic area in Rhode Island, approximately 9% of the population had serological evidence of previous *B. microti* infection compared with 11% of previous Lyme disease. Most human cases of babesiosis occur in the summer and in areas where the vector tick, rodents, and deer are in close proximity to humans. Rarely, babesiosis is acquired through transfusion of blood products (including whole blood, packed red cells, cryopreserved red cells, and platelets) or organ transplantation. Transplacental/perinatal transmission of babesiosis also has been described.

Pathogenesis

Our understanding of the pathogenesis of human babesiosis is incomplete and is primarily based on animal studies. Cytoadherence of *Babesia*-infected erythrocytes to vascular epithelium may diminish access of host immune factors to *Babesia*, at least in part by preventing transit of infected erythrocytes through the spleen where they are destroyed, thus preventing *Babesia* from completing their life cycle and invading other erythrocytes. Excessive cytoadherence may lead to erythrocyte sequestration and obstruction of microvasculature with subsequent tissue anoxia, as has been demonstrated in cattle infected by *B. bovis*. Similarly, production of host proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-1 are thought to help destroy intracellular *Babesia*; however, excessive cytokine production associated with moderate to severe disease may account for the majority of clinical manifestations and complications. T cells, B cells, macrophages, neutrophils, antibody, and complement are important in clearing parasitemia but also may contribute to disease pathogenesis.

Clinical manifestations

The clinical severity of babesiosis ranges from subclinical infection to fulminating disease resulting in death. In clinically apparent cases, symptoms of babesiosis begin after an incubation period of 1 to 9 weeks from the beginning of tick feeding or 1 week to 6 months (usually 3 to 7 weeks) after transfusion. In most cases, there is a gradual onset of malaise and fatigue followed by intermittent temperatures as high as 40.9°C/105.6°F and one or more of the following symptoms: chills, sweats, headache, and myalgia. Less commonly noted are arthralgia, anorexia, nausea, vomiting, sore throat, abdominal pain, and/or weight loss, nonproductive cough, emotional lability, hyperesthesia, conjunctival injection, and photophobia. The findings on physical examination generally are minimal, often consisting only of fever. Splenomegaly, hepatomegaly, or both are noted occasionally. Slight pharyngeal erythema, jaundice, retinopathy with splinter hemorrhages, and retinal infarcts also have been reported. Rash is seldom noted, although ecchymoses and petechiae have been described in severe disease.

Symptoms usually persist for a few weeks to several months, with prolonged recovery of up to 18 months in severe cases. Parasitemia may continue even after a person feels well and may persist for >2 years without symptoms in immunocompetent patients or relapsing illness in immunocompromised patients. Although prolonged symptomatic disease or death may occur in immunocompromised hosts, complete recovery is the rule.

Patients at increased risk for more severe babesial disease include those with asplenia, malignancy, or concomitant HIV/AIDS infection; those at the extremes of age (neonates and the elderly); those with hemoglobinopathies; those with chronic heart, lung, liver, or hematologic disease; or those on immunosuppressive therapy. People infected through blood transfusion or organ donation, or who experience *B. divergens* infection also have more severe disease. Concurrent babesiosis and Lyme disease infection has been reported in 2% to 19% of patients experiencing Lyme disease and results in more severe illness than Lyme disease alone. Moderate to severe babesiosis may occur in children, but infection usually results in mild disease and is generally less debilitating than in adults. Numerous cases of neonatal babesiosis have been described, usually following transfusion with infected blood and sometimes resulting in severe illness. Symptoms and signs include lethargy, tachypnea, pallor, poor feeding, splenomegaly, hepatomegaly, jaundice, and generalized macular rash.

Complications

Severe babesiosis can occur, consisting of fulminant illness lasting about a week and ending in death or a prolonged convalescence. Although more common in immunocompromised hosts or those experiencing *B. divergens* infection, severe babesiosis can occur in otherwise healthy individuals who are infected with *B. microti*. In a retrospective study of 136 patients with *B. microti* infection from Long Island, New York, 7 patients (5%) died. The patients with fatal illness ranged in age from 60 to 82 years, and only 1 was known to be immunocompromised. Signs and symptoms in severe cases include high fever, severe hemolytic anemia, hemoglobinemia and hemoglobinuria, jaundice, ecchymoses, petechiae, congestive heart failure, pulmonary edema, renal failure, adult respiratory distress syndrome, and coma. Patients with malignancy (especially B-cell lymphoma), HIV/AIDS infection, and/or immunosuppressive therapy (especially rituximab) may experience a chronic form of babesiosis that is poorly responsive to multiple courses of standard antibabesial therapy.

Diagnosis

Babesiosis should be suspected in any patient with unexplained febrile illness who has recently lived or traveled in endemic regions during the months of May through September. There is often no recollection of a tick bite because the unengorged *I. scapularis* nymph is difficult to discern with the naked eye (~2 mm in length). Babesiosis also should be considered in any patient with unexplained febrile illness who has had a blood transfusion within the previous 6 months.

Laboratory findings reflect the invasion and subsequent lysis of erythrocytes by the parasite and the immune response to infection. They include moderate to severe hemolytic anemia, an elevated reticulocyte count, thrombocytopenia, an elevated erythrocyte sedimentation rate, elevated serum bilirubin and liver enzyme concentrations, elevated serum blood urea nitrogen and creatinine concentrations, and proteinuria. The leukocyte count is normal to decreased, with a "left shift." Atypical lymphocytes also may be noted on manual differential blood smear examination.

Specific diagnosis of babesiosis is made by microscopic demonstration of the organism using Giemsa-stained thin blood smears or amplification of *Babesia* DNA using polymerase chain reaction (PCR). Giemsa-stained *Babesia* parasites appear as round,

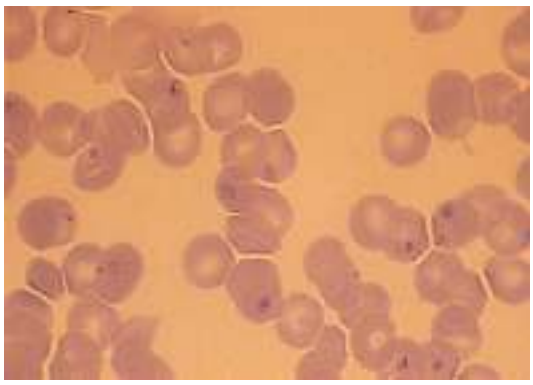

FIGURE 200.3 Ring forms of *Babesia microti* in human blood film (1,000×).

oval, or pear-shaped microorganisms with a blue cytoplasm and a red chromatin membrane (Figure 200.3). Multiple blood fields should be examined because only a few erythrocytes are infected in the early stage of the illness when most people seek medical attention. Fewer than 1% of erythrocytes may be parasitized initially and may escape detection. Parasitemia seldom exceeds 10% in normal hosts but may reach as high as 85% in people who are immunocompromised. Thick blood smears may be examined, but the organisms appear as simple chromatin dots that may be mistaken for stain precipitate or iron inclusion bodies. Accordingly, only someone with extensive experience in interpreting thick smears should perform this method. The ring form is most common and is very similar to the intraerythrocytic ring forms of *Plasmodium falciparum*. Although the presence of tetrad forms ("Maltese cross") is diagnostic, such elements are seldom encountered. Similarly, the absence of hemozoin (malarial pigment) is often considered to be generally diagnostic for the small blood stage parasites (piroplasms), but early ring stages of the plasmodia also lack pigment. Laboratory diagnosis of severe cases includes the presence of high parasitemia, erythrocytes infected by multiple parasites, and basket-shaped merozoites that are often extracellular.

Physicians also can confirm babesial infection by use of PCR, antigen capture assays, serologic testing, and small animal inoculation. The PCR assay is a sensitive and specific test for detection of babesia DNA, and real-time PCR provides an index of parasite number. Both immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies can be detected using an immunofluorescent assay (IFA) or enzyme-linked immunosorbent assay (ELISA). Antibody may be undetectable early in the course of disease, and the presence of antibody may reflect past rather than acute disease. Only a fourfold rise in antibody titer between acute and convalescent sera can confirm the diagnosis. During the acute phase of the illness, titers usually exceed 1:1024 but decline to 1:64 or less within 12 months. Thus, a *Babesia* IFA titer of ≥1:1024 usually signifies active or recent infection. A serological cutoff point of 1:64 generally is considered to be diagnostic of past or current infection. Although cross-reactions occur with different *Babesia* spp. and *Plasmodium* spp. with the IFA test, these titers are almost always low (≤1:16). The diagnosis of acute babesiosis is suspect in symptomatic patients whose serum contains antibody to *Babesia* but whose blood lacks identifiable babesial parasites on smear or babesial DNA by PCR. In sum, diagnosis is made by a combination of epidemiologic, clinical, and laboratory criteria.

For *B. divergens* babesiosis, specific antibodies do not become detectable until at least 1 week after onset of illness. Because this infection is rapidly fulminating, serological diagnosis is not practical in the diagnosis of acute infection, but serological conversion serves as an aid in retrospective diagnosis during convalescence. The high parasitemias that are present are easily detected by blood smear in the acute phase of infection. Infection by *B. duncani* may readily be detected by blood smear or PCR. This species may be cultivated in vitro. Unlike the IFA for *B. microti,* a higher cutoff value (>1:160) is required to impart specificity, for unknown reasons. In humans and in rodent models, tetrad forms are frequently seen in blood smears, but otherwise this agent is difficult to distinguish from *B. microti*.

Coinfection with the agents of Lyme disease (*B. burgdorferi*), human granulocytic anaplasmosis (*A. phagocytophilum*), or both may occur in patients experiencing babesiosis in areas where these pathogens are endemic. Babesiosis coinfection should be considered in Lyme disease patients who present with more severe initial symptoms than are commonly observed with Lyme disease alone or who do not respond to standard therapy.

Treatment

Early efforts to treat patients with babesiosis were unsuccessful, including use of the antimalarial drug chloroquine. The combination of clindamycin and quinine was the first effective antimicrobial therapy but is now an alternative to the treatment of choice, atovaquone and azithromycin. In the only prospective, randomized trial of antibabesial therapy in humans, the combination of atovaquone and azithromycin was compared with clindamycin and quinine for treatment of adults with non–life-threatening *B. microti* infection. The atovaquone and azithromycin combination was found to be as effective in clearing parasitemia and resolving symptoms as the clindamycin and quinine combination. Both drug combinations were given by mouth for 7 days. After 3 months, there was no microscopic evidence of *Babesia* or amplifiable *B. microti* DNA in either group. Significantly fewer adverse effects were associated with the atovaquone and azithromycin combination. Three-fourths of patients receiving clindamycin and quinine experienced adverse drug reactions, and one-third were forced to decrease the dose or discontinue the medication. Adverse effects of therapy included hearing loss, tinnitus, syncope, hypotension, and gastrointestinal symptoms (anorexia, vomiting, and diarrhea). In contrast, only 18% of subjects in the azithromycin and atovaquone group experienced symptoms consistent with adverse drug reaction, and only 1 (2%) subject required a decrease in dosage or discontinuation of medication. The primary conclusion of this study was that antibabesial therapy based on the atovaquone and azithromycin drug combination generally is superior to that based on clindamycin and quinine because efficacy is similar for the two antimicrobial combinations but the atovaquone and azithromycin regimen is much better tolerated than the clindamycin and quinine regimen. Physicians were encouraged to consider the use of atovaquone and

TABLE 200.1 **TREATMENT REGIMENS FOR BABESIOSIS PATIENTS**

Patient Category	Treatment Regimen	
	Adult doses	**Pediatric doses**
Ambulatory patients: mild to moderate disease [a]	**Preferred** Atovaquone 750 mg (with a fatty meal) orally Q12h plus azithromycin 500 mg orally on day 1, then 250 mg Q24h for 7 to 10 days. **Alternative** [c] Clindamycin 600 mg orally Q8h plus quinine sulfate 650 mg orally Q8h for 7 to 10 days.	**Preferred** [b] Atovaquone 20 mg/kg (up to 750 mg/dose) orally Q12h plus azithromycin 10 mg/kg (up to 500 mg/dose) orally on day 1, then 5 mg/kg (up to 250 mg/dose) Q24h for 7 to 10 days. **Alternative** [c] Clindamycin 7-10 mg/kg (up to 600 mg/dose) orally Q6h-8h plus quinine sulfate 8 mg/kg (up to 650 mg/dose) orally Q8h for 7 to 10 days.
Hospitalized patients: acute severe disease [d]	**Preferred** [c] Atovaquone 750 mg orally Q12h plus azithromycin 500 mg IV Q24h until symptoms abate, then convert to all oral therapy (see step-down therapy). **Alternative** [c] Clindamycin 600 mg IV Q6h plus quinine sulfate 650 mg orally Q8h until symptoms abate, then convert to all oral therapy (see step-down therapy). If infection relapses, consider one of the regimens listed in Table 3.	**Preferred** [f] Atovaquone 20 mg/kg (up to 750 mg/dose) orally Q12h plus azithromycin 10 mg/kg (up to 500 mg/dose) IV Q24h until symptoms abate, then convert to all oral therapy (see step-down therapy). **Alternative** [c] Clindamycin 7-10 mg/kg (up to 600 mg/dose) IV Q6h-8h plus quinine sulfate 8 mg/kg (up to 650 mg/dose) orally Q8h until symptoms abate, then convert to all oral therapy (see step-down therapy). If infection relapses, consider one of the regimens listed in Table 3.
Hospitalized patients: step-down therapy (transition to oral therapy)	**Preferred** Atovaquone 750 mg (with a fatty meal) orally Q12h plus azithromycin 250-500 mg orally Q24h. Treatment of acute disease plus step-down therapy typically lasts 7-10 days in total. A high dose of azithromycin (500-1000 mg) orally should be considered for immunocompromised patients. **Alternative** [c] Clindamycin 600 mg orally Q8h plus quinine sulfate 650 mg orally Q8h. Treatment of acute disease plus step-down therapy typically lasts 7-10 days in total.	**Preferred** Atovaquone 20 mg/kg (up to 750 mg/dose) orally Q12h plus azithromycin 5-10 mg/kg (up to 500 mg/dose) orally Q24h. Treatment of acute disease and step-down therapy typically last 7-10 days in total. **Alternative** [c] Clindamycin 7-10 mg/kg (up to 600 mg/dose) orally Q6h-8h plus quinine sulfate 8 mg/kg (up to 650 mg/dose) orally Q8h. Treatment of acute disease plus step-down therapy typically lasts 7-10 days in total.
Highly immunocompromised patients	Start with one of the regimens recommended for hospitalized patients: acute severe disease and follow with one of the step-down therapies but treat for at least 6 consecutive weeks, including 2 final weeks during which parasites are no longer detected on peripheral blood smear [3]. When oral azithromycin is used, a 500-1000 mg daily dose should be considered. If infection relapses, consider one of the regimens listed in Table 3.	

[a] These patients usually are immunocompetent, experience mild to moderate symptoms, have a parasitemia <4%, and do not require hospital admission.
[b] Azithromycin modestly increases the risk of pyloric stenosis for infants less than 6 weeks old [4].
[c] Clindamycin plus quinine is preferred when parasitemia and symptoms have failed to abate following initiation of atovaquone plus azithromycin. Some physicians have used parenteral quinidine instead of oral quinine; however, quinidine is no longer available in the United States. All quinine doses listed are for the sulfate salt, which is the only quinine salt available in the United States; 650 mg quinine sulfate is equivalent to 542 mg quinine base.
[d] Exchange transfusion should be considered for patients with high-grade parasitemia (>10%) or moderate to high-grade parasitemia and any one or more of the following: severe hemolytic anemia and/or severe pulmonary, renal, or hepatic compromise. Expert consultation with a transfusion services physician or hematologist in conjunction with an infectious diseases specialist is strongly advised.
[e] Azithromycin 1,000 mg given *orally*, in combination with other antibiotics, has been used successfully to clear *Babesia microti* infection in immunocompromised patients. Some physicians have used a one-time dose of azithromycin 1,000 mg *intravenously* for severe babesiosis. While this dose has been shown to be safe, there are no published reports of the use this 1000 mg dose for severe babesiosis [5]. If intravenous azithromycin 1,000 mg is given to an immunocompromised patient, subsequent doses should be reduced to 500 mg daily.
[f] This regimen has not yet been reported for the treatment of children with severe babesiosis.

azithromycin in adult patients experiencing non–life-threatening babesiosis and in others who could not tolerate clindamycin and quinine. Subsequent studies have shown that the atovaquone and azithromycin combination also is effective for patients experiencing life-threatening babesiosis. This combination is now recommended as first-line therapy for all babesiosis patients. The currently recommended dosing for atovaquone and azithromycin is shown in Table 200.1. Treatment usually is given for 7 to 10 days but may need to be extended for immunocompromised individuals. Higher doses and intravenous administration of azithromycin are also indicated for severe disease in these patients. Clindamycin and quinine is given to patients who do not respond to atovaquone and azithromycin because of the development of drug resistance or who experience untoward reaction to the drug combination. Dosing is listed in Table 200.1. This combination frequently produces untoward reactions, such as tinnitus, QT prolongation, allergic reaction, vertigo, and gastrointestinal upset. Treatment failures have been reported in patients with splenectomy, HIV-infected patients, and in those receiving concurrent corticosteroid therapy.

The combination of pentamidine (240 mg IV/d) and trimethoprim-sulfamethoxazole (3 g/d) was found to be moderately effective in clearing parasitemia and symptoms due to *B. divergens*. Potential adverse reactions to pentamidine that include pain at the site of injection, formation of sterile abscess, hyperglycemia or hypoglycemia, and nephrotoxicity limit the use of this combination.

Red blood cell exchange transfusion should be considered for babesiosis patients with high parasitemia (>10%), significant hemolysis, or renal or pulmonary compromise. Partial or complete exchange transfusion has been shown to rapidly decrease parasitemia by removing parasite-infected red blood cells from the circulation and correcting anemia. It also helps remove vasoactive elements such as pro-inflammatory cytokines and thromboplastic substances that may contribute to renal failure, disseminated intravascular coagulation, and other complications. Nonetheless, no prospective controlled trials have been carried out to confirm the efficacy of exchange transfusion in decreasing disease complications and death. Due to the risks associated with multiple blood exposures, these techniques should not be considered as routine therapy but only used for those severely ill with babesiosis.

Babesiosis patients should be monitored closely during therapy. In most cases, improvement will occur within 1 or 2 days after antiprotozoal therapy is begun. Symptoms generally resolve within 1 or 2 months after atovaquone and azithromycin or clindamycin and quinine therapy is completed. In severely ill patients, the hematocrit and percentage of erythrocytes parasitized should be monitored daily or every other day until the patient has improved and the parasitemia has decreased to less than 4%. Some patients may have persistence of low-grade parasitemia for months following antibiotic therapy.

Physicians should consider retreatment of patients with antibabesial therapy if patients show evidence of parasitemia in their blood for >3 months after initial therapy, especially if parasitemia is increasing. Physicians also should consider the possibility of coinfection with Lyme disease, human granulocytic anaplasmosis, or both in babesiosis patients who have a rash or experience persistent symptoms despite appropriate antibabesial therapy. Such patients may benefit from the addition of doxycycline therapy as neither clindamycin and quinine nor atovaquone and azithromycin has been shown to be effective for the treatment of Lyme disease or human granulocytic anaplasmosis.

Prevention

Prevention of babesiosis can be accomplished by avoiding *Babesia* endemic areas from May through September where ticks, deer, and mice are known to thrive. It is especially important for those at increased risk in endemic areas, such as asplenic individuals, to avoid tall grass and brush where ticks may abound. Use of clothing that covers the lower part of the body and that is sprayed or impregnated with diethyltoluamide (DEET), dimethyl phthalate, or permethrin (Permanone) is recommended for those who travel in the foliage of endemic areas. DEET has been shown to be more effective than other repellents against ticks, but the risk of adverse effects is greater. Thus, although DEET can help to prevent tick bites and is generally well tolerated when applied to the skin properly, care must be taken with repeated use of high-concentration products.

A search for ticks on people and pets should be carried out and the ticks removed using tweezers to grasp the mouthparts while carefully removing the tick. Prophylactic antibiotics after a tick bite to prevent babesiosis are not indicated. The effects of reduction of the tick, mouse, or deer populations in endemic areas on the incidence of human babesiosis have not been evaluated. Blood donors with a history of babesiosis or who test positive on blood donor screening for *Babesia* infection are excluded from donating blood to prevent transfusion-related cases. Effective vaccines have been developed to prevent *B. divergens* and *B. bovis* infections in cattle, but no vaccines are currently available for the prevention of human babesiosis.

Suggested reading

Abraham A, Brasov I, Thekkiniath J, et al. Establishment of a continuous in vitro culture of Babesia duncani in human erythrocytes reveals unusually high tolerance to recommended therapies. *Biol Chem*. 2018;293:19974–19981.

Fox LM, Wingerter S, Ahmed A, et al. Neonatal babesiosis. Case report and review of the literature. *Pediatr Infect Dis J.* 2006; 25:169–173.

Hatcher JC, Greenberg PD, Antique J, et al. Severe babesiosis in Long Island: Review of 34 cases and their complications. *Clin Infect Dis*. 2001:32:1117–1125.

Herwaldt BL, Linden JV, Bosserman E, et al. Transfusion-associated babesiosis in the United States: A description of cases. *Ann Intern Med*. 2011;155:509–519.

Krause PJ, Auwaerter PG, Bannuru RR, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA): 2020 Guideline on Diagnosis and Management of Babesiosis. *Clin Infect Dis*. 2021;72:185–189.

Krause PJ, Gewurz BE, Hill D, et al. Persistent and relapsing babesiosis in immunocompromised patients. *Clin Infect Dis.* 2008;46:370–376.

Krause PJ, Lepore T, Sikand VJ, et al. Atovaquone and azithromycin for the treatment of human babesiosis. *N Engl J Med*. 2000;343:1454–1458.

Krause PJ, Spielman A, Telford S, et al. Persistent parasitemia after acute babesiosis. *N Engl J Med*. 1998;339:160–165.

Krause PJ, Telford SR, Spielman A, et al. Concurrent Lyme disease and babesiosis: Evidence for increased severity and duration of illness. *JAMA*. 1996;275:1657–1660.

Meldrum SC, Birkhead GS, White DJ, et al. Human babesiosis in New York state: An epidemiological description of 136 cases. *Clin Infect Dis*. 1992;15:1019–1023.

Persing DH, Herwaldt BL, Glaser C, et al. Infection with a Babesia-like organism in northern California. *N Engl J Med*. 1995;332:298–303.

Simon MS, Westblade LF, Dziedziech A, et al. Clinical and molecular evidence of atovaquone and azithromycin resistance in relapsed *Babesia microti* infection associated with rituximab and chronic lymphocytic leukemia. *Clin Infect Dis*. 2017;65:1222–1225.

Smith R, Hunfeld KP, Krause PJ. Management strategies for human babesiosis. *Expert Rev Anti Infect Ther.* 2020 May;4:1–12.

Spielman A, Clifford CM, Piesman J, et al. Human babesiosis on Nantucket Island, U.S.A.: Description of the vector, *Ixodes* (Ixodes) *dammini*, n. *sp. (Acarina: Ixodidae). J Med Entomol*. 1979;15:218–234.

Thekkiniath J, Mootien S, Lawres L. BmGPAC, an antigen capture assay for detection of active *Babesia microti* infection. *J Clin Microbiol*. 2018;25;56(10):e00067–18.

Vannier E, Krause PJ. Human babesiosis. *New Engl J Med*. 2012;366:2397–2407.

Wittner M, Rowin KS, Tanowitz HB, et al. Successful chemotherapy of transfusion babesiosis. *Ann Intern Med*. 1982:96:601–604.

Wormser GP, Prasad A, Neuhaus E, et al. Emergence of resistance to azithromycin-atovaquone in immunocompromised patients with *Babesia microti* infection. *Clin Infect Dis.* 2010;50:381–386.

201

Trypanosomes and leishmania

Anastacio de Sousa, Selma M. B. Jeronimo, and Richard Pearson

American trypanosomiasis (Chagas disease), human African trypanosomiasis (HAT, sleeping sickness), and leishmaniasis are caused by related protozoa of the family *Trypanosomatidae*, order Kinetoplastida (see Table 201.1). They have a unique mitochondrial structure, the kinetoplast; are transmitted in nature by insect vectors; and exist in multiple morphologic forms in their human hosts and insect vectors. They are important causes of morbidity and mortality in endemic areas of the world: Chagas disease in South and Central America, sleeping sickness in sub-Saharan Africa, and leishmaniasis in scattered areas on every continent except Antarctica. Although uncommon in industrial countries in North America and Europe, these diseases have been the source of increased attention in recent years. Infection with *Trypanosoma cruzi*, the cause of Chagas disease, is well-documented among Latin American immigrants to North America and Europe and poses a risk to them, children of infected mothers, and to recipients of donated blood or transplanted organs. Cases of African sleeping sickness have fallen to historic lows over the past two decades as a consequence of sustained control efforts, and the disease has been targeted for eradication by the World Health Organization (WHO). Cutaneous leishmaniasis is seen among tourists returning from endemic areas in Latin America and the Middle East as well as in military personnel who have served in Iraq, Afghanistan, and other endemic areas. Imported cases of visceral leishmaniasis to the United States in travelers or immigrants from the Indian subcontinent, East Africa, South America or southern Europe, some in association with HIV/AIDS, occur, but are rare. While canine visceral leishmaniasis has been reported in the United States among foxhounds and other dogs, linked to vertical transmission in female dogs that were infected in Europe, there have been no reports of leishmanial infection in persons exposed to them.

Despite several important recent advances, the treatment of Chagas disease, African trypanosomiasis, and leishmaniasis leaves much to be desired. Many of the drugs (Table 201.2) used for them are associated with frequent and potentially severe untoward effects, some require parenteral administration, and many must be administered over prolonged periods of time. Some of the drugs have been approved by the US Food and Drug Administration (FDA) for these diseases while others listed in Table 201.2 are investigational or used off-label. Several investigational drugs can be obtained from the US Centers for Disease Control and Prevention (CDC) Drug Service along with detailed information about administration and side effects; they are administered under Investigational New Drug (IND) protocols. The high cost of some of those medications and the lack of availability of others are important determinants in therapeutic decisions in impoverished endemic areas. Hopefully, more effective, less toxic approaches to chemotherapy and/or protective vaccines will become available in the future.

American trypanosomiasis (Chagas disease)

Chagas disease, caused by *T. cruzi*, is transmitted by triatomine (reduviid or kissing) bugs that reside in buildings in rural areas of Latin America and occasionally in contaminated juices or foods. *T. cruzi* infects a large number of animal species as well as humans. There are an estimated 6 to 7 million persons infected in the world. The parasite develops in the intestine of the triatomine bug and is passed in feces when it takes a

TABLE 201.1 **DISEASES CAUSED BY PROTOZOA OF THE FAMILY *TRYPANOSOMATIDAE***

Disease	Causative agent	Transmission	Vector	Reservoir
American trypanosomiasis (Chagas disease)	*Trypanosoma cruzi*	Americas	Triatomine (Reduviid) bugs; occasionally infected juices or foods	Multiple species of animals
African trypanosomiasis (sleeping sickness)	*Trypanosoma brucei gambiense*	West and Central Africa	Tsetse flies (*Glossina* species)	Humans, domestic animals (minor role)
	Trypanosoma brucei rhodesiense	East Africa		Large game animals
Leishmaniasis (visceral, cutaneous, disseminated, mucosal)	*Leishmania* species	Worldwide	Sand flies (*Phlebotomus* species in the America and *Lutzomyia* species elsewhere)	Rodents, canines (dogs, foxes), or humans depending on the *Leishmania* species

blood meal. The bite causes itching, and parasites may enter the skin through the imperceptible bite site when the person scratches. They may also be transferred to the conjunctiva, where they can enter in the absence of a lesion.

The invasion that follows can elicit a local inflammatory nodule or chagoma. When parasites invade through the conjunctiva, unilateral, painless, periorbital edema (Romaña's sign) may develop. After a period of local multiplication, trypomastigotes disseminate through the bloodstream, causing acute Chagas disease with fever, other constitutional symptoms, carditis, and, rarely, meningoencephalitis. Death can result, but the acute phase is often mild or asymptomatic. Symptoms usually resolve over 4 to 8 weeks as host immune responses develop. The indeterminate phase of infection follows in which persons are entirely asymptomatic but continue to harbor the parasite. Eventually, 20% to 30% of infected individuals progress to chronic Chagas disease with cardiac, esophageal, or large intestinal involvement. Progressive, disseminated Chagas disease with carditis and/or brain abscesses has been reported in a limited number of persons with AIDS, following transplants. or associated with other immunocompromising conditions. *T, cruzi* is present in the bloodstream and organs of persons throughout the period of infection. Transmission can occur through transfusion of contaminated blood or transplantation of contaminated organs. This has posed ongoing problems in endemic areas in Latin America and is of concern in North America and Europe related to immigration. Chagas disease can also be acquired through the gastrointestinal tract following ingestion of food or juices contaminated with *T, cruzi* released from the insect vector. Outbreaks have been reported in Brazil. Congenital transmission and accidental laboratory infections are well-documented.

The diagnosis of acute Chagas disease is frequently made by identifying the parasite microscopically in blood or body tissues (Figure 201.1) or by molecular probes for parasite DNA. Several serologic assays have been developed to detect antitrypanosomal antibodies in persons with indeterminate phase or chronic Chagas disease. The tests tend to be sensitive, but not always specific. They are routinely used in blood banks in endemic areas of Latin America. A screening test for anti-*T. cruzi* immunoglobulin G antibodies approved by the FDA is used to detect infected blood and organ donors in the United States. However, screening assays for anti-*T. cruzi* antibodies can cross-react with leishmanial and other antigens, and a second antibody test is done to confirm the diagnosis. Screening of potential blood and organ donors has brought to medical attention a number of infected immigrants now living in the United States, Canada and Europe.

The drugs of choice for the treatment of Chagas disease are benznidazole or nifurtimox. Both are now FDA approved. Benznidazole has been the mainstay of therapy in Latin American countries. Nifurtimox has been used in the United States. Untoward effects are common with both drugs and may necessitate premature discontinuation of therapy.

Nifurtimox (Bayer 2502, Lampit; Bayer) is typically given for 60 days (see Table 201.2 for dosage). The drug is better tolerated in children and adolescents than in adults; higher doses per kilogram of body weight are used in younger patients. Neurologic and gastrointestinal side effects are common. They include sleep disturbances, restlessness, tremor, memory loss, paresthesias, weakness, polyneuritis, and, rarely, seizures, as well as anorexia, nausea, vomiting, abdominal pain, and weight loss. Other, rare side effects include fever, pulmonary infiltrates, and effusions.

Benznidazole (Rochagan, Roche) is administered for a period of 60 days. Higher doses are used in children. Side effects are frequent and include gastrointestinal disturbances, psychiatric manifestations, dose-dependent neuropathy, and cutaneous hypersensitivity reactions. On rare occasions hepatitis or neutropenia develops.

Treatment is indicated for all cases of acute or reactivated Chagas disease and for indeterminate or congenital infection up to age 18 years. Treatment is also recommended for adults up to 50 years old with chronic infection who do not already have advanced cardiomyopathy. For those >50 years with chronic *T. cruzi* infection, the decision to treat is individualized, weighing the potential benefits and risks, based on the patient's age, clinical status, and preference.

Once the cardiac, esophageal, or large intestinal manifestations of advanced Chagas disease develop, neither drug appears to alter the outcome. Supportive therapy includes cardiotropic drugs for congestive heart failure and arrhythmias, pacemaker placement for heart block, and palliative endoscopic botulinum toxin injections or surgical procedures for esophageal disease or surgery for intestinal megadisease. Nifurtimox has been used to treat disseminated

TABLE 201.2 **TREATMENT OF TRYPANOSOMIASIS AND LEISHMANIASIS**

Drug of choice	Adult dosage	Pediatric dosage
American trypanosomiasis/Chagas disease (*Trypanosoma cruzi)*		
Benznidazole[a]	5–7 mg/kg/d in 2 divided doses × 60 d	2-12 yr: 5–8 mg/kg/d in 2 doses × 60 d ≥12 yr: same as adult x 60 d
Or Nifurtimox[a]	8–10 mg/kg/d in 3 doses × 60 d	Body Weight 2.5 kg to <40 kg: 10-20 mg/kg/d in 3 doses × 60 d Body Weight ≥ 40 kg 8-10 mg/kg/d in 3 doses for 60 d
East African sleeping sickness (*Trypanosoma brucei rhodesiense*)		
First (hemolymphatic) stage		
Suramin[a,b]	4-5 mg/kg (test dose) slowly IV, then 20 mg/kg IV (max 1 g) on days 1, 3, 7, 14, and 21	2 mg/kg (max 100 mg; test dose) slowly IV, then 10-15 mg/kg (max 1 g) IV on days 1,3,7,14, and 21
Second (central nervous system involvement) stage		
Melarsoprol[a,b,c]	2.2 mg/kg/d (max 180–200 mg/d) IV × 10 d	2.2 mg/kg/d (max 180–200 mg/d) IV× 10 d
West African sleeping sickness (*Trypanosoma brucei gambiense*)		
First (hemolymphatic) stage		
Pentamidine[d,e]	4 mg/kg/d IM or IV (over 2 hr) × 7 d	4 mg/kg/d IM or IV (over 2 hr) × 7d
Second (central nervous system involvement) stage Nifurtimox-eflornithine combination therapy (WHO) Nifurtimox[a,b,c] 15 mg/kg per day in 3 doses × 10 d *Plus* Eflornithine[a,f] 400 mg/kg/d IV in 2 doses × 7d Alternative Melarsoprol, dosed as per *T. brucei rhodesiense*		
Eflornithine[a,f]	400 mg/kg/d IV in 4 doses × 14 d	400 mg/kg/d IV in 4 doses × 14 d
Leishmaniasis (*Leishmania species*)		
Visceral[g]		
Liposomal amphotericin B[h,i]	3 mg/kg IV (d 1–5, 14, and 21)	3 mg/kg IV (d 1–5, 14, and 21)
Or Miltefosine[k]	50 mg PO TID × 28 d	≥12 yr and 30–44 kg: 50 mg PO BID × 28 d or ≥45 kg adult dose for 28 days
Alternatives: Sodium stibogluconate[a,b]	20 mg sb/kg/d IV or IM × 28 d[j]	20 mg sb/kg/d IV or IM × 28 d[j]
Or		
Meglumine antimoniate[a]	20 mg sb/kg/d IV or IM × 28 d[j]	20 mg sb/kg/d IV or IM × 28 d[j]
Or		
Amphotericin B deoxycholate[d]	0.5–1 mg/kg IV daily or every second day for total dose of 15–20 mg/kg	1 mg/kg IV daily or every second day for a total dose of 15–20 mg/kg
Cutaneous[l]		
Local therapy:	Cryotherapy (with liquid nitrogen) Thermotherapy (use of localized current field radiofrequency heat) Intralesional administration of Sb^V (not covered by CDC's protocol for Pentostam) Application of paromomycin (as an ointment containing 15% paromomycin; not commercially available in the United States)[m]	

(*continued*)

TABLE 201.2 **CONTINUED**

Drug of choice	Adult dosage	Pediatric dosage
Systemic therapy: Liposomal amphotericin B	3 mg/kg/d IV for 6–10 doses	3 mg/kg/d IV for 6–10 doses
Or Miltefosine,[n] dosed as for visceral leishmaniasis	20 mg sb/kg/d IV or IM × 20 d[h]	20 mg sb/kg/d IV or IM × 20 d[j]
Or Sodium stibogluconate [a,b]		
Or		
Meglumine antimoniate[a]	20 mg sb/kg/d IV or IM × 20 d[j]	20 mg sb/kg/d IV or IM × 20 d[j]
Or		
Amphotericin B deoxycholate [d]	0.5–1.0 mg/kg daily or every other day for a total dose of approx. 20 mg/kg	0.5–1.0 mg/kg daily; or every other day for a total dose of approx. 20 mg/kg
Or		
See text for fluconazole, pentamidine and fluconazole		
Mucosal[p]		
Liposomal amphotericin[d]	3 mg/kg/d for a total dose of 20-60 mg/kg	3 mg/k/d for a total dose of 20-60 mg/kg
Or Miltefosine[q]	50 mg PO TID × 28 d	≥12 yr and 30–44 kg: 50 mg PO BID × 28 d ≥45 kg: 50 mg PO TID × 28 d
Or Alternative Sodium stibogluconate[a,b]	20 mg sb/kg/d IV or IM × 28 d[j]	20 mg sb/kg/d IV or IM × 28 d[j]
Or		
Meglumine antimoniate[a]	20 mg sb/kg/d IV or IM × 28 d[j]	20 mg sb/kg/d IV or IM × 28 d[j]
Or		
Amphotericin B deoxycholate[d]	0.5–1 mg/kg IV daily or every second day for a total dose of 20-45 mg/kg	0.5–1 mg/kg IV daily or every second day for a total dose of 20-45 mg/kg

[a] Based on the recommendations of the Centers for Disease Control and Prevention, last reviewed April 8, 2021
[b] Available under an Investigational New Drug (IND) protocol from the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta, GA Questions regarding treatment should be directed to Parasitic Diseases Inquiries (404-718-4745; e-mail chagas@cdc.gov).
[c] In frail patients, begin with as little as 18 mg and increase the dose progressively. Pretreatment with suramin has been advocated by some for debilitated patients. Corticosteroids have been used to prevent arsenical encephalopathy. Up to 20% of patients with *T. b. gambiense* fail to respond to melarsoprol.
[d] An approved drug, but considered investigational for this condition by the FDA.
[e] For treatment of *T. b. gambiense*, pentamidine and suramin have equal efficacy, but pentamidine is better tolerated.
[f] Eflornithine is effective for the treatment of *T. b. gambiense*, particularly in combination with nifurtimox, but not *T. b. rhodesiense*. See https://www.cdc.gov/parasites/sleepingsickness/health_professionals/index.html (last viewed April 13, 2021). Eflornithine is available in limited supply only from the World Health Organization (WHO) and the CDC. Flexinidazole is recommended by the WHO for treatment of first- and second-stage *T. b. gambiense* disease in endemic areas (WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. August 2019), but it is not available or recommended for use in the US.
[g] Visceral infection is most commonly caused by *Leishmania donovani* and *L. infantum* (previously known as *L. chagasi* in Latin America). Treatment may vary based on symptoms, host immune status, species, and resistance pattern in the area where infection was acquired.
[h] Several lipid formulations of amphotericin B have been used for treatment of visceral leishmaniasis. Largely based on clinical trials in patients infected with *L. infantum*, the FDA approved liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis. Amphotericin B lipid complex (Abelcet) and amphotericin B cholesteryl sulfate (Amphotec) are considered investigational.
[i] The FDA-approved dosage regimen for immunocompromised patients (e.g., HIV infected) is 4 mg/kg/d (d 1–5) and 4 mg/kg/d on d 10, 17, 24, 31, and 38. The relapse rate is high; maintenance therapy may be indicated, but there is no consensus as to dosage or duration.
[j] May be repeated or continued; a longer duration or higher dose may be needed for some patients treated with liposomal amphotericin.
[k] Gastrointestinal adverse effects are common, and the drug is contraindicated in pregnancy and breastfeeding. Resistance has been reported. Miltefosine is approved for *L. donovani* infection acquired in the Indian subcontinent.
[l] Cutaneous infection is most commonly due to the Old World species *L. major*, *L. tropica,* and *L. aethiopica* and New World species *L. mexicana*, *L. amazonensis, L. (Viannia) braziliensis, L. (Viannia) panamensis*, and others. The choice of treatment varies based on the location and characteristics of the lesion(s), host immune status, infecting *Leishmania* spp., and area of the world where infection was acquired. If lesions are small, few in number, cosmetically inconsequential, and not caused by *Leishmania* spp. associated with mucosal disease, they can be followed expectantly, particularly if there is evidence of self-healing, or the lesions may be treated locally. An oral or parenteral systemic option is used for the rest. The final choice depends on the infecting species or geographic location of acquisition and the relative toxicity of the treatment modality.
[m] Topical paromomycin should be used only in geographic regions where cutaneous leishmaniasis species have low potential for mucosal spread.
[n] Oral miltefosine is approved for the treatment of cutaneous and mucosal leishmaniasis due to *L. (V.) panamensis*, *L. (V.) braziliensis*, and *L. (V.) guyanensis*. See note k for adverse effects.
[o] Several azoles have been used with variable effects. Early reports suggested that fluconazole 200 mg/d for 6 weeks was effective in American military personnel with *L. major*, but failures have been reported with that dose when lesions are caused by other *Leishmania* spp. Fluconazole at higher doses, 8 mg/kg for 4–6 weeks, has been reported to be effective in the treatment of *L. (V.) braziliensis* in an observational study in Brazil.
[p] American mucosal leishmaniasis is most often due to *L. (V.) braziliensis*, but may be seen in persons infected with *L. (V.) panamensis, L. (V.) guyanensis,* and other species. The selection among treatment options is based on symptoms, host immune status, infecting *Leishmania* spp., and site where the infection was acquired.
Abbreviations: CDC = Centers for Disease Control and Prevention; FDA = Food and Drug Administration; IV = intravenously; IM = intramuscularly; sb = pentavalent antimony.

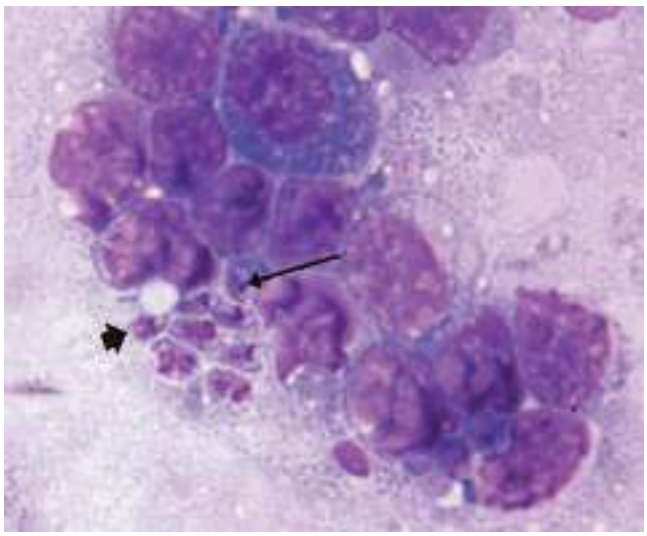

FIGURE 201.1 An imprint from a lymph node biopsy of a child with acute Chagas disease showing amastigotes (*arrowhead*), with large kinetoplast (*arrow*). Culture in LIT from the node and from whole blood grew *Trypanosoma cruzi*.

infection in persons who have undergone cardiac transplantation for chagasic cardiomyopathy in the United States.

Human African trypanosomiasis

HAT (sleeping sickness) is caused by *Trypanosoma brucei gambiense*, which is endemic in West and Central Africa, and *T. brucei rhodesiense* in East Africa. Uganda is the only country where both exist. The African trypanosomes are transmitted by tsetse flies, which are found only in rural areas of sub-Saharan Africa. Humans are the primary reservoir of *T. b. gambiense*, whereas *T. b. rhodesiense* is found in large game animals and sometimes domestic cattle. There has been a dramatic (≥95%) decrease in reported cases of African trypanosomiasis since 1999. There were only 977 reported cases in 2018, although the actual number was likely higher due to underreporting. Transplacental transmission and transmission through contaminated blood or transplanted organs can occur, but are uncommon. *T. b. gambiense* (West African trypanosomiasis) accounts for approximately 98% of cases of HAT worldwide, but it is rarely encountered in industrialized countries. In the United States, there is on average one case of HAT per year; most cases are due to American tourists returning with *T. b. rhodesiense* (East African trypanosomiasis). An indurated chancre may develop at the site of parasite inoculation. It is more likely to occur in *T. b. rhodesiense* than *T. b. gambiense* infection and in expatriates than in residents of endemic areas.

The first (hemolymphatic) stage of *T. b. gambiense* infection is characterized by recurrent bouts of fever, headaches, edema of the face, myalgias, arthralgias, other constitutional symptoms, rash in some patients, and lymphadenopathy. Swollen posterior cervical nodes are known as *Winterbottom's sign*. Trypanosomes may be seen in the blood or aspirates of lymph nodes. After a period of several weeks to months the second stage begins when they invade the central nervous system, producing meningoencephalitis. Symptoms and findings include headaches, which may be severe; loss of concentration; personality changes; memory loss; seizures; difficulty walking; increased sleep; and eventually obtundation, coma, wasting, and death.

In *T. b. rhodesiense* infection, systemic symptoms develop a few days to several weeks after the tsetse fly bites. A chancre may be present at the bite site. Fever, headache, severe fatigue, irritability, lymphadenopathy, myalgias, and arthralgias follow. Invasion of the central nervous system can occur early during infection resulting in death within several weeks or months if treatment is not initiated. The courses may be indistinguishable, but *T. b. rhodesiense* infection is usually more acute and severe, and lymphadenopathy is not as prominent as it is with *T. b. gambiense* infection.

All cases of HAT must be treated. Given the complexity of the regimens and toxicity of the drugs, consultation with experts at the CDC or elsewhere is recommended. Persons with first-stage HAT (hemolymphatic disease) due to *T. b. gambiense* are treated with pentamidine isethionate, which is administered parenterally (Table 201.2). Those with first-stage *T. b. rhodesiense* HAT are treated with suramin. Pentamidine and suramin are of comparable efficacy for *T. b. gambiense*, but pentamidine is less toxic.

Pentamidine isethionate is administered daily, intramuscularly (IM) or intravenously (IV). If infused too rapidly, IV pentamidine can produce hypotension and shock. Gastrointestinal disturbances, pain at the injection site when the drug is given IM, liver enzyme abnormalities, and nephrotoxicity are other side effects. Some patients develop life-threatening hypoglycemia due to pancreatic β cell injury and insulin release; insulin-dependent diabetes may follow. Rare side effects include acute pancreatitis, hyperkalemia, anaphylaxis, and ventricular arrhythmias.

Toxicity is frequent with suramin and includes gastrointestinal disturbances such as nausea and vomiting; neurologic side effects such as photophobia, hyperesthesias, and peripheral neuropathy; and urticaria and pruritus. Administration of the drug is occasionally associated with shock, renal toxicity, optic atrophy, or blood dyscrasias. Severe reactions can occur in persons who are coinfected with *Onchocerca volvulus*. A test dose of suramin is given IV prior to the administration of treatment doses because of rare, but potentially severe hypersensitivity reactions.

Eflornithine, which has been called the "resurrection drug," is used for second-stage (central nervous system) disease caused by *T. b. gambiense*. It is given IV. It can be used as monotherapy (Table 201.2), but the combination of eflornithine plus nifurtimox (see the section on Chagas disease) has higher cure rates and a lower risk of mortality. Unfortunately, supplies of eflornithine are limited worldwide, and while effective, it is not used for first-stage disease. Eflornithine-based regimens are not effective for *T. b. rhodesiense* infection.

Melarsoprol (*Arsobal*, Rhone-Poulenc Rorer) is the only effective drug for persons with second-stage HAT (central nervous system involvement) due to *T. b. rhodesiense* (see Table 201.2). It can also be used for second-stage *T. b. gambiense* infection if eflornithine is not available, but it is far more toxic than eflornithine-based regimens. Melarsoprol is administered IV. Untoward effects are common. In

addition to encephalopathy, which occurs in as many as 18% of recipients and is fatal in 3% to 10%, treatment is frequently associated with nausea, vomiting, abdominal pain, peripheral neuropathy, hypertension, allergic reactions, and, rarely, shock. Administration of prednisolone, 1 to 2 mg/kg/d, may reduce the severity of arsenical encephalopathy and the risk of death by approximately half. A number of dosage regimens have been studied. Lower doses of melarsoprol have been used in cachectic patients.

Finally, flexinidazole is recommended by the WHO for treatment of first- and second-stage *T. b. gambiense* disease in endemic areas, but it is neither available nor recommended for use in the US. New therapeutic approaches are needed.

Leishmaniasis (cutaneous, mucosal, disseminated, and visceral)

Leishmaniasis refers to the spectrum of disease caused by 20 *Leishmania* spp. that infect humans and other vertebrate hosts. The three major clinical syndromes include cutaneous, mucosal, and visceral leishmaniasis, but a variety of other presentations, including post–kala-azar dermal leishmaniasis, disseminated cutaneous leishmaniasis, diffuse cutaneous leishmaniasis, and viscerotropic leishmaniasis, have been described. *Leishmania* spp. are transmitted by sand flies in nature. In many areas of the world, leishmaniasis is a zoonosis with dogs, other canines, or rodents serving as reservoirs, and humans become infected when they venture into endemic habitats. An outbreak of canine visceral leishmaniasis has been reported in the United States among foxhounds and some other dogs. Infection seems to occur by dog-to-dog or in utero transmission. There have been no human cases. In some sites such as India, humans are the only reservoir of visceral leishmaniasis. The manifestations of disease depend on interactions between the infecting *Leishmania* sp. and the genetically determined cell-mediated immune responses of its human host (Figures 201.2–201.9).

In persons with cutaneous leishmaniasis, parasites multiply in macrophages at the site of inoculation in the skin and in draining lymph nodes. The morphology of the resulting lesion is variable. Often, a nodule develops, expands, and then ulcerates over a course of weeks. Lesions may be single or multiple. Some have a "pizza-like" appearance with a raised, erythematous, outer border, a central area of red granulation tissue, and a yellowish or brown overlying crust. Others are "volcano-like" or flat and plaque-like. Lesions can persist for months to years but eventually heal, leaving a burn-like scar as evidence of disease. In mucosal leishmaniasis due to *L. (Viannia) braziliensis* and related species in Latin America, mucosal lesions of the nose, oral pharynx, and occasionally adjacent sites develop months to years after the initial skin lesion has healed. Disseminated leishmaniasis due to *L. braziliensis* or *L. amazonensis* infection is associated with 10 to several hundred papules, nodules, or ulcerative skin lesions.

The majority of persons infected with *L. donovani* or *L. infantum* (formerly known as *L. chagasi* in Latin America), are asymptomatic, despite parasitemia in some instances, and have spontaneously resolving infections. In the subset of persons who develop progressive visceral leishmaniasis, known as *kala-azar*, parasites

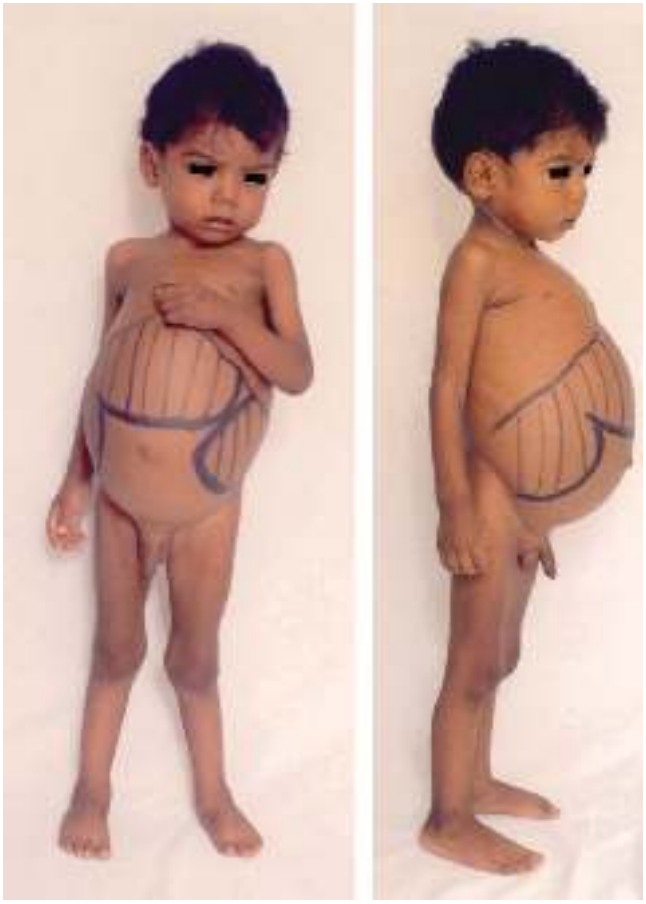

FIGURE 201.2 (A and B) Brazilian child with advanced visceral leishmaniasis and massive hepatosplenomegaly.

disseminate throughout the reticuloendothelial system. They are found within macrophages in the liver, spleen, bone marrow, lymph nodes, and occasionally other organs. Patients with advanced visceral leishmaniasi typically present with massive splenomegaly,

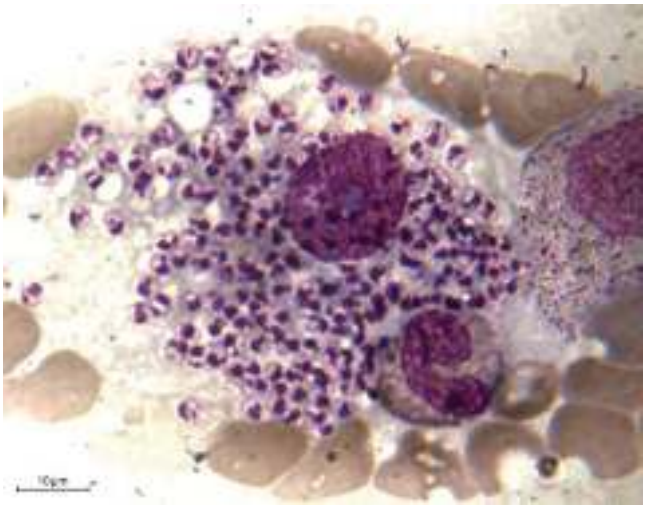

FIGURE 201.3 A macrophage with >100 amastigotes from a bone marrow aspirate of an AIDS patient with kala-azar.

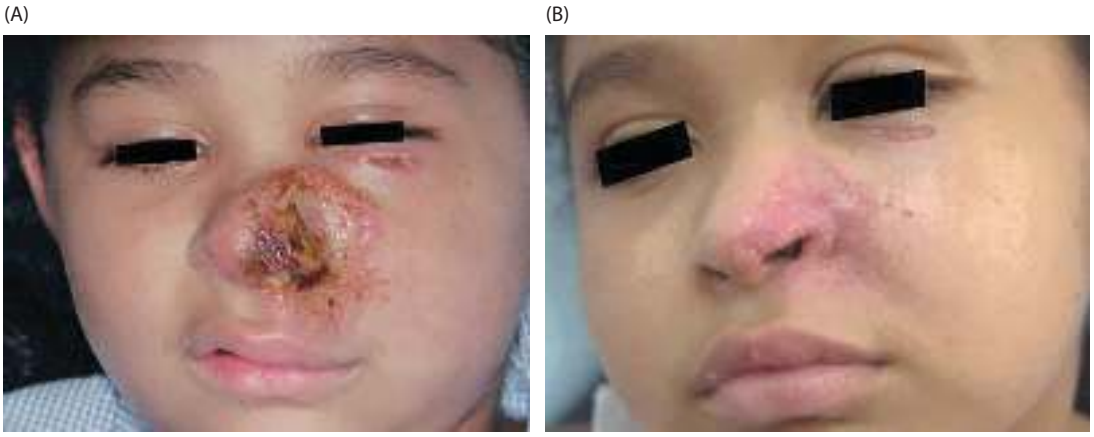

FIGURE 201.4 (A and B) A child with cutaneous leishmaniasis with involvement of the nose, due to *Leishmania* (*Viannia*) *braziliensis*. Before and after treatment.

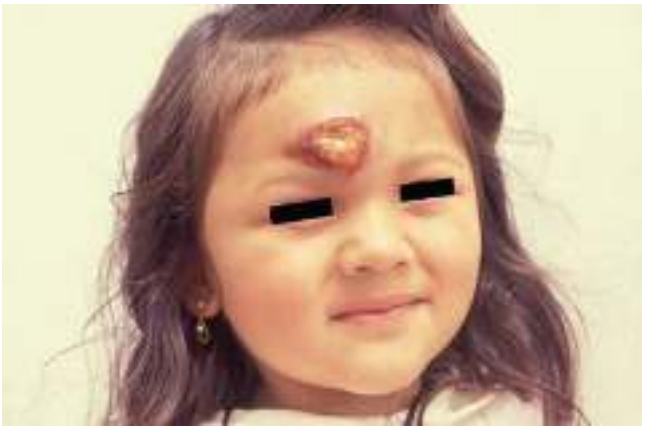

FIGURE 201.5 Brazilian child with cutaneous leishmaniasis due to *Leishmania* (*Viannia*) *braziliensis*.

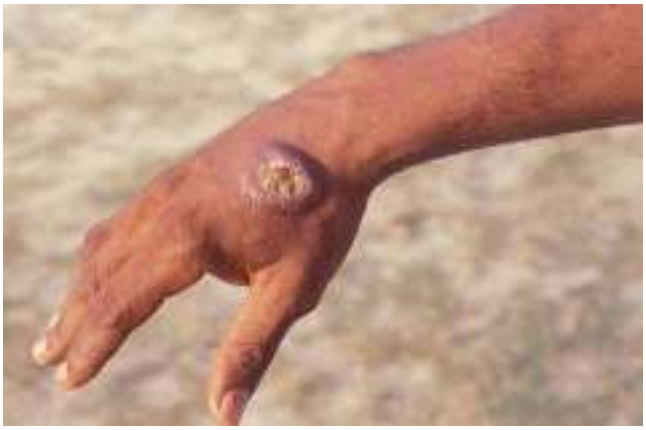

FIGURE 201.7 Patient with cutaneous leishmaniasis, due to *Leishmania* (*Viannia*) *braziliensis*. Hand involvement.

FIGURE 201.6 A Brazilian woman with cutaneous leishmaniasis, with lymphatic involvement (sporotricoid type) due to *Leishmania* (*Viannia*) *braziliensis*. Lymphatic involvement (*arrowheads*) and site of a punch biopsy (*arrow*). Leishmania amastigotes were seen in imprint and promastigotes grown in Novy-MacNeal-Nicolle (NNN) media.

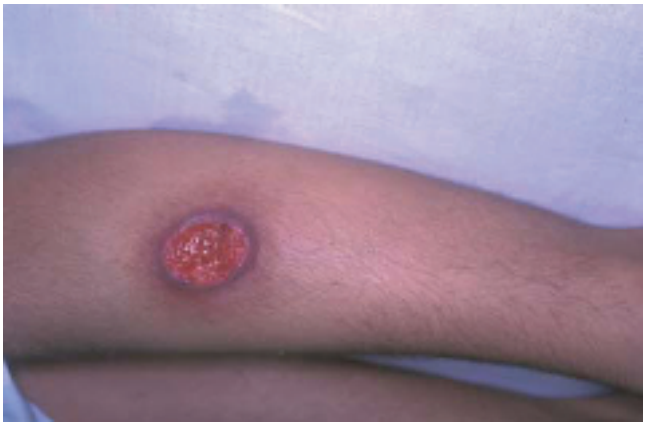

FIGURE 201.8 Patient with cutaneous leishmaniasis, due to *Leishmania* (*Viannia*) *braziliensis*. Leg involvement.

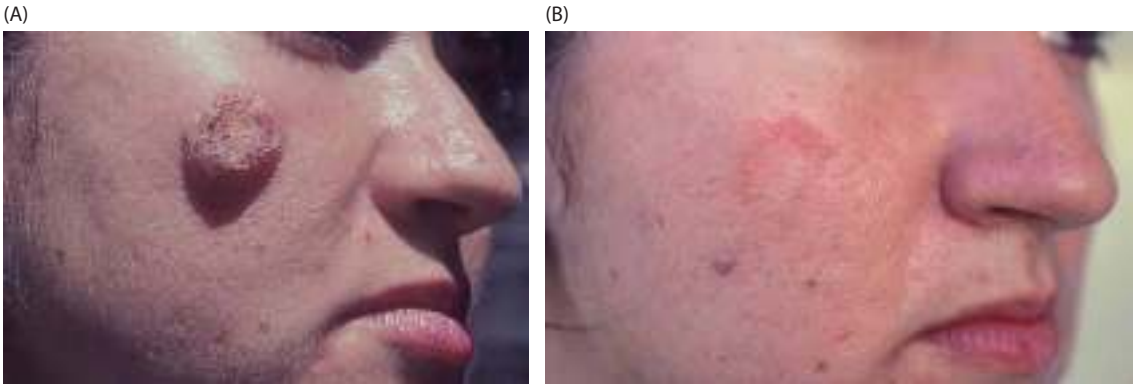

FIGURE 201.9 (A and B) Cutaneous leishmaniasis due to *Leishmania* (*Viannia*) *braziliensis* before and after treatment.

hepatomegaly, fever, weight loss, constitutional symptoms, and hypergammaglobulinemia. Visceral leishmaniasis emerged in Spain, southern France, and Italy, and later in Brazil, India, Ethiopia, and elsewhere as an opportunistic infection in persons with AIDS. Persons with concurrent visceral leishmaniasis and AIDS may present in the classical manner, but atypical presentations are common. Splenomegaly may be absent, and gastrointestinal and pleuropulmonary involvement are often seen.

The diagnosis of cutaneous or visceral leishmaniasis is suggested by a history of exposure in an endemic region and the clinical findings. It is confirmed by identifying *Leishmania* amastigotes by smear, culture, or molecular tests for DNA, in blood, bone marrow, splenic aspirates, lymph nodes, or other tissue from patients with visceral leishmaniasis or in biopsies of skin or mucosal lesions from those with cutaneous or mucosal leishmaniasis. Anti-leishmanial antibodies are usually present in high titer in persons with visceral leishmaniasis, but may be absent in persons with AIDS. Several assays are available to measure antibodies; an enzyme-linked immunosorbent assay using a recombinant 39-kDa kinesin-like antigen is sensitive and specific for visceral leishmaniasis. Serology is not diagnostic in cutaneous leishmaniasis, as antileishmanial antibodies are variably present and at low titer. The leishmanin (Montenegro) skin test (Figure 201.10) is not approved or available in the United States and has been discontinued in most countries. It is negative in patients with visceral leishmaniasis, but it usually becomes positive after successful treatment. The test is typically positive in persons with cutaneous and mucosal leishmaniasis. Interferon-release assays are under development.

Liposomal amphotericin B (AmBisome, Fugisawa) and miltefosine are approved in the United States for treatment of visceral leishmaniasis. Liposomal amphotericin B is highly effective and the drug of choice in industrialized countries. Its cost and availability have limited its use in some impoverished endemic areas. Other lipid-associated compounds have also been reported to be effective, but they have been less well studied. Amphotericin B deoxycholate is an alternative, but it is more toxic than liposomal amphotericin B.

The emergence of pentavalent antimony resistance in India and adjacent countries and the desire for an oral regimen stimulated the search for new drugs. Miltefosine, a phosphocholine analog that is administered orally, is now FDA-approved for the treatment of visceral leishmaniasis due to *L. donovani* acquired in India and adjacent areas; for cutaneous leishmaniasis due to *L. braziliensis, L. guyanensis,* and *L. panamensis*; and for mucosal leishmaniasis due to *L. braziliensis*. Gastrointestinal side effects are common, but have not prevented the completion of therapy in most patients. Transient elevations of liver enzymes and creatinine have been noted. Miltefosine is embryotoxic and contraindicated during pregnancy and breastfeeding. Women in the reproductive age range must be provided effective birth control. Resistance has been reported.

Sodium sibogluconate (Pentostam) and meglumine antimoniate (Glucantime), both pentavalent antimony compounds, have been used for decades to treat leishmaniasis. Pentostam is available through the CDC Drug Service in the United States. These drugs are dosed on the basis of their pentavalent antimony content; Pentostam contains 100 mg of pentavalent antimony/mL and Glucantime contains 85 mg/mL. Side effects increase with age and include gastrointestinal symptoms, pancreatitis, myalgias, headache, malaise, and cardiac toxicity including sudden death in older people and those receiving higher than recommended doses. Antimony resistance and treatment failures are now common in the Indian subcontinent and some other regions. In areas where pentavalent antimony resistance has not emerged, either Glucantime or Pentostam remain an alternative for the treatment of visceral leishmaniasis.

Relapses of visceral leishmaniasis may occur after treatment with any of the drugs just discussed. Relapses are usually observed within 6 months

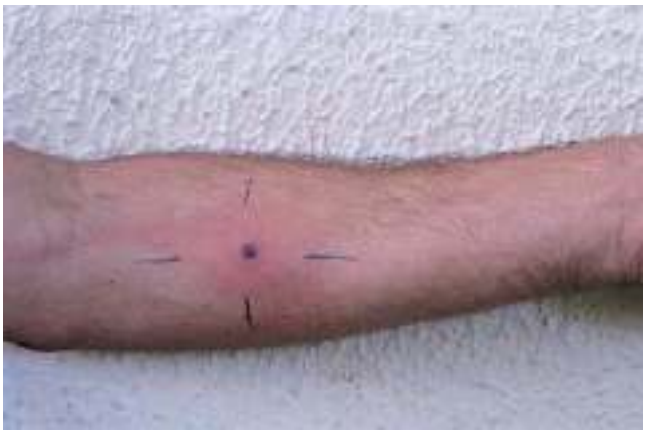

FIGURE 201.10 Positive Montenegro test (leishmanin skin test), 50 mm, with central necrosis, in a patient with mucosal leishmaniasis.

of the completion of therapy. Persons who relapse can be treated with a second course of the same drug or an alternative regimen. Liposomal amphotericin B is the treatment of choice in persons with AIDS. Relapses are more common after treatment with other drugs. It is important to optimize antiretroviral therapy. Suppressive anti-leishmanial therapy has also been used in people with AIDS or other severe, immune compromising conditions and more than one relapse, but there have been no controlled trials to ascertain the optimal drug or regimen.

Persons with visceral leishmaniasis in the developing world can be severely wasted when they present, and they can die from secondary bacterial or viral infections. Attention should focus on addressing their nutritional needs as well as treating concurrent bacterial or viral infections with appropriate antimicrobial drugs.

Cutaneous leishmaniasis typically has a self-resolving course. If lesions are small, few in number, cosmetically inconsequential, and not caused by *Leishmania* spp. associated with mucosal disease, they can be followed expectantly, particularly when there is evidence of self-healing. When that is not the case, lesions can be treated topically, provided the infecting *Leishmania* species is not associated with mucosal disease, or systemically. The choice of treatment depends on the infecting *Leishmania* species; the number, location, and size of the skin lesions; and the availability of the therapeutic modality.

Options for local treatment include thermal therapy, cryotherapy for very small lesions, or topical application of paromomycin (15%) in an effective vehicle. Intralesional injections with Pentostam are used for uncomplicated lesions of Old World leishmaniasis in Europe and Asia, but Pentostam is currently available only for systemic administration in the United States.

When skin lesions are large, multiple, cosmetically significant, or caused by *L.* (*V.*) *braziliensis* or related New World species associated with mucosal leishmaniasis, systemic treatment is used. The only oral drug approved by the FDA for treatment of cutaneous leishmaniasis is miltefosine, specifically for *L. braziliensis, L. guyanensis,* and *L. panamensis* infections. Historically, either Pentostam or Glucantime, 20 mg of pentavalent antimony/kg/d, for 20 days was used, but both drugs are associated with substantial toxicity. Oral fluconazole has been effective in some settings, but not all. Fluconazole, 200 mg/d for 6 weeks, was associated with a high response rate in persons with cutaneous leishmaniasis due to *L. major*, but *L. major* infections often heal spontaneously in a matter of weeks to months without treatment. In an observational study in northeastern Brazil, persons with cutaneous leishmaniasis due to *L. braziliensis* responded to high-dose, prolonged fluconazole (8 mg/kg/d for 4–6 weeks) therapy.

Liposomal amphotericin B, or alternatively amphotericin deoxycholate, can be effective in the treatment of cutaneous leishmaniasis, but both are costly and potentially toxic. Pentamidine has activity against *Leishmania* spp., but its side effects, which include severe, life-threatening hypoglycemia and later diabetes mellitus, preclude its use for uncomplicated cutaneous leishmaniasis. Whatever the therapy, cutaneous lesions respond slowly and often take weeks to epithelialize. An atrophic, burn-like scar is often left as evidence of disease.

Persons with mucosal leishmaniasis can be treated initially with liposomal amphotericin B or miltefosine. The latter is FDA approved for treatment of mucosal disease due to *L. braziliensis.* Alternatives include Pentostam or Glucantime, alone or in combination with pentoxifylline in areas where pentavalent antimony resistance is rare; or amphotericin B deoxycholate. Treatment failures and relapses are not unusual in patients with mucosal disease. Plastic surgical repairs should be delayed for 12 months after treatment to ensure clinical cure, Grafts may be lost if relapses occur in the months following surgery.

Suggested reading

Aronson N, Herwaldt BL, Libman M, et al. Diagnosis and treatment of leishmaniasis. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). *Am J Trop Med Hyg*. 2017;96(1):24–45.

Bern C. Antitrypanosomal therapy for chronic Chagas disease. *N Engl J Med*. 2011;364(26): 2527–2534.

Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: A systematic review. *JAMA*. 2007;298:2171–2181.

Buscher P, Cecchi G, Jamonneau V, Priotto G. Human African trypanosomiasis. *Lancet*. 2017;390(10110):2397–2409.

Centers for Disease Control and Prevention. African Trypanosomiasis (sleeping sickness). https://www.cdc.gov/parasites/sleepingsickness/index.html

Cota GF, de Sousa MR, Fereguetti TO, Rabello A. Efficacy of anti-leishmania therapy in visceral leishmaniasis among HIV infected patients: A systematic review with indirect comparison. *PLoS Negl Trop Dis*. 2013;7(5):e2195.

Ferreira RT, Melandre AM, Cabral ML, et al. Extraction of *Trypanosoma cruzi* DNA from food: A contribution to the elucidation of acute Chagas disease outbreaks. *Rev Soc Bras Med Trop*. 2016 Apr;49(2):190–195.

Grinnage-Pulley T, Scott B, Petersen CA. A mother's gift: Congenital transmission of *Trypanosoma* and *Leishmani*a Species. *PLoS Pathog*. 2016 Jan 28;12(1):e1005302.

Kennedy PG. Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping sickness). *Lancet Neurol*. 2013;12(2):186–194.

Reveiz L, Maia-Elkhoury AN, Nicholls RS, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis: A systematic review update. *PLoS ONE*. 2013;8(4):e61843.

Schaut RG, Robles-Murguia M, Juelsgaard R, et al. Vectorborne transmission of *Leishmania infantum* from hounds, United States. *Emerg Infect Dis*. 2015 Dec;21(12):2209–2212.

Silva-Dos-Santos D, Barreto-de-Albuquerque J, Guerra B, Moreira OC, et al. Unraveling Chagas disease transmission through the oral route: Gateways to Trypanosoma cruzi infection and target tissues. *PLoS Negl Trop Dis.* 2017 Apr 5;11(4):e0005507.

Toepp AJ, Bennett C, Scott B, et al. Maternal *Leishmania infantum* infection status has significant impact on leishmaniasis in offspring. *PLoS Negl Trop Dis*. 2019 Feb 13;13(2):e0007058.

Valença-Barbosa C, Fernandes FA, Santos HL, et al. Molecular identification of food sources in triatomines in the Brazilian Northeast: Roles of goats and rodents in Chagas disease epidemiology. *Am J Trop Med Hyg.* 2015 Nov;93(5):994–997.

World Health Organization. Human African trypanosomiasis. https://www.who.int/trypanosomiasis_african/en/

World Health Organization. WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. August 2019. https://www.who.int/trypanosomiasis_african/resources/9789241550567/en/

202

Intestinal protozoa

M. Paul Kelly

Intestinal protozoal infection produces substantial morbidity and mortality in people of all ages, particularly in tropical and subtropical parts of the world. Amebiasis, giardiasis, cryptosporidiosis, and those infections associated with AIDS are important problems for health in many parts of the world, but some protozoa found in the human digestive system do not cause disease. Vaccines are not yet available for protection against these infections, and many are difficult to treat. The intestinal protozoa that produce important human infections are summarized in Table 202.1. There are differences between protozoa in their impact in patients with AIDS: cryptosporidiosis is an AIDS-defining infection, but neither the incidence nor the severity of amebiasis or giardiasis are affected by HIV.

Entamoeba histolytica

Entamoeba histolytica causes dysentery, chronic colonic amebiasis, and hepatic amebiasis. The last topic is dealt with in Chapter 203, "Extraintestinal amoebic infection." Amebic dysentery is a syndrome of bloody diarrhea caused by invasion of the colonic wall by trophozoites of *E. histolytica*. It is common in many parts of the world, especially West and southern Africa, Central America, and south Asia. In the United States, 3,000 to 4,000 cases are reported each year. There is now consensus that the species formerly recognized as *E. histolytica* in fact comprises two species: *E. histolytica* and *Entamoeba dispar*. The first is the pathogenic protozoan long associated with human invasive disease and with hepatic amebiasis, and the latter is a morphologically identical nonpathogenic protozoan first recognized as the nonpathogenic zymodeme of *E. histolytica*. The latter does not require treatment, but it cannot be differentiated from *E. histolytica* morphologically. Diagnosis of invasive amebiasis is achieved by the identification of hematophagous trophozoites in very fresh stool smears or in colonic biopsies; the latter may also show typical flask-shaped ulcerations. Serologic testing using an immunofluorescent antibody test is now an important contribution to the diagnosis of a seriously ill patient, particularly in distinguishing colonic dilation resulting from amebiasis from that caused by ulcerative colitis. Serology does not distinguish between *E. histolytica* and *E. dispar*. Diagnosis using the polymerase chain reaction (PCR), which detects specific DNA sequences of genetic material, is increasingly available, and it does allow species identification.

Treatment of invasive amebiasis is shown in Table 202.2. Treatment can be divided into two stages: (1) eradication of tissue forms with metronidazole, tinidazole, or nitazoxanide and (2) eradication of luminal carriage with diloxanide furoate. Dehydroemetine and iodoquinol, used formerly for the treatment of amebiasis, are toxic and no longer used.

Intestinal amebiasis may be complicated by acute toxic colitis, presenting in a similar manner to the dilation of acute severe ulcerative colitis. The patient will be febrile and unwell, sometimes with signs of peritoneal irritation, and a plain abdominal radiograph will indicate dilation. Intravenous fluids must be given, the patient kept NPO, and metronidazole and a broad-spectrum antibiotic given intravenously. Worsening dilation of the colon or perforation will necessitate surgery, but, in the event of perforation, the

TABLE 202.1 **INTESTINAL PROTOZOA**

The sarcodina (amebae)	Pathogenic	*Entamoeba histolytica*
	Nonpathogenic	*Entamoeba dispar*
		Entamoeba moshkovskii
		Entamoeba chattoni
		Endolimax nana
		Iodamoeba butschlii
		Dientamoeba fragilis
The mastigophora (flagellates)	Pathogenic	*Giardia lamblia*
	Nonpathogenic	*Trichomonas hominis*
		Chilomastix mesnili
		Embadomonas intestinalis
		Enteromonas hominis
The ciliophora		*Balantidium coli*
The coccidia		*Cryptosporidium parvum*
		Cystoisospora belli (formerly Isospora belli)
		Sarcocystis species
		Cyclospora cayetanensis
The microsporidia		*Enterocytozoon bieneusi*
		Encephalitozoon intestinalis
Stramenopile		*Blastocystis hominis*

outcome is poor. If treatment with metronidazole is started early in patients with severe amebic colitis, medical management should nearly always suffice, but surgery should not be delayed if perforation is impending.

Chronic amebiasis may be difficult to distinguish from intestinal tuberculosis or Crohn's disease but responds to metronidazole and diloxanide as discussed. Surgery is sometimes necessary because stricturing may persist.

Giardia lamblia

Giardia lamblia infection, first recognized by Van Leeuwenhoek in 1681, is a cause of acute and persistent diarrhea and possibly malnutrition in children in many tropical and subtropical countries. It is also a well-recognized cause of travelers' diarrhea. In many cases it is self-limiting, but the course may be prolonged in immunoglobulin deficiencies. Asymptomatic infection is common. Diagnosis is by stool microscopy, although when this is negative and the clinical suspicion is strong, trophozoites may be detected in small intestinal fluid and mucosal biopsy specimens obtained by endoscopy (Figure 202.1). Fecal *Giardia* antigen enzyme-linked immunosorbent assays (ELISA) and PCR are now increasingly used in many routine diagnostic laboratories.

Several drugs are now available for the treatment of giardiasis but none is regarded as safe in pregnancy, and treatment failures are not uncommon, requiring a second and sometimes a third course of therapy. Five classes of chemotherapy are available (Table 202.3): nitroimidazoles (metronidazole and tinidazole), benzimidazoles (albendazole, secnidazole), nitazoxanide, nitrofurans (furazolidone), and paromomycin, which is the treatment of choice in pregnancy because it is not absorbed. If single agents fail repeatedly, combination therapy may be tried, but there are few controlled data to guide drug choice, dose, or duration.

Balantidium coli

Balantidium coli infection manifests as a severe, sometimes life-threatening colitis indistinguishable from amebic dysentery. It is uncommon but occurs in Central and South America, Iran, Papua New Guinea, and the Philippines, usually in communities that live in

TABLE 202.2 **DRUG TREATMENT OF AMEBIASIS**

		Adult dosage	Child dosage
Tissue infection			
First choice	Metronidazole[a]	750 mg TID for 10 d	50 mg/kg/d for 10 d[b]
	Tinidazole[a]	2 g/d for 3 d	60 mg/kg/d for 3 d
Second choice	Nitazoxanide	500 mg BID for 3 d	Age 2–3 years: 100 mg BID; age 4–11 years: 200 mg BID for 3 d
	Paromomycin	30 mg/kg/d for 10 d[b]	30 mg/kg/d for 10 d[b]
Luminal carriage			
First choice	Diloxanide furoate	500 mg TID for 10 d	20 mg/kg/d for 10 d[b]
Second choice	Paromomycin	30 mg/kg/d for 10 d[b]	30 mg/kg/d for 10 d[b]

[a] Must be followed by eradication of luminal carriage.
[b] In three doses.

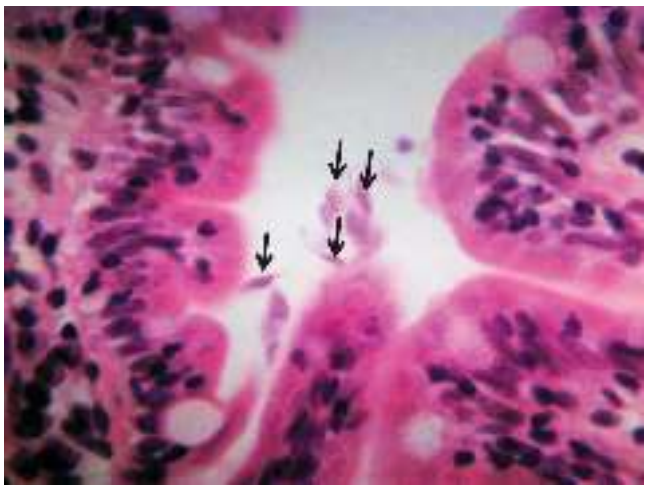

FIGURE 202.1 Trophozoites of *Giardia lamblia* in the lumen in a small intestinal biopsy (6 mm section stained with hematoxylin and eosin).

close proximity to pigs, which are an important reservoir. Diagnosis is made by identification of the large trophozoites in feces or in rectal biopsies. Treatment is with tetracycline, 500 mg four times daily for 10 days (Table 202.4). Metronidazole and paromomycin are alternatives.

Cryptosporidiosis

Infection with *Cryptosporidium parvum* or *C. hominis* is likely to present as acute, self-limiting watery diarrhea in children or in travelers or as a waterborne epidemic. Most episodes require no specific therapy, but attention to fluid and electrolyte balance is important. Cryptosporidiosis is associated with persistent diarrhea, even in apparently immunocompetent children, and, in HIV-infected individuals, it often persists until death. Cryptosporidiosis is also common in malnourished children in the tropics, irrespective of HIV infection. In patients with HIV-related diarrhea, cryptosporidiosis can be found in 10% to 30% of cases in industrialized countries and 10% to 40% of cases in tropical populations. However, since the introduction of highly active antiretroviral therapy (ART) with multidrug regimens, this infection is much less frequent in those regions where ART programs have been scaled up. It remains a significant clinical challenge in patients in the tropics, where patients often present with advanced AIDS or compliance is often poor. Diagnosis is usually made by microscopy of fecal smears using a modified Ziehl–Neelsen stain, which reveals the red-staining 5-μm oocysts(Figure 202.2), but ELISA and PCR tests are being adopted.

Although many drugs have been tried, only two have been shown to have any value in controlled trials: paromomycin and nitazoxanide. Hyperimmune bovine colostrum is a form of passive immunotherapy but is not in clinical use. Paromomycin (30 mg/kg/d in three doses) has been found to be of very limited efficacy. Nitazoxanide (1 g BID for 14 days) has been demonstrated to be effective in children and adults without AIDS in randomized controlled trials. Uncontrolled data from the US compassionate use program indicate that prolonged courses of 500 to 1,500 mg nitazoxanide twice daily can be useful, but meta-analyses do not confirm this. There is still an urgent need for drugs that are effective in the severely immunocompromised host, and new drugs are in development. Interestingly, there is direct evidence that cryptosporidiosis can be prevented by simple measures: intensive hand washing reduced diarrheal disease, including cryptosporidiosis, in American AIDS patients, but to the author's knowledge this finding has not been replicated in a tropical setting.

Cystoisospora belli

Cystoisospora belli is uncommon in industrialized countries but may be found in up to 40% of patients with AIDS-related diarrhea in Africa. In HIV-infected individuals it causes a clinical syndrome of persistent diarrhea and wasting, which is indistinguishable from that attributed to other intracellular enteropathogenic protozoa (cryptosporidiosis, microsporidiosis). There were reports of isosporiasis before HIV infection appeared. Diagnosis rests on the identification in fecal smears of elongated, large sporocysts, which appear red with the modified Ziehl–Neelsen stain.

Trimethoprim-sulfamethoxazole (TMP-SMX) has been reported to be effective at a dosage of 160/800 mg four times daily for 10 days. In patients with AIDS, this needs to be followed with the same drug in a dose of 160/800 mg three times weekly indefinitely as prophylaxis against recurrence. Otherwise, recurrence is seen in 50% of patients with HIV infection at 2 months. An alternative drug is sulfadoxine-pyrimethamine (500/25 mg weekly) as

TABLE 202.3 **DRUG TREATMENT OF GIARDIASIS**

Drug	Adult dosage	Child dosage	Efficacy
Metronidazole	500 mg TID for 3 d	5 mg/kg TID for 10 d (maximum 750 mg/d)	>90%
Tinidazole	2 g single dose	75 mg/kg single dose	>90%
Albendazole	400 mg/d for 5 d		>85%
Nitazoxanide	100–200 mg 2× daily		85%
Furazolidone	100 mg QID for 10 d	2 mg/kg TID for 10 d	>80%
Paromomycin	500 mg 3× daily for 5–10 d		

TABLE 202.4 **TREATMENT OF CILIOPHORA, COCCIDIA, AND MICROSPORIDIA**

Organism	Drug regimen
Ciliophora	
Balantidium coli	Tetracycline, 500 mg QID for 10 d
Coccidia	
Cryptosporidium parvum	Nitazoxanide, 500 mg 2× daily for 3 d
Cystoisospora belli	Trimethoprim–sulfamethoxazole, 1 DS tab PO QID for 10 d; Prophylaxis: 1 DS tab 3×/week (or once daily to aid compliance)
Sarcocystis species	As for *C. belli*
Cyclospora cayetanensis	Trimethoprim-sulfamethoxazole, 1 DS tab PO BID for 7 d
Microsporidia	
Enterocytozoon bieneusi	Fumagillin, 60 mg daily for 14 d
Encephalitozoon intestinalis	Albendazole, 400 mg BID for 14 d
Blastocystis hominis	
	The status of this organism as a pathogen is still the subject of controversy, so it is uncertain whether it requires treatment. It is our practice to attempt eradication with metronidazole, 750 mg TID for 10 d, when there are gastrointestinal symptoms and no other cause is apparent

secondary prophylaxis. Patients intolerant of sulfonamides could be given diclazuril, but only anecdotal evidence of its efficacy is available. In the author's experience it does not respond to nitazoxanide.

Sarcocystis species

Sarcocystis infection, which may give rise to a persistent diarrhea, is treated in the same way as *C. belli*. This infection is very uncommon.

Dientamoeba fragilis

Most infections with *Dientamoeba fragilis* are asymptomatic and do not require treatment. When required, treatment is as for amebiasis.

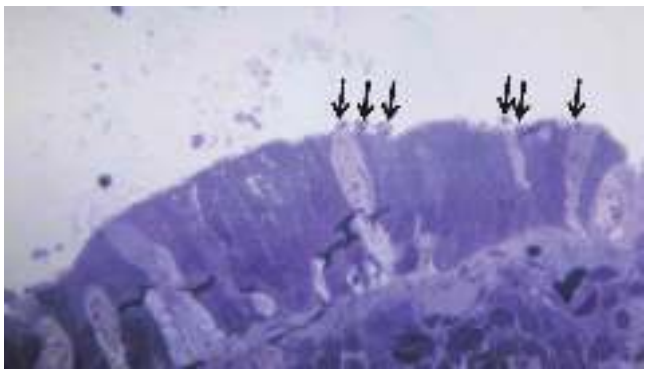

FIGURE 202.2 *Cryptosporidium* sp. trophozoites in small intestinal mucosa of an AIDS patient (semi-thin section stained with toluidine blue).

Cyclospora cayetanensis

Cyclospora cayetanensis causes travelers' diarrhea (especially in travelers to South America and Nepal) and foodborne outbreaks. In fecal smears, the oocysts resemble those of *C. parvum* in taking up carbol fuchsin in the modified Ziehl–Neelsen stain, but the oocysts are larger than *C. parvum* at 8 to 10 μm and they autofluoresce. Eradication is achieved using TMP-SMX (160/800 mg BID) for 7 days. If infection persists, then TMP-SMX should be continued for a further 3 to 5 days. In patients who are intolerant of TMP-SMX, ciprofloxacin can be used but it is less effective.

Microsporidia

Two microsporidia are pathogenic in the human gastrointestinal tract: *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* (formerly known as *Septata intestinalis*). These organisms have recently been reclassified and are actually fungi, but we consider them here because their clinical manifestations are so similar to intracellular protozoal infections such as cryptosporidiosis and isosporiasis. They are intracellular parasites that generally infect severely immunocompromised individuals. The most common manifestation is a persistent diarrhea associated with weight loss, but a syndrome of sclerosing cholangitis is also described. Diagnosis relies on detection of the parasite in duodenal biopsies obtained at endoscopy (Figure 202.3) or on the finding of the spores in the feces using a variety of stains. *E. intestinalis* may cause a disseminated infection with renal spore excretion.

Treatment of *E. intestinalis* infection is with albendazole, 400 mg twice daily for 1 month, but maintenance treatment may be

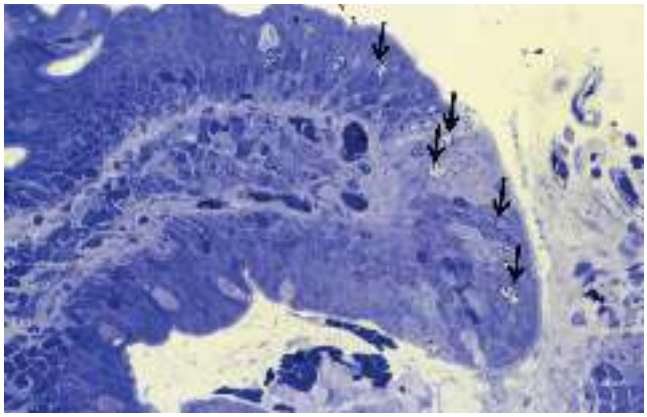

FIGURE 202.3 *Encephalitozoon intestinalis* in a small intestinal biopsy of an AIDS patient (semi-thin section stained with toluidine blue).

needed if relapse occurs following the cessation of therapy, although eradication may be achieved in some patients. *E. bieneusi* infection responds much less well, but fumagillin, 60 mg/d for 14 days, results in symptomatic improvement and parasite clearance in some patients. Fumagillin is toxic.

Suggested reading

Abubakar I, Aliyu SH, Arumugam C, Hunter PR, Usman NK. Prevention and treatment of cryptosporidiosis in immunocompromised patients. *Cochrane Database Syst Rev*. 2007;24:CD004932.

Ahmadpour E, Safarpour H, Xiao L, et al. Cryptosporidiosis in HIV-positive patients and related risk factors: A systematic review and meta-analysis. Cryptosporidiose chez les patients VIH-séropositifs et facteurs de risque associés: Revue systématique et méta-analyse. *Parasite*. 2020;27:27. doi:10.1051/parasite/2020025.

Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: A randomized controlled trial. *Lancet*. 2002;360:1375–1380.

Checkley W, White AC Jr, Jaganath D, et al. A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium. *Lancet Infect Dis*. 2015;15(1):85–94. doi:10.1016/S1473-3099(14)70772-8.

Granados CE, Reveiz L, Uribe LG, Criollo CP. Drugs for treating giardiasis. *Cochrane Database Syst Rev*. 2012;12:CD007787.

Hemphill A, Müller N, Müller J. Comparative pathobiology of the intestinal protozoan parasites *Giardia lamblia*, *Entamoeba histolytica*, and *Cryptosporidium parvum*. *Pathogens* 2019;8:116.

Hoge CW, Shlim DR, Ghimire M, et al. Placebo-controlled trial of cotrimoxazole for *Cyclospora* infections among travellers and foreign residents in Nepal. *Lancet*. 1995;345:691–693.

Jumani RS, Spector JM, Izadnegahdar R, Kelly P, Diagana TT, Manjunatha UH. Innovations in addressing pediatric diarrhea in low resource settings. *ACS Infect Dis*. 2020;6(1):14–24. doi:10.1021/acsinfecdis.9b00315.

Kelly P. Intestinal protozoa. In Farrar J et al, eds. *Manson's tropical diseases*, 23rd ed. London: Elsevier; 2013: 664.

Field AS, Milner DA Jr. Intestinal microsporidiosis. *Clin Lab Med*. 2015;35(2):445–459. doi:10.1016/j.cll.2015.02.011.

Ortega-Pierres MG, Argüello-García R. Giardia duodenalis: Role of secreted molecules as virulent factors in the cytotoxic effect on epithelial cells. *Adv Parasitol*. 2019;106:129–169. doi:10.1016/bs.apar.2019.07.003.

Tan KS. New insights on classification, identification, and clinical relevance of *Blastocystis* spp. *Clin Microbiol Rev*. 2008;21:639–665.

Extraintestinal amebic infection

Rosa Andrade

Extraintestinal manifestations of invasive amebic disease are less common than amebic colitis, where amebic liver abscesses (ALA) are the most frequent manifestation. ALA arises from hematogenous dissemination of intestinal amebic trophozoites presumably through the portal circulation, and they may present months to years after an episode of amebic colitis.

Other extra-abdominal manifestations, such as thoracic and brain amebiasis, are frequently associated with the direct dissemination of trophozoites from an ALA. They are diagnosed clinically and supported with relevant epidemiologic risks and serologic, antigen-based, or molecular testing. Untreated extraintestinal manifestations are usually fatal. However, outcomes have improved since the introduction of nitroimidazoles, such as metronidazole, as the mainstay treatment for invasive amebiasis.

Amebic liver abscess

Entamoeba histolytica infections are mostly asymptomatic. Only 4% to 10% of infections become symptomatic over the course of a year. An ALA can complicate invasive amebic colitis in approximately 5% of cases. Travelers to the endemic countries are at risk for developing amebiasis and liver disease. Longer stays are associated with increased risk. Of travelers who develop an ALA after leaving an endemic area, 95% do so within 5 months; however, they can occur anywhere from 4 days to 20 years after leaving the endemic area. Therefore, a detailed travel history is essential to assist with the diagnosis.

Adult men are 7 to 10 times more likely to have ALA (often between the ages of 20 and 40) than women. However, this difference is not observed in children. Notably, men who have sex with men are an at-risk population, given their overall increased risk for intestinal amebiasis. Testosterone may explain this increased susceptibility to ALA in men as observed in a mice model of *E. histolytica* infection. In this model, testosterone inhibited the release of interferon-γ from natural killer T cells, which are critical for the control of ALA. Additionally, people with cell-mediated immune defects including chronic steroid users, pregnant women, alcoholics, the malnourished, and those with malignancies may also be at increased risk of invasive amebiasis.

The clinical presentation of ALA is characterized by fever and right upper quadrant pain as the most frequent complaints and the most consistent findings on examination (Table 203.1).

The duration of disease influences the symptoms, as patients with symptoms for >2 weeks tend to be afebrile and have weight loss and more focal abdominal pain. The classic finding of point tenderness in the right upper quadrant or intercostal tenderness has been frequently noted in earlier literature but is likely neither sensitive nor specific.

Young patients with an ALA are more likely than older patients to present in the acute phase with prominent symptoms of <10 days duration. Older patients from endemic areas are more likely to have a subacute course lasting 6 months, with weight loss and hepatomegaly.

Most ALA are solitary lesions, and approximately 80% are found in the right lobe of the liver, thus explaining the location of the pain. The pain may also occur in the epigastrium, right lower chest, or the

TABLE 203.1 **CLINICAL FINDINGS FOR PATIENTS WITH AMEBIC LIVER ABSCESS**

Clinical findings	%
Fever	85–90
Right upper quadrant pain	84–90
Hepatomegaly	30–50
Weight loss	33–50
Diarrhea	20–33
Cough	10–30
WBC count >12,000/μL	80
Elevated level of alkaline phosphatase	70

WBC, white blood cell.
From Petri and Singh. Diagnosis and management of amebiasis. *Clin Infect Dis*. 1999; 29:1117–1125.

right shoulder tip (referred pain). Left-sided abdominal pain, corresponding to an abscess in the left lobe of the liver, is less common. Localized swelling or generalized hepatomegaly may be noted on exam depending on the size and location of the abscess or abscesses. Abscesses high in the right lobe of the liver may not result in hepatomegaly but, if of significant size, can lead to elevation of the right hemidiaphragm, which is evident on a chest radiograph.

Laboratory findings in a patient with amebic liver disease include leukocytosis (white blood cell [WBC] count >12 000/mm^3), an elevated alkaline phosphatase, and, occasionally, elevated transaminases. It is uncommon to see an elevated bilirubin, and thus jaundice in a febrile patient with right upper quadrant pain should point the clinician toward another diagnosis. A mild degree of anemia (anemia of chronic disease) is present in many cases, particularly with symptoms for >2 weeks. Peripheral eosinophilia is rare and should suggest an alternative parasitic infection such as echinococcosis and hepatic fascioliasis (liver fluke).

Diagnosis

Most cases of extraintestinal amebiasis occur in the absence of active amebic colitis. Their diagnosis relies in a combination of appropriate clinical symptoms, epidemiologic risk factors, characteristic imaging findings, positive serologic, antigen detection, or molecular testing.

Serologic testing for antibodies to *E. histolytica* is >80% sensitive in disease of >1 week duration and nearly 99% sensitive in recovering patients. A negative test essentially rules out the diagnosis except in early infection (≤1 week). It is important to use an enzyme immunoassay (EIA) or agar gel dilution to test serology as an indirect hemagglutination often remains positive for years at high titer, and residents of an endemic region may have positive antibodies to *E. histolytica* that do not represent acute disease. Serum antigen detection tests for the *E. histolytica* Gal/GalNAc lectin gave a positive result in >95% of patients with ALA in a study of Bangladeshi patients before treatment, comparing favorably to currently available serum antibody tests. Importantly, after treatment with metronidazole, circulating antigen levels were rarely detected (15%), making the test potentially useful for the diagnosis of acute disease in endemic countries. Molecular diagnosis using polymerase chain reaction (PCR) assays are highly sensitive and specific for ALA. They are currently part of multiplex PCR assays for multiple enteric pathogens, but this test remains expensive and depends on skilled laboratory personnel.

Diagnostic aspiration of an ALA is seldom needed. However, it is indicated to rule out a pyogenic liver abscess or in those at high risk for abscess rupture. Patients at high risk of abscess rupture have an abscess cavity with a diameter >5 cm or one located in the left lobe, which could rupture into the pericardium. The classic amebic pus resembles "anchovy paste" or "chocolate sauce" which refers to the thick, acellular, proteinaceous debris consisting of necrotic hepatocytes and a few polymorphonuclear cells obtained by successful aspiration. Amebic trophozoites are magenta-colored by periodic acid-Schiff staining, making them easy to visualize, but finding trophozoites in an aspirate only occurs in 20% to 30% of cases, with a higher yield from the edge of the abscess.

Several imaging modalities that detect a space-occupying lesion in the liver support the diagnosis of ALA in the presence of a positive amebic serology. Imaging frequently demonstrates a single round or oval, homogeneous, hypoechoic lesion. Low-attenuation lesions with septations or an observable fluid level or debris may also be seen (see Figures 203.1 and 203.2). Chest radiographs in approximately 50% of patients with ALA demonstrate an elevated right hemidiaphragm or other abnormality such as discoid atelectasis. Ultrasonography, computer tomography (CT)scanning, and magnetic resonance imaging (MRI) are all quite sensitive, but none are specific because they cannot distinguish an ALA from a pyogenic abscess.

The differential diagnosis of ALA includes pyogenic abscess; hepatocellular carcinoma, especially with necrosis; and echinococcal cyst. On imaging, the differential can often be narrowed to pyogenic abscess versus amebic liver abscess, with the clinical and radiographic findings being largely indistinguishable. Some epidemiologic differences may help to increase the likelihood of pyogenic liver abscess: age >50 years old, no sex predominance, underlying diabetes mellitus, biliary disease, and lack of travel to an endemic country. Nevertheless, these clues do not rule out amebic liver abscess, especially in a patient living in an endemic region.

Treatment

Nitroimidazoles, such as metronidazole and tinidazole, are the mainstay of treatment for invasive amebiasis worldwide due to their effectiveness in affected tissue. Metronidazole is effective in a dose of 750 mg three times daily for 7 to 10 days for adults, and 35 to 50 mg/kg/d in three doses for 7 to 10 days for children (Table 203.2).

Metronidazole is generally well-tolerated, but the disulfiram-like reaction to alcohol is important to mention to patients. Minor side effects such as nausea, vomiting, anorexia, and a metallic taste

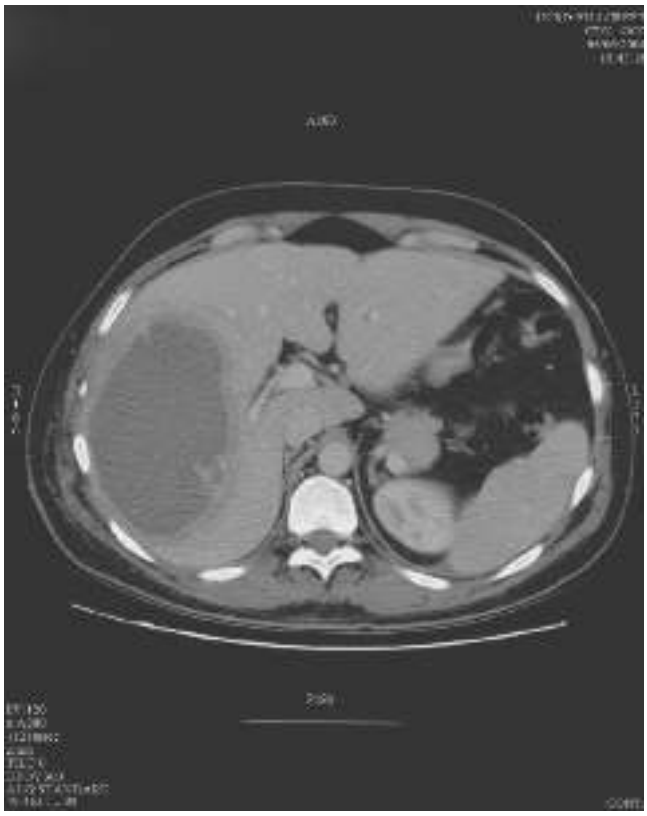

FIGURE 203.1 Contrast CT scan image of an amebic liver abscess. The abscess appears as a hypoattenuating mass within the right lobe of the liver with an irregular, multiseptated rim with a thin rim of surrounding edema.

occur more frequently than rare neurologic adverse effects such as vertigo, seizures, and encephalopathy. The drug should be discontinued if these latter effects or, rarely, neutropenia occur. Long-term use of metronidazole is also known to cause peripheral neuropathy.

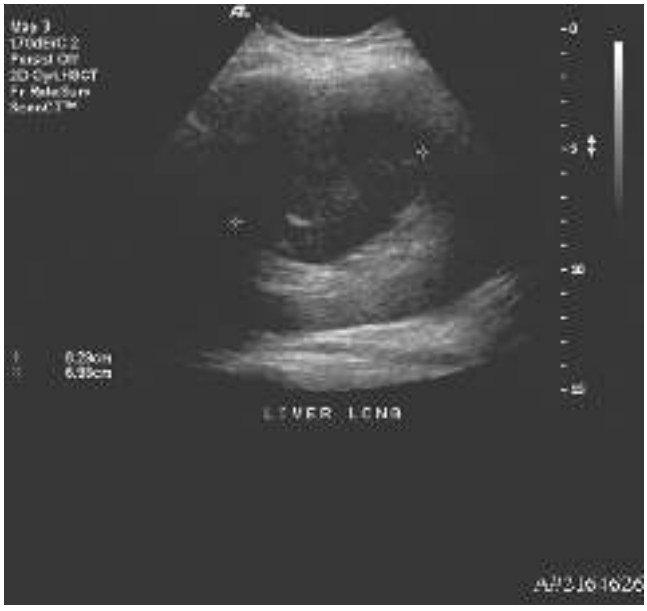

FIGURE 203.2 Ultrasound of the same amebic liver abscess as Figure 203.1

However, the short duration of amebiasis treatment precludes this adverse event.

Tinidazole, a newer nitroimidazole compound, is also effective for the treatment of ALA. It has a longer half-life and is better tolerated, allowing for a shorter treatment course. The recommended dose of tinidazole for amebic liver abscess is 2 g/d for 3 to 5 days in adults and 50 mg/kg/d for 3 to 5 days in children.

The nitroimidazoles remain >90% effective treating amebic liver abscess, and no clinical cases of metronidazole-resistant amebiasis have been documented to date. Treatment with these agents typically results in defervescence, decreased abdominal pain, and normalization of the WBC count within 3 days.

Ultrasonographic or CT-guided aspiration of amebic liver abscesses is typically reserved for patients not responding to 3 to 5 days of medical therapy with persistent fever or pain, imminent rupture of an abscess >5 cm, or a left lobe abscess that may rupture into the pericardium.

All treatment regimens with a tissue amebicide should be followed by treatment with a luminal amebicide to eliminate intestinal carriage of the organism that could lead to relapse if not treated.

In the United States, treatment for 7 days with paromomycin, a nonabsorbable aminoglycoside, is the preferred luminal amebicide. It is safe in pregnancy, has minimal gastrointestinal side effects, and ototoxicity and nephrotoxicity rarely occur. Diloxanide furoate is also effective and well-tolerated and has few side effects but is not commercially available in the United States. Iodoquinol is likewise effective but has some serious side effects such as optic neuritis and peripheral neuropathy and requires a 20-day course. Nitazoxanide, a 5-nitrothiazolyl derivative, is active against *E. histolytica in vitro* and *in vivo* as suggested in a double-blind, placebo-controlled trial; however, it has not been directly compared to the standard luminal amebicides already mentioned.

The usual response to medical therapy of an ALA is a rapid resolution of fever and pain. There is no reason for follow-up ultrasound early in the course as lesions may enlarge acutely, but they ultimately resolve entirely within a year. Serology by EIA typically reverts to negative within 6 months.

Amebic extra-abdominal invasive disease

Pulmonary amebiasis

Other extra-abdominal manifestations such as thoracic and brain involvement are frequently associated with direct dissemination from an amebic liver abscess. The amebic intrathoracic disease is the leading extra-abdominal manifestation that occurs in approximately 10% of ALA patients. Depending on the ALA location, amebic intrathoracic disease can present as empyema, bronco-hepatic fistulas, or extension of pleuropulmonary abscesses into the pericardium. This latter presentation has a 15% to 20% mortality after the ALA ruptures through the diaphragm.

Pulmonary amebiasis may develop as a serous, sympathetic effusion in the right pleural cavity due to a right-sided liver abscess.

TABLE 203.2 **DRUG TREATMENT OF AMEBIC LIVER ABSCESS**[a]

Drug of choice	Adult dose	Pediatric dose	Side effects
Metronidazole	750 mg IV/PO TID × 7–10 d	35–50 mg/kg/d in 3 doses × 7–10 d	Common: nausea, vomiting, metallic taste Occasional: peripheral neuropathy, vertigo, seizures, encephalopathy Disulfiram effect: nausea, vomiting with alcohol ingestion
Tinidazole[b]	2 g IV/PO qd × 5 d	60 mg/kg/d (maximum 2 g) × 5 d	Similar side effect profile as metronidazole: better tolerated with less nausea and vomiting

[a] All treatments should be followed by luminal amebicidal agent, described in text and detailed in Chapter 202, "Intestinal protozoa."
[b] Used only as alternative to metronidazole.

Rupture of a liver abscess into the chest cavity can lead to empyema, producing signs such as cough, dyspnea, and pleuritic chest pain. Thoracentesis will reveal the classic anchovy paste fluid described in ALA aspirations. Classically, patients who develop bronchopleural fistula will expectorate the contents of the liver abscess. Although unpleasant, before the availability of amebicidal agents, this occurrence was deemed a good prognostic sign, as it was an effective means of draining the abscess. In addition, hematogenous spread of amebic trophozoites can rarely cause disease in the lung parenchyma, leading to consolidation and sometimes lung abscess. Treatment of pleuropulmonary disease involves using a tissue amebicide, such as metronidazole, and, in the case of empyema, drainage with a chest tube. Amebic pneumonia and lung abscesses from hematogenous spread are successfully treated with metronidazole alone.

Amebic pericarditis

The second most common intrathoracic manifestation of invasive amebiasis is pericarditis (1–3% of patients with ALA), which has a 40% mortality. It is the most serious complication of a left-lobe ALA which ruptures into the pericardium leading to pericarditis and, potentially, cardiac tamponade. A left-lobe liver abscess threatening the pericardial sac may cause irritation and a serous effusion. The rapidity of the amebic pus leakage into the pericardial sac determines both the signs and symptoms that develop. A slow leak gives more insidious symptoms of gradually increasing shortness of breath, unmitigated fever, and patient deterioration. In contrast, a rapid rupture into the pericardium may cause cardiac tamponade and the associated chest pain, tachypnea, pulsus paradoxus, elevated neck veins, and hypotension.

The evaluation of amebic pericarditis begins with establishing the diagnosis of invasive amebic infection with positive serologic testing in a patient with left-lobe liver abscess and a compatible epidemiologic history. An electrocardiogram will show evidence of pericarditis, and chest radiography demonstrates an elevated and immobile left diaphragm. Confirming the diagnosis is only definitively accomplished by aspiration of the pericardium, which, along with effective tissue amebicides, is the treatment of choice. A concomitant large liver abscess should also be aspirated and repeat aspirations performed if needed to eliminate the risk of further pericardial accumulation. Fibrous constriction is unusual after the just described treatment, and surgical treatment is unnecessary in most cases.

Amebic peritonitis

In about 2% of patients with ALA, intraperitoneal abscess and peritonitis complicate the case. The associated physical exam findings of an acute abdomen are usually present. Compared to amebic peritonitis due to perforation of the colon from amebic colitis, patients with ruptured liver abscesses and peritonitis have better outcomes because there is not concomitant colonic bacterial flora contaminating the peritoneum. Treatment of amebic peritonitis due to liver abscess rupture requires metronidazole and therapeutic paracentesis to drain infected collections.

Amebic brain abscess

Approximately 0.66% to 4.7% of patients with ALA may develop an amebic brain abscess. Untreated, an amebic brain abscess has a high mortality rate (90%). Amebic brain abscesses have been described in the frontal, parietal, temporal, and occipital lobes and the cerebellum. Typically, a patient with an amebic brain abscess can present with unspecific symptoms: headache, vomiting, and altered mental status. Signs of amebic brain abscess included most commonly meningeal signs, facial nerve (VII) palsy, motor paralysis, and seizure. Most patients had abnormal cerebrospinal fluid, although there was no distinctive or characteristic abnormality. CT scanning of the head often reveals multiple space-occupying lesions, which may be circumscribed areas of low-attenuation without a clear rim or enhancement early in the course of disease. Treatment involves a prolonged course of metronidazole, which has good central nervous system penetration, and possibly surgical drainage depending on the size of the lesion(s) and severity of the symptoms.

Other manifestations of invasive amebic disease

Amebic splenic abscesses, resulting from the hematogenous spread of amebic trophozoites, can be visualized with ultrasound or CT scan and treated medically with metronidazole. Splenectomy is occasionally required.

Urinary tract amebiasis, manifesting as perinephric abscesses, is again due to the hematogenous spread of amebic trophozoites and is treated with metronidazole. Genital amebiasis is more common in women than men, with vaginitis, vulvovaginal amebiasis, cervicitis, and salpingitis all having been reported. These cases may be sexually transmitted; consequently, ulcerative penile lesions in a sexual partner should be evaluated for possible amebiasis. Invasive carcinoma of the penis and carcinoma of the cervix are often initially suspected because the clinical appearance of amebic ulcerative lesions mimics those of these malignancies. An epidemiologic study in Japan found a link between genital amebiasis and men who have sex with men engaging in anal sex with partners with amebic colitis. The treatment for these manifestations of the disease is again with metronidazole, and sexual partners should always be treated as well. Finally, cases of cutaneous amebiasis, presenting as painful ulcers in both children and adults, have also been described in the literature. These presentations are often, but not always, associated with intestinal amebiasis and respond to metronidazole.

Suggested reading

Haque R, Huston CD, Hughes M, Houpt E, Petri WA Jr. Amebiasis. *N Engl J Med*. 2003;348:1565–1573.

Lotter H, Helk E, Bernin H, Jacobs T, Prehn C, et al. Testosterone increases susceptibility to amebic liver abscess in mice and mediates inhibition of IFN gamma secretion in natural killer T cells. *PLoS ONE*. 2013;8(2):e55694. doi:10.1371/journal.pone.0055694.

Shirley D-A T, Farr L, Watanabe K, Moonah S. A review of the global burden, new diagnostics, and current therapeutics for amebiasis. *Open Forum Infect Dis*. 2018 Jul 1;5(7):ofy161. https://doi.org/10.1093/ofid/ofy161

Section 25

Antimicrobial therapy: General considerations

Principles of antibiotic therapy

John S. Czachor

Over the past three to four decades, there has been a disturbing trend of antibiotic resistance among a wide variety of pathogens that are causing serious disease in patients residing in the community, in long-term care facilities, and in hospitals. The lines of acquisition, however, have begun to blur with increasingly less separation between nosocomial and community settings. Multidrug resistance has become an everyday occurrence, so much so that both the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have instituted antibiotic risk notifications and grading systems ranking the severity of various threats to our health (https://www.cdc.gov/drugresistance/biggest_threats.html https://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed). Antibiotic drug-resistant microorganisms are now a global problem, made worse by the ease of travel and transmission of these microbes. The advent of medical tourism adds an unintended complication to this scenario as well.

The pharmaceutical industry has responded to this grave concern, although there has been an overall decline in the number of new antibiotics introduced compared to the past decade. A number of compelling reasons have been given for this situation, including fewer pharmaceutical companies, the costly vetting/research process of bringing a drug to market, the perceived lower profitability of antimicrobial agents, and the relative delayed initial use of a new product. In any instance, the need for newer and more effective antibiotics has become essential for the future, and there does seem to be an uptick in the numbers of agents approved for use. New classes of antimicrobial agents—and finding different uses for recognized antibiotics, such as aerosolized amikacin—have augmented our choices.

Another event that has merited attention is the continuously evolving novel indications for antibiotics for both infectious and noninfectious disorders. The newer macrolides have anti-inflammatory properties that allow them to be used, for example, in cystic fibrosis. The use of ampicillin combined with ceftriaxone is now the benchmark to treat infective endocarditis caused by *Enterococcus faecalis* infections with high-level resistance to aminoglycosides. Finally, there are a number of antimicrobial compounds that are prescribed for nonbacterial dermatologic conditions, such as dapsone for dermatitis herpetiformis.

When selecting an antibiotic, the clinician must reflect on a variety of issues. Some of the more common factors that merit consideration include the patient's drug allergy history, the relative safety of the medication, the potential of the antibiotic to cause a significant drug–drug interaction, the mechanism of the drug's elimination from the body, the agent's historical "track record" in the therapy of the specific infection being treated, the route of administration of the antibiotic, and, finally, the cost of the medication. With oral administration of antibiotics there are the additional concerns of patient compliance and adequate drug absorption.

Pharmacokinetics and pharmacodynamics

The term "pharmacokinetics" refers to the disposition of an antibiotic throughout the human body. This encompasses such principles as absorption, bioavailability, distribution, protein binding, metabolism, and

elimination. "Pharmacodynamics" refines the concept of pharmacokinetics by describing the interaction between the concentration of the antibiotic at the site of the infection over time and its subsequent effect on the infection itself. Pharmacodynamics is useful for establishing optimum dosing regimens. The absorption of most oral antibiotics occurs by passive diffusion in the small intestine. Some antibiotics, including vancomycin, aminoglycosides, and aztreonam, are not adequately absorbed when given orally. On occasion, this can be advantageous. Oral neomycin can be prescribed as a preoperative preparation prior to large bowel surgery or in the treatment of hepatic encephalopathy, whereas the poorly absorbed oral vancomycin and fidaxomicin are used for the therapy of *Clostridium difficile*-related colitis. Other drugs, such as cefpodoxime proxetil and cefuroxime axetil, are administered as prodrugs to facilitate absorption. Food interferes with the absorption of some antimicrobials (e.g., penicillin, ampicillin, cephalexin, tetracycline, and azithromycin).

A fundamental tenet of antimicrobial activity is that it must achieve therapeutic concentrations at the tissue source of the infection. Multiple factors influence the distribution of antibiotics from plasma to these sites: the nature of the capillary bed (those fenestrated by small pores vs. those unfenestrated capillaries of the brain, leptomeninges, and vitreous humor), the agent's lipid solubility and degree of protein binding (as only unbound drug is antibacterially active and capable of diffusing across capillaries), and the presence of active transport pumps (located in the choroid plexus of the brain, retina, kidneys, and biliary ducts).

Antibacterial agents are eliminated from the body through hepatic and biliary excretion (ceftriaxone and piperacillin), hepatic metabolism (clindamycin, chloramphenicol, metronidazole, erythromycin, sulfonamides, some tetracyclines, isoniazid, rifampin, linezolid), and predominantly renal excretion (most penicillins and cephalosporins, imipenem, aminoglycosides, nitrofurantoin, most tetracyclines, vancomycin, trimethoprim-sulfamethoxazole [TMP-SMX], daptomycin). It is essential that the clinician be aware of renal compromise from congestive heart failure, hypertension, diabetes, medication, and physiologic alteration with age because this will mandate a dosage reduction for those compounds predominantly eliminated by renal excretion. The estimated glomerular filtration rate (GFR; using the Cockroft–Gault equation or the Modification of Diet in Renal Disease [MDRD] equation) has traditionally been used to help determine appropriate drug doses for antimicrobials eliminated primarily by renal excretion when the measured creatinine clearance is not available. A newer formula, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), may be the best to estimate GFR.

Concentration-dependent antimicrobial agents function such that optimal bacterial killing occurs while the concentration of the antibiotic is above the minimum inhibitory concentration (MIC) of the organism. The aminoglycosides are one example of this type and are usually administered as once-daily dosing (unless prescribed for synergistic purposes), taking advantage of the observation that the ratio of the maximum peak drug concentration to organism MIC (8 to 12) correlates with clinical response. Other concentration-dependent antimicrobials include fluoroquinolones, daptomycin, and metronidazole. Alternatively, those compounds that are concentration-independent or time-dependent measure their success by the percentage of time the drug concentration exceeds the MIC of an organism. Drugs in this class include vancomycin, clindamycin, the macrolides, and the β-lactam group. There may be some benefit for continuous intravenous administration of the β-lactam antibiotics, thereby maintaining sustained drug levels above the MIC of the pathogen, particularly in the severely ill or immunocompromised patient.

The postantibiotic effect (PAE) is another pharmacodynamic concept that may impact antimicrobial choice. This refers to the persistent suppression of bacterial regrowth following limited exposure to an antibiotic and can be considered the time it takes for the organism to recover from this exposure. Classically, drugs that affect protein synthesis or nucleic acid synthesis, such as the fluoroquinolones, aminoglycosides, tetracyclines, macrolides, chloramphenicol, and rifampin, have significant PAEs against gram-negative organisms, although the only β-lactam antibiotics that share this property are the carbapenems.

Selection of therapy

Table 204.1 delineates some of the more important host and drug features that influence antibiotic selection. Additional concerns

TABLE 204.1 **SELECTION OF THERAPY**

Host factor	Special antibiotic concern
Drug allergy	Safety record
Site of infection	Success record
Pregnancy	Most likely organism(s) and susceptibility
Epidemiologic information	
Renal function	Bactericidal/bacteriostatic
Recent antibiotic exposure	Penetration into privileged sites (CNS, endocardium)
Infection acquisition (community/ECF/hospital)	Potential to cause major untoward event
Concomitant medication	

Abbreviations: CNS = central nervous system; ECF = extended care facility.

BOX 204.1

Combination therapy

Tuberculosis
Disseminated *Mycobacterium avium* complex
Helicobacter pylori
Endocarditis (α-hemolytic streptococcus, enterococcus)
Life-threatening infection caused by *Pseudomonas aeruginosa*
Empiric treatment
- -Pneumococcal meningitis until susceptibility confirmed
- -Febrile, severely neutropenic host
- -Polymicrobic infection
- -Life-threatening infection with inapparent source

relate to adherence to the therapeutic regimen and cost of the medication. Antibiotics that can be administered infrequently lend themselves to out-of-hospital administration. Daptomycin, ertapenem, telavancin, and ceftriaxone can usually be infused as infrequently as once a day. Both dalbavancin and oritavancin have prolonged half-lives which offer unique one-time dosing. The development of newer oral antimicrobial agents that can be given as infrequently as once or twice per day achieves enhanced compliance. Compounds such as the fluoroquinolones, metronidazole, and linezolid/tedizolid have excellent absorption, resulting in high serum levels without the need for intravenous administration. Some medications, although still available, including chloramphenicol and erythromycin estolate, are infrequently prescribed, having fallen out of favor due to adverse effects, unfavorable pharmacokinetics and/or pharmacodynamics, or a limited spectrum of activity.

Antibiotic combinations are sometimes used to manage selected infections (Box 204.1). There are potential disadvantages, however, to the administration of antibiotic combinations, such as increased untoward events, heightened costs, and superinfection.

Practice guidelines and antibiotic stewardship

In the past, with few exceptions, choosing an antibiotic has been left to the whims of clinicians. Seldom has the optimal duration of antibacterial treatment been defined by evidence-based medicine. Practice guidelines have emerged in response to questions regarding the quality, consistency, and expense of medical care. Guidelines are generally created based on the best available scientific evidence melded with expert opinion and cohesively assembled in a usable format for practitioners. Selected medical societies and organizations, as well as easily accessible websites, have become the repositories for the recommended information. Access to these guidelines has helped to transform how medicine is practiced today. Guidelines for various infectious conditions already exist, whereas others are being created and refined.

Just as important as the guidelines has been the recognition of the need for optimal, cost-effective, and rational use of antibiotics. Stewardship has evolved from guidelines to encompass antimicrobial utilization for all conditions and can be found in hospitals, long-term care facilities, long-term acute care facilities, ambulatory surgical centers, dialysis centers, and other medical settings. Institutions employing stewardship are coordinating interventions, often in conjunction with pharmacy assistance, to promote appropriate antibiotic selection as well as their proper dose, duration, and route of administration. Benefits of antibiotic stewardship include improved clinical outcomes, reduced medical costs, fewer toxic and adverse effects, and decreased selection of antibiotic-resistant microorganisms.

Antibiotics and the human microbiome

Recently, we have begun to unravel the mystery and the science behind the human microbiome. Our own innate microorganisms help us in so many ways, and yet, with antibiotic use, we alter their function and composition. This change in these microbes, known as *dysbiosis*, has far-reaching effects beyond the immediate concerns of antibiotic-associated diarrhea, *Clostridium difficile* colitis, and establishing a reservoir for antibiotic resistance. In fact, the effects of antibiotic therapy on the microbes within the gut may persist for a longer time than previously appreciated, perhaps even months to years. Increased susceptibility to infections; a link to atopic, inflammatory, and autoimmune diseases; and effects on the regulation of host metabolism, energy homeostasis, and adiposity, all have been associated with dysbiosis. The role of dysbiosis affecting chronic inflammation is being delineated as well. *Probiotics* have been seen by many as a restorative option once antibiotics have been prescribed. It is unclear, however, which preparation and/or composition of probiotic provides the best replenishment for the gut microbiota. A greater understanding and appreciation of the effects of antibiotics on the human microbiome is essential knowledge if we are to use antibiotics appropriately and wisely.

Special populations

The pregnant patient, the lactating patient, and those of reproductive potential

Physiologic changes in the urinary tract and complications of parturition predispose the pregnant woman to urinary tract infections as well as chorioamnionitis and endometritis. Antibiotic selection for the pregnant woman must take into consideration the potential for drug-induced toxicities for both the woman and her developing fetus. Antibiotics were traditionally classified based on animal studies and epidemiologic data often generated from pregnant women who were exposed to antibacterial agents because of clinical need. The antibiotics were then assigned a letter from A to D or X to quantify their relative risk. On the horizon, however, is

the soon to be introduced regulation from the US Food and Drug Administration (FDA) that fundamentally changes how we address pregnancy and antimicrobial concerns. Referred to as the Pregnancy and Lactation Labeling Rule (PLLR), the intent is to provide prescribers clear and in-depth information on the risks and benefits of a drug administered either during pregnancy or lactation. Gone is the old alphabet system, which will be replaced by risk summary information from the manufacturer regarding the specific antibiotic's effects on pregnancy, lactation, and potential untoward effects on females and males of reproductive potential. For further information, visit https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf.

The elderly patient

A number of factors distinguish the administration of antibiotics in elderly patients: concern about compliance with the medication because of poor memory, impaired vision, diminished hearing, or difficulty in opening child-resistant containers; the decrease of renal function with normal aging and the need to make appropriate dosage adjustment of medications to prevent antibiotic-related toxicities; the potential for drug–drug interactions because many geriatric patients take numerous medications daily; and the presence of concomitant medical disorders that can adversely influence antibiotic distribution and penetration. Elderly patients appear to experience adverse drug reactions from antibacterial compounds more frequently than do younger patients. Older patients with comorbid conditions often may be excluded from clinical trials, and therefore evidence coming from these studies may only be partly applicable to this particular group. As the elderly are more frequently admitted to the hospital, many times with an infection, antibiotic use follows. With many preexisting medications in place, the risk of potentially dangerous pharmacological interactions involving antimicrobial agents is among the most frequent and undesirable consequences of polypharmacy in older persons.

Antibiotic use in continuous renal replacement therapy

For critically ill patients with infection, acute renal insufficiency often develops. Acute renal failure is associated with increased morbidity and mortality in patients with sepsis. Continuous renal replacement therapy (CRRT), an alternative to traditional hemodialysis and better tolerated by hemodynamically unstable patients, decreases the incidence of adverse biomarkers. Appropriate dosing of antimicrobial agents for patients receiving CRRT remains poorly defined as the pharmacokinetics of drug removal in critically ill patients undergoing CRRT is complex. Those antibiotics with low protein-binding capacity and/or poor tissue penetration have enhanced removal. Mechanical or operational factors associated with CRRT play a role in antibiotic therapy in these patients as well, and increasing the blood flow or dialysate flow rate of CRRT may increase drug clearance. However, recent consensus is that using the CRRT modality, whether it be convective or diffusive, does not affect patient infectious outcomes. A more important variable is the effluent flow rate, which, when kept within the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, results in a target goal attainment of antibiotic levels. Tables 204.2 and 204.3 list antibiotic dose alterations for patients with CRRT.

TABLE 204.2 **DRUGS NOT REQUIRING DOSAGE ALTERATION DURING CONTINUOUS RENAL REPLACEMENT THERAPIES**

Aztreonam	Linezolid
Azithromycin	Meropenem
Cefepime	Metronidazole
Ceftriaxone	Moxifloxacin
Clindamycin	Oxacillin
Doxycycline	Quinupristin-dalfopristin
Imipenem	Rifampin

Route of administration

Antibiotics are administered intravenously when the patient has systemic perfusion issues (septic shock, hypotension), has bacterial infection at a unique or protected site (e.g., leptomeninges, endocardium, a deep neck infection, epiglottitis, endophthalmitis, myopericarditis, mediastinitis, septic thrombophlebitis), has an infection that is imminently life-endangering (e.g., meningococcemia, Rocky Mountain spotted fever, plague, bacteremia), has an infection that precludes oral administration because of nausea/vomiting or impaired function of the gastrointestinal tract (peritonitis, appendicitis, ascending cholangitis, pancreatic abscess), or has an infection that cannot be managed with an oral compound. Traditionally, physicians have prescribed an intravenous antibiotic simply because

TABLE 204.3 **DRUGS REQUIRING DOSAGE ALTERATION DURING CONTINUOUS RENAL REPLACEMENT THERAPIES (CRRT)**[a]

Amikacin	Penicillin
Ampicillin/sulbactam	Piperacillin
Cefazolin	Piperacillin-tazobactam
Ciprofloxacin	Ticarcillin-clavulanate
Daptomycin	Tobramycin
Gentamicin	TMP-SMX
Levofloxacin	Vancomycin

[a] Dose reduction as compared to normal renal function.
Abbreviations: CRRT = continuous renal replacement therapies, TMP-SMX = trimethoprim–sulfamethoxazole.

a patient was admitted to the hospital. However, the decision to hospitalize a patient does not automatically dictate that the antibacterial therapy must be administered intravenously. Unless one of the indications previously listed is present, some serious infections can be successfully managed by oral antibiotics.

Adverse reactions

Antibiotic-induced untoward events are a concern not only because they result in host injury but also because these adverse events interrupt and complicate treatment, thereby requiring the administration of alternative and often more expensive and potentially toxic medication. Antibiotic-induced untoward events can also serve as a source of medical litigation.

Adverse events attributed to antibiotics are usually caused by three mechanisms: exaggerated response to the known pharmacologic effects of the drug, immunologic reactions to the drug or its metabolites, and toxic effects of the medication or its metabolites. Many of the antibiotic-related adverse events are initiated by an extension of the drug's normal pharmacology, and these events are often avoided by appropriate dosage adjustment.

In addition to the direct influence of the antibiotic, host factors such as genetic constitution, integrity of drug elimination mechanisms, and concomitant medical disorders can affect the frequency and severity of antibiotic-induced untoward events. For example, with HIV-infected patients, TMP-SMX causes more non–dose-related gastrointestinal intolerance, fever, and altered liver function, while ampicillin-induced rash is more common in those patients with infectious mononucleosis.

Antibiotic allergy

Antibiotic-induced allergic reactions are immunologically mediated and most commonly involve the skin, presenting as pruritus, a maculopapular eruption, or urticaria. More significant antibiotic-induced allergic reactions include erythema multiforme major (Stevens–Johnson syndrome), toxic epidermal necrolysis, exfoliative dermatitis, angioedema, and anaphylaxis. Antibiotic-induced allergic reactions are not confined to the skin: bone marrow suppression of all three cell lines, pulmonary hypersensitivity reactions, renal and liver manifestations, and muscle involvement have been routinely documented.

Among the most feared allergic reactions to penicillins and cephalosporins are angioedema and anaphylaxis. These events are usually attributed to drug-specific immunoglobulin E (IgE) antibodies from prior drug administration, but these serious untoward events can also result from direct release of mast-cell mediators following the first dose of antibiotic. Vancomycin and fluoroquinolones can also cause direct mast cell release in the absence of drug-specific IgE antibodies. Skin testing has been very accurate in identifying penicillin-related IgE antibodies and for determining the risk for patients experiencing an immediate reaction (see Chapter 210, "Hypersensitivity to antibiotics").

There is room for discussion regarding penicillin allergy. Frequently, patients are unaware of the exact manifestation of this problem. Perhaps it occurred as a child, and there is nobody to historically confirm the allergy, nor is there allergy testing as an option to verify the allergy. Many times, the patient cannot recall the untoward effect. The question for the clinician is whether a β-lactam class drug may be safely administered. Studies addressing this concern have consistently shown that true penicillin allergy is uncommon based on allergy testing, but the conundrum presented is what to do if no such testing is available? The percentage of cross-reactivity to other -lactam antibiotics has been slowly reduced over time. For cephalosporins, rates of cross-reactivity are approximately 1% to 2%, and the risk lessens as the compounds go from first-generation to fourth-generation. Although structurally similar to the β-lactam antibiotics, aztreonam can be safely administered to patients who have experienced an anaphylactic reaction following the administration of a member of the penicillin family. In the past, it was considered potentially harmful to administer a carbapenem to patients with a history of immediate hypersensitivity to penicillin, though recent investigations and experience suggest that the allergic crossover is approximately 1%. There always remain useful desensitization protocols for those who are in dire need of penicillin or β-lactam class antibiotics but who have immediate hypersensitivity reactions. It is noteworthy to remember, however, that any drug desensitization can be complicated by severe allergic reactions.

Drug monitoring

Monitoring the adequacy of antibiotic treatment involves the physician critically assessing the patient's response on a regular basis, as determined by the resolution of both the systemic and local inflammatory response and, in part, measured by results obtained from laboratory studies, microbiology data, and radiologic exams. In general, antibiotic concentrations in blood are not routinely measured. Aminoglycoside antibiotics are an exception, however, because serum concentrations of these compounds are performed to ostensibly reduce the risk of nephrotoxicity and ototoxicity and ensure appropriate therapeutic levels. Better outcomes for treating patients with gram-negative bacteremia are noted if peak levels of gentamicin and tobramycin exceed 5 μg/mL, and peak amikacin concentrations exceed 20 μg/mL. Avoiding elevated aminoglycoside levels may result in decreased ototoxic and nephrotoxic effects. Serial audiometric testing to assess ototoxicity should be considered for those patients receiving long-term administration of aminoglycosides and vancomycin. Some practitioners also measure vancomycin troughs to assist their choice of dosage interval and drug amount, and appropriate levels may reduce the incidence of ototoxicity. Some antifungals agents, in particular the azole class, often require serum level monitoring to ensure optimum concentrations of the drug for good outcomes.

Outpatient parenteral antibiotic therapy

Outpatient parenteral antibiotic therapy (OPAT) is designed either to avoid hospitalization or to continue treatment initiated in the hospital and provide therapy that is therapeutically equivalent to the inpatient setting while enhancing the patient's quality of life and achieving significant cost savings. The decision to initiate OPAT is influenced by the availability of an adequate oral treatment; the patient's clinical status and acceptance of this form of treatment; the home environment and support systems; the option for an infusion center or advanced treatment area; the potential for treatment plan compliance; the availability of competent, professional follow-up; and reimbursement status. OPAT has been a safe and effective form of treatment for patients with a wide array of infectious diseases, and antibiotics such as ceftriaxone, vancomycin, daptomycin, ertapenem, and aminoglycosides lend themselves to OPAT because these compounds can be administered infrequently. The advent of dalbavancin and oritavancin has expanded the dosing options available to practitioners because of their unique half-lives allowing for extended intervals between doses. In addition to antibiotic-related adverse events, outpatient intravenous antibiotic infusion poses the risk of vascular access–related complications, such as venous thrombosis, and catheter-related bloodstream infections.

Switch (step-down) therapy

The availability of numerous safe and effective oral antimicrobials that are well absorbed and can be administered infrequently provides the opportunity for *switch* or *step-down therapy*. This approach, available to the patient who has stabilized and appears to be "turning the corner," as manifested by resolution of fever with improved appetite and strength as well as the reduction of the signs and symptoms caused by the infection, has been successfully used to treat patients with the most commonly identified community-acquired infections. Switch therapy frees the patient from the inconvenience, discomfort, and risks of intravenous access; results in considerable cost savings; and permits earlier hospital discharge. Switch therapy requires patient compliance with the medication and adequate intestinal absorption of the antimicrobial, coupled with the appropriate follow-up from the clinician.

A similar concept to step-down is to "streamline" or narrow the spectrum of activity of the antibiotic once susceptibility testing is completed. Often this can be one intravenously administered medication switching to another parenteral drug or possibly to an oral antibiotic. This is a common practice within the realm of antibiotic stewardship. Rapid testing for resistance markers or genes may result in a shorter time of broad-spectrum antibiotic treatment and perhaps reduce the potential for side effects, drug interactions, and effects on the microbiome.

Antibacterial prophylaxis

Appropriately administered antibiotic prophylaxis is the standard of care for patients who undergo selective surgical procedures. The ideal prescribed agent should cause minimal untoward events, not select for virulent organisms, achieve adequate local tissue levels, be relatively inexpensive, demonstrate inhibitory activity for the bacteria anticipated to cause postoperative infection, and should be infused (usually 30–60 minutes before the surgery begins) so that therapeutic concentrations are present prior to the initial operative incision (see Chapter 112, "Surgical prophylaxis").

In addition to their indication for the prevention of postoperative infections, antibacterial agents have been effective for the prevention (primary/secondary) of several nonsurgical disorders, including repetitive cellulitis, rheumatic fever, syphilis, traveler's diarrhea, tuberculosis, invasive meningococcal disease, pertussis, diphtheria, plague, and recurrent cystitis in women. Although no definite studies have confirmed that antibiotic prophylaxis provides protection against the development of endocarditis during bacteremia-producing procedures, it is currently recommended that patients with certain cardiac conditions receive antibiotic prophylaxis when subjected to selective dental, respiratory tract, gastrointestinal tract, and genitourinary tract bacteremia-producing procedures (see Chapter 111, "Nonsurgical antimicrobial prophylaxis" and Chapter 37, "Endocarditis").

Antimicrobial failure

When a patient is not responding to antimicrobial therapy, there is a temptation to administer an alternative compound with an extended spectrum of activity. This approach is often valid, particularly for the seriously ill patient. It is essential, however, for the clinician to establish an accurate diagnosis because noninfectious disorders often masquerade as infection. For example, hypersensitivity to an insect bite, acute gout, a fixed drug reaction, skin manifestations of Lyme disease, necrotizing fasciitis, and anaerobic myonecrosis can initially resemble traditional bacterial cellulitis; Charcot joint in the diabetic simulates osteomyelitis; pulmonary infarction, lung cancer, acute respiratory distress syndrome, aspiration of gastric contents, drug-induced pneumonitis, and congestive heart failure can imitate an infectious pneumonia; and vasculitis can resemble endocarditis. There should be consideration given to those factors that have the potential to impede successful antibiotic treatment (obstruction, necrotic tissue, undrained abscess, or an infected prosthetic device), the possibility of a polymicrobic infection, the development of drug resistance or a superinfection, or infection in a "privileged site," such as meningitis, endocarditis, or chronic bacterial prostatitis, disorders that require antimicrobials with unique penetration properties.

The clinician should also consider drug compliance and adequacy of drug dosage and recognize that selective infections, such as bacterial endocarditis, bacterial meningitis, and life-threatening

infections in granulocytopenic hosts, require a bactericidal antibiotic. An additional factor that can impact antibiotic treatment for patients is the recognition that numerous patients self-prescribe antibiotics prior to their first encounter with physicians. This practice can alter the anticipated microbiologic pathogens, the manifestations of the infection, and the clinical response of the infection.

In addition to antibiotics, survival of seriously ill, hospitalized infected patients often requires early institution of adjunctive treatments. Therapies that merit consideration include vigorous fluid administration, cardiovascular support with a vasopressor or an inotropic agent, oxygen delivery via lung-protective ventilation, and aggressive renal replacement therapy including CRRT.

Inappropriate administration

There are no convincing scientific data to support the administration of antibiotics to otherwise healthy patients who experience rhinitis and nonbacterial pharyngitis, laryngitis, acute bronchitis, or acute sinusitis. These infections are predominantly self-limited viral disorders. Antibiotic administration to these patients will serve only to add to healthcare-related costs, promote the spread of antibiotic-resistant organisms, and place patients at risk of adverse drug reactions. Additional disorders for which antibiotics are not indicated include witnessed aspiration pneumonitis, colonized noninfected wounds, and asymptomatic bacteriuria, unless the latter condition is identified in a pregnant woman or those about to undergo an invasive genitourinary procedure.

Antibiotic therapy is not appropriate treatment for the patient with persistent unexplained fever. These patients merit a thorough evaluation consisting of a comprehensive medical history and physical examination complemented with the judicious application of laboratory and radiographic studies. Empiric administration of an antibiotic to the patient with protracted fever may serve to obscure and/or delay the correct diagnosis and result in untoward drug-induced events.

When making decisions regarding the administration of antibiotics, clinicians should be guided by accurate susceptibility data for those clinically significant isolates recovered from appropriately collected specimens, as well as expert consultation and evidence-based medicine as published in accepted practice guidelines.

Acknowledgments

This chapter includes contributions from the late Richard A. Gleckman.

Suggested reading

Corsonello A, Abbatecola AM, Fusco S, et al. The impact of drug interactions and polypharmacy on antimicrobial therapy in the elderly. *Clin Microbiol Infect*. 2015;21:20–26.

Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26:1–12.

Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev*. 2010;74(3):417–433.

Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44:159–177.

Estes L. Review of pharmacokinetics and pharmacodynamics of antibacterial agents. *Mayo Clin Proc*. 1998;78:1114–1122.

Francino MP. Antibiotics and the human gut microbiome: Dysbiosis and accumulation of resistances. *Front Microbiol*. 2016;6:1543:1–11.

Sakoulas G, Geriak M, Nizet V. Is a reported penicillin allergy sufficient grounds to forgo the multidimensional antimicrobial benefits of β-lactam antibiotics? *Clin Infect Dis*. 2019;68(1):157–164.

Shaw AR, Mueller BA. Antibiotic dosing in continuous renal replacement therapy. *Adv Chronic Kidney Dis*. 2017;24(4):219–227.

Zinner SH. The search for new antimicrobials: Why we need new options. *Expert Rev Anti Infect Ther*. 2005;3:907–913.

Antibacterial agents

Richard R. Watkins

The modern antibiotic era began with the discoveries of penicillin by Fleming in 1928 and sulfonamides by Domagk in 1932.Since then, more than a dozen different classes of antibacterial agents have been developed for use in humans. This chapter describes the various antibacterial agents, emphasizing their mechanisms of action, clinical indications, and mechanisms of bacterial resistance (Box 205.1).

Penicillins and monobactams

The core structure of the penicillins consists of a thiazolidine ring attached to a β-lactam ring and an R-group side chain. The thiazolidine–β-lactam ring provides antibacterial activity, while the side chain determines the antimicrobial spectrum and pharmacologic characteristics. Penicillins are bactericidal agents that inhibit penicillin-binding proteins (PBPs), which are involved in the synthesis of peptidoglycan. PBPs vary in their concentrations among bacteria and in their binding affinity for β-lactam antibiotics. This largely explains why β-lactam antibiotics differ in their efficacy and antibacterial spectrum. One type of PBP is β-lactamase, which hydrolyzes and inactivates the β-lactam ring. The penicillins may be conveniently grouped into the following classes: natural penicillins, penicillinase-resistant penicillins, aminopenicillins, and extended-spectrum penicillins. In addition, some of the penicillins have been combined with β-lactamase inhibitors including clavulanic acid, sulbactam, and tazobactam, which widen their antibacterial spectrum of activity.

The natural penicillins, penicillin G and penicillin V, are so named because they can be purified directly from cultures of the mold *Penicillium*. Penicillin G is unstable in acid and inactivated by gastric contents. It is administered by intramuscular, subcutaneous, intrathecal, or intravenous (IV) injection. Benzathine penicillin G, the treatment for primary, secondary, and latent syphilis, is slowly absorbed from tissue after intramuscular injection and detectable in serum for up to 30 days. However, levels are inadequate for treating neurosyphilis and IV formulations should be used. Most bacteria have developed resistance to the natural penicillins. Those that remain susceptible include *Streptococcus pyogenes*, viridans group streptococci, some enterococci, some *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Neisseria meningitidis*, some *Haemophilus influenzae*, *Clostridium* (except *Clostridioides difficile*), *Actinomyces israelii*, and *Leptospira*. Penicillin V is only available for oral use and treats most of the same organisms as penicillin G, although it is less active against *Haemophilus* and *Neisseria*. Nafcillin, a penicillinase-resistant penicillin, is active against methicillin-sensitive *Staphylococcus aureus* (MSSA), penicillin-susceptible strains of *S. pneumoniae*, and most anaerobic gram-positive cocci. Importantly, nafcillin does not treat enterococcus and *Listeria*. Oral formulations of penicillinase-resistant penicillins include dicloxacillin (which is frequently used for skin and soft tissue infections [SSTIs]) and cloxacillin. The aminopenicillins, ampicillin and amoxicillin, have improved activity against enterococci compared to penicillin G. Amoxicillin is better orally absorbed than ampicillin, while the latter is effective in treating meningitis due to *L. monocytogenes*, *N. meningitidis*, and group B streptococci. Ampicillin has been combined with the β-lactamase inhibitor sulbactam and is often given for mixed bacterial infections, such as intra-abdominal infections and obstetric and gynecologic infections. Amoxicillin-clavulanate is an oral formulation that is also given when multiple organisms

BOX 205.1

Overview of antibacterial agents

Penicillins and monobactams
Cephalosporins
Carbapenems
Aminoglycosides
Quinolones
Tetracyclines
Macrolides
Pleuromutilins
Glycopeptides, lipopeptides, and streptogramins
Oxazolidinones
Sulfonamides
Metronidazole and clindamycin
Rifamycins
Polymyxins
Miscellaneous agents
Chloramphenicol
Nitrofurantoin
Fosfomycin
Topicals

need to be treated, such as animal or human bite wounds. The extended-spectrum penicillins include piperacillin, ticarcillin, and carbenicillin. Piperacillin is almost always given in combination with the β-lactamase inhibitor tazobactam. It has a wide range of activity including streptococci, anaerobes, enterococci, many Enterobacterales as well as *Pseudomonas aeruginosa*. Piperacillin-tazobactam is utilized for many serious infections including hospital-acquired pneumonia, neutropenic fever, polymicrobial SSTIs, intra-abdominal infections, complicated urinary tract infections (UTIs), and often empirically for sepsis. Of note, use of piperacillin-tazobactam has been identified as a risk factor for *Candida glabrata* and *Candida krusei* fungemia. Ticarcillin-clavulanate is another parenteral broad-spectrum agent with similar indications as piperacillin-tazobactam, although less active against enterococci.

Monobactams consist of a single β-lactam ring with side chains. Currently the only commercially available monobactam is aztreonam. Monobactams are active exclusively against gram-negative aerobic bacteria. Aztreonam is not absorbed from the gastrointestinal tract and is usually given by the IV route. It is the only β-lactam that can be given to patients with allergies to penicillin or other β-lactam antibiotics since there is no cross-reactivity between them. An inhaled formulation of aztreonam has been developed for chronic use in cystic fibrosis patients with endobronchial *P. aeruginosa* infection. The combination of aztreonam and the non–β-lactam β-lactamase inhibitor avibactam is in late stage development for antibiotic-resistant infections.

Bacteria employ a number of resistance mechanisms against the penicillins and monobactams. The most common is the production of β-lactamase, which covalently reacts with and lyses the β-lactam ring. Four different classes of β-lactamases have been identified, designated A through D. Other mechanisms include efflux pumps which push penicillin out across the bacterial outer membrane, porins which do not allow passage of penicillins into the cytoplasm, and production of low-affinity PBPs.

Cephalosporins

The second major group of β-lactams, cephalosporins, are widely used in clinical practice. Currently there are >20 cephalosporins available worldwide. They are composed of a β-lactam ring fused to a six-member dihydrothiazine ring. This structure bestows more intrinsic resistance against β-lactamases compared to the five-member ring of penicillin. Cephalosporins are commonly classified according to generation, with agents in each generation having a similar antibacterial spectrum of activity. Successive generations gain activity against aerobic gram-negative bacteria. Enterococci are intrinsically resistant to cephalosporins, although the methicillin-resistant *S. aureus* (MRSA)-active cephalosporins have lower minimum inhibitory concentrations (MICs) against ampicillin-sensitive strains. The mechanism of action of cephalosporins is similar to other β-lactam agents, namely binding to and inhibiting PBPs, which in turn prevents peptidoglycan synthesis. Cephalosporins are bactericidal drugs and cause persistent suppression of bacterial growth for several hours, called the *post-antibiotic effect* (PAE), in gram-positive bacteria, but not in gram-negative organisms. Their rapidity of bacterial killing is determined by the amount of time that the drug concentration exceeds the MIC, with maximal killing at four times the MIC.

The first-generation cephalosporins include cefazolin, cefadroxil, and cephalexin, with the first administered parenterally and the latter two orally. Cefazolin is commonly used for infections caused by MSSA and streptococci, such as SSTIs, endocarditis from susceptible strains, and surgical prophylaxis for foreign-body insertion and other clean and clean-contaminated surgical procedures with a high risk for infection. The oral first-generation agents have good oral bioavailability and are effective for many SSTIs. They are often used to transition to oral therapy after parenteral cefazolin or in the outpatient setting. They are not active against *H. influenzae* or *Moraxella catarrhalis* and should not be used for respiratory infections. Second-generation cephalosporins are divided into two groups, the true cephalosporins (cefuroxime) and the cephamycins (cefoxitin and cefotetan). Cefuroxime was frequently used in the past for respiratory tract infections, but its poor activity against penicillin-resistant *S. pneumoniae* has now limited its effectiveness. The cephamycins have good activity against aerobic gram-negative and anaerobic organisms and are first-line agents for intra-abdominal, gynecologic, and mixed skin infections. The parenteral third-generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime, and ceftizoxime) have a number of important clinical indications. Ceftriaxone and cefotaxime are active against penicillin-resistant pneumococcus and are recommended for treatment of community-acquired pneumonia (CAP; when combined with azithromycin) and meningitis. Ceftriaxone is the drug of choice for gonococcal infections and is combined with

doxycycline to treat pelvic inflammatory disease. Both ceftriaxone and cefotaxime are active against *Borrelia burgdorferi* and are effective for neurologic Lyme disease. Also, these agents have good activity against Enterobacteriales, although caution should be used with monotherapy against *Citrobacter*, *Serratia*, and *Enterobacter* species as they can develop inducible resistance through chromosomal β-lactamase production. Ceftazidime has good activity against *P. aeruginosa* but limited activity against *S. aureus*. Ceftazidime-avibactam has further coverage against resistant gram-negative bacilli including ceftazidime-resistant strains, and *Acinetobacter baumannii*. Several oral third-generation cephalosporins are available (cefpodoxime, cefixime, cefdinir, and cefditoren) and are commonly prescribed for respiratory infections, sinusitis, and otitis media. Currently the only available fourth-generation cephalosporin in the United States is cefepime. This drug has an enhanced spectrum of activity against gram-negative organisms including those with reduced sensitivity to third-generation drugs. Cefepime is recommended as monotherapy for patients with neutropenic fever, although it is often combined with an aminoglycoside. Ceftaroline and ceftobiprole are advanced-generation cephalosporins with broad gram-positive and gram-negative in vitro activity and comparable efficacy to vancomycin against MRSA. They are also active against ampicillin-sensitive enterococci but not against *P. aeruginosa* or *Acinetobacter* spp. Ceftaroline has been approved in the United States to treat CAP and SSTIs, including those caused by MRSA and MSSA. Ceftolozane-tazobactam is another advanced cephalosporin-β-lactamase inhibitor combination primarily used to treat antibiotic-resistant *P. aeruginosa*. Finally, cefiderocol is indicated for complicated urinary tract infections due to multidrug-resistant gram-negative bacteria, including *Pseudomonas aeruginosa*, when no other options are available.

Carbapenems

Among the most broad-spectrum antibiotics, carbapenems are often reserved for serious infections. There are four available agents in this class: ertapenem, meropenem, imipenem, and doripenem. Also, the combinations of meropenem-vaborbactam and imipenem-cilastatin-relebactam have been recently approved. Their chemical structure is slightly different from other β-lactams in that the sulfur is replaced by a methylene group and the ring contains a double bond. Imipenem is a substrate for the kidney enzyme dehydropeptidase-1. It is coadministered with cilastin, a dehydropeptidase-1 inhibitor. Carbapenems have a similar mechanism of action (i.e., binding to high-molecular-weight PBPs) and are not hydrolyzed by most penicillinases. All have excellent activity against many gram-positive cocci. Penicillin-susceptible *Enterococcus faecalis* is susceptible to imipenem with MICs of ≤2 μg/mL but resistant to the other carbapenems. *Enterococcus faecium* is resistant to all carbapenems, as are methicillin-resistant staphylococci. *Neisseria* spp., *Haemophilus* spp., and Enterobacteriales are all highly susceptible to carbapenems, including strains that produce extended-spectrum β-lactamases (ESBLs). Doripenem is the most active against *P. aeruginosa*, while ertapenem is inactive. Ertapenem also has poor activity against *Acinetobacter*. *Stenotrophomonas maltophilia* and *Burkholderia cepacia* are intrinsically resistant to all four carbapenems. As a class, carbapenems are highly active against anaerobic bacteria. The addition of the cyclic boronic acid inhibitor vaborbactam extends the spectrum of meropenem to include some carbapenem-resistant organisms. Relebactam, a class A/C β-lactamase inhibitor, can restore activity against imipenem-cilastatin–resistant organisms, including some carbapenem-resistant *Klebsiella* and *P. aeruginosa*.

Because of their activity against many gram-positive, gram-negative, and anaerobic bacteria, carbapenems treat a wide range of infections. Moreover, they are often a good choice for patients who have recently received other antibiotics or for empiric coverage of sepsis. From an antibiotic stewardship perspective, carbapenems are advantageous since they can replace multiple antibiotics with one drug. For instance, ertapenem, with its long half-life that permits once-daily dosing, is often given to treat polymicrobial infections. However, the convenience of carbapenems must be carefully balanced against the potential for the emergence of resistance. Adverse events are similar to other β-lactams, although as a class there is an increased risk for seizures, particularly with imipenem.

Resistance to carbapenems usually occurs through overproduction of efflux pumps, altering PBPs, diminished outer membrane permeability, or production of β-lactamases. Several species of Enterobacteriales carry the plasmid-borne carbapenemases KPC-1, KPC-2, and KPC-3, which are capable of degrading carbapenems. *P. aeruginosa* also has a distinct efflux pump that is capable of removing numerous antibiotics, including meropenem, doripenem, and ertapenem but not imipenem. The carbapenemase New Delhi metallo-β-lactamase-1 (NDM-1) has spread worldwide. It is a class B carbapenemase (also called a metallolactamase) that requires zinc at its active site.

Aminoglycosides

The first aminoglycoside to be produced was streptomycin in 1944. It was followed by neomycin, then gentamicin, tobramycin, and amikacin. In 2018, plazomicin was approved for adults with complicated UTIs and limited or no alternative treatment options. Aminoglycosides are bactericidal agents that exhibit concentration-dependent killing. They bind to the 30S subunit of the prokaryotic ribosome, preventing protein synthesis from mRNA. This occurs through penetration of the bacterial cytoplasmic membrane by an oxygen-dependent active transport mechanism. Because of this action, aminoglycosides work poorly in anaerobic environments such as abscesses. These agents demonstrate a significant PAE, which increases with the peak serum concentration. Aminoglycosides are rarely used as single agents and are usually combined with another antimicrobial, such as a β-lactam or vancomycin. This helps prevent the emergence of resistance and gains the benefit of synergy. In cases of endocarditis, gentamicin should be administered using multiple daily dosing. However, for other types of infections there are several advantages of once-daily administration over multiple daily dosing. Animal studies have shown a lower rate of drug-related toxicities as well as a more robust PAE with once-daily dosing. Studies in humans

have also demonstrated that once-daily dosing is efficacious, causes less nephrotoxicity, and is more cost-effective compared to multiple daily dosing regimens. The toxicities of aminoglycosides are well established and include nephrotoxicity (incidence 5–10%), ototoxicity, vestibular toxicity, and neuromuscular blockade. Therefore, these agents should be used cautiously in patients with myasthenia gravis, electrolyte abnormalities such as hypocalcemia and hypomagnesemia, or with concurrent drugs that interfere with neuromuscular transmission, such as calcium channel blockers. Renal failure associated with aminoglycosides is usually reversible and often resolves once the drug is discontinued. Ototoxicity is more likely to be permanent.

Among their clinical indications, aminoglycosides have in vitro activity against strains of MSSA, although resistance can develop quickly unless used in combination with another active drug. Gentamicin is active against species of *Enterococcus*, but tobramycin and amikacin are not. Pneumococci and all other streptococci are resistant to aminoglycosides, as are anaerobic bacteria. Certain aminoglycosides have activity against mycobacteria; for instance, streptomycin inhibits *Mycobacteria tuberculosis* and amikacin inhibits *Mycobacteria avium-intracellulare*. Most species of Enterobacteriales, *P. aeruginosa*, *Serratia*, and *Acinetobacter* are susceptible to plazomicin, amikacin, gentamicin, and tobramycin but resistance rates vary between institutions. Notably, plazomicin has potent in vitro activity against carbapenem-resistant *A. baumannii*. *Stenotrophomonas maltophilia* and *Burkholderia cepacia* are resistant to aminoglycosides. Streptomycin is effective therapy for *Yersinia pestis* and *Francisella tularensis*, and gentamicin plus doxycycline is used to treat brucellosis.

Overall, the prevalence of bacterial resistance to the aminoglycosides remains low. There are three main mechanisms for resistance to these agents: (1) point mutations in 16S ribosomal RNA, (2) efflux pumps that prevent accumulation of the drug, and (3) bacterial enzymes that modify the drug to bind poorly to ribosomes. Enterococci are intrinsically resistant due to their facultative anaerobic metabolism. ESBLs are carried on plasmids that also carry resistance genes for aminoglycosides.

Quinolones

The first quinolone, nalidixic acid, was generated as a by-product during the production of chloroquine. Investigators discovered it had activity against certain gram-negative bacteria. Modifications of the compound, including the addition of fluorine, led to further quinolones with aerobic gram-positive, additional aerobic gram-negative, and some anaerobic activity. Quinolones available for human use include ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, gemifloxacin, and most recently delafloxacin. They are rapidly bactericidal agents that stop bacterial DNA synthesis by inhibiting two enzymes, topoisomerase IV and DNA gyrases. Like aminoglycosides, quinolones cause PAE against gram-negative bacilli, lasting approximately 2 to 6 hours. The bioavailability of quinolones is high (close to 100%), making for an easy transition from the IV to oral route. They have a high distribution in tissues including lung, bile, prostate, and stool. Except for moxifloxacin, concentrations in the kidney and urine are high. Although bone concentration is less than serum, quinolones have been successfully used to treat osteomyelitis and prosthetic joint infections, especially when combined with rifampin in the latter. The clinical uses for quinolones are presented in Table 205.1. Common toxicities associated with this class include gastrointestinal upset, dizziness, delirium (especially in the elderly), and rashes, while prolongation of the QT interval, arrhythmias, and tendonitis are rare but potentially serious. They should not be given with dairy products or metals like aluminum, calcium, or magnesium as these can reduce absorption of the drugs. Likewise, caution should be used in patients concurrently on warfarin, with close monitoring of prothrombin times because an increased risk of bleeding has been reported.

Bacterial resistance to quinolones occurs mainly from spontaneous mutations in genes that code for DNA gyrase or topoisomerase IV. Less commonly, resistance mutations occur in genes that encode membrane porin channels, leading to reduced diffusion as well as overexpression of efflux pumps. Studies have shown an increased risk for the development of resistance while on therapy in *P. aeruginosa* and *S. aureus*.

Tetracyclines

Originally derived from soil microorganisms, tetracyclines have broad-spectrum activity against gram-positive and gram-negative bacteria, intracellular bacteria, and some parasites. They are bacteriostatic agents, have anti-inflammatory properties, and inhibit protein synthesis by binding to the 30S subunit of the bacterial ribosome. Currently available drugs in this class include doxycycline, minocycline, and tetracycline, while saracycline is a narrow spectrum tetracycline derivative. A similar class is the glycylcyclines, which are derivatives of minocycline and have a modified side chain at position 9. These include tigecycline and eravacycline. The recently approved drug omadacycline belongs to the aminomethylcycline subclass of tetracycline. Both doxycycline and minocycline have high bioavailability, while the bioavailability of tetracycline is reduced when taken with food. Like quinolones, their absorption is decreased by multivalent cations like calcium and magnesium. The routes of elimination differ between the agents, with tetracycline cleared through the urine, doxycycline through the feces, minocycline through the liver, and tigecycline through the biliary/fecal route and, to a lesser extent, the urine. Toxicities are uncommon and include gastrointestinal upset, esophageal ulcers, rashes, and photosensitivity reactions. Minocycline can cause vertigo, more often in women. Tetracyclines should be avoided in pregnant women and children <8 years because of teeth staining. Patients should be encouraged to take oral tetracyclines with a full glass of water and remain upright for at least 30 minutes to decrease the risk for esophageal irritation.

Tetracyclines have a multitude of clinical uses. Doxycycline is included in the Infectious Diseases Society of America guidelines for the management of CAP for monotherapy in outpatients and in combination with a β-lactam for inpatients. Given recent reports associating arrhythmias with macrolides and quinolones,

TABLE 205.1 CHARACTERISTICS OF QUINOLONES

Drug	Principle route of metabolism	Common clinical indications and uses
Ciprofloxacin	Renal	UTIs, prostatitis, atypical pneumonia, HAP, travelers' diarrhea, gastroenteritis, peritonitis prophylaxis with cirrhosis, chronic osteomyelitis; excellent activity against gram negatives including *P. aeruginosa*
Levofloxacin	Renal	AECOPD, CAP, HAP, *P. aeruginosa* infections
Moxifloxacin	Hepatic	Aspiration pneumonia, AECOPD, CAP, abdominal infections, mixed anaerobic infections
Ofloxacin	Renal	UTIs, prostatitis, travelers' diarrhea
Gemifloxacin	Renal	AECOPD, CAP
Delafloxacin	Renal	ABSSSI, CAP

Abbreviations: UTI = urinary tract infection; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; AECOPD = acute exacerbations of chronic obstructive pulmonary disease; ABSSSI = acute bacterial skin and skin structure infections.

doxycycline seems to be a safe and effective alternative. It is often used to treat mild MRSA SSTIs. Moreover, doxycycline has been associated with a lower risk for *C. difficile* infection than other antibiotics. Tetracyclines are first-line therapy for Lyme disease, Rocky Mountain spotted fever, Q fever, cat scratch disease, anaplasmosis, ehrlichiosis, bartonellosis, brucellosis, pelvic ulcer disease, and in combination therapy for *Helicobacter pylori*. They also serve as alternative therapy for several conditions when patients are allergic or otherwise intolerant to first-line agents, including syphilis, leptospirosis, and Whipple's disease. Saracycline is a narrow-spectrum agent approved for moderate to severe acne vulgaris. Tigecycline is a broad-spectrum antibiotic with activity against MRSA, vancomycin-resistant enterococci (VRE), and many gram-negative bacilli including multidrug-resistant strains of *Acinetobacter*. However, it does not treat "the three P's" *Pseudomonas*, *Proteus*, and *Providencia*, or *Morganella*. Tigecycline is indicated to treat intra-abdominal infections, CAP, and SSTIs. Approximately 25% of patients develop nausea, which may necessitate discontinuation of therapy. Eravacycline is usually reserved for antibiotic-resistant infections. It has activity against some carbapenem-resistant organisms, ESBL-producing organisms, and *A. baumannii*, but it lacks activity versus *P. aeruginosa*. Eravacycline also treats MRSA and VRE. Omadacycline has activity against a broad range of gram-positive and select gram-negative pathogens and is approved to treat CAP and SSTIs.

Tetracycline resistance occurs mainly by acquisition of exogenous genes for efflux pumps and ribosomal protection proteins. Tigecycline has a higher affinity for ribosomes and can overcome ribosomal protection proteins, although it remains susceptible to multidrug-resistance pumps.

Macrolides

The macrolide group of antibiotics includes erythromycin, azithromycin, clarithromycin, and fidaxomicin. The first three drugs are used to treat a wide range of infections, while fidaxomicin is only used to treat *C. difficile* (Table 205.2). In addition to their primary indications, macrolides are often used as alternative agents for several conditions, such as Lyme disease in pregnancy and streptococcal pharyngitis in penicillin-allergic patients.

The first macrolide to be discovered, erythromycin, previously had good activity against many gram-positive organisms, but resistance has decreased its clinical efficacy. Erythromycin still maintains excellent activity against *Bordetella pertussis* and atypical respiratory pathogens. It is also used as a prokinetic agent for gastroparesis. However, gastrointestinal side effects and frequent dosing limit its use. Azithromycin has been the most commonly prescribed antibiotic in the United States for adults in recent years. It is better tolerated than erythromycin and, for many of its indications, is taken once a day for a 5-day course. Unfortunately, azithromycin has been associated with an increased risk of cardiovascular death, estimated at 47 additional cardiovascular deaths per 1 million courses.

All macrolides exhibit anti-inflammatory and immunomodulatory properties. Evidence suggests they are beneficial in certain chronic noninfectious illnesses such as cystic fibrosis and bronchiectasis. Their role in cardiovascular disease is controversial and requires further clarification.

Resistance to erythromycin, azithromycin, and clarithromycin is mediated through efflux pumps, mutations in genes for 50S ribosomal proteins, and enzymatic inactivation by phosphotransferases. A single strain of *C. difficile* with an elevated fidaxomicin MIC taken from a cured patient was found to have a single mutation in the β subunit of the RNA polymerase.

Pleuromutilins

Lefamulin is the first pleuromutilin to be used systemically in humans. Its mechanism of action is the inhibition of protein synthesis by preventing the binding of tRNA for peptide transfer. Lefamulin is approved for the treatment of CAP in adults and is available in both oral and IV formulations. It has potent in vitro activity against both typical and atypical CABP pathogens, as well as viridans streptococci, *Enterococcus faecium*, and MRSA. Lefamulin is also being investigated for acute bacterial skin and soft tissue

TABLE 205.2 **CHARACTERISTICS OF MACROLIDES**

Drug	Mechanism of action	Common clinical uses	Adverse reactions
Erythromycin	Binds bacterial 50S ribosome and inhibits RNA-dependent protein synthesis	*Bordetella pertussis* Atypical respiratory pathogens Prokinetic agent for gastroparesis	Nausea, vomiting, rashes, ototoxicity (high doses), QT prolongation
Azithromycin	Binds bacterial 50S ribosome and inhibits RNA-dependent protein synthesis	Pharyngitis Bacterial sinusitis CAP Otitis media MAC treatment and prophylaxis NGU Q fever SSTIs	Diarrhea, nausea, abdominal pain, cholestatic hepatitis, arrhythmias
Clarithromycin	Binds bacterial 50S ribosome and inhibits RNA-dependent protein synthesis	Pharyngitis Bacterial sinusitis CAP Otitis media *H. pylori* MAC and other mycobacterial infections (except MTb) Q fever SSTIs	Diarrhea, nausea, abdominal pain, arrhythmias
Fidaxomicin	Inhibits bacterial RNA polymerase	*C. difficile* infection; lower relapse rate compared to vancomycin except with NAP1/B1/027 strain	Nausea, vomiting, abdominal pain, gastrointestinal hemorrhage

Abbreviations: CAP = community-acquired pneumonia; MAC = *Mycobacterium avium* complex; MTb = *Mycobacterium tuberculosis*; NGU = nongonococcal urethritis; SSTIs = skin and soft-tissue infections.

infections. The most common side effects observed in clinical trials were infusion reactions and diarrhea. Patients with liver or kidney injury prescribed lefamulin are at increased risk of QT prolongation. Lefamulin should be avoided in patients with QT prolongation at baseline, who have a known ventricular arrhythmia, are taking class IA or IIIA antiarrhythmic drugs, or are taking other drugs that are known to cause QT prolongation.

Glycopeptides, lipopeptides, and streptogramins

Vancomycin, derived from the word "vanquish," was the first glycopeptide introduced for clinical use. The other glycopeptide is teicoplanin, which is available in Europe and Asia but not the United States. Glycopeptides are bactericidal agents that inhibit cell wall synthesis in dividing bacteria by binding to precursors of the peptidoglycan chain. Vancomycin has activity against most strains of staphylococci (including MRSA), streptococci, and enterococcus. Most strains of *L. monocytogenes* are susceptible although some with high MICs have been reported. *Leuconostoc*, *Lactobacillus*, and *Pediococcus* are intrinsically resistant. Vancomycin is used for many serious infections including meningitis, endocarditis, MRSA pneumonia, cellulitis, osteomyelitis, and gram-positive bacteremia. Oral vancomycin, which is not systemically absorbed, is used to treat moderate to severe *C. difficile* infections and recurrences. Adverse reactions to the drug are uncommon and include infusion-related reactions such as rash (red man syndrome), neutropenia, thrombocytopenia, ototoxicity, and nephrotoxicity. Resistance in enterococci is mediated by the *van* genes, which are found mostly in *E. faecalis* and can be transmitted to other bacteria such as staphylococci. It is increasingly common for strains of *S. aureus* to exhibit rising MICs to vancomycin (so-called *MIC creep*). Indeed, high rates of clinical failure with vancomycin have been observed with MRSA bacteremia when the vancomycin MIC is ≥2 μg/mL.

Telavancin is a semisynthetic lipoglycopeptide derived from vancomycin. It has a bactericidal concentration-dependent method of killing and a dual mechanism of action, inhibiting cell wall synthesis and disrupting membrane integrity. Telavancin exhibits potent in vitro activity against many gram-positive organisms, including staphylococcus, streptococcus, both vancomycin-susceptible and -resistant enterococcus, and gram-positive anaerobes. In the United States, telavancin is approved for the treatment of patients with complicated SSTIs. Women of childbearing age should have a pregnancy

test prior to starting telavancin because of possible teratogenicity. Dalbavancin is another lipoglycopeptide with broad gram-positive activity that is approved for SSTIs. It has a long half-life and is given once weekly for two doses. The semisynthetic glycopeptide ortivancin is similar to dalbavancin in terms of spectrum of activity and clinical indications. It is given as a single 1,200 mg dose administered IV over 3 hours.

The lipopeptide daptomycin is a rapidly acting, bactericidal agent that forms calcium-dependent ion channels in the cytoplasmic membrane of gram-positive organisms, causing loss of intracellular potassium and cell death. Daptomycin has a similar spectrum of activity as vancomycin and can be used to treat SSTIs, *S. aureus* bloodstream infections and right-sided endocarditis, osteomyelitis, and septic arthritis. Pulmonary surfactant inactivates daptomycin, and it should not be used for pneumonia. It is usually well-tolerated but reversible myopathy can occur. Therefore, monitoring of creatine phosphokinase (CPK) should be done weekly and concurrent statin therapy should be avoided. Resistance to daptomycin has been associated with MRSA strains with decreased susceptibility to vancomycin. Many bacteria with elevated daptomycin MICs demonstrate phenotypic changes in their cell membranes.

The streptogramins consist of two different macrocyclic compounds that each bind to the 50S subunit of the bacterial ribosome, inhibiting protein synthesis. Currently quinupristin-dalfopristin is the only streptogramin available in the United States. It is active against most gram-positive organisms (except *E. faecalis*) and a few gram-negatives including *Neisseria gonorrhoeae*, *N. meningitidis*, *M. catarrhalis*, and *H. influenzae*. Resistance occurs through conformational changes in the 50S subunit, enzymatic inactivation, and production of efflux pumps. The clinical use of quinupristin-dalfopristin has been limited by its frequent side effects (arthralgias, myalgias, hyperbilirubinemia), many drug interactions, and because it needs to be administered through a central line due to frequent thrombophlebitis and pain when given peripherally.

Oxazolidinones

Linezolid is the first of the oxazolidinones, a completely synthetic class of antibacterial agents with broad gram-positive activity. Unlike vancomycin, daptomycin, and quinupristin–dalfopristin, linezolid is available in both IV and oral formulations. It is a bacteriostatic agent that inhibits protein synthesis by binding to 23S rRNA in the catalytic site of the 50S ribosome. It is approved for the following indications: (1) VRE infections, including bacteremia; (2) nosocomial pneumonia caused by MSSA, MRSA, and *Streptococcus pneumoniae*; (3) complicated SSTIs, including diabetic foot infections without concurrent osteomyelitis caused by MSSA, MRSA, *Streptococcus pyogenes*, or *Streptococcus agalactiae*; (4) uncomplicated SSTIs caused by MSSA or *S. pyogenes*; and (5) CAP caused by MSSA or *S. pneumoniae*. Adverse events are uncommon and usually mild, including headache, nausea, and diarrhea. More serious ones can also occur, usually if linezolid is given for >28 days. These include anemia, thrombocytopenia, lactic acidosis, optic neuritis, and peripheral neuropathy. It is therefore recommended that a weekly CBC be done while on therapy. Linezolid can cause serotonin syndrome when taken concurrently with selective serotonin reuptake inhibitors (SSRIs) and should be avoided. Resistance to linezolid has been observed in strains of MRSA and VRE with mutations in the 23S ribosomal RNA domain V region and is usually associated with prior exposure to the drug. Once-daily tedizolid has fewer drug–drug interactions than linezolid and is approved to treat complicated SSTIs.

Sulfonamides

The first class of antibacterials in clinical use, sulfonamides are still widely prescribed. There are two agents currently available: trimethoprim-sulfamethoxazole (TMP-SMX) and dapsone. They are bacteriostatic and inhibit folic acid synthesis, thus stopping bacterial growth. Trimethoprim is a dihydrofolate reductase inhibitor that potentiates the activity of sulfonamides but also has antibacterial properties itself. Sulfonamides have broad in vitro activity against many gram-positive and gram-negative bacteria. TMP-SMX is most often used to treat UTIs, including pyelonephritis, cystitis, and prostatitis. It can also be given as prophylaxis for patients with recurrent UTIs. Furthermore, TMP-SMX is effective for treating SSTIs due to community-associated MRSA, with >90% of strains currently susceptible. It is first-line therapy for patients with *Pneumocystis jirovecii* pneumonia (PCP), as well as PCP prophylaxis. IV TMP-SMX is often used in severe cases. Dapsone is the treatment of choice for leprosy and for PCP prophylaxis in patients intolerant of TMP-SMX. Hemolytic anemia can occur on dapsone especially in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, so a G6PD level should be obtained before therapy is started. Adverse reactions associated with TMP-SMX include rashes (rarely Stevens–Johnson syndrome), fever, gastrointestinal upset, hepatitis, cytopenias, and hyperkalemia.

Because of long-standing usage (>70 years), widespread resistance to the sulfonamides has developed. It is mediated by overproduction of para-aminobenzoic acid (PABA) or structural changes in dihydropteroate synthetase, or by plasmids that code for the production of drug-resistant enzymes or decreased bacterial cell wall permeability.

Metronidazole and clindamycin

Developed in the 1950s, metronidazole is commonly used for parasitic and anaerobic infections. It is bactericidal and acts by interfering with electron transport proteins via reduction of its nitro group, leading to free radical formation and cell death. Oral metronidazole is well absorbed and serum levels are comparable to IV therapy. Metronidazole is active against nearly all gram-negative anaerobic bacteria, including *Bacteroides fragilis*; gram-positive anaerobes such as *C. difficile* and *H. pylori*; and parasites such as *Giardia*, *Entamoeba*, and *Trichomonas vaginalis*. Clinically it is used to treat a variety of anaerobic infections such

as brain abscesses, bacteremia, endocarditis, bacterial vaginosis, bone and joint infections, and infections of the head and neck. Oral metronidazole is effective against mild *C. difficile* infection, but recurrences are common (approximately 25%) and oral vancomycin is now recommended as first-line treatment. Of note, it should not be used as a single agent in treating lung abscesses because of the frequent presence of aerobic gram-positive cocci, against which it lacks activity. Adverse reactions associated with metronidazole include gastrointestinal upset, rashes, neutropenia, and neurologic complaints such as headache, dizziness, and peripheral neuropathy. Alcohol should be avoided as it can lead to a disulfiram-like reaction. Resistance is rare and results from a decreased capacity of the electron transport chain to reduce the nitro group of metronidazole. Certain strains of *H. pylori* acquire resistance from mutational inactivation of the *rdxA* gene.

Clindamycin is a chemical modification of lincomycin, the original member of the lincosamide group. Similar to the macrolides, clindamycin binds to the 50S subunit of the bacterial ribosome and inhibits protein synthesis. It has in vitro activity against many aerobic gram-positive bacteria, including staphylococci and streptococci, and anaerobes, although resistance is becoming more common. In particular, approximately 25% of clinical strains of *B. fragilis* are resistant to the drug. Clindamycin is used to treat lung abscesses, intra-abdominal and gynecologic infections, and gas gangrene from *Clostridium perfringens*. Topical formulations are effective for acne vulgaris and vaginal ones for bacterial vaginosis. It has good activity against MSSA but less so with MRSA. A D test should be done on strains of MRSA or *S. pyogenes* resistant to erythromycin; a positive D test indicates resistance to clindamycin will also occur. It can also be given as an adjunctive agent to bind toxins produced by *S. pyogenes* and *S. aureus*. Finally, clindamycin can serve as an alternative to penicillin or macrolides for most indications for patients with drug allergies. The major toxicity associated with clindamycin is *C. difficile* infection, which is not infrequent and now limits its clinical usage. Resistance to the drug occurs mainly through 50S ribosomal modification and enzymatic inactivation.

Rifamycins

A versatile class of drugs, the rifamycins have many indications but are usually used in combination with other antibiotics. There are four drugs currently available: rifampin, rifabutin, rifapentine, and rifaximin. Rifamycins act by inhibiting the β-subunit of bacterial RNA polymerase. They are potent inducers of the cytochrome P450 system. This leads to many drug interactions including HIV medications, warfarin, cardiovascular drugs such as β-blockers and statins, and immunosuppressive agents such as tacrolimus and glucocorticoids. Rifamycins are also associated with many adverse reactions. They cause an orange-red discoloration of tears and other secretions. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea are common, while rashes, hepatitis, cytopenias, uveitis, and a lupus-like syndrome can also occur.

There are different clinical indications for each of the rifamycins. Rifampin is the oldest and most commonly used. It can be given as an alternative to isoniazid for treatment of latent tuberculosis, as one of the four drugs to treat active tuberculosis, in combination with dapsone for leprosy, as monotherapy for prophylaxis against meningococcal disease, or in combination therapy for prosthetic valve endocarditis or osteomyelitis (especially with foreign bodies) from *Staphylococcus*. Furthermore, rifampin can be used to eradicate MRSA colonization along with another drug such as doxycycline. Rifabutin and rifapentine are mainly used to treat mycobacterial infections. Rifaximin is poorly absorbed and is indicated for travelers' diarrhea. Moreover, it is sometimes used for recurrent or refractory *C. difficile* infection, usually for 2 weeks after finishing a standard course of oral vancomycin. Rifaximin is also effective for treating and preventing hepatic encephalopathy.

Resistance to rifamycins occurs mainly through single-step mutations in the gene that codes for RNA polymerase. Because this process occurs rapidly, rifamycins are not used to treat infections by themselves, except for the few indications jus noted.

Polymyxins

First discovered in the 1940s, polymyxins were used to treat serious gram-negative infections until around 1980, when safer agents with less nephrotoxicity became available. They have reemerged in recent years, often as agents of last resort, due to the ongoing spread of multidrug-resistant bacteria. The two drugs in this class currently available are polymyxin B and colistin. They are rapidly bactericidal and act like a detergent by punching holes in the bacterial cell membrane. Polymyxins have broad activity against aerobic gram-negative bacteria, including most strains of *P. aeruginosa* and *A. baumannii*. However, *Proteus*, *Serratia*, *Providencia*, *Burkholderia*, *Moraxella*, *Vibrio*, *Morganella*, *Helicobacter*, and *Edwardsiella* are resistant. Colistin is often used parenterally to treat serious multidrug-resistant gram-negative bacterial infections such as ventilator-associated pneumonia. Aerosolized colistin is also available and mainly given to treat colonization or infection of the bronchial system in patients with cystic fibrosis. A dose-related nephrotoxicity is a common side effect and is usually reversible with discontinuation of the drug. Also, neurologic side effects can occur, such as paresthesias, peripheral neuropathy, and muscle weakness. Resistance to polymyxins develops through modification of lipopolysaccharides on the bacterial cell wall.

Miscellaneous agents

Chloramphenicol is rarely used in North America and Europe, although an inexpensive oral formulation is widely available in underdeveloped countries. It has excellent activity against aerobic gram-positive and gram-negative bacteria, anaerobes (including *Clostridium* and *B. fragilis*), and atypical bacteria. However, serious toxicities limit its clinical utility. The most common is reversible

bone marrow suppression. Development of aplastic anemia from chloramphenicol is rarer but can be irreversible. Because of these, it should only be used for serious, life-threatening infections (e.g., bacterial meningitis) when alternative drugs are contraindicated.

Nitrofurantoin is an oral agent used to treat and prevent UTIs. It is bactericidal and acts by inhibiting translation and pyruvate metabolism. More than 90% of *Escherichia coli* and *Citrobacter* strains are susceptible, and it has excellent activity against group B streptococci, *Staphylococcus saphrophyticus*, and enterococci including VRE. However, most other strains of Enterobacteriales are resistant. For uncomplicated cystitis, a 10-day course of therapy is usually given because shorter courses have been associated with suboptimal cure rates. Daily nitrofurantoin (100 mg) is effective therapy for both young and postmenopausal women with asymptomatic and symptomatic bacteriuria. Toxicities include gastrointestinal symptoms, pulmonary reactions including fibrosis, hepatitis, hemolytic anemia, and peripheral neuropathy. Patients on long-term prophylaxis should be monitored for these conditions.

Fosfomycin is another oral agent for lower UTIs whose usage has been increasing in recent years because of bacterial resistance to other agents. It is bactericidal and inhibits cell wall synthesis through inactivation of the bacterial enzyme MurA. Resistance occurs through mutations in the bacterial membrane transporter for the drug. Fosfomycin has broad-spectrum antibacterial activity. Among susceptible pathogens are *E. coli* (including ESBL-producing strains), *Citrobacter*, *Proteus*, and *Enterococcus* (including VRE). Rates of susceptibility vary in *Klebsiella* and *Enterobacter*, while strains of *Pseudomonas* are often resistant. Fosfomycin is given as a one time mega-dose that is formulated as a powder and dissolved in a glass of water. It can also be given as a prophylactic agent for recurrent UTIs once every 10 days.

Topicals

Topical antibiotics are important agents for both treating and preventing infections of the skin, as well as to eradicate chronic carriage of MRSA. The two most common agents used for this purpose are povidone-iodine and chlorhexidine, with the latter becoming more widely available and popular in recent years.

Available topical antibacterials include silver sulfadiazine, which is mainly used as a burn wound dressing. Activated silver has broad-spectrum antimicrobial activity and some anti-inflammatory properties. Silver sulfadiazine decreases colonization of wounds but there is no clear evidence that it treats infections or improves wound healing. Bacitracin is active against many gram-positive bacteria including staphylococci, streptococci, and clostridia. It is effective for treating impetigo but may also lead to slower wound healing. Mupirocin is another agent with in vitro activity against gram-positive organisms, especially MRSA. It is used to treat impetigo, folliculitis, and infected wounds and ulcers, and to decolonize the nares in patients colonized with *S. aureus*. Unfortunately, the development of mupirocin resistance in MRSA is becoming increasingly common. Neomycin is an aminoglycoside with activity against both gram-positive and gram-negative organisms including *S. aureus*, *S. pyogenes*, *E. coli*, *Proteus*, and *Serratia* while *P. aeruginosa* is usually resistant. It can cause contact sensitivity and resistance may develop. Neomycin is not recommended for patients with decreased renal function as it can be systemically absorbed, leading to ototoxicity. Polymyxin B is bactericidal against several aerobic gram-negative organisms including *P. aeruginosa* but not species of *Proteus*, *Serratia*, and *Providencia*. It is often used in combination with another agent such as bacitracin. Fusidic acid is another topical with only gram-positive activity. It gets good tissue penetration and is useful for treating boils. Retapamulin has in vitro activity against staphylococci (including MRSA) and streptococci and exhibits a potent post-antibiotic effect lasting 3 to 4 hours. It is indicated for treating impetigo in adults and children.

Future directions

The spread of antibiotic-resistant bacteria is a major challenge for public health in the twenty-first century. Indeed, some experts believe we will soon enter a post-antibiotic era. To forestall this dire prediction, judicious usage of antibiotics is necessary, along with prudent infection control methods that reduce the spread of multidrug-resistant pathogens. Developing new antibiotics is a priority that should be actively supported by the pharmaceutical industry, professional societies, and government agencies.

Suggested reading

Gilbert DN, Chambers HF, Saag MS, et al. *The Sanford guide to antimicrobial therapy,* 50th ed. Sperryville, VA: Antimicrobial Therapy, Inc.; 2020.

Lewis K. The science of antibiotic discovery. *Cell*. 2020;181:29–45.

Vila J, Moreno-Morales J, Ballesté-Delpierre C. Current landscape in the discovery of novel antibacterial agents. *Clin Microbiol Infect*. 2020;26:596–603.

Watkins RR, Deresinski S. Omadacycline: A novel tetracycline derivative with oral and intravenous formulations. *Clin Infect Dis*. 2019;69:890–896.

Watkins RR, Holubar M, David MZ. Antimicrobial resistance in methicillin-resistant *Staphylococcus aureus* to newer antimicrobial agents. *Antimicrob Agents Chemother*. 2019;63:e01216–19.

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Principles and practice of antimicrobial stewardship

Cheston B. Cunha

Introduction

The primary goal of antimicrobial stewardship is to optimize antibiotic use while using cost-effective interventions to minimize antibiotic resistance and control *Clostridium difficile* infection. Before the formal creation of antimicrobial stewardship programs (ASPs), infectious disease (ID) clinicians acted as the antibiotic stewards in hospitals. More recently, the US Centers for Disease Control and Prevention (CDC) has mandated ASPs for all US hospitals and more emphasis has been placed on mitigating the damage of suboptimal antibiotic use.

Principles of antimicrobial stewardship programs

The CDC has determined seven core measures that all ASPs should follow. The hospital must designate a single ID clinician who will direct the hospital's ASP efforts. To be effective, the ID clinician leader must possess the requisite interpersonal, diplomatic, and leadership skills that form the basis for the enthusiastic support of the medical staff. The ID clinician leader should have special expertise in various aspects of antimicrobial therapy (i.e., pharmacokinetics, resistance, pharmacoeconomics, and *C. difficile*). Most successful ASPs interventions focus on seven key areas where antimicrobial use can be optimized (Table 206.1). If these problem areas are the focus of ASPs, unnecessary and suboptimal antimicrobial use will be reduced and benefit for patients and institutions will be maximized.

To create and maintain an effective hospital-wide ASP, the ASP team leader needs full and ongoing financial support for the ASP from the hospital administration. Support includes a staff of ID/AS trained clinical pharmacists (PharmDs) who are a vital component of ASPs. There must be a sufficient number of PharmDs for the size of the hospital to ensure the effectiveness of the ASP. The ID team leader and PharmDs need committed IT support to effectively accomplish daily stewardship activities and larger stewardship projects. These key activities include a daily prospective audit with feedback to clinicians, data collection to track and monitor antibiotic use, resistance, and *C. difficile* infections, as well as ASP cost-savings to the institution.

Just as important, the success of an ASP depends on the understanding and support of medical staff. The medical staff needs to understand the principles of antibiotic therapy put forth in ASP initiatives if they are to accept and support ASP recommendations for the benefit of patients and the hospital.

Most physicians need relevant, targeted antibiotic education to understand optimal versus adequate antimicrobial therapy (i.e., pharmokinetics [PK]-/pharmodynamic [PD]- based dosing; see Table 206.2), IV versus PO administration, dosing adjustments in renal/hepatic insufficiency, factors in tissue penetration, shortest duration of therapy for cure, antibiotic resistance potential, and antibiotic *C. difficile* potential. Antibiotic myths and misconceptions abound. All too often, antibiotic

TABLE 206.1 ANTIMICROBIAL STEWARDSHIP PRINCIPLES AND PRACTICE: BEYOND THE GUIDELINES

Monotherapy vs. combination therapy

- Monotherapy is preferred whenever possible to cover the most likely pathogen or cultured pathogen clinically relevant to the site of infection.
- Combination therapy should be avoided if possible. Always try to preferentially use monotherapy.
- Monotherapy is usually less expensive than combination therapy and has less potential for adverse effects and drug–drug interactions.
- Combination therapy is often used for potential synergy (rarely occurs and, if used, must be based on microbiology laboratory synergy studies), to increase spectrum (preferable to use monotherapy with same spectrum), or to prevent resistance (except for TB, ineffective in most cases).

Narrow vs. broad-spectrum therapy

- Narrow vs. broad spectrum doesn't prevent resistance; for example, in treating *E. coli* urosepsis, switching from a carbapenem (broad-spectrum) to ampicillin (narrow-spectrum) may actually increase resistance potential.
- Narrow- vs. broad-spectrum is not always clinically superior to well-chosen broad-spectrum therapy, such as switching from ceftriaxone (broad-spectrum) to penicillin (narrow-spectrum in treating *S. pneumoniae* has no clinical rationale or clinical advantage and has no effect on controlling resistance.
- Antibiotic resistance is not related to spectrum narrowness or broadness; for example, levofloxacin has a broad spectrum but low resistance potential whereas ampicillin has a narrow spectrum but high resistance potential.

Colonization vs. infection

- Treat infection, not colonization.
- Provide empiric coverage primarily directed against the most probable pathogens causing the infection at the body site.
- Avoid "covering" multiple organisms cultured (pathogens and nonpathogens) at the body site cultured.
- Colonization of respiratory secretions, wounds, or urine with "water" (*S. maltophilia, B. cepacia, P. aeruginosa*) or skin organisms (MSSA, MRSA, CoNS, VSE, VRE) is the rule.

Antibiotic resistance

- The best way to control resistance is a selectively restricted formulary; restricted only to "high resistance potential' antibiotics, such as imipenem (not meropenem or ertapenem), ceftazidime (not other third- or fourth-generation), gentamicin/tobramycin (not amikacin).
- Some antibiotics may be restricted for other reasons; for example, excessive vancomycin (IV not PO) use predisposes to VRE emergence, and vancomycin may cause cell wall thickening in *S. aureus* resulting in permeability-related resistance (to vancomycin and other antibiotics; e.g., daptomycin).
- Overrestriction of antibiotics may impair timely effective therapy and does not, per se, decrease resistance.
- Preferentially select antibiotics (all other things being equal) with a "low resistance potential." Avoid, if possible, "high resistance potential" antibiotics, such as macrolides (for respiratory infections), TMP-SMX (for UTIs).
- Since resistance is, in part, concentration-dependent, subtherapeutic or low antibiotic tissue concentrations (all other things being equal) predispose to resistance.
- Suboptimal dosing or usual dosing with inadequate tissue penetration, such as into the body fluids or undrained abscesses (source control is key) predisposes to resistance.

C. difficile diarrhea/colitis

- Preferentially select antibiotics (all other things being equal) with low *C. difficile* potential.
- Predisposing factors to *C. difficile* include relatively few antibiotics (e.g., clindamycin, β-lactams, ciprofloxacin).
- Most antibiotics have little/no *C. difficile* potential (e.g., aminoglycosides, aztreonam, macrolides, TMP-SMX, colistin, polymyxin B, daptomycin, Q/D, doxycycline, minocycline, tigecycline, vancomycin, linezolid).
- Some antibiotics are protective against *C. difficile* (e.g., doxycycline, tigecycline).
- Always consider non-antibiotic factors that may predispose to *C. difficile* (e.g., cancer chemotherapy, anti-depressants, statins, PPIs).
- Also consider person-to-person spread or acquisition for the environment.

PO and IV to PO switch antibiotic therapy

- Wherever possible, treat with entirely oral antibiotic therapy instead of IV therapy.
- Switch from IV to PO antibiotic therapy after clinical defervescence (usually <72 h).
- Early IV to PO switch therapy eliminates phlebitis and IV line-associated infections.

TABLE 206.1 **CONTINUED**

Pharmacoeconomic considerations
The least expensive therapy is usually not the best therapy.
The least expensive antibiotic (acquisition cost) may, in fact, be expensive (re: total cost) when considering the cost implications to the institution of dosing frequency, *C. difficile* potential, resistance potential, and degree of activity against the known or likely pathogen, and the cost of potential therapeutic failure vis-à-vis ↑ length of stay (LOS) and medicolegally.
Stewardship savings are best achieved by decreasing duration of antibiotic therapy and by treating entirely with oral antibiotic therapy or early IV to PO switch therapy.

CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PPI, proton pump inhibitor; Q/D, daily dose; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection; VRE, vancomycin-resistant *Enterococcus*; VSE, vancomycin-susceptible *Enterococcus*.
Adapted from Cunha CB. Antimicrobial stewardship principles & practice. In Cunha CB, Cunha BA, eds. *Antibiotic essentials*, 17th ed. New Delhi: Jay Pee Medical Publishers; 2020: 13–16.

therapy is regarded as a cure and is an immediate response for all febrile disorders. In these cases, multiple antimicrobials are often prescribed in an attempt to "cover the patient." Polypharmacy is nearly always unnecessary and increases costs and adverse events potential.

The most successful ASPs rely on a multidisciplinary approach that includes the critical support of the microbiology laboratory, infection control, and hospital epidemiology.

Colonization versus infection

One of the most frequently encountered problems for clinicians is to differentiate *colonization* from actual *infection*. When an organism is recovered from a culture site (e.g., urine cultures in asymptomatic individuals, superficial wound cultures, etc.), most clinicians feel compelled to treat the organism. Often, the more resistant the organism, the stronger the urge to treat it. Colonization, with very few

TABLE 206.2 **PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) CONSIDERATIONS**

Antibiotics		**Optimal dosing strategies**
Concentration-dependent antibiotics (C_{max}:MIC)		
Quinolones Aminoglycosides Vancomycin (if MIC >1 μg/mL use 2 g (IV) q12h)	Doxycycline Tigecycline Polymyxin B Colistin	Use highest effective dose without toxicity
Time-dependent antibiotics (T > MIC)		
Penicillins: Maintain concentrations > MIC for ≥60% of the dosing interval β-lactams: Maintain concentrations > MIC for ≥75% of the dosing interval Carbapenems: Maintain concentrations > MIC for ≥ 0% of the dosing interval		Use high doses (which increase serum concentrations which also increases T > MIC for more of the dosing interval)

MIC, minimum inhibitory concentration.
Adapted from Cunha CB, Cunha BA, eds. *Antibiotic essentials*, 17th ed. New Delhi: Jay Pee Medical Publishers; 2020.

exceptions, should not be treated. Because colonization may be difficult to eradicate, multiple, prolonged courses of antimicrobials are frequently given to patients; this results in no benefit to patients and increased costs to the healthcare system while increasing local resistance and *C. difficile* rates.

Antibiotic resistance

The majority of resistance in hospitals comes from the community (e.g., nursing homes/chronic care facilities) and the food supply (antibiotics are commonly used in the food supply). Hospital-acquired resistance is still a concern, and, to minimize the risk of this, hospitals should preferentially select formularies with "low resistance potential" antibiotics. There are many misconceptions about resistance (i.e., resistance is class-related or is related to volume or duration of use). Rather than considering overall antimicrobial "tonnage" as a risk for generating resistance, the potential of individual antimicrobials should be taken into account. Antibiotics may be considered as having a "low or high resistance" potential. The "low resistance potential" antibiotics (e.g., doxycycline) induce little or no resistance independent of volume or duration of use, whereas "high resistance potential" antibiotics (e.g., ceftazidime) may induce resistance even with limited use. Obviously, if high resistance potential drugs are used in large volume, the likelihood of worsening resistance in a hospital/community increases dramatically. Within each antibiotic class are low and high resistance potential antibiotics; for example among third-generation cephalosporins, ceftazidime has a high resistance potential while ceftriaxone has a low resistance potential, thus showing that resistance is not related, per se, to antibiotic class (see Tables 206.3 and 206.4).

C. difficile diarrhea

C. difficile diarrhea (CDD) is an area that ASPs must also impact. Unnecessary antimicrobial administration can lead to increased rates of CDD in an institution. Also, it is not well appreciated that antibiotics have different *C. difficile* potentials (i.e., high risk for CDD vs. low risk). While it is often difficult to determine the precise CDD risk of an antimicrobial, clindamycin and the β-lactams (excluding ceftriaxone) are the most frequent antibiotic causes of CDD. Most other antibiotics have low *C. difficile* potential (e.g., macrolides, tetracyclines, aztreonam, aminoglycosides, trimethoprim-sulfamethoxazole [TMP-SMX]). Some antibiotics are actually protective against *C. difficile* (e.g., doxycycline, tigecycline). *C. difficile*-protective drugs (e.g., the tetracyclines) should be favored by formularies to minimize CDD. In selecting an antibiotic, clinicians must consider *C. difficile* potential as well as resistance potential.

TABLE 206.3 **ANTIBIOTIC RESISTANCE POTENTIAL**

High resistance potential antibiotics
(***antibiotics to avoid***)

IV Antibiotics	**PO Antibiotics**
Ciprofloxacin	Gentamicin or tobramycin
Organism often resistant: *E. coli*	Organism often resistant: *P. aeruginosa*
TMP-SMX	Ceftazidime
Organism often resistant: *E. coli*	Organism often resistant: *P. aeruginosa*
Imipenem	Ciprofloxacin
Organism often resistant: *P. aeruginosa*	Organism often resistant: *E. coli*
	TMP-SMX
	Organism often resistant: *E. coli*

Low resistance potential antibiotics
(***preferred antibiotics***)

IV Antibiotics		**PO Antibiotics**	
Meropenem	Levofloxacin	Doxycycline	Nitrofurantoin
Amikacin	Aztreonam	Minocycline	Methenamine salts[a]
Ceftriaxone	Cefepime	Levofloxacin	Fosfomycin
Doxycycline	Colistin		
Tigecycline	Polymyxin B		

[a]For uncomplicated lower UTIs.
TMP-SMX, trimethoprim/sulfamethoxazole.
Adapted from Cunha CB, Cunha BA, eds. *Antibiotic essentials*, 17th ed. New Delhi: Jay Pee Medical Publishers; 2020.

TABLE 206.4 **RESISTANCE POTENTIAL OF SELECTED ANTIBIOTICS**

High resistance potential antibiotics to avoid	Usual organism(s) resistance to each antibiotic	Preferred low resistance potential antibiotic alternatives in same class	Preferred low resistance potential antibiotic alternatives in different classes
Aminoglycosides			
Gentamicin Tobramycin	*P. aeruginosa*	Amikacin	Levofloxacin, Colistin, Cefepime
Cephalosporins			
Ceftazidime	*P. aeruginosa*	Cefepime	Levofloxacin, Colistin, Polymyxin B
Tetracyclines			
Tetracycline	*S. pneumoniae*	Doxycycline, Minocycline	Levofloxacin, Moxifloxacin
Quinolones			
Ciprofloxacin	*S. pneumoniae*	Levofloxacin, Moxifloxacin	Doxycycline
Ciprofloxacin	*P. aeruginosa*	Levofloxacin	Amikacin, Colistin, Cefepime
Glycopeptides			
Vancomycin	MSSA MRSA	None	Linezolid, Daptomycin, Minocycline, Tigecycline
Carbapenems			
Imipenem	*P. aeruginosa*	Meropenem, Doripenem	Amikacin, Cefepime, Colistin, Polymyxin B
Macrolides			
Azithromycin	*S. pneumoniae*	None	Doxycycline, Levofloxacin, Moxifloxacin
Dihydrofolate			
Reductase Inhibitors			
TMP-SMX	*S. pneumoniae*	None	Doxycycline, Levofloxacin, Moxifloxacin

Adapted from Cunha CB, Cunha BA, eds. *Antibiotic essentials*, 17th ed. New Delhi: Jay Pee Medical Publishers; 2020.

Clinical and pharmacoeconomic benefits

Optimal antibiotic therapy is based on the aforementioned principles, but other ASP interventions also benefit the patient and the hospital (i.e., IV to PO switch therapy and PO therapy). The advantages of IV to PO switch/PO therapy include decreased drug costs (PO antibiotics cost less, at any given dose, than their IV equivalents) as well as decreasing the incidence of phlebitis (shorter duration of IV lines). IV to PO switch programs increase patient satisfaction (shorter IV days and earlier discharge) and decreases hospital length of stay, which is a significant cost savings to hospitals. Well-chosen PO therapy is increasingly becoming the standard for multiple infections. There has been increasing data supporting the use of PO therapy over IV which should give clinicians and ASPs increasing confidence in the many benefits of IV to PO and PO therapy.

Practice of antimicrobial stewardship programs

While the problems faced by and the general approach to these problems is similar among all ASPs, specific programs must differ among hospitals. Depending on the hospital size, location (rural, suburban, urban), teaching versus community focus, staff antibiotic prescribing habits, presence or absence of full-time ID clinicians, resistance patterns, etc., the individual priorities and strategies of each ASP must vary. What is a successful ASP intervention in one hospital may be ineffective in another. The ASP ID team leader and clinical ID-trained PharmD staff must tailor ASP interventions to the hospital's unique set of antibiotic use–related concerns. The success of ASPs relies on determining the most effective strategy for a specific antibiotic-related problem at a specific institution. The effectiveness of various ASP interventions is assessed and modified based on the findings of effective audit

and feedback. Audit with feedback identifies effective/ineffective interventions and may suggest modifications or entirely new and innovative approaches.

Suggested reading

Cunha BA. Effective antibiotic-resistance control strategies. *Lancet* 2001;357:1307–1308.

Cunha BA, Hage JE, Schoch PE, Cunha CB, Bottone EJ, Torres DC. Overview of antimicrobial therapy. In Cunha CB, Cunha BA, eds. *Antibiotic essentials*, 17th ed. New Delhi: Jaypee Brothers Medical Publishers Ltd.; 2020: 1–16.

Cunha CB. Antimicrobial stewardship in critical care. In Cunha BA, Cunha CB, eds. *Infectious diseases and antimicrobial stewardship in critical care medicine,* 4th ed. Boca Raton, FL: CRC Press; 2020: 377–386.

Cunha CB. Principles of antimicrobial stewardship. In LaPlante KL, Cunha CB, Morrill HJ, Rice LB, Rice B. Mylonakis E, eds. *Antimicrobial stewardship: Principles and practice*. London: CABI Press; 2017: 1–8.

Cunha CB, Opal SM. Antimicrobial stewardship: Strategies to minimize antibiotic resistance while maximizing antibiotic effectiveness. *Med Clin N Am.* 2018;102:831–843.

Cunha CB, Varughese CA, Mylonakis E. Antimicrobial stewardship programs (ASPs): The devil is in the details. *Virulence.* 2013;4:147–149.

Cyriac JM, James E. Switch over from intravenous to oral therapy: A concise overview. *J Pharmacol Pharmacother.* 2014;5:83–87.

Doron S, Davidson LE. Antimicrobial stewardship. *Mayo Clin Proc.* 2011;86:1113–1123.

John JF Jr, Fishman NO. Programmatic role of the infectious diseases physician in controlling antimicrobial costs in the hospital. *Clin Infect Dis.* 1997;24:471–485.

McCallum AD, Sutherland RK, Mackintosh CL. Improving antimicrobial prescribing: Implementation of an antimicrobial i.v.-to-oral switch policy. *J R Coll Physicians Edinb.* 2013;43:294–300.

Nowak MA, Nelson RE, Breidenbach JL, Thompson PA, Carson PJ. Clinical and economic outcomes of a prospective antimicrobial stewardship program. *Am J Health Syst Pharm.* 2012;69:1500–1508.

Ohl CA, Luther VP. Health care provider education as a tool to enhance antibiotic stewardship practices. *Infect Dis Clin North Am.* 2014;28:177–193.

Salsgiver E, Bernstein D, Simon MS, et al. Knowledge, attitudes and practices regarding antimicrobial use and stewardship among prescribers at acute-care hospitals. *Infect Control Hosp Epidemiol.* 2018;39:316–322.

Wagner B, Filice GA, Drekonja D, et al. Antimicrobial stewardship programs in inpatient hospital settings: A systematic review. *Infect Control Hosp Epidemiol.* 2014;35:1209–1228.

207

Antifungal therapy

Dimitrios Farmakiotis and Ralph Rogers

Introduction

The patient population at risk for invasive fungal infections is rapidly growing. This is the result of more effective treatments for hematologic malignancies, which lead to prolonged periods of neutropenia, but also newly recognized syndromes associated with the use of novel therapies, such as a variety of fungal infections in patients receiving tyrosine kinase inhibitors (ibrutinib) or endemic mycoses (histoplasmosis) associated with tumor necrosis factor (TNF-α) inhibitors. Invasive fungal infections are also increasingly recognized in immunocompetent or "immunomodulated" individuals, such as the outbreak of *Cryptococcus gatii* infections in Northwestern United States and British Columbia, chronic cavitary and semi-invasive aspergillosis in patients with chronic obstructive pulmonary disease (COPD), and post-influenza and ICU-related aspergillosis. Recent advances in our understanding of fungal pathogenesis and the development of potent, relatively nontoxic antifungal agents have led to significantly improved outcomes and even cure of severe fungal infections that were almost uniformly fatal three decades ago. Therefore, knowledge of clinical mycology and antifungal treatment basics is paramount across different specialties other than infectious diseases, such as oncology-hematology, rheumatology, transplantation medicine, and critical care. Figure 207.1 provides an overview of fungal pathogens for the clinician, and Table 207.1 summarizes the spectra, pharmacokinetics, and main toxicities of the most commonly used antifungal drugs. Figure 207.2 provides and algorithm for the empiric treatment of fungal infections. This chapter focuses on the three main classes of antifungal agents used in clinical practice: polyenes (amphotericin B formulations), echinocandins, and (tri)azoles.

Amphotericin B

Amphotericin B is the main antifungal in the class of polyenes and was the first antifungal agent discovered that was effective for the treatment of systemic fungal diseases. It probably has the broadest spectrum, is highly cidal, and remains the primary antifungal agent in clinical use today for many severe or recalcitrant fungal infections. The original formulation of amphotericin B deoxycholate (AmBD, Fungizone, 1959) has several associated dose-limiting toxicities, and three alternate lipid-associated formulations have since been developed: amphotericin B lipid complex (ABLC, Abelcet, 1995), amphotericin B colloidal dispersion (ABCD, Amphotec, 1996), and liposomal amphotericin B (L-AmB, Ambisome, 1997), which are less toxic, but adverse effects still pose frequent limitations in their use compared to other classes of antifungals. The predominant formulations in clinical use today (AmBD and L-AmB) will be the main focus of this section.

History, mechanism, adverse effects

Amphotericin B (AmB) was first described in 1956 after its isolation from a Streptomycete (*Streptomyces nodosus*) found in a soil sample obtained from the Orinoco River region of Venezuela. Its name reflects

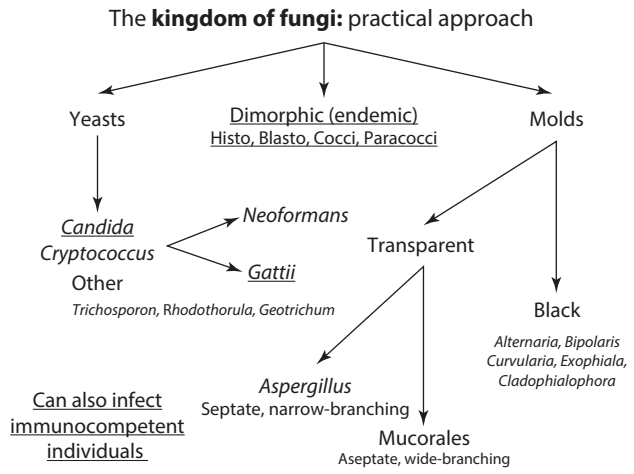

FIGURE 207.1 An overview of fungal pathogens.

its amphipathic nature (having both a hydrophobic and hydrophilic group) and being the second of two new antimicrobials isolated from this sample (with amphotericin A having less antifungal activity). AmB is highly insoluble in water and so was originally formulated with sodium deoxycholate (AmBD) to form a colloid and allow for intravenous infusion. In an effort to reduce nephrotoxicity, three lipid-associated formulations were developed: ABLC, which consists of AmB complexed with two lipids in a large ribbon-like structure; ABCD, which consists of AmB bound to cholesteryl sulfate in a much smaller disc-like structure; and L-AmB, which consists of small unilamellar liposomes each containing AmB. These lipid formulations have demonstrated a decrease in nephrotoxicity as compared with AmBD while maintaining similar clinical efficacy but are in general more expensive.

Although amphotericin B has been used clinically for decades, there is not yet a firm understanding of its mechanism of action. The drug is thought to act on the cell membrane, as might be expected given its amphipathic structure. However, various studies show disparate, but not necessarily mutually exclusive, mechanisms of action. One hypothesis, the "barrel-stave" model, suggests that AmB self-assembles into channel-like structures (or nanopores) that span the lipid bilayer and allow for ionic permeability and subsequent cell death. This long-standing model is supported by studies demonstrating that these transmembrane channels tend to be more stable in the presence of ergosterol rather than cholesterol, providing an explanation for the relatively increased action of amphotericin B

TABLE 207.1 **OVERVIEW OF ANTIFUNGAL AGENTS**

	Azoles (–conazole)							
***Candida* spp.**	**Flu**	**Itra**	**Vori**	**Posa***	**Isavu***	**5FC[1]**	**Echinocandins**	**AmB***
Albicans	S	S	S	S	S	(S)	S	S
Glabrata	DD/R	DD/R	DD/R	DD/R	DD/R	(S)	S (I/R)	S
parapsilosis	S	S	S	S	S	(S)	S/I	S
Tropicalis	(S)	(S)	(S)	(S)	(S)	(S)	(S)	(S)
Krusei	R	S	S	S	S	R	S	S
Lusitaniae	(S)	(S)	(S)	(S)	(S)	(S)	(S)	(R)
PK/PD: Penetration and Cidality								
Urine	+	–	–	–	–	–	(–)[2]	D+ L(–)[2]
CSF/eye	++	+	++	+	(–)[3]	+	–	+
Cidality[4]	–	–	–	–	–	–	+	+
Toxicities and Drug–Drug Interactions								
Liver	+	+	++	+(+)	(–)	+	(–)[5]	(–)
Kidney	–	–	(–)	–	–	–	– (? ↓K)	++
CYP/QTc	+	+	++	+(+)	–	–	–	(–)
Other		Hypertension	Skin Cancer Periostitis			Anemia		Infusion Reactions

Underlined: Active against Aspergillus spp.
* Active against the Mucorales.
[1]5FC is almost exclusively used in combinations for synergy, except uncomplicated cystitis from susceptible *Candida* spp., where it can be used as monotherapy.
[2] Limited penetration, case reports of success.
[3] Limited data, mostly from animal models suggesting some brain penetration.
[4] Refers mainly to *Candida*; against *Aspergillus* mold-active triazoles and AmB are cidal and echinocandins static.
[5] Less hepatotoxic than azoles; caspofungin and micafungin are hepatically metabolized, anidulafungin is not.
5FC, flucytosine; CSF, cerebrospinal fluid; CYP, Cytochrome-P; D, deoxycholate ("classic"), L, liposomal AmB; DD, dose-dependent; I, intermediate; K, potassium; PK/PD, pharmacokinetics/pharmacodynamics; QTc, corrected QT interval on EKG; R, resistant; S, susceptible.

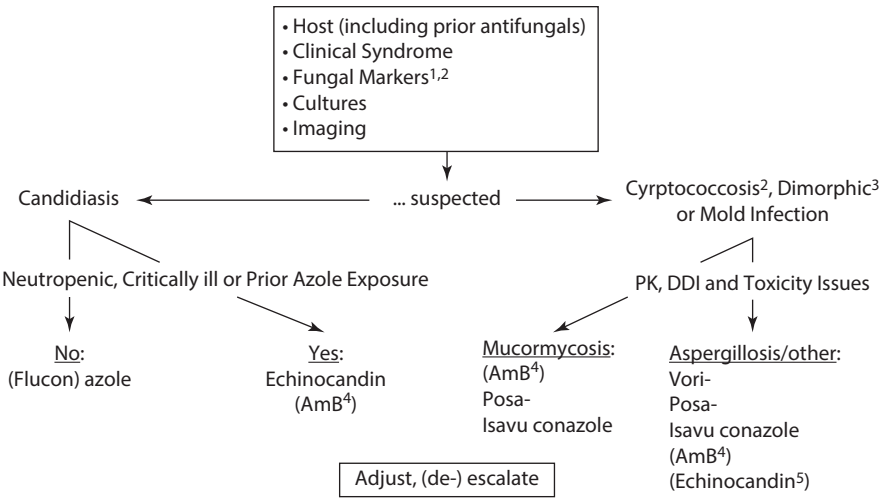

FIGURE 207.2 Algorithm for the empiric treatment of fungal infections.

[1]Cryptococcal antigen, 2Aspergillus galactomannan, 3beta-D-glucan (Fungitel). [2]Induction treatment for meningitis or severe disease consists of AmB + flucytosine (5FC). [3]For disseminated and severe disease, use AmB. [4]AmB: Amphotericin B, use with close monitoring of electrolytes, adequate hydration, minimization of other nephrotoxins, consider premedication for infusion reactions. [5]High-dose, not recommended in general as monotherapy for aspergillosis.

against fungal cells as compared to bacterial or human cells. Another hypothesis, the "sterol-sponge" model, suggests that binding of ergosterol by AmB and subsequent ergosterol sequestration are sufficient to promote fungal cell death independent of membrane permeabilization given the dependence of multiple critical aspects of fungal physiology on the presence of ergosterol. Further research into the specific mechanisms of AmB on-target and off-target actions is ongoing in an effort to further understand the mechanism(s) of clinical resistance as well as to aid in the potential development of less toxic derivatives.

Adverse effects of AmB (and the subsequent development of effective and less toxic antifungal agents; namely, azoles and echinocandins) have contributed to this agent no longer being used as first-line therapy for many fungal infections. One of the most frequent and most severe dose-related effects of AmB is nephrotoxicity, with early studies showing an incidence as high as 83%. This effect is manifested clinically by azotemia, renal tubular acidosis, and electrolyte abnormalities (hypokalemia, hypomagnesemia) and, not uncommonly, can progress to acute renal failure. The toxicity is thought to be due to formation of membrane pores in tubular cells by AmB with ensuing tubular cell injury, compounded by decreased renal blood flow (and subsequent decrease in glomerular filtration rate), via activation of the tubuloglomerular feedback system. Some studies have shown that salt loading prior to AmB infusion can help minimize nephrotoxicity, perhaps by ameliorating the tubuloglomerular feedback response. Similarly, use of the lipid-associated formulations is also associated with decreased incidence of nephrotoxicity due to the decreased distribution of the drug to the kidneys. One large randomized study showed a decrease in the incidence of nephrotoxicity from 34% to 19% with the use of L-AmB as compared to AmBD.

Infusion-related adverse effects are also relatively common, with distinct syndromes associated with both AmBD and L-AmB. AmBD infusions are commonly followed within 1 to 3 hours by fever, chills/rigors, headache, muscle aches, and nausea; this syndrome is thought to be due to induction of pro-inflammatory cytokines by AmB. In contrast, L-AmB infusions are occasionally associated with a syndrome of chest pain, dyspnea, hypoxia, abdominal pain, flushing, and urticaria, all starting within minutes of initiating an infusion; this syndrome is thought to be due to a "pseudo-allergic" complement-mediated reaction to the liposomal moiety rather than related to AmB itself. AmBD infusion reactions are often ameliorated by premedication with an anti-inflammatory agent or by slowing the infusion rate, whereas L-AmB infusion reactions can often be ameliorated by an antihistamine and are often less severe or absent with subsequent doses. Premedication with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or meperidine, and, according to some investigators using a different lipid formulation of AmB (ABLC vs. L-AmB) might also help. ABCD has a similar or higher rate of these infusion reactions than AmBD and is no longer manufactured or distributed. One other potential adverse effect of AmB is hypoproliferative anemia; hepatotoxicity is rare.

Pharmacology, drug interactions

Amphotericin B is poorly absorbed after oral administration and thus is generally given intravenously. After an infusion of AmBD, the AmB moiety dissociates and thereafter remains highly bound (>90%) to lipoproteins when circulating in plasma, though the majority of AmB is distributed widely to tissues (including the kidneys). There is no significant metabolism of AmB, and most of the drug is eventually excreted unchanged in urine and feces, albeit very slowly (terminal $t_{1/2} \approx 5$ days). In contrast, after an infusion of L-AmB, the liposomes are largely sequestered in the plasma compartment but are also eventually excreted unchanged in urine and feces, with a terminal $t_{1/2}$ of approximately 6 days. A standard dose of L-AmB (3–6 mg/kg/d) achieves a much higher peak plasma concentration than a standard dose of AmBD (0.3–1.5 mg/kg/d) due both to the higher dose given (and tolerated) as well as to the distribution of the drug. However, by virtue of being associated with a liposome rather than simply being bound to a lipoprotein, there is

overall decreased exposure of the renal tubules to "free" AmB with L-AmB as compared to AmBD; thus, even with a higher plasma concentration of L-AmB, there is less nephrotoxicity.

There are no renal or hepatic dosing adjustments for any formulations of AmB given the lack of renal or hepatic metabolism or significant contributions to drug clearance. AmBD distributes to most tissues, although the concentration of AmB at some sites is much lower than that of plasma given the limited diffusion potential of a lipoprotein-bound drug. L-AmB is largely sequestered in the plasma compartment but similarly is thought to be available at most sites of infection due to inflammatory changes allowing for local extravasation of liposomes. Neither AmBD nor any of the lipid-associated formulations have any significant interactions with other medications, though care should be taken to avoid simultaneous administration with other nephrotoxic or hypokalemia-inducing agents.

Therapeutic use, clinical resistance

Amphotericin B is active against a broad array of fungal pathogens; additionally, it is used clinically as an alternative agent for the treatment of leishmaniasis, a protozoal disease. It is active against almost all *Candida* (except *C. lusitaniae* strains) and *Aspergillus* spp. (except *A. terreus* strains), as well as *Cryptococcus* spp., the dimorphic/endemic fungi, and many non-*Aspergillus* hyaline (transparent or pale) molds including the Mucorales. AmB is also active against some (but not all) dematiaceous (dark brown or black) molds (e.g., *Alternaria*, *Bipolaris*, *Exophiala* spp.), the etiologic agents of phaeohyphomycosis or chromoblastomycosis. The formulations of AmB can generally be used interchangeably for most infections without regards to efficacy, with the exception of genitourinary infections which are thought to be more appropriately treated with AmBD rather than L-AmB given the reduced excretion of the latter in urine. Local instillation (intraperitoneal, intrathecal, intravitreal, bladder irrigation, or through nephrostomy tube) of AmB is occasionally necessary for severe or recalcitrant infections. While alternate classes of effective antifungal agents (i.e., azoles and echinocandins) have replaced AmB as first-line antifungal therapy for many infections due to their decreased toxicity, AmB remains an effective treatment option for many infections and, not uncommonly, is the only antifungal agent available with clinical activity against some more atypical or resistant fungal pathogens.

A more approachable assessment of the breadth of activity of AmB involves examining fungal pathogens encountered clinically which are less susceptible or frankly resistant to AmB. Resistance to AmB among *Candida* spp. is generally rare, but an elevated minimum inhibitory concentration (MIC) and/or a clinically resistant phenotype is not uncommonly seen in *C. lusitaniae* and the emerging pathogen *C. auris* (as well as the closely related but less commonly encountered *C. haemulonii*). Resistance is thought to be most often due to a mutation in an enzyme involved in the ergosterol biosynthesis pathway (e.g., ERG2, ERG3, ERG5, ERG6, or ERG11) which results in decreased production of ergosterol and thus decreased susceptibility to AmB. In general, these mutations also lead to decreased virulence and/or decreased susceptibility to external stressors, which is thought to have prevented the emergence of widespread clinical AmB resistance in most *Candida* spp. It is unclear why AmB resistance is more common in the *Candida* species mentioned earlier, although some reports have demonstrated a relationship between AmB resistance and phenotypic switching in *C. lusitaniae* (perhaps allowing for the expression of an intrinsically resistant phenotype in the presence of AmB) as well as demonstrated some preliminary evidence of alternate mechanisms of AmB resistance in *C. auris*. Resistance to AmB among *Aspergillus* spp. is also generally rare but does occur in *A. terreus*. Rather than a decrease in ergosterol content of the fungal cell membrane as observed with some *Candida* spp., resistance to AmB in *A. terreus* is thought to be primarily due to an increased intrinsic stress response capability. Recent reports have highlighted a troubling trend of increasing AmB resistance in other common *Aspergillus* spp., including *A. fumigatus*.

Data describing resistance to AmB for other fungal pathogens is much sparser. Notably, in vitro antifungal susceptibility testing is limited in its ability to predict clinical outcomes, with many other factors playing roles that are perhaps more relevant when considering atypical fungal infections in immunocompromised hosts (e.g., virulence of pathogen, clinical syndrome, host immune status). Many *Fusarium* spp. (especially *F. solani* complex) demonstrate elevated MICs to AmB, although there are no formal interpretive clinical breakpoints, no clear mechanism of resistance has been uncovered, and there is no clear correlation between elevated MIC and clinical failure. In some guidelines, voriconazole rather than L-AmB is the first-line agent recommended for treatment of fusariosis. *Scedosporium* spp. (including teleomorphic forms previously named *Pseudallescheria* spp.) and the now renamed *Lomentospora prolificans* also demonstrate elevated MICs to AmB. Similarly to *Fusarium* spp., no clear mechanism of resistance to AmB has been identified for *Scedosporium* spp., although the clinical relevance of an elevated MIC is a bit more straightforward given the generally poor clinical outcomes of this infection despite AmB treatment. Voriconazole rather than AmB again remains the first-line agent recommended for the treatment of scedosporiosis, especially infections with *S. apiospermum* (*S. prolificans* is notorious for multidrug resistance), although surgical debridement is often the mainstay of therapy if possible, given the lack of clinical efficacy for many antifungals. Treatment of scedosporiosis with combinations of antifungal agents, often including AmB and terbinafine, is also relatively common practice.

Echinocandins

Three echinocandin antifungal agents are currently available for clinical use: caspofungin (Cancidas, 2001), micafungin (Mycamine, 2005), and anidulafungin (Eraxis, 2006). Two other glucan synthase inhibitors are in development (rezafungin and ibrexafungerp, see further discussion in the "Novel Antifungals" section of this chapter). Echinocandins are the antifungal agents of choice for invasive candidiasis, not only because of their superior cidality against *Candida* and clinical efficacy but also due to their tolerability and minimal interactions with other medications.

History, mechanism, adverse effects

The first echinocandin compound described was a lipopeptide with anti-yeast activity isolated from an *Aspergillus* strain (*A. nidulans var. echinulatus*, now *A. spinulosporus*) in 1974. This early compound and its derivatives proved too toxic for clinical use, but a similar group of compounds was eventually isolated from another ascomycete (*Zalerion arboricola*) in 1992, which subsequently gave rise to the echinocandin agents currently in use. Given the origin of these echinocandin precursors, the limited clinical efficacy against *Aspergillus* (see later discussion) found within this class of antifungal agents is not altogether surprising.

Echinocandins act by inhibiting (1,3)-β-D-glucan synthase (GS), the enzyme responsible for the synthesis of (1,3)-β-D-glucan (BDG), a major component of the fungal cell wall. Additional components of the fungal cell wall include various other glucans, mannans (including galactomannan), and chitin. Cell wall components vary among disparate fungal species (e.g., *Candida albicans*: 30–39% BDG, 43–53% [1,6]-β-D-glucan, 2–6% chitin; *Aspergillus fumigatus*: 20–35% BDG, 20–25% galactomannan, 7–15% chitin); moreover, the relative abundance of each component can vary in response to environmental stimuli (e.g., antifungal exposure). For fungal species in which BDG is a predominant component of the cell wall, such as *Candida* spp., the decreased production of BDG after exposure to an echinocandin results in a weak and osmotically fragile fungal cell wall, leading to fungal cell lysis. For some other fungal species in which BDG is present but in relatively lower abundance, particularly in molds such as *Aspergillus* spp., the inhibition of BDG production by an echinocandin causes lysis of the cell wall at rapidly growing hyphal tips but in general does not halt the overall growth of the fungal organism. Opposite to mold-active triazoles, echinocandins are fungicidal against *Candida* and fungistatic against *Aspergillus*.

All of the echinocandins are generally well-tolerated. Notably, there are no mammalian homologues for GS, thus no expected on-target adverse effects. Beyond mild to moderate generalized symptoms such as headache or gastrointestinal discomfort primarily reported in clinical trials, hepatotoxicity is the one adverse effect noted most frequently with clinical echinocandin use, though the reported prevalence of this complication varies (3.8–37%) and likely depends at least in part on an individual's preceding level of hepatic dysfunction. Although caspofungin and micafungin both undergo hepatic metabolism while anidulafungin does not, aside from a potential impact on dosing regimens, these differences in metabolism have not been shown to impact the relative frequency of hepatotoxicity between different echinocandins. Hypokalemia has been reported sporadically, but its association with echinocandin administration is not well-established.

Pharmacology, drug interactions

Echinocandins are only available for parenteral use given their large molecular weight and poor absorption when administered orally. All are highly protein-bound, which results in relatively long half-lives and allows for once-daily dosing. Their large molecular weight, protein-bound status, and minimal lipophilicity all contribute to poor penetration into tissue compartments without fenestrated capillaries (e.g., brain/CSF, eye, prostate). Importantly, since none of these agents undergoes appreciable renal excretion, there is minimal active drug found in urine. Echinocandins do not undergo renal metabolism, so no dose adjustments are necessary for renal insufficiency. Caspofungin and micafungin both undergo hepatic metabolism to form inactive metabolites which are eventually excreted via urine and feces, though only caspofungin has an indicated dose reduction for hepatic dysfunction. Anidulafungin does not undergo hepatic metabolism and is instead primarily degraded in the plasma to an inactive form which is eventually excreted primarily in the feces. Preliminary data suggest that optimal dosing of echinocandins in obese individuals may necessitate a dose increase. Higher doses are also recommended by some experts against aspergillosis and in serious *Candida* infections, such as endocarditis.

Drug interactions with echinocandins are relatively rare. None of these agents is primarily metabolized by cytochrome P450 (CYP) enzymes, so they are neither affected by nor affect other CYP inducers, inhibitors, or competitors. Decreased concentrations of caspofungin have been found when coadministered with rifampin, thought to be due to increased hepatic uptake (rather than metabolism) of caspofungin via the OATP1B1 transporter due to the induction of OATP1B1 by rifampin. Other studies have demonstrated that cyclosporin may increase caspofungin levels, that caspofungin may decrease tacrolimus levels, and that micafungin may increase sirolimus and itraconazole levels, all via unknown mechanisms. However, these drug–drug interactions are not considered nearly as clinically significant as those with most azoles.

Therapeutic use, clinical resistance

The echinocandins are primarily active against *Candida* spp. and are recommended for use as first-line therapy for the treatment of invasive candidiasis. They are active against the majority of *Candida* spp. and are used to treat *Candida* infections at all anatomic sites with the exception of brain/central nervous system (CNS), eye, urine, and prostate. They are also effective for treatment of febrile neutropenia and antifungal prophylaxis in neutropenic patients. The echinocandins also have some fungistatic activity against *Aspergillus* spp. and can be used for salvage therapy (alone or in combination with other classes of antifungal agents) for selected and sometimes refractory cases of invasive aspergillosis. They are active against the mycelial forms of dimorphic fungi (e.g., *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*) but are much less active against their yeast-like forms and thus are generally not used clinically to treat infections due to these pathogens. Echinocandins lack activity against *Cryptococcus* spp. The *Mucorales* and other non-*Aspergillus* non-dematiaceous molds are generally not susceptible to echinocandins.

Most data regarding mechanisms of echinocandin resistance have been derived from work with *Candida* spp. In contrast to the azoles, for which intrinsic resistance (due at least in some part to many years of agricultural azole herbicide use) is relatively common, intrinsic echinocandin resistance in *Candida* spp. is rare. Instead, echinocandin resistance is generally associated with repeated or prolonged exposure to these agents. The development of clinical resistance is closely linked to the acquisition of a mutation in an FKS

gene (FKS1 or FKS2). These genes encode catalytic subunits of GS, the target of echinocandins, and mutations in certain hotspot areas lead to decreased echinocandin susceptibility. Beyond a target gene mutation, no other common resistance mechanisms have been found; notably, echinocandins are not substrates for multidrug transporters. However, some cellular stress responses, such as an increase in chitin synthesis, are also thought to contribute to resistance by promoting echinocandin tolerance and allowing time for the development of FKS mutations.

Globally, echinocandin resistance is relatively rare among common *Candida* spp. including *C. albicans* (0–0.2%), *C. parapsilosis* (0–0.5%), *C. tropicalis* (0–1.3%), and *C. krusei* (0%). Resistance is more common in *C. glabrata* (0.8–2.5%), and especially so when measured at some centers with many immunocompromised patients and prevalent echinocandin use (10–22%). Echinocandin resistance in *C. glabrata* is often also associated with concurrent fluconazole resistance (up to 36% in one study). The increased rate of echinocandin (and azole) resistance in *C. glabrata* is thought to be at least in part due to alterations in a DNA mismatch repair gene (MSH2) allowing for the more rapid emergence of escape mutations in this organism ("mutator phenotypes"). Uncommon *Candida* spp. clinical isolates demonstrate varying echinocandin resistance patterns, with one cross-sectional study demonstrating rates of MIC greater than the epidemiologic cutoff values (ECV) as follows: *C. lusitaniae*: 6/55 (11%), *C. dubliniensis*: 0/50 (0%), *C. guilliermondii*: 1/19 (5.3%), *C. kefyr*: 1/16 (6.3%). Interpretation of these elevated MICs is limited by the lack of published clinical breakpoints due to the rare isolation and decreased virulence of some of these organisms. *C. auris*, an emerging pathogen associated with nosocomial infections, typically has intrinsic fluconazole resistance and not uncommonly also has acquired pan-azole resistance and/or amphotericin B resistance. It is worrisome that some of these isolates have also shown relatively high rates of echinocandin resistance (2–7%), leaving limited options for effective antifungal therapy, which makes the emergence of multidrug-resistant (MDR) *C. auris* a public health emergency.

Triazoles

Triazoles were the second major class of systemic antifungal agents developed (after amphotericin B). There are five agents currently in clinical use: fluconazole (Diflucan, 1990), and the mold-active triazoles: itraconazole (Sporanox, 2001), voriconazole (Vfend, 2003), posaconazole (Noxafil, 2006), and isavuconazole (Cresemba, 2015). Triazoles are first-line therapy for many infections due to *Aspergillus* spp. given their fungicidal activity against this pathogen, but they have been supplanted from first-line therapy for invasive candidiasis by the echinocandins given that triazoles are fungistatic against *Candida* spp. and the increasing prevalence of triazole-resistant *Candida* clinical isolates.

History, mechanism, adverse effects

The synthetically derived imidazoles (e.g., clotrimazole, miconazole) have been used for the treatment of superficial fungal infections since 1969, but their use for systemic mycoses is restricted by their limited efficacy and systemic toxicity. Ketoconazole, a triazole (produced by N-substitution of the imidazole ring) developed in 1978, was the first orally active broad-spectrum antifungal agent available for clinical use. Similarly to imidazoles, its use as a systemic antifungal has fallen out of favor due to toxicities not present in later triazole derivatives. Fluconazole (FLC), a miconazole derivative, and itraconazole (ITC), a ketoconazole derivative, were subsequently developed and remain the "first-generation" triazoles in clinical use today. Further modifications of FLC and ITC produced the "second-generation" triazoles, voriconazole (VCZ) and posaconazole (PCZ), respectively. Most recently introduced into clinical use is the "third-generation" triazole isavuconazole (ISA), which has a structure most similar to FLC and VCZ. VCZ, PCZ and ISA are often referred to as the "newer" triazoles because of extended spectrum and favorable pharmacokinetics.

Triazole antifungal agents act by inhibiting the biosynthesis of ergosterol, an integral component of the fungal cell membrane. More specifically, they act by inhibition of lanosterol 14α-demethylase (encoded by genes ERG11 in *Candida* or CYP51 in *Aspergillus*), a key enzyme involved in the conversion of lanosterol to ergosterol in fungi, and the conversion of lanosterol to cholesterol in humans. Inhibition of this enzyme leads to a decrease in available ergosterol and, more importantly, the production of toxic metabolites by alternate metabolic pathways. Thus, triazole administration results in growth arrest and a fungistatic effect seen across most of the fungal kingdom, especially yeasts. However, in some mold (specifically many *Aspergillus*) species, there is also a subsequent fungicidal effect of some triazoles due to an ensuing period of overexuberant fungal cell wall biosynthesis without any corresponding development of hyphal protrusions; this leads to fungal cell wall stress, rupture, and, finally, fungal death.

The major adverse effect associated with the use of all triazoles is hepatotoxicity, which often manifests as asymptomatic elevation in liver function tests but in rare cases can also progress to acute liver failure. Each of the triazole agents has a differing incidence of associated hepatoxicity, with a relatively low incidence for FLC and a relatively higher incidence for VCZ. This hepatoxicity is thought to be dose-dependent (at least with VCZ), and thus the incidence of toxicity is also affected by several pharmacokinetic parameters. Alopecia is also relatively common with extended triazole therapy (including at least FLC and VCZ), and QTc prolongation (FLC, ITC, VCZ, PCZ) or shortening (ISA) have also been described. The adverse-effect profile of VCZ is somewhat unique. Early side effects include relatively common reports of visual disturbances (often transient as a result of early retina stimulation with the first doses), but also frank hallucinations and peripheral neuropathy. Long-term adverse effects associated with prolonged VCZ use are painful periostitis (due to fluoride accumulation, a component of VCZ formulations, often manifesting as isolated elevation of alkaline phosphatase levels) and development of cutaneous malignancies associated with VCZ skin phototoxicity, especially in vulnerable patient populations with additional risk factors, such as organ transplant recipients on calcineurin inhibitors and stem cell transplant recipients with graft-versus-host disease.

Pharmacology, drug interactions

The "short-tailed" triazoles (FLC, VCZ, ISA) all have excellent bioavailability (>90%), though VCZ is best absorbed on an empty stomach, whereas absorption of the "long-tailed" triazoles (ITC, PCZ) is less straightforward. ITC is well absorbed after a full fatty meal, is also best absorbed at low gastric pH, but notably has only 54% relative bioavailability with an empty stomach. Furthermore, ITC solution has 133% relative bioavailability as compared to ITC capsules. PCZ is formulated as an oral suspension as well as delayed-release tablets. The PCZ oral suspension has similar characteristics as ITC, with bioavailability maximized by administration with a high-fat meal and low gastric pH, but otherwise has relatively lower and unpredictable absorption. In contrast, absorption of the PCZ delayed-release tablet is unaffected by food intake and gastric acidity, providing uniformly adequate drug levels. FLC, VCZ, PCZ, and ISA are all also available in parenteral formulations; both VCZ and PCZ parenteral formulations contain cyclodextrin so their use is limited in patients with renal insufficiency. ISA is given as isavuconazonium sulfate (the water-soluble prodrug of isavuconazole) in both the oral and parenteral formulations, which rapidly disassociates to release the active drug soon after administration. It also has excellent absorption that is not affected by food intake or gastric acidity.

ITC, VCZ, PCZ, and ISA are highly protein-bound (99%, 58%, 98%, and 99%, respectively) and have extensive tissue distribution, whereas FLC is minimally protein-bound (12%) and has a distribution that approximates total body water. FLC does not undergo significant metabolism but is instead primarily excreted unchanged in the urine; it therefore requires dosage adjustments for renal impairment (but not for hepatic impairment) and is also the only triazole reliably effective for *Candida* urinary tract infections. In contrast, ITC, VCZ, and ISA undergo extensive hepatic metabolism (ITC and ISA via CYP3A4, VCZ via CYP2C19), with inactive metabolites of each excreted in urine or feces. PCZ undergoes limited hepatic metabolism via UGT1A rather than via a CYP enzyme and is primarily excreted unchanged in the feces. ITC and VCZ have recommended dosage adjustments for hepatic impairment whereas PCZ and ISA do not. All triazoles have generally good penetration into most tissues; however, given its relatively small size, low lipophilicity, and low affinity for plasma proteins, FLC has superior penetration to aqueous compartments such as the cerebrospinal fluid (CSF), eye, and urine. VCZ also has some CSF penetration (50%) given its relatively lower affinity for plasma proteins as compared to some of the other triazoles, but is almost absent (<5%) from the urinary compartment. ITC, PCZ, and ISA each have suboptimal (compared to VRC) CSF and very poor urine penetration. All of the triazoles have long terminal half-lives allowing either once- or twice-daily dosing.

Therapeutic drug monitoring (TDM) is recommended for VCZ given its narrow therapeutic window and metabolism by CYP2C19, an enzyme with several relatively common genetic polymorphisms which can widely vary the rate of VCZ metabolism. TDM has also been recommended for ITC and PCZ (especially the oral suspension) given the variable oral absorption of these agents; it is unclear if TDM is necessary for the PCZ delayed-release tablets or ISA given the uniformly adequate drug levels found with these formulations. However, PCZ or ISA levels can be measured and the authors of this chapter have found them useful in selected cases, such as patients with absorption issues or concerns for toxicity or significant drug–drug interactions (e.g., induced catabolism of ISA by phenobarbital).

The triazoles are notorious for interacting with other medications, due primarily to interactions with CYP enzymes, leading to increased levels of other drugs metabolized by these enzymes (e.g., warfarin, NSAIDs, angiotensin receptor blockers [ARBs] for 2C9; proton pump inhibitors [PPIs], selective serotonin reuptake inhibitors [SSRIs], methadone for 2C19; and statins, amiodarone, cyclosporine, tacrolimus, and sirolimus for 3A4). Moreover, ITC and ISA are metabolized via CYP3A4 and VCZ is metabolized via CYP2C19, therefore inducers (e.g., rifampin or some antiepileptics) or inhibitors (e.g., clopidogrel or some protease inhibitors) of these CYP enzymes act to decrease or increase, respectively, the levels of these three triazoles. While some drug–drug interactions are predictable (e.g., the reliably increased cyclosporine, tacrolimus, and sirolimus levels encountered with triazole use), given the multitude of potential interactions it is wise to always carefully address drug interactions when using triazoles. For tacrolimus and sirolimus, usually a 50% and 66% dose reduction with FLC or VRC/PCZ coadministration is recommended, depending on pre-administration levels and goal.

Therapeutic use, clinical resistance

FLC is active against most yeasts, including many *Candida* spp. and *Cryptococcus* spp., but is generally not active against molds. ITC is used clinically for the treatment of the dimorphic fungi and has anti-*Aspergillus* activity. VCZ is active against most yeasts (including some FLC-resistant *Candida* spp., such as *C. krusei* that is intrinsically resistant to FLC). VCZ is considered the first-line antifungal agent for infections due to *Aspergillus* spp. (including the often AmB-resistant *A. terreus*) and can also be used for the treatment of other hyaline and dematiaceous molds including *Fusarium* spp. and *Scedosporium apiospermum*. PCZ and ISA have additional activity against *Mucorales* spp. FLC is the only triazole agent used for the treatment of urinary tract infections given the limited renal excretion of the other agents. FLC and VCZ are the two triazole agents used most often for treatment of fungal infections in the CNS given their relatively increased CSF penetration as compared to the other triazoles. Posaconazole is also used for antifungal prophylaxis during induction chemotherapy for acute myeloid leukemia and in hematopoietic stem cell transplant recipients with graft-versus-host disease.

There is an ongoing trend of increased resistance to triazole agents, due both to increased rates of triazole use in humans for prophylaxis and treatment as well as to the widespread use of biosimilar fungicides in veterinary and agricultural practice. Resistance to triazoles can be either intrinsic or acquired and is generally due to target modification, increased target production,

or antifungal efflux. In *Candida* spp., intrinsic FLC resistance due to an ERG11 modification is seen consistently in both *C. krusei* and *C. auris*. Acquired pan-triazole resistance, not uncommon in *C. glabrata* and *C. auris*, can develop as a result of a distinct ERG11 modification or via a gain of function mutation in a regulatory gene resulting in overexpression of ERG11 (too much target) or of a CDR efflux pump (not enough antifungal). These mutations are thought to be more common in *C. glabrata* than in other *Candida* spp due to its haploid genome, and, possibly, an intrinsic mutation in MSH2 (a DNA repair gene). In *Aspergillus* spp., intrinsic FLC resistance is ubiquitous due to a polymorphism of CYP51 (as compared to the ERG11 homolog in *Candida* spp). Intrinsic resistance to multiple triazole agents is associated with *A. fumigatus* isolates which have the TR34-L98H or TR46-Y121F/T289A genotypes (representing paired mutations in the CYP51 promoter as well as the CYP51 gene) and are thought to have developed due to selective pressure from ongoing environmental fungicide use. *A. fumigatus* resistance to triazoles is an important emerging concern of clinical significance in Europe, less so in the United States. Acquired triazole resistance is most often associated with prolonged triazole treatment and is usually due to one of many known resistance-conferring single-point mutations in CYP51. Less is known about resistance mechanisms in other *Aspergillus* spp. and in other molds.

Other antifungal agents

Nystatin

Similar to amphotericin B, nystatin is a polyene with similar mechanism of action. However, its use is limited to topical application for skin infections (nystatin powder) and oropharyngeal candidiasis (nystatin oral suspension, "swish and spit or swallow"). Some centers use it as antifungal prophylaxis in a high-risk (transplant) patients, although fluconazole is superior, to avoid CYP-mediated drug–drug interactions, especially with calcineurin or mTOR inhibitors (see earlier discussion).

Flucytosine (5FC)

Flucytosine is metabolized to 5-fluro-uracil (5FU), acting then as an antimetabolite that inhibits fungal DNA synthesis. As such, the genetic barrier to development of resistance is very low, and monotherapy is only recommended for uncomplicated urinary tract infections from susceptible *Candida* strains. However, it is useful in combination therapy, its combination with AmB being the standard of care for the initial ("induction") treatment of serious cryptococcal infections, including cryptococcal meningitis. The combination of AmB+5FC is also recommended for the management of some serious *Candida* infections, such as endocarditis. TDM of 5FC levels can have a role in dose adjustments if prolonged administration is required. The main adverse events associated with 5FC are myelosuppression (especially hypoproliferative anemia) and hepatotoxicity. 5FC needs to be renally adjusted.

Terbinafine

Similar to azoles, terbinafine, an allylamine, acts on the fungal cell wall, disrupting ergosterol synthesis by inhibition of a different enzyme, squalene monooxygenase (2,3-epoxidase). It is highly lipophilic and therefore accumulates in the skin, nails, and fatty tissues. Its main indication as monotherapy is onychomycosis. Clinicians also use it in combination regimens against difficult to treat and potentially resistant mold infections such as fusariosis and scedosporiosis. It can cause hepatotoxicity.

Antifungals under development

The antifungal armamentarium has rapidly expanded over the past few decades at an unprecedented rate, and many new molecules are currently being investigated with promising results. Nikkomycin Z (VFS-1) targets the synthesis of the cell wall component, chitin, and has activity against *Coccidioides immitis* and *Blastomyces dermatitidis* alone and against *Candida* spp., *C. neoformans*, and *A. fumigatus* in combination with azoles. T-2307 is an aromatic diamidine with some structural similarities to pentamidine, which acts on the mitochondrial membrane, and it has potent activity against *Candida* spp., including *Candida* strains that are resistant to other antifungals, *C. neoformans* and *A. fumigatus*.

Rezafungin (also known as biafungin or CD101) is a long-acting echinocandin that is administered weekly. Despite its long half-life, it achieves high serum concentrations for long periods of time and has not been shown in preliminary studies to select resistant strains more than existent echinocandins. Ibrexafungerp (SCY-078) is an oral β-D-glucan inhibitor that also seems to have in vitro activity against some resistant *Candida* strains, including isolates with decreased susceptibility to echinocandins. Olorofim (F901318) is an orotomide that targets dihydroorotate dehydrogenase (DHODH) in the de novo pyrimidine biosynthesis pathway. It lacks anti-*Candida* activity, but is effective against *Aspergillus* spp. and, potentially, other molds. A detailed review of novel compounds with potential antifungal action is beyond the scope of this chapter and has been included in other recent comprehensive publications.

Suggested reading

Alastruey-Izquierdo A, Alcazar-Fuoli L, Rivero-Menendez O, et al. Molecular identification and susceptibility testing of molds isolated in a prospective surveillance of triazole resistance in Spain (FILPOP2 Study). *Antimicrob Agents Chemother.* 2018;62(9):e00358–18.

Alastruey-Izquierdo A, Mellado E, Pelaez T, et al. Population based survey of filamentous fungi and antifungal resistance in Spain (FILPOP Study). *Antimicrob Agents Chemother.* 2013;57(7):3380–3387.

Alexander B, Johnson M, Pfeiffer C, et al. Increasing echinocandin resistance in Candida glabrata: Clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. *Clin Infect Dis.* 2013;56(12):1724–1732.

Al Hatmi A, CurfsBreuker I, SybrenDeHoog G, et al. Antifungal susceptibility testing of Fusarium: A practical approach. *J Fungi.* 2017;3(2):19.

Anderson T, Clay M, Cioffi A, et al. Amphotericin forms an extramembranous and fungicidal sterol sponge. *Nat Chem Biol.* 2014;10(5):400–406.

Arendrup M, Patterson T. Multidrug resistant Candida: Epidemiology, molecular mechanisms, and treatment. *J Infect Dis.* 2017;216(Suppl 3):S445–51.

Ashbee H, Barnes R, Johnson E, et al. Therapeutic drug monitoring (TDM) of antifungal agents: Guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother.* 2014;69(5):1162–1176.

Ashu E, Korfanty G, Samarasinghe H, et al. Widespread amphotericin B resistant strains of Aspergillus fumigatus in Hamilton, Canada. *Infect Drug Resist*. 2018;11:1549–1555.

Badiee P, Badali H, Boekhout T, et al. Antifungal susceptibility testing of Candida species isolated from the immunocompromised patients admitted to ten university hospitals in Iran: Comparison of colonizing and infecting isolates. *BMC Infect Dis.* 2017;17(1):727.

Barone J, Koh J, Bierman R, et al. Food interaction and steady-state pharmacokinetics of itraconazole capsules in healthy male volunteers. *Antimicrob Agents Chemother.* 1993;37(4):778–784.

Barrone J, Moskovitz B, Guarnieri J, et al. Enhanced bioavailability of itraconazole in hydroxypropyl-B-cyclodextrin solution versus capsules in healthy volunteers. *Antimicrob Agents Chemother.* 1998;42(7):1862–1865.

Bekersky I, Fielding R, Dressler D, et al. Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin deoxycholate in humans. *Antimicrob Agents Chemother.* 2002;46(3):828–833.

Bennett J. Amphotericin B toxicity: Review of selected aspects of pharmacology. *Ann Intern Med.* 1964;61(2):335–340.

Bennett J. Clotrimazole: New drug for systemic mycoses? *Ann Intern Med.* 1970;73(4):653–654.

Benz F, Knusel F, Nuesch J, et al. Echinocandin B, a new polypeptide antibiotic from Aspergillus nidulans var echinulatus. *Helv Chim.* 1974;57(8):2459–2477.

Bordallo-Cardona M, Marcos-Zambrano L, Sanchez-Carrillo C, et al. Mutant prevention concentration and mutant selection window of micafungin and anidulafungin in clinical Candida glabrata isolates. *Antimicrob Agents Chemother.* 2018;62(3):e01982–17.

Boukari K, Balme S, Janot J, et al. Towards new insights in the sterol/amphotericin nanochannels formation: A molecular dynamic simulation study. *J Membr Biol.* 2016;249(3):261–270.

Brammer K, Farrow P, Faulkner J. Pharmacokinetics and tissue penetration of fluconazole in humans. *Rev Infect Dis.* 1990;12(Supp 3):S318–26.

Buil J, Snelders E, Denardi L, et al. Trends in azole resistance in Aspergillus fumigatus, the Netherlands, 1994–2016. *Emerg Infect Dis.* 2019;25(1):176–178.

Butler W. Amphotericin B toxicity: Changes in renal function. *Ann Intern Med.* 1964;61(2):344–349.

Cancidas (caspofungin). *Prescribing information*. Whitehouse Station, NJ: Merck & Co, Inc.; April 2016.

Castanheira M, Deshpande L, Davis A, et al. Monitoring antifungal resistance in a global collection of invasive yeasts and molds: Application of CLSI epidemiologic cutoff values and whole genome sequencing analysis for detection of azole resistance in Candida albicans. *Antimicrob Agents Chemother.* 2017;61(10):e00906–17.

Castanheira M, Messer S, Rhomberg P, et al. Antifungal susceptibility patterns of a global collection of fungal isolates: Results of the SENTRY antifungal susceptibility program (2013). *Diagn Microbiol Infect Dis.* 2016;85(2):200–204.

Chowdhary A, Prakash A, Sharma C, et al. A multicentre study of antifungal susceptibility patterns among 350 Candida auris isolates (2009–2017) in India: Role of the ERG11 and FKS1 genes in azole and echinocandin resistance. 2018;73(4):891–899.

Cobo F, LaraOva A, Rodriguez-Granger J, et al. Infections caused by Scedosporium/Lomentospora species: Clinical and microbiological findings in 21 cases. *Med Mycol.* 2018;56(8):917–925.

Cowen L, Sanglard D, Howard S, et al. Mechanisms of antifungal drug resistance. *Cold Spring Harb Perspect Med.* 2014;5(7):a019752.

Davis M, Nguyen M, Donnelley M, et al. Tolerability of long-term fluconazole therapy. *J Antimicrob Chemother.* 2018;doi:10.1093/jac/dky501.

DeKruijff B, Demel R. Polyene antibiotic-sterol interactions in membranes of Acholeplasma laidlawii cells and lecithin liposomes. III: Molecular structure of the polyene antibiotic-cholesterol complexes. *Biochim Biophys Acta.* 1974;339(1):57–70.

Durani U, Tosh P, Barreto J, et al. Retrospective comparison of posaconazole levels in patients taking the delayed-release tablet versus the oral suspension. *Antimicrob Agents Chemother.* 2015;59(8):4914–4918.

Ermishkin L, Kasumov M, Potzeluyev M. Single ionic channels induced in lipid bilayers by polyene antibiotics amphotericin B and nystatine. *Nature.* 1976;262(5570):698–699.

Escandon P, Chow N, Caceres D, et al. Molecular epidemiology of Candida auris in Columbia reveals a highly related, countrywide colonization with regional patterns in amphotericin B resistance. *Clin Infect Dis.* 2019;68(1):15–21.

Espinel-Ingroff A, Colombo A, Cordoba S, et al. International evaluation of MIC distributions and epidemiological cutoff value (ECV) definitions for Fusarium species identified by molecular methods for the CLSI broth microdilution method. *Antimicrob Agents Chemother.* 2015;60(2):1079–84.

Espinel-Ingroff A, Cuenca-Estrella M, Fothergill A, et al. Wild-type MIC distributions and epidemiological cutoff values for amphotericin B and Aspergillus spp for the CLSI broth microdilution method (M38-A2 document). *Antimicrob Agents Chemother.* 2011;55(11):5150–5154.

Farmakiotis D, Tverdek FP, Kontoyiannis DP. The safety of amphotericin B lipid complex in patients with prior severe intolerance to liposomal amphotericin B. *Clin Infect Dis* 2013;56(5):701–703.

Farmakiotis D, Tarrand J, Kontoyiannis D. Drug-resistant Candida glabrata infection in cancer patients. *Emerg Infect Dis.* 2014;20(11):1833–1840.

Farmakiotis D, Kontoyiannis DP. Epidemiology of human pathogenic yeast antifungal resistance: Current viewpoint and practical recommendations for management. *Int J Antimicrob Agents.* 2017;50(3):318–324.

Food and Drug Administration (FDA). FDA drug safety communication: FDA limits use of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems. US Food and Drug Administration. 2013 Jul 26. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-limits-usage-nizoral-ketoconazole-oral-tablets-due-potentially

Feldmesser M, Kress Y, Mednick A, et al. The effect of the echinocandin analogue caspofungin on cell wall glucan synthesis by Cryptococcus neoformans. *J Infect Dis.* 2000;182(6):1791–1795.

Felton T, Troke P, Hope W. Tissue penetration of antifungal agents. *Clin Microbiol Rev.* 2014;27(1):68–88.

Fisher M, Hawkins N, Sanglard D, et al. Worldwide emergence of resistance to antifungal drugs challenges human health and food security. *Science*. 2018;360:739–742.

Free S. Chapter 2: Fungal cell wall organization and biosynthesis. *Adv Genetics.* 2013;81:33–82.

Gallis H, Drew R, Pickard W. Amphotericin B: 30 years of clinical experience. *Rev Infect Dis.* 1990;12(2):308–329.

Geissel B, Loiko V, Klugherz I, et al. Azole-induced cell wall carbohydrate patches kill Aspergillus fumigatus. *Nat Commun.* 2018;9(1):3098.

Ghannoum M, Rice L. Antifungal agents: Mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. *Clin Microbiol Rev.* 1999;12(4):501–517.

Gigliotti F, Shenep J, Lott L, et al. Induction of prostaglandin synthesis as the mechanism responsible for the chills and fever produced by infusing amphotericin B. *J Infect Dis.* 1987;156(5):784–789.

Gold W, Stout A, Pagano J, et al. Amphotericins A and B, antifungal antibiotics produced by a streptomycete. I: In vitro studies. *Antibiotics Annual. 1955-1956*;3:579–586.

Gray K, Palacios D, Dailey I, et al. Amphotericin primarily kills yeast by simply binding ergosterol. *Proc Natl Acad Sci.* 2012;109(7):2234–2239.

Guarro J. Fusariosis, a complex infection caused by a high diversity of fungal species refractory to treatment. *Eur J Clin Microbiol Infect Dis.* 2013;32(12):1491–1500.

Gulmez D, Dogan O, Boral B, et al. In vitro activities of antifungal drugs against environmental Exophiala isolates and review of the literature. *Mycoses.* 2018;61(8):561–569.

Hall R, Swancutt M, Meek C, et al. Weight drives caspofungin pharmacokinetic variability in overweight and obese people: Fractal power signatures beyond two-thirds or three-fourths. *Antimicrob Agents Chemother.* 2013;57(5):2259–2264.

Hamill R. Amphotericin B formulations: A comparative review of efficacy and toxicity. *Drugs.* 2013;73:919–934.

Hashemizadeh Z, Badiee P, Ali Malekhoseini S, et al. Observational study of associations between voriconazole therapeutic drug monitoring, toxicity, and outcome in liver transplant patients. *Antimicrob Agents Chemother.* 2017;61(12):e01211–17.

Healey K, Perlin D. Fungal resistance to echinocandins and the MDR phenomenon in Candida glabrata. *J Fungi.* 2018;4(3):105.

Healey K, Zhao Y, Perez W, et al. Prevalent mutator genotype identified in fungal pathogen Candida glabrata promotes multi-drug resistance. *Nat Commun.* 2016;7:11128.

Heeres J, Meerpoel L, Lewi P. Conazoles. *Molecules*. 2010;15(6):4129–4188.

Huang W, Liao G, Baker G, et al. Lipid flippase subunit CDC50 mediates drug resistance and virulence in Cryptococcus neoformans. *MBio*. 2016;7(3):e00478–16.

Ingham C, Schneeberger P. Microcolony imaging of Aspergillus fumigatus treated with echinocandins reveals both fungistatic and fungicidal activities. *PLoS One.* 2012;7(4):e35478.

Jeffrey-Smith A, Taori S, Schelenz S, et al. Candida auris: A review of the literature. *Clin Microbiol Rev.* 2018;31(1):e00029–17.

Jung DS, Farmakiotis D, Yiang J, et al. Uncommon Candida species fungemia in cancer patients, Houston, Texas, USA. *Emerg Infect Dis.* 2015;21(11):1942–1950.

Keniya M, Sabherwal M, Wilson R, et al. Crystal structures of full-length lanosterol 14a-demethylases of prominent fungal pathogens Candida albicans and Candida glabrata provide tools for antifungal discovery. *Antimicrob Agents Chemother.* 2018;62(11):e01134–18.

Krishna G, Ma L, Martinho M, et al. Single-dose phase I study to evaluate the pharmacokinetics of posaconazole in new tablet and capsule formulations relative to oral suspension. *Antimicrob Agents Chemother.* 2012;56(8):4196–4201.

Lackner M, DeHoog G, Verwejj P, et al. Species-specific antifungal susceptibility patterns of Scedosporium and Pseudallescheria species. *Antimicrob Agents Chemother.* 2012;56(5):2635–2642.

Lamoth F, Alexander B. Antifungal activities of SCY-078 (MK-3118) and standard antifungal agents against clinical non-Aspergillus mold isolates. *Antimicrob Agents Chemother.* 2015;59(7):4308–4311.

Leonardelli F, Macedo D, Dudiuk C, et al. Aspergillus fumigatus intrinsic fluconazole resistance is due to the naturally occurring T301I substitution in CYP51Ap. *Antimicrob Agents Chemother.* 2016;60(9):5420–5426.

Lepesheva G, Hargrove T, Kleshchenko Y, et al. CYP51: A major drug target in the cytochrome P450 superfamily. *Lipids*. 2008;43(12):1117–1125.

Levine H, Cobb J. Oral therapy for experimental coccidiomycosis with R41400 (ketoconazole), a new imidazole. *Am Rev Respir Dis.* 1978;118(4):715–721.

Levine M, Chandrasekar P. Adverse effects of voriconazole: Over a decade of use. *Clin Transplant.* 2016;30(11):1377–1386.

Levine S, Walsh T, Martinez A, et al. Cardiopulmonary toxicity after liposomal amphotericin B infusion. *Ann Intern Med.* 1991;114(8):664–666.

Lin A, Goldwasser E, Bernard E, et al. Amphotericin B blunts erythropoietin response to anemia. *J Infect Dis.* 1990;161(2):348–351.

Llanos A, Cieza J, Bernardo J, et al. Effect of salt supplementation on amphotericin B nephrotoxicity. *Kidney Int.* 1991;40(2):302–308.

Lockhart S, Etienne K, Vallabhaneni, et al. Simultaneous emergence of multidrug resistant Candida auris on 3 continents confirmed by whole genome sequencing and epidemiological analyses. *Clin Infect Dis.* 2017;64(2):134–140.

LoRe V, Carbonari D, Lewis J, et al. Oral azole antifungal medications and risk of acute liver injury, overall and by chronic liver disease status. *Am J Med.* 2016;129(3):283–291.

Lovero G, Borghi E, Balbino S, et al. Molecular identification and echinocandin susceptibility of Candida parapsilosis complex bloodstream isolates in Italy, 2007-2014. *PLoS One.* 2016;11(2):e0150218.

Malani A, Kerr L, Obear J, et al. Alopecia and nail changes associated with voriconazole therapy. *Clin Infect Dis.* 2014;59(3):e61–e65.

Maligie M, Selitrennikoff C. Cryptococcus neoformans resistance to echinocandins: (1,3)-B-glucan synthase activity is sensitive to echinocandins. *Antimicrob Agents Chemother.* 2005;49(7):2851–2856.

Manavathu E, Cutright J, Chandrasekar P, et al. Organism dependent fungicidal activities of azoles. *Antimicrob Agents Chemother.* 1998;42(11):3018–3021.

Marcos-Zambrano L, Puig-Asensio M, Perez-Garcia F, et al. Candida guilliermondii complex is characterized by high antifungal resistance but low mortality in 22 cases of candidemia. *Antimicrob Agents Chemother.* 2017;61(7):e00099–17.

Maseda E, Grau S, Luque S, et al. Population pharmacokinetics/pharmacodynamics of micafungin against Candida species in obese, critically ill, and morbidly obese critically ill patients. *Crit Care.* 2018;22(1):94.

McClenny N, Fei H, Baron E, et al. Change in colony morphology of Candida lusitaniae in association with development of amphotericin B resistance. *Antimicrob Agents Chemother.* 2002;46(5):1325–1328.

Miceli M, Kauffman C. Isavuconazole: A new broad-spectrum triazole antifungal agent. *Clin Infect Dis.* 2015;61(10):1558–1565.

Miller M. Reversible hepatotoxicity related to amphotericin B. *Can Med Assoc J.* 1984;131(10):1245–1247.

Miller N, Dick J, Merz W. Phenotypic switching in Candida lusitaniae on copper sulfate indicator agar: Association with amphotericin B resistance and filamentation. *J Clin Microbiol.* 2006;44(4):1536–1539.

Moore J, Healy J, Kraft W. Pharmacologic and clinical evaluation of posaconazole. *Expert Rev Clin Pharmacol.* 2015;8(3):321–334.

Mycamine (micafungin). *Prescribing information*. Deerfield, IL: Astellas Pharma US, Inc.; June 2013.

Nakai T, Uno J, Ikeda F, et al. In vitro antifungal activity of micafungin (FK463) against dimorphic fungi: Comparison of yeast-like and mycelial forms. *Antimicrob Agents Chemother.* 2003;47(4):1376–1381.

Neumann A, Czub J, Baginski M. On the possibility of the amphotericin B-sterol complex formation in cholesterol- and ergosterol containing lipid bilayers: A molecular dynamics study. *J Phys Chem.* 2009;113(48):15875–15885.

Nishiyama Y, Uchida K, Yamaguchi H. Morphological changes of Candida albicans induced by micafungin (FK463), a water-soluble echinocandin-like lipopeptide. *J Electron Microsc.* 2002;51(4):247–255.

Nucci M, Anaissie E. Fusarium infections in immunocompromised patients. *Clin Microbiol Rev.* 2007;20(4):695–704.

Osherov N, Kontoyiannis DP. The anti-Aspergillus drug pipeline: Is the glass half full or empty? *Med Mycol* 2017;55(1):118–124.

Ostrosky-Zeichner L, Sobel JD (eds.), Boucher HW (consulting ed.). Fungal infections. *Infect Dis Clin North Am* 2016;30(1).

Pappas P, Kauffman C, Andes D, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the IDSA. *Clin Infect Dis.* 2016;62(4):e1–e50.

Pappas P, Kauffmann C, Perfect J, et al. Alopecia associated with fluconazole therapy. *Ann Intern Med.* 1995;123(5):354–357.

Patel G, Crank C, Leikin J. An evaluation of hepatotoxicity and nephrotoxicity of liposomal amphotericin B (L-AMB). *J Med Toxicol.* 2011;7(1):12–15.

Patil A, Majumdar S. Echinocandins in antifungal pharmacotherapy. *J Pharm Pharmacol.* 2017;69(12):1635–1660.

Patterson T, Thompson G, Denning D, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Disease Society of America. *Clin Infect Dis.* 2016;63(4):e1–60.

Perfect J, Savani D, Durack D. Comparison of itraconazole and fluconazole in treatment of Cryptococcal meningitis and Candida pyelonephritis in rabbits. *Antimicrob Agents Chemother.* 1986;29(4):579–583.

Perlin D, RautemaaRichardson R, AlastrueyIzquierdo A. The global problem of antifungal resistance: Prevalence, mechanisms, and management. *Lancet Infect Dis.* 2017;17:e383–92.

Perlin D. Echinocandin resistance in Candida. *Clin Infect Dis.* 2015;61(S6):S612–7.

Perlin D. Mechanisms of echinocandin antifungal drug resistance. *Ann N Y Acad Sci.* 2015;1354(1):1–11.

Pettit N, Miceli M, Rivera C, et al. Multicentre study of posaconazole delayed-release tablet serum level and association with hepatotoxicity and QTc prolongation. *J Antimicrob Chemother.* 2017;72(8):2355–2358.

Pfaller M, Messer S, Woosley L, et al. Echinocandin and triazole antifungal susceptibility profiles for clinical opportunistic yeast and mold isolates collected from 2010-2011: Application of new CLSI clinical breakpoints and epidemiological cutoff values for characterization of geographic and temporal trends of antifungal resistance. *J Clin Microbiol.* 2013;51(8):2571–2581.

Pham C, Igbal N, Bolden C, et al. Role of FKS mutations in Candida glabrata: MIC values, echinocandin resistance, and multidrug resistance. *Antimicrob Agents Chemother.* 2014;58(8):4690–4696.

Posch W, Blatzer M, Wilflingseder D, et al. Aspergillus terreus: Novel lessons learned on amphotericin B resistance. *Med Mycol.* 2018;56(Supp 1):73–82.

Purkins L, Wood N, Kleinermans D, et al. Effect of food on the pharmacokinetics of multiple-dose oral voriconazole. *Br J Clin Pharmacol.* 2003;56 (Supp 1):17–23.

Ramirez-Garcia A, Pellon A, Rementeria A, et al. Scedosporium and Lomentospora: An updated overview of underrated opportunists. *Med Mycol.* 2018;56(Supp 1):102–125.

ReichertLima F, Lyra L, Pontes L, et al. Surveillance for azoles resistance in Aspergillus spp highlights a high number of amphotericin B resistant isolates. *Mycoses*. 2018;61(6):360–365.

Richardson K, Brammer K, Marriott M, et al. Activity of UK-49858, a bis-triazole derivative, against experimental infections with Candida albicans and Trichophyton mentagrophytes. *Antimicrob Agents Chemother.* 1985;27(5):832–835.

Ries L, Rocha M, DeCastro P, et al. The Aspergillus fumigatus CrzA transcription factor activates chitin synthase gene expression during the caspofungin paradoxical effect. *MBio*. 2017;8(3):e00705–17.

Ringden O, Jonsson V, Hansen M, et al. Severe and common side-effects of amphotericin B lipid complex (Abelcet). *Bone Marrow Transplant.* 1998;22(7):733–734.

Risley J. Cholesterol biosynthesis: Lanosterol to cholesterol. *J Chem Ed.* 2002;79(3):377–384.

Roden M, Nelson L, Knudsen T, et al. Triad of acute infusion-related reactions associated with liposomal amphotericin B: Analysis of clinical and epidemiological characteristics. *Clin Infect Dis.* 2003;36(10):1213–1220.

Rogers P, Jenkins J, Chapman S, et al. Amphotericin B activation of human genes encoding for cytokines. *J Infect Dis.* 1998;178(6):1726–1733.

Sabra R, Branch R. Mechanisms of amphotericin B induced decrease in glomerular filtration rate in rats. *Antimicrob Agents Chemother.* 1991;35(12):2509–2514.

Sandhu P, Lee W, Xu X, et al. Hepatic uptake of the novel antifungal agent caspofungin. *Drug Metab Dispos.* 2005;33(5):676–682.

Saravolatz L, Johnson L, Kauffman C. Voriconazole: A new triazole antifungal agent. *Clin Infect Dis.* 2003;36(5):630–637.

Sau K, Mambula S, Latz E, et al. The antifungal drug amphotericin B promotes inflammatory cytokine release by a Toll-like receptor and CD14 dependent mechanism. *J Biol Chem.* 2003;278(39):37561–37568.

SchmittHoffmann A, Roos B, Heep M, et al. Single-ascending-dose pharmacokinetics and safety of the novel broad-spectrum antifungal triazole BAL4815 after intravenous infusions (50, 100, and 200 milligrams) and oral administrations (100, 200, and 400 milligrams) of its prodrug, BAL8557, in healthy volunteers. *Antimicrob Agents Chemother.* 2006;50(1):279–285.

Schwartz R, Sesin D, Joshua H, et al. Pneumocandins from Zalerion arboricola. *J Antibiot.* 1992;45(12):1853–1866.

Seidel D, Meisner A, Lackner M, et al. Prognostic factors in 264 adults with invasive Scedosporium spp and Lomentospora prolificans infection reported in the literature and Fungiscope. *Crit Rev Microbiol.* 2019;1–21.

Shalani K, Kumar N, Drabu S, et al. Advances in synthetic approach to and antifungal activity of triazoles. *Beilstein J Org Chem.* 2011;7:668–677.

Shields R, Kline E, Healey K, et al. Spontaneous mutational frequency and FKS mutation rates vary by echinocandin agent against Candida glabrata. *Antimicrob Agents Chemother.* 2018;63(1):e01692–18.

Sipsas N, Gamaletsou M, Anastasopoulou A, et al. Therapy of mucormycosis. *J Fungi.* 2018;4(3):90.

Taj Aldeen S, Salah H, AlHatmi A, et al. In vitro resistance of clinical Fusarium species to amphotericin B and voriconazole using EUCAST antifungal susceptibility method. *Diag Microbiol Infect Dis.* 2016;85(4):438–443.

Tortorano A, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on the diagnosis and management of hyalohyphomycosis:

Fusarium spp, Scedosporium spp, and others. *Clin Microbiol Infect.* 2014;20(Supp 3):27–46.

Vekeman F, Weiss L, Aram J, et al. Retrospective cohort study comparing the risk of severe hepatotoxicity in hospitalized patients treated with echinocandins for invasive candidiasis in the presence of confounding by indication. *BMC Infect Dis.* 2018;18(1):438.

Verweij P, Chowdhary A, Melchers W, et al. Azole resistance in Aspergillus fumigatus: Can we retain the clinical use of mold-active antifungal azoles. *Clin Infect Dis.* 2016;62(3):362–368.

Vincent B, Lancaster A, ScherzShouval R, et al. Fitness trade-offs restrict the evolution of resistance to amphotericin B. *PLoS Biol.* 2013;11(10):e1001692.

Walsh T, Finberg R, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med.* 1999;340(10):764–771.

Wang J, Chang C, YoungXu Y, et al. Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infections. *Antimicrob Agents Chemother.* 2010;54(6):2409–2419.

Wang J, Chang C, YoungXu Y, et al. Systemic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infection. *Antimicrob Agents Chemother.* 2010;54(6):2409–2419.

Wasmman R, TerHeine R, VanDongen E, et al. Pharmacokinetics of anidulafungin in obese and normal-weight adults. *Antimicrob Agents Chemother.* 2018;62(7):e00063–18.

Wei X, Zhang Y, Lu L. The molecular mechanism of azole resistance in Aspergillus fumigatus: From bedside to bench and back. *J Microbiol*. 2015;53(2):91–99.

Wiederhold N, Pennick G, Dorsey S, et al. A reference laboratory experience of clinically achievable voriconazole, posaconazole, and itraconazole concentrations within the bloodstream and cerebral spinal fluid. *Antimicrob Agents Chemother.* 2014;58(1):424–431.

Xing Y, Chen L, Feng Y, et al. Meta-analysis of the safety of voriconazole in definitive, empirical, and prophylactic therapies for invasive fungal infections. *BMC Infect Dis.* 2017;17(1):798.

Yano T, Itoh Y, Kawamura E, et al. Amphotericin B induced renal tubular cell injury is mediated by Na+ influx through ion-permeable pores and subsequent activation of mitogen-activated protein kinases and elevation of intracellular Ca2+ concentration. *Antimicrob Agents Chemother.* 2009;53(4):1420–1426.

Yoon S, Vazquez J, Steffan P, et al. High-frequency, in vitro reversible switching of Candida lusitaniae clinical isolates from amphotericin B susceptibility to resistance. *Antimicrob Agents Chemother.* 1999;43(4):836–845.

Young L, Hull C, Heitman J. Disruption of ergosterol biosynthesis confers resistance to amphotericin B in Candida lusitaniae. *Antimicrob Agents Chemother.* 2003;47(9):2717–2724.

Zimmermann T, Yeates R, Laufen H, et al. Influence of concomitant food intake on the oral absorption of two triazole antifungal agents, itraconazole and fluconazole. *Eur J Clin Pharmacol.* 1994;46(2):147–150.

208

Antiviral therapy

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Successful antiviral therapy continues to be one of many challenges facing the healthcare provider today. All viruses parasitize host cell enzymes and structures to varying degrees. Designing or discovering drugs that specifically target viral enzymes without affecting host cell machinery is difficult. This is crucial because a lack of specificity increases the risk of toxicity. Additionally, many viruses establish a latent infection in the host, during which time they are essentially quiescent. Elimination of latent viruses from the host has not been possible to date. Some of the most serious viral infections today stem from the reactivation of latent viruses during periods of impaired cell-mediated immunity. Additionally, an ongoing challenge in antiviral therapy is the development of drug resistance due to viral mutagenicity.

The availability of antiviral agents has significantly reduced the incidence of morbidity and mortality. Most of the currently available antiviral agents target the virus by exploiting differences between the viral and host replication processes. Many viruses have their own specific DNA polymerases, which are more susceptible to inhibition by specific drugs than are the cellular DNA replication enzymes. Consequently, many antiviral agents are nucleoside or nucleotide analogs that inhibit these enzymes and cause chain termination when incorporated into replicating genetic material. In addition, some of these compounds accumulate preferentially in virus-infected cells or are activated by virus-encoded enzymes, increasing their specificity. Nevertheless, similar to antibacterial agents, most antiviral agents remain far from being a panacea due to dose-related toxicities and potential for development of resistance.

This chapter reviews the clinical utility, pharmacokinetics, adverse effects, and drug–drug interactions of antiviral agents for the treatment of herpes simplex virus (HSV), varicella-zoster virus (VZV), influenza, hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus (CMV), respiratory syncytial virus (RSV), and coronavirus disease 2019 (COVID-19) (Table 208.1). Antiretrovirals associated with the treatment of human immunodeficiency virus (HIV) are discussed in Chapter 98, "HIV infection: antiretroviral therapy."

Herpes simplex virus: Systemic therapies

Acyclovir

Acyclovir, a guanine derivative, has in vitro activity against several viruses, but in clinical practice it is used primarily for the treatment and prevention of HSV-1, HSV-2, and VZV. Acyclovir is preferentially taken up by HSV-infected cells and is phosphorylated by viral thymidine kinase, which is necessary for conversion to the active triphosphate form. It competitively inhibits viral DNA polymerase and causes DNA chain termination when incorporated into replicating DNA.

Oral acyclovir may be used for primary episodes of genital herpes to reduce the time of viral shedding and time to healing at a dose of 200 mg five times per day or 400 mg three times daily for 7 to 10 days. The latter regimen is preferred for patients with HIV and may be preferred for patients with poor adherence due to decreased frequency of administration. It can also be used for treatment of recurrent episodes

TABLE 208.1 **ANTIVIRAL DRUGS APPROVED BY THE US FOOD AND DRUG ADMINISTRATION (FDA)**

HSV/VZV	Influenza	HBV	HCV	CMV	RSV	COVID-19
Acyclovir	Oseltamivir	Lamivudine	Ledipasvir/sofosbuvir	Ganciclovir	Palivizumab	Remdesivir
Valacyclovir	Peramivir	Entecavir	Sofosbuvir/velpatasvir	Valganciclovir		
Famciclovir	Zanamivir	Tenofovir	Elbasvir/grazoprevir	Cidofovir		
Docosanol	Baloxavir	Adefovir	Sofosbuvir/velpatasvir / voxilaprevir	Foscarnet		
Penciclovir	Amantadine	Telbivudine	Glecaprevir/pibrentasivir	L4etermovir		
Trifluridine	Rimantadine	Peginterferon- α2a	Ombitasvir/paritaprevir/ ritonavir/dasabuvir			
			Daclatasvir			
			Ribavirin			

Abbreviations: CMV = cytomegalovirus, COVID-19 = coronavirus disease 2019, HBV = hepatitis B virus, HCV = hepatitis C virus, HSV = herpes simplex virus, RSV = respiratory syncytial virus, VZV = varicella-zoster virus.

with several dosing regimens such as 400 mg orally three times daily for 5 days, 800 mg orally twice daily for 5 days, or 800 mg orally three times daily for 2 days. Duration of therapy for initial episodes and recurrences may be extended if there is insufficient clinical improvement. All regimens for recurrence should be initiated within 24 hours of lesion development or prodrome onset. Last, acyclovir can be used as chronic suppressive therapy to decrease the incidence of recurrent genital HSV at a dose of 400 mg orally twice daily. Chronic suppressive therapy should be evaluated annually to reassess the need for suppression as incidence of recurrence decreases over time. Antiviral therapy improves time to healing and duration of symptoms but does not completely eradicate latent virus. Dosing of oral acyclovir for herpes labialis is similar.

Acyclovir is available in two topical forms. A topical ointment demonstrated mild benefit for initial genital HSV episode, but failed to show a benefit for recurrent episodes. A topical acyclovir cream is applied 5 times a day for 4 days for primary herpes labialis, but its impact on the natural course of the infection is limited to a decrease in median duration of symptoms by only 0.5 days. For these reasons, topical therapies are not recommended. For the severe mucosal and cutaneous lesions most commonly seen in patients with immunodeficiencies, hospital admission and acyclovir 5 mg/kg intravenously (IV) every 8 hours is warranted.

IV acyclovir reduces mortality in HSV encephalitis and should be used at high dosages (10 mg/kg IV q8h) for 14 to 21 days. It is typically dosed based on ideal body weight; however, some data suggest that ideal body weight dosing in patients with a body mass index (BMI) >40 kg/m^2 may lead to lower serum concentrations and drug exposure. Adjusted body weight may be more appropriate in patients with BMIs of >40 kg/m^2 if there is not significant clinical improvement when dosing based on ideal body weight.

Acyclovir is also active against VZV, but treatment of VZV infections requires higher dosages than treatment of uncomplicated HSV infections because acyclovir undergoes less efficient activation to the triphosphate form by VZV thymidine kinases. Acyclovir, 800 mg five times daily for 7 to 10 days, should be used in patients with herpes zoster (shingles) to prevent dissemination and to shorten the time to healing. In immunocompromised patients, localized infection can be treated with the same oral dosing of acyclovir just mentioned. However, if there is severe, disseminated, or complicated disease, 10 mg/kg IV every 8 hours is indicated. Therapy duration is approximately 7 days, but may need to be extended pending clinical course. Oral agents such as acyclovir or valacyclovir may be used as stepdown therapy to complete the course. Unfortunately acyclovir therapy does not convincingly alter the subsequent development of complications such as postherpetic neuralgia (PHN). VZV can also present with ophthalmologic involvement and can cause acute retinal necrosis, both of which require prompt medical evaluation and treatment. Acyclovir ophthalmic ointment is commercially available and indicated for HSV-related keratitis.

Acyclovir 800 mg orally five times daily for 5 to 7 days is effective in the treatment of primary varicella or chickenpox, shortening the duration and severity of illness when begun within 24 hours after the onset of rash. The recommended dose for the treatment of immunocompromised patients with an uncomplicated infection is the same as the preceding, but for severe, disseminated, or complicated infection 10 mg/kg IV every 8 hours for 7 to 10 days is appropriate.

Acyclovir is also indicated for mucocutaneous HSV prophylaxis in solid organ and bone marrow transplant recipients who are not already receiving prophylaxis against CMV. Acyclovir 400 to 800 mg orally twice daily is recommended for 30 days in solid organ transplant and at least until resolution of neutropenia in bone marrow transplant patients. The incidence of acyclovir resistance in HSV and VZV is low in the general population but should be considered in patients who fail to respond to therapy. Resistance is mediated by changes in viral thymidine kinase or DNA polymerase and is most commonly seen in immunocompromised patients. For cases of acyclovir-resistant HSV, consider use of topical cidofovir 1% gel, trifluridine 1% solution, foscarnet 1% solution, or imiquimod 5% cream for mucocutaneous cases and IV foscarnet or cidofovir for more severe cases. Topical cidofovir, trifluridine, and foscarnet are not commercially available in the United States and

must be compounded. In the case of acyclovir-resistant VZV, use IV foscarnet or cidofovir.

Pharmacokinetics

Acyclovir has poor water solubility and hence poor oral bioavailability (10–20%) but good tissue distribution. The low oral bioavailability is unaffected by administration with food and necessitates frequent administration, which is partly resolved by using either the IV formulation or the prodrug valacyclovir. The serum half-life is 2.5 to 3 hours, depending on renal function. Acyclovir is predominantly excreted as unchanged drug in the urine, and dose adjustment is necessary in patients with impaired renal function. Dose adjustments begin at a creatinine clearance (CrCl) of <25 mL/min/1.73 m^2 and 50 mL/min/1.73 m^2 for oral and IV acyclovir, respectively. Acyclovir is safe for use in pregnant and breastfeeding women with active or a history of HSV infection.

Adverse effects

Central nervous system adverse effects range from confusion to seizures and coma, especially in the settings of renal insufficiency, underlying altered mental status, and advanced age. Renal failure may occur from acyclovir precipitation in the renal tubules. Therefore, when administering high IV doses, it is important to ensure adequate hydration of the patient. Common adverse effects of oral acyclovir include nausea and vomiting (2.7%), diarrhea (2.4%), and malaise (11.5%).

Drug interactions

Acyclovir is primarily excreted in the urine as unchanged drug (60–90%), but a small portion is metabolized by cytochrome P450 1A2 (CYP1A2). As a result, concomitant therapy with medications that inhibit CYP1A2, decrease renal function, or compete for renal transporter may lead to increased acyclovir exposure. For example, coadministration of acyclovir with theophylline, aminoglycosides, or probenecid may increase acyclovir exposure although dose adjustment is usually not necessary because of the wide therapeutic index of oral acyclovir. Consider dose adjustment of IV acyclovir in patients who are at higher risk for toxicity (e.g., elderly, poor renal function at baseline).

Valacyclovir

Valacyclovir is metabolized to acyclovir after oral administration, and oral bioavailability of the active form is 55%.Valacyclovir is indicated for primary (1 g BID for 7–10 days) and recurrent (500 mg BID for 3 days or 1 g once daily for 5 days) genital HSV. Treatment of recurrent episodes is ideally initiated within 24 hours of lesion development or prodrome onset. The efficacy of valacyclovir for genital HSV is similar to that of acyclovir, but the improved bioavailability reduces the number of administrations required per day. There is no IV formulation of valacyclovir; for severe, complicated, or disseminated infections IV acyclovir may be used initially. The dose of valacyclovir for suppression of HSV is 500 mg or 1 g once daily. For patients with HIV (PWH), 500 mg twice daily is recommended. The need for suppression should be reassessed annually as incidence of recurrence decreases over time. Herpes labialis can be treated with 2 g twice daily for 1 day; however, a longer treatment duration of 1 g twice daily for 5 to 10 days is required for PWH. Treatment duration may need to be extended pending clinical improvement. Early initiation of treatment has shown to reduce the mean duration of symptoms by 1 day. Antiviral therapy does not completely eradicate HSV or influence incidence of recurrent episodes.

In terms of treatment of VZV (both shingles and primary varicella infection) a higher dose of 1 g three times daily for 7 days is indicated, but therapy may be extended until there are no new lesions and lesions have crusted. Data demonstrate in a reduction in duration of VZV symptoms by one day with valacyclovir therapy when compared to placebo. Valacyclovir 500 mg twice daily can also be used for prophylaxis in solid organ and bone marrow transplant patients to prevent reactivation of HSV in patients not receiving anti-CMV therapy. If there is concern for valacyclovir-resistant VZV or HSV, please refer to the acyclovir section for management. When treating VZV meningitis/encephalitis, a higher dose of 2 g every 6 hours should be used.

Pharmacokinetics

Valacyclovir is readily absorbed from the GI tract after oral intake and is almost completely converted to acyclovir and L-valine via first-pass intestinal and hepatic metabolism. Acyclovir is then primarily excreted in the urine (89%). The half-life of active acyclovir is 2.5 to 3 hours but can be prolonged in renal impairment. Dose adjustments of valacyclovir begin at CrCl of 50 mL/min and 30 mL/min for herpes zoster/labialis and genital HSV, respectively. No hepatic dose adjustments are required. Acyclovir remains the drug of choice in pregnancy as it is the most well studied, but valacyclovir may be an alternative if there are concerns for acyclovir intolerance or pill burden.

Adverse effects

The major toxicities are similar to those of acyclovir including confusion, seizures, and altered mental status. Common adverse reactions were similar to acyclovir and include headache (14%), dizziness (2%), and nausea (6%).

Drug interactions

As valacyclovir is a prodrug of acyclovir, the drug interaction profile is similar. Please see acyclovir section on drug–drug interactions.

Famciclovir

Famciclovir is an inactive prodrug of penciclovir, which has a spectrum of activity similar to that of acyclovir. After oral administration, famciclovir is rapidly metabolized to penciclovir, which is then triphosphorylated by viral thymidine kinase and has a mechanism of action similar to acyclovir. Famciclovir's bioavailability is 77%, which

is considerably higher than that of acyclovir, and consequently it has less frequent administration. It is also indicated for the treatment of initial (250 mg TID for 7–10 days), recurrence (1 g BID for 1 day, 125 mg BID for 5 days, or 500 mg once followed by 250 mg BID for 2 days) and also for suppression of recurrent genital HSV (250 mg q12h). For PWH, genital HSV initial episodes, recurrences, and suppression requires 500 mg twice daily. Treatment duration in PWH is 7 to 10 days and 5 to 10 days for initial episodes and recurrences, respectively. Treatment of recurrent genital HSV should begin within 24 hours of symptom or prodrome onset. The need for suppressive therapy should be reassessed annually as incidence of recurrence decreases over time. It is also used for recurrent herpes labialis in immunocompetent patients (1,500 mg as a single dose at the first sign of recurrence) and PWH (500 mg BID for 5–10 days). Longer durations of therapy may be required pending clinical course. Antiviral therapy does not completely eradicate HSV or influence incidence of recurrent episodes. No IV formulation is available, and, for severe, complicated, or disseminated infections use IV acyclovir.

Famciclovir is approved for treatment of herpes zoster in immunocompetent and immunocompromised populations (500 mg TID for 7 days) and provides similar clinical benefit to acyclovir. Duration of therapy may need to be extended if there is insufficient clinical response after 7 days. One study found a decreased duration of PHN when comparing famciclovir to placebo, but no significant difference was found when it was studied against acyclovir. Famciclovir can be used as step-down therapy after IV acyclovir in severe cases to complete the treatment course. If there is concern for famciclovir-resistant VZV or HSV, please refer to the acyclovir section for management.

Pharmacokinetics

Famciclovir is a prodrug that is converted via aldehyde oxidase into active penciclovir upon administration. Administration of famciclovir with food decreases penciclovir maximal concentration and increases its time to peak penciclovir concentration; however, total drug exposure remains the same. Penciclovir is primarily excreted renally as unchanged drug (73%). The serum half-life is 2.5 to 3 hours, but the intracellular half-life is 10 to 20 times longer. Dose adjustment is necessary in patients with reduced renal function and begins at a CrCl of 60 mL/min for most indications, but no hepatic dose adjustments are necessary. Acyclovir remains the drug of choice in pregnancy as it is the most well-studied, but famciclovir may be an alternative if there are concerns for acyclovir intolerance or pill burden.

Adverse effects

Common adverse effects include headache (8.5–39%), nausea (2.2–12.5%), diarrhea (1.2–9%) and vomiting (0.7–4.8%).

Drug interactions

Probenecid may lead to increased famciclovir serum concentrations through competition for renal transporters used for elimination. Famciclovir is not a CYP3A4 substrate.

Herpes simplex virus: Topical therapies

Docosanol

Docosanol is a saturated fatty alcohol that reduces the duration of cold sores associated with HSV by approximately 1 day in clinical studies. Its mechanism of action is prevention of HSV entry into the host cell through inhibition of viral fusion. Docosanol 10% is available without a prescription in the United States and is applied topically to the cold sore five times a day at the first sign of infection for up to 10 days. The most commonly reported side effects include headache and local skin irritation.

Penciclovir

Penciclovir is another nucleoside analog with mechanism of action and spectrum of activity similar to that of acyclovir. It is available only as a topical preparation at a concentration of 1% for recurrent herpes labialis. Famciclovir is an oral prodrug of penciclovir. In clinical trials, topical penciclovir shortened the duration of symptoms by 0.5 days if applied within 1 hour of the beginning of symptoms and again every 2 hours while awake for 4 days. Thus the combination of its unimpressive clinical performance and cumbersome dosing have decreased its use in clinical practice.

Trifluridine

Trifluridine 1% is a fluorinated thymidine analog that interferes with DNA synthesis and is used topically for the treatment of HSV keratitis or for acyclovir-resistant mucocutaneous HSV. Trifluridine may cause local irritation and palpebral edema when used for HSV keratitis.

Influenza therapies

Oseltamivir

Oseltamivir phosphate was approved in 1999 as the first oral neuraminidase inhibitor. Inhibition of influenza's neuraminidase prevents release of newly formed virus and infection of surrounding cells. It was originally approved for the treatment of uncomplicated influenza. Initial clinical trials demonstrated a 1.3-day shorter time to improvement when compared to placebo. However, it is now also recommended for severe or complicated cases in the outpatient and hospital setting. Clinical efficacy is greatest when initiating therapy within 48 hours of illness onset, but oseltamivir has shown some benefit in hospitalized patients with illness onset of 4 to 5 days prior to administration. The dose for treatment of influenza is 75 mg orally twice daily for 5 days, but extended duration may be necessary in hospitalized patients with severe and prolonged illness. Oseltamivir can also be used for prophylaxis of influenza at a dose of 75 mg orally once daily for 10 days started within 48 hours of exposure. A longer duration of prophylaxis can be used in institutional or hospital settings, such as continuing therapy for 7 days

after last known exposure. Cross-resistance with other neuraminidase inhibitors can occur.

Pharmacokinetics

Oseltamivir is well absorbed by the GI tract with an oral bioavailability of at least 75%. Oral oseltamivir is well absorbed in critically ill patients, and data demonstrate serum concentrations similar to those in ambulatory patients. It is converted to the carboxylate salt by hepatic esterases, but there is no metabolism by CYP enzymes. Volume of distribution ranges from 23 to 26 liters, and it has low plasma protein binding. Oseltamivir carboxylate is eliminated in the urine by both glomerular filtration and tubular secretion, and so renal dose adjustments are required at CrCl of 60 mL/min. No hepatic dose adjustment is required. Oseltamivir is the preferred agent for the treatment of influenza in pregnant women.

Drug interactions

Oseltamivir may reduce the efficacy of the live attenuated influenza vaccine, and the vaccine should not be administered 2 weeks before or 48 hours after administration. Inactivated influenza vaccine may be administered at any time.

Adverse effects

Associated adverse events include vomiting (9%), nausea (10%), abdominal pain (2%), and dizziness (2%). Serious but rare adverse effects are serious skin hypersensitivity reactions and neuropsychiatric events.

Peramivir

Peramivir was approved in 2015 as a single-dose IV neuraminidase inhibitor for the treatment of acute uncomplicated influenza. Inhibition of influenza's neuraminidase prevents release of newly formed virus and infection of surrounding cells. In clinical trials for acute uncomplicated influenza, single-dose peramivir demonstrated a shorter time to recover by 21 hours when compared to placebo. Of note, the vast majority of patients (99%) enrolled in this study had influenza A; there were an insufficient number of patients with influenza B. It failed to show a benefit as a single dose in serious influenza requiring hospitalization. However, data are conflicting on the efficacy of multiple-dose peramivir in hospitalized patients. The dose is 600 mg intravenously once and should be initiated within 48 hours of symptom onset. Clinical utility in the outpatient setting is limited by route of administration. Cross-resistance with other neuraminidase inhibitors has been seen. Peramivir does not undergo metabolism and is predominantly eliminated via the kidneys (90%) with a half-life of 20 hours. Renal dose adjustment is required for patients with CrCl of <50 mL/min. Safety and efficacy in pregnancy and lactation has not been established. Serious but rare adverse effects include serious skin hypersensitivity and neuropsychiatric events. Other adverse effects in clinical studies were diarrhea (8%), increases in creatine phosphokinase (>6 times the upper limit of normal) (4%), and elevations in alanine aminotransferase (ALT; >2.5 times the upper limit of normal) (3%). Peramivir may reduce the efficacy of the live attenuated influenza vaccine, and the vaccine should not be administered 2 weeks before or 48 hours after administration. Inactivated influenza vaccine may be administered at any time.

Zanamivir

Zanamivir is an inhaled neuraminidase inhibitor that is indicated for the treatment of influenza A and influenza B in patients who have been symptomatic for no longer than 48 hours. Inhibition of influenza's neuraminidase prevents release of newly formed virus and infection of surrounding cells. The clinical benefit seen of zanamivir in clinical studies was a decrease in median time to symptom improvement by approximately 24 hours. Zanamivir is dosed as two inhalations (10 mg) every 12 hours for 5 days for the treatment of influenza. It is also indicated for the prophylaxis of influenza. The dosing for prophylaxis is lower at two inhalations (10 mg) once daily. A duration of 10 days is recommended for prophylaxis of household contacts, and a longer duration can be used for community or institutional outbreaks. There is a significant risk of bronchospasm in patients with underlying respiratory conditions such as asthma and chronic obstructive pulmonary disease. Consequently, the clinical utility of zanamivir is limited because it cannot be used in those patient populations at one of the highest risks of complications from influenza. In addition, post-marketing reports of neuropsychiatric events such as delirium have been reported. Common adverse effects include diarrhea (3%), nausea (3%), and headaches (2%). A small percentage of zanamivir is systemically absorbed, but no dose adjustments are required for renal or hepatic impairment. Safety and efficacy in pregnancy and lactation has not been established. Coadministration with the live attenuated influenza vaccine may decrease effectiveness of the vaccine; the vaccine should not be administered 2 weeks before or 48 hours after administration. Inactivated influenza vaccine may be administered at any time.

Baloxavir

Baloxavir is a polymerase acidic endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza. Inhibition of the endonuclease prevents viral gene transcription which decreases viral replication. It was approved in 2018 for adults and pediatric patients >12 years as a first in class agent with a novel mechanism of action. For patients weighing <80 kg, a single dose of 40 mg is a sufficient treatment course. Patient weighing ≥80 kg or more should receive 80 mg as a single dose. Therapy should be initiated within 48 hours of symptom onset. Baloxavir retains activity against neuraminidase-resistant strains of influenza; cross-resistance is not expected because the mechanism of action is different. Initial clinical trials demonstrated a 28-hour decrease in time to alleviation of symptoms when compared to placebo; however, no difference was noted in comparison to oseltamivir. Results were similar in studies of hospitalized patients. Baloxavir is highly protein bound, undergoes metabolism by UGT1A1 and CYP3A4, and has a long half-life of 79 hours. There are no recommendations for dosing in CrCl of <50 mL/min, but only 15% of the dose is eliminated in

the urine. No hepatic dose adjustment is required. Safety and efficacy in pregnancy and lactation has not been established. Baloxavir can be administered without regard to food, but should not be administered with polyvalent cations due to chelation and subsequent reduction drug exposure. It may also decrease the effectiveness of the live attenuated influenza vaccine. The incidence of adverse effects were low with diarrhea (3%), bronchitis (2%), and nausea (1%) being the most common.

Amantadine and rimantadine

Amantadine is used to treat Parkinson's disease and as an antiviral agent that prevents uncoating of influenza A virus by inhibiting the M2 channel protein. Rimantadine is a structural analog of amantadine with the mechanism of action. They do not have activity against influenza B. Widespread resistance exists to these agents among circulating influenza A strains. It is therefore no longer recommended for prevention or treatment.

Hepatitis B therapies

Lamivudine

Lamivudine is a cytosine analog most commonly used as part of antiretroviral regimens for treatment of HIV. Incorporation of monophosphorylated lamivudine into replicating HBV causes chain termination, and the triphosphorylated form inhibits HBV DNA polymerase. The dose for treatment of HBV is 100 mg/d and has been shown to result in serologic conversion, virologic response, and histologic improvement. Of note, this dose is lower than the 300 mg/d dose recommended for HIV. Although lamivudine has demonstrated clinical benefit, monotherapy for both HIV and HBV is not recommended as treatment emergent resistance will occur. Therefore, lamivudine is no longer first-line therapy in many national guidelines. The preferred regimen for HBV/HIV coinfection is lamivudine or emtricitabine (another cytosine analog) in combination with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). Screening for HIV coinfection should occur prior to initiation of lamivudine as monotherapy of occult HIV results in rapid appearance of lamivudine-resistant HIV. If a patient has a history of HBV lamivudine resistance, the preferred therapy is tenofovir monotherapy or tenofovir in combination with lamivudine (or emtricitabine).

Pharmacokinetics

Lamivudine is rapidly absorbed after oral intake, but administration with food decreases maximal concentration. The majority of lamivudine is eliminated unchanged in the urine, and dose adjustment is recommended at CrCl of <50 mL/min. The mean elimination half-life is typically between 5 and 7 hours but may be longer in patients with renal impairment. No hepatic dose adjustment is required, and lamivudine is safe for use in pregnancy.

Adverse effects

Lamivudine is well-tolerated in general. Serious adverse events are rare, but include lactic acidosis, hepatic steatosis, pancreatitis, and exacerbation of HBV after discontinuation. Common adverse effects include malaise and fatigue (24%), nausea and vomiting (15%), and headache (21%).

Drug interactions

Because lamivudine is mainly eliminated by active organic cationic secretion into the urine as unchanged drug, the possibility exists of interactions with other drugs eliminated by a similar mechanism. However, no clinically relevant interactions are known that would require dose adjustments. Lamivudine and emtricitabine are both cytosine analogs with similar activity; they should not be used in combination.

Entecavir

Entecavir is a guanosine analog that works by inhibiting HBV DNA polymerase. For the treatment of chronic HBV patients with compensated liver disease who are nucleoside-treatment naïve, the dosing is 0.5 mg orally once daily. Although tenofovir is preferred in the setting of lamivudine failure or in lamivudine and/or telbivudine resistance, entecavir 1 mg orally once daily can be used. The higher dosing of 1 mg/d is also recommended for patients with decompensated liver disease. In the case of entecavir resistance, it is recommended to add tenofovir or change to emtricitabine-tenofovir. Like lamivudine, HIV resistance may emerge in chronic hepatitis B patients treated with entecavir but with unrecognized or untreated HIV infection. If entecavir therapy is required in a patient with HIV, ensure that the patient is on a fully suppressive HIV regimen to prevent development of resistance.

Pharmacokinetics

Entecavir has a bioavailability of 100% following oral administration under fasted conditions. Patients should be counseled to take entecavir 2 hours prior or 2 hours after a meal. Food delays absorption and decreases maximal concentration and overall drug exposure by 44% to 46% and 18% and 20%, respectively. It is predominantly eliminated by the kidney as unchanged drug and undergoes glomerular filtration and tubular secretion. It requires renal dose adjustment beginning at CrCls of <50 mL/min.

Adverse effects

Commonly reported side effects include headaches (2–4%), fatigue (1–3%), dizziness (< 1%), and gastrointestinal (GI) symptoms (1%). Severe acute exacerbations of hepatitis have occurred when treatment has been discontinued.

Drug interactions

Entecavir may be potentiated by drugs that decrease renal function or compete for active tubular secretion.

Tenofovir

Tenofovir is an adenosine analog that competitively inhibits HBV DNA polymerase. There are two different formulations of tenofovir: tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). TDF was originally approved in the United States in 2001 for the treatment of HIV-1 in combination with other agents and later gained approval for the treatment of chronic hepatitis B in 2008. After oral administration, serum TDF is converted into tenofovir through hydrolysis and is intracellularly activated to its disphophate form. The dose of TDF for the treatment of HIV and HBV is 300 mg once daily; however, it must be adjusted for renal impairment. Long-term use of TDF is associated with nephrotoxicity and decreases in bone mineral density leading to osteopenia/osteoporosis. To overcome these adverse effects, TAF was developed and marketed for HIV in 2015 (as a part of the combination tablet elvitegravir-cobicistat-emtricitabine-tenofovir alafenamide) and for chronic hepatitis B in 2016. TAF's enhanced safety profile is due to primarily intracellular conversion of TAF to tenofovir. As a result, there is a 90% decrease in systemic tenofovir exposure. The dose of TAF for treatment of chronic hepatitis B is 25 mg once daily; however, the dose is reduced to 10 mg if given as a fixed-dose combination with boosting agents for the treatment of HIV. Similar to TDF, TAF is renally eliminated. Patient with progressively worsening renal function on tenofovir-based therapies should be switched to an alternative agent such as entecavir if there are no contraindications.

Both TDF and TAF are currently first-line agents in many national guidelines and preferred if there is coinfection with HIV (in combination with a cytosine analog). They are well-tolerated overall and have a high genetic barrier to resistance for HBV. Key monitoring parameters include renal function and bone mineral density. TAF is preferred over TDF in patients with poor baseline renal function or osteopenia/osteoporosis. Given that both formulations of tenofovir are indicated for the treatment of HIV, baseline HIV testing should be performed prior to initiation to prevent monotherapy of HIV infection.

Pharmacokinetics

Following oral intake, both TDF and TAF are converted to their active forms through hydrolysis and phosphorylation, as described previously. Food increases absorption of both TDF and TAF by 65% and 15%, respectively. TDF can be administered without regard to food; however, TAF should be administered with food. Tenofovir is renally excreted by both glomerular filtration and tubular secretion. The half-life of TDF is 17 hours, but only 0.5 hours for TAF. The dosing interval should be adjusted in patients with CrCl of <50 mL/min for TDF; TAF is not recommended in patients with a CrCl of <15 mL/min. There are no dose adjustments for hepatic impairment, but TAF is not recommended in Child Pugh Class B or C. TDF is safe for use in pregnancy; however, there are limited data with TAF.

Adverse effects

The most common adverse effects associated with long-term use are decreases in renal function and loss of bone mineral density. Other adverse effects of TDF in patients with HBV include nausea (20%), vomiting (13%), and dizziness (13%). Clinical data in PWH show improvement in renal function and bone mineral density when switching therapy from TDF to TAF. Fanconi's syndrome, a rare but serious adverse effect, is associated with both TDF and TAF. An exacerbation of HBV can occur when treatment is discontinued.

Drug interactions

Tenofovir may potentiate or be potentiated by drugs that decrease renal function or compete for active tubular secretion. TAF is a substrate of P-glycoprotein (P-gp) and is contraindicated with strong inducers of P-gp, such as rifampin, phenytoin, and carbamazepine. However, pharmacokinetic data demonstrate that TDF can be used safely without dose adjustment with strong P-gp inducers such as rifampin.

Adefovir

Adefovir dipivoxil is an adenosine analog that inhibits both HIV reverse transcriptase and HBV DNA polymerase. It is converted into its active disphosphate form by cellular kinases, which competitively inhibits HBV DNA polymerase and causes chain termination if incorporated into replicating DNA. It was initially developed as a nucleotide reverse transcriptase inhibitor for the treatment of HIV; however, the dose of 60 mg once daily was associated with significant nephrotoxicity. It was then developed for the treatment of chronic hepatitis B infection at a lower dose of 10 mg once daily. Renal dose adjustment is required beginning at a CrCl of 50 mL/min. HIV testing should be obtained prior to initiation because adefovir does have activity against HIV, and resistance may develop if there is unrecognized coinfection with HIV. Adverse effects include nephrotoxicity and exacerbations if HBV is discontinued. Adefovir is no longer a preferred agent in several national guidelines for the treatment of HBV because it has been shown to be inferior to both entecavir and tenofovir.

Telbivudine

Telbivudine is a thymidine analog with activity against HBV DNA polymerase. Its mechanism of action also involves activation through intracellular triphosphorylation and causes chain termination if incorporated into replicating DNA. It is indicated for the treatment of chronic hepatitis B infection in adult patients at a dosage of 600 mg once daily. It has a low genetic barrier to resistance, and long-term monotherapy is associated with the resistance and virologic breakthrough. Cross-resistance may occur in patients who have developed resistance to lamivudine. For these reasons, it is no longer a first-line agent in many national guidelines. This agent undergoes renal

elimination and requires dose adjustment at CrCls of <50 mL/min. Telbivudine is well-tolerated overall but can cause elevations in serum creatinine kinase, peripheral neuropathy, and exacerbations of HBV if discontinued.

Peginterferon-α2a

Interferons are naturally occurring glycoproteins with antiviral and immunomodulatory activities. They were the mainstay of treatment for a number of viral infections; however, in current practice, they have been replaced by agents with an improved safety and/or efficacy profile. For example, interferon-based therapies for the treatment of HCV have almost been completely supplanted by use of direct-acting antiviral (DAA) therapies. DAAs can be administered orally, have fewer adverse effects, and vastly outperform interferon in terms of efficacy. One of the last remaining indications for interferon therapy is in the treatment of HBV infection.

Peginterferon-α2a is administered as 180 μg subcutaneously once weekly for 48 weeks in the treatment of HBV. The main advantage of peginterferon-α2a over nucleotide analogues is that there is a finite duration of therapy. Duration of nucleotide therapy is unclear and often indefinite as discontinuation risks virologic relapse and decompensation. The exact mechanism of action against HBV is not clear. Treatment with peginterferon-α2a yields sustained seroconversion of HBV Be antigen in 20% to 31% of cases. HBV genotypes A and B are most responsive to interferon therapy compared to other genotypes. There is a warning for worsening neuropsychiatric, autoimmune, ischemic, and infectious disorders, and close monitoring is suggested. Other major toxicities commonly observed are depression (18%), flu-like symptoms (14%), fever (37–54%), myalgias (37%), fatigue (56%), and alopecia (18–23%). The long half-life of 50 to 160 hours allows for weekly dosing. Liver function tests should be monitored closely, and the dose may need to be decreased if ALT increases to greater than five times the upper limit of normal. It should not be used in patients with autoimmune hepatitis or hepatic decompensation (Child Pugh Class B or C). Dose adjustments are also required if patients develop myelosuppression, depression, or CrCl of <30 mL/min.

Hepatitis C therapies: Single-tablet regimens

Ledipasvir/Sofosbuvir

Ledipasvir/sofosbuvir (LDV/SOF) was approved in the United States in 2014 as the first single-tablet regimen for the treatment of HCV genotype 1 and later received approval for genotypes 4 through 6. LDV inhibits the NS5A protein, and the active metabolite of SOF inhibits the NS5B RNA-dependent RNA polymerase and causes chain termination. Inhibition of both of these essential enzymes halts HCV viral replication. This regimen is coformulated with LDV 90 mg and SOF 400 mg and administered orally once daily without regard to food. The duration of therapy is dependent on patient factors such as treatment history, HIV status, HCV genotype, baseline HCV viral load, and cirrhosis status. Therapy can be as short as 8 weeks for patients mono-infected with HCV who are treatment-naïve with genotype 1, non-cirrhotic, and have a baseline HCV viral load of <6 million IU/mL. Most patients receive 12 weeks of therapy, but for those with decompensated cirrhosis, the addition of ribavirin for 12 weeks or extension to 24 weeks of therapy is required.

Pharmacokinetics

Both agents are rapidly absorbed from the GI tract. LDV requires an acidic environment for absorption, and acid suppressive therapy may reduce absorption. Administration with food increases SOF exposure by twofold but does not affect its maximal concentration or exposure of the active metabolite. Food has no effect on the absorption of LDV. Plasma protein binding of ledipasvir is 99.8% and 65% for sofosbuvir. After absorption, SOF is hepatically activated into its triphosphate form known as GS-461203. This compound is then further metabolized to the inactive GS-331007, which is eliminated through the urine. Although sofosbuvir is ultimately eliminated renally, no renal dose adjustment is required as clinical data have demonstrated the safety of the 400 mg dose of sofosbuvir in patients with chronic kidney disease and end-stage renal disease on hemodialysis. LDV is eliminated unchanged primarily through the biliary tract, with a half-life of 47 hours. The safety and efficacy of LDV/SOF in pregnancy and lactation has not yet been established.

Adverse effects

The combination of ledipasvir/sofosbuvir is well tolerated overall, especially in combination with interferon-based therapies. The most common adverse effects noted in clinical trials of patients with compensated liver disease were fatigue (13–18%), headache (11–17%), nausea (6–9%), and diarrhea (3–7%). Rarely, reactivation of HBV leading to fulminant hepatitis, hepatic failure, and death has been reported in patients coinfected with HBV who were not currently receiving HBV therapy. Therefore, it is important to screen for HBV exposure and coinfection prior to initiation of HCV therapy and manage as clinically indicated.

Drug interactions

Coadministration of SOF-containing regimens with amiodarone may lead to severe symptomatic bradycardia and is not recommended. The mechanism of this interaction is unknown. Acid-suppressive therapies reduce absorption of LDV and should be reassessed prior to initiation of LDV/SOF. A maximum dose of omeprazole 20 mg once daily is recommended and should be administered simultaneously with LDV/SOF under fasted conditions to avoid decreased absorption. The maximal dose of famotidine is 40 mg twice daily and must be administered simultaneously with LDV/SOF and/or 12 hours apart.

Both agents are substrates of P-gp and breast cancer resistance protein (BRCP). Drug exposures may be significantly increased or decreased by inhibitors or inducers of these transporters. For

example, LDV/SOF is not recommended with strong P-gp inducers such as rifampin, phenytoin, and carbamazepine. However, LDV/SOF is the only single-tablet regimen that can be given with efavirenz-based antiretroviral therapy. Renal function must be monitored closely with concomitant TDF therapy as drug exposure of TDF increases by 98% when administered with LDV/SOF. No clinically significant interaction is seen with TAF.

In addition to being a substrate, LDV is also an inhibitor of P-gp and BRCP. Therefore, administration with other P-gp and BRCP substrates may lead to supratherapeutic serum concentrations and drug exposure. The clinical relevance of this interaction is seen when examining the effects of coadministration with HMG-CoA reductase inhibitors, such as rosuvastatin. The combination of LDV/SOF and rosuvastatin is not recommended as there is an increased risk of HMG-CoA reductase inhibitors adverse effects such as myalgia, myopathy, and rhabdomyolysis.

Sofosbuvir/Velpatasvir

In 2016, the US Food and Drug Administration (FDA) approved sofosbuvir/velpatasvir (SOF/VEL) 400/100 mg once daily for the treatment of HCV genotypes 1 through 6. Velpatasavir is an NS5A inhibitor, and sofosbuvir is an inhibitor of the NS5B RNA-dependent RNA polymerase as discussed previously. The coformulated tablet is dosed as one tablet once daily without regard to food. Treatment duration is typically 12 weeks for patients without cirrhosis or compensated cirrhosis. It is important to screen for baseline resistance-associated substitutions (RAS) in genotype 3 for treatment-naïve patients with compensated cirrhosis and for peginterferon/ribavirin-experienced patients without cirrhosis. If the Y93H RAS is detected in these populations, the addition of ribavirin is indicated. In patients with decompensated cirrhosis, duration is 12 weeks in conjunction with ribavirin or 24 weeks without ribavirin.

Pharmacokinetics

Velpatasvir achieves its maximal concentration 3 hours after administration, and food increases absorption of velpatasvir by 21% to 34% depending on the fat and caloric content of the meal. Like ledipasvir, velpatasvir is also highly protein-bound. Metabolism of velpatasvir occurs via CYP2B6, CYP2C8, and CYP3A4. Elimination is via the biliary tract, with a half-life of approximately 15 hours. For a discussion of SOF pharmacokinetics, please see the pharmacokinetics section of LDV/SOF. No renal dose adjustment is required of either SOF or VEL. The safety and efficacy of SOF/VEL in pregnancy and lactation has not yet been established.

Adverse effects

Data from phase 3 clinical trials show that the combination of SOF/VEL is well-tolerated. The most common adverse effects in patients with compensated liver disease were headache (22%) and fatigue (15%). Less common adverse effects included nausea (9%), asthenia (5%), and insomnia (5%). Rarely, reactivation of HBV leading to fulminant hepatitis, hepatic failure, and death can occur after initiation of SOF/VEL. Patients should be screened for HBV exposure and coinfection at baseline and managed appropriately as clinically indicated.

Drug interactions

Because this regimen contains SOF, it should not be coadministered with amiodarone as there is a significant risk of severe symptomatic bradycardia. Acid-suppressive medications decrease absorption of velpatasvir and should be avoided if possible. If acid-suppressive therapy is required, omeprazole at a dose of no greater than 20 mg once daily can be administered 4 hours after ingestion of VEL/SOF with a meal. This administration strategy does not significantly affect treatment outcome. Of note, these administration requirements are more complex than that of LDV/SOF, and so LDV/SOF may be preferred if a patient with genotype 1 or 4 to 6 requires proton pump inhibitor therapy. A similar interaction with famotidine is also present. Up to 40 mg of famotidine twice daily can be administered simultaneously with and/or 12 hours after VEL/SOF to mitigate the drug–drug interaction.

VEL is a substrate of P-gp and BRCP, organic anion transporter 1B1 (OATP1B1), and OATP1B3. Unlike ledipasvir, velpatasvir undergoes hepatic metabolism by CYP2B6, CYP2C8, and CYP3A4. Strong inducers or inhibitors of these transporters or enzymes will reduce or increase serum concentrations and drug exposure of VEL, respectively. The classic CYP and P-gp inducers such as rifampin, phenytoin, and carbamazepine are contraindicated with this regimen. SOF/VEL is not compatible with efavirenz-based antiretroviral therapy.

VEL is also an inhibitor P-gp, BRCP, OATP1B1, OATP1B3, and OATP2B1. Substrates of these transporters may have increased serum concentrations if coadministered. SOF/VEL also increases exposure to TDF by 30% to 80%, so close monitoring of renal function is necessary if TDF is a part the patient's HIV or HBV regimen. Consider alternative HIV or HBV therapy with TAF. A significant drug–drug interaction is present with HMG-CoA reductase inhibitors atorvastatin and rosuvastatin. SOF/VEL increases the maximal concentration of rosuvastatin by 2.61-fold and the area under the curve by 2.69-fold. No more than 10 mg of rosuvastatin should be used with SOF/VEL therapy.

Elbasvir/Grazoprevir

Elbasvir/grazoprevir (EBR/GZR) is a single-tablet regimen which combines EBR, an NS5A inhibitor, with GZR, an NS3/4A protease inhibitor. The NS3/4A protease is responsible for proteolytic cleavage of HCV polyproteins, and inhibition halts viral replication. It was initially approved in the United States in 2016, for the treatment of HCV genotypes 1 and 4. For patients with genotype 1a, the most common genotype in the United States, RAS testing is required. If genotype 1a RAS are detected, the addition of ribavirin and extended duration to 16 weeks are required or an alternative regimen should be selected. A single coformulated tablet of EBR/

GZR 50/100 mg is given orally once daily for 12 weeks without regard to food.

Pharmacokinetics

Times to peak concentrations for GZR and EBR are 2 and 3 hours, respectively. A high-fat, high-calorie meal decreases EBR exposure by 11% and increases GZR exposure by 1.5-fold; however, these changes are not clinically significant, and the regimen can be administered without regard to food. Both agents are highly protein-bound and have long half-lives of between 24 and 31 hours. Metabolism occurs hepatically, primarily through CYP3A4, and elimination is through the biliary tract. Therefore, no renal dose adjustments are required. EBR/GZR can be used safely in patient with cirrhosis but is contraindicated in patients with a history of or active decompensated cirrhosis. The safety and efficacy of EBR/GZR in pregnancy and lactation has not yet been established.

Adverse effects

In clinical studies leading to EBR/GZR approval, adverse effects were minimal and incidence was low. The most common adverse effects were fatigue (11%) and headache (10%) in patients receiving EBR/GRZ alone. Rarely, reactivation of HBV leading to fulminant hepatitis, hepatic failure, and death has been reported in patients coinfected with HBV who were not currently receiving HBV therapy. Therefore, it is important to screen for HBV exposure and coinfection prior to initiation of HCV therapy and manage as clinically indicated.

Drug interactions

There is no black box warning regarding use of EBR/GZR with amiodarone as there is with sofosbuvir-containing regimens. However, GZR is an inhibitor of CYP3A4 and may increase drug exposure of amiodarone, leading to bradycardia. Combination therapy of EBR/GZR and amiodarone therapy is not recommended unless the patient can be monitored very closely for signs and symptoms of bradycardia. Acid-suppressive therapies such as omeprazole and famotidine do not significantly impact absorption of EBR/GZR. Therefore, EBR/GZR is considered an agent of choice when a patient requires acid-suppressive therapies.

EBR and GZR are substrates of CYP3A4 and P-gp. Additionally, GZR is affected by OATP1B1/3. EBR/GRZ is contraindicated with strong inducers of CYP3A4 and P-gp such as rifampin, phenytoin, and carbamazepine. In addition, EBR/GRZ has clinically significant interactions with antiretroviral therapy as well; it should not be coadministered with efavirenz (CYP3A4 inducer) and HIV protease inhibitors like darunavir because they are strong CYP3A4 inhibitors. Antiretroviral therapy should be modified or another DAA should be selected in this scenario.

Although EBR and GZR are P-gp substrates, data demonstrate they are minimally affected by intestinal P-gp and therefore have minimal effect on other P-gp substrates such as digoxin. A pharmacokinetic study demonstrated no significant difference in digoxin drug exposure when administered with EBR/GZR. For this reason, consider use of EBR/GZR in patients who require concomitant therapy with narrow therapeutic index P-gp substrates. As with other DAAs, drug–drug interactions are present with HMG-CoA reductase inhibitors. A maximum dose of 20 mg of atorvastatin should not be exceeded while on EBR/GZR therapy as the latter can increase atorvastatin drug exposure by 94%.

Sofosbuvir/Velpatasvir/Voxileprevir

Sofosbuvir/velpatasvir/voxilaprevir 400/100/100 mg (SOF/VEL/VOX) is a pangenotypic regimen initially approved in 2017, primarily for the treatment of patients who had failed a previous NS5A-containing regimen. SOF/VEL/VOX can also be used for patients who failed a non-NS5A sofosbuvir-containing regimen in genotypes 1a and 3. It contains an agent from each class of the DAA group: SOF (NS5B inhibitor), VEL (NS5A inhibitor), VOX (NS3/4A protease inhibitor). Dosing consists of one tablet orally daily administered with food for 12 weeks. SOF/VEL/VOX can even be used as retreatment in patient who previously failed SOF/VEL/VOX. In this scenario, the addition of ribavirin and extension to 24 weeks is recommended on the basis of expert opinion.

Pharmacokinetics

The pharmacokinetics of SOF/VEL have been discussed previously (see SOF/VEL section). Administration with food increases absorption of VOX by 112% to 435% relative to fasted conditions. It is also highly protein-bound, and metabolism occurs via CYP3A4. Elimination is biliary with a half-life of 33 hours. The safety and efficacy of SOF/VEL/VOX in pregnancy and lactation has not yet been established. No renal dose adjustment is required. SOF/VEL/VOX is contraindicated in patients with a history of or active decompensated liver disease.

Adverse effects

Treatment discontinuations due to adverse effects were rare in clinical trials. Common adverse effects included headache (21–23%), fatigue (17–19%), and diarrhea (10–13%). Rarely, reactivation of HBV leading to fulminant hepatitis, hepatic failure, and death has been reported in patients coinfected with HBV who were not currently receiving HBV therapy. Therefore, it is important to screen for HBV exposure and coinfection prior to initiation of HCV therapy and manage as clinically indicated.

Drug interactions

Drug interactions with amiodarone and acid-suppressive therapies of SOF and VEL have been previously discussed. SOF/VEL/VOX is primarily metabolized by CYP3A4 and contraindicated with strong CYP3A4 and P-gp inducers such as rifampin, phenytoin, and carbamazepine. Additionally, HIV protease inhibitors such as darunavir and atazanavir should not be coadministered with VOX. Cyclosporine significantly increases the serum concentration of VOX. HMG-CoA reductase inhibitor interactions exist with SOF/VEL/VOX. Rosuvastatin and pitavastatin are not recommended, and the lowest effective dose of atorvastatin is suggested by the

prescribing information. No more than pravastatin 40 mg can be used with SOF/VEL/VOX.

Hepatitis C therapies: Multi-tablet regimens

Glecaprevir/Pibrentasvir

Glecaprevir/pibrentasvir (GLE/PIB) is a combination of an NS5A inhibitor and an NS3/4A protease inhibitor. It was approved in 2017 by the FDA for HCV genotypes 1 through 6 as 100/40 mg tablets administered as three tablets (total 300/120 mg) orally once daily with food. Duration of therapy is typically 8 weeks for uncomplicated patients, but some patients may require 12 or 16 weeks. The longer durations of 12 weeks is reserved for those who are coinfected with HIV and have cirrhosis or those who are treatment-experienced with pegylated interferon and ribavirin for genotypes 1, 2, and 4 through 6 and have cirrhosis. Interferon- and ribavirin treatment-experienced patients with genotype 3 require 16 weeks of GLE/PIB.

Pharmacokinetics

Both agents of this regimen have a time to maximal concentration of 5 hours after administration. As mentioned earlier, this regimen requires food for absorption. Food increases systemic exposure by 83% to 163% and 40% to 53% for GLE and PIB, respectively. Similar to other regimens, GLE and PIB are highly protein-bound. GLE undergoes metabolism by CYP3A, but PIB does not undergo metabolism. Elimination occurs through the biliary tract with a half-life of 6 hours for GLE and 13 hours for PIB. Use of GLE/PIB in patients with a history of or active decompensated cirrhosis is contraindicated. The safety and efficacy of GLE/PIB in pregnancy and lactation has not yet been established.

Adverse effects

In approval studies, GLE/PIB was very well tolerated, and common adverse effects included headache (13%), fatigue (11%), and nausea (8%). Rarely, reactivation of HBV leading to fulminant hepatitis, hepatic failure, and death has been reported in patients coinfected with HBV who were not currently receiving HBV therapy. Therefore, it is important to screen for HBV exposure and coinfection prior to initiation of HCV therapy and manage as clinically indicated.

Drug interactions

Absorption of glecaprevir is affected by proton pump inhibitors such as omeprazole. Omeprazole 20 mg once daily reduced glecaprevir exposure by 29%. A higher dose of omeprazole 40 mg further decreased glecaprevir drug exposure by 51%. However, product labeling does not recommend dosage adjustment with omeprazole as long as dosage does not exceed 40 mg once daily. Pibrentasvir absorption and drug exposure is not affected by omeprazole. Coadministration of GLE/PIB with famotidine has not been studied.

GLE and PIB are affected by transporters P-gp, BRCP, and OATP1B1/3. Consequently, strong inhibitors or inducers of these transporters will significantly increase or decrease GLE/PIB exposure, respectively. They are also weak inhibitors of CYP3A, CYP1A2, and uridine glucuronosyltransferase 1A1 (UGT1A1). Drug exposure of amiodarone may be increased by GLE/PIB, and close monitoring is recommended. GLE/PIB is contraindicated with HIV protease inhibitors (strong CYP3A4 inhibitors) and the non-nucleoside reverse transcriptase inhibitor efavirenz (CYP3A4 inducer). Other strong inducers such as rifampin, phenytoin, and carbamazepine are also contraindicated. A unique interaction exists between GLE/PIB and ethinyl estradiol; coadministration may increase the risk of ALT elevations. This interaction is not seen with progestin-only contraceptives such as norethindrone. GLE/PIB can also significantly increase exposure of HMG-CoA reductase inhibitors. For example, they increase atorvastatin exposure by 8.3-fold, increasing the risk of myalgia, myopathy, and rhabdomyolysis. Coadministration with atorvastatin is not recommended; select an alternative agent or consider withholding atorvastatin while on GLE/PIB therapy.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir

The regimen of coformulated ombitasvir, paritaprevir, and ritonavir copackaged with dasabuvir achieved FDA approved in 2014. Ombitasvir is an NS5A inhibitor, paritaprevir is an NS3/4A protease inhibitor, and dasabuvir is an NS5B inhibitor. Ritonavir is not active against HCV, but is used to increase the serum concentrations and drug exposure of paritaprevir, similar to its current role in treatment of HIV. Two tablets of the coformulated ombitasvir, paritaprevir, and ritonavir 12.5/75/50 mg are taken once daily in the morning. The dasabuvir is administered as its own tablet as 250 mg twice daily with food. The regimen is indicated for treatment of genotype 1b in patients without cirrhosis. Ribavirin must be added for patients with genotype 1b with cirrhosis and for treatment of genotype 1a. Treatment duration is either 12 or 24 weeks. This regimen contains ritonavir, which also has activity against HIV. It is important to screen for HIV prior to initiation or ensure that the patient coinfected with HIV is on a suppressive regimen to avoid the selection for HIV protease inhibitor resistance mutations.

Food increases absorption of all components of this regimen, and therefore it should not be administered on an empty stomach. Ombitasvir, paritaprevir, ritonavir, and dasabuvir are not recommended in moderate hepatic impairment (Child-Pugh B) and contraindicated in severe hepatic impairment (Child-Pugh C). No renal dose adjustments are required. Safety and efficacy in pregnancy and lactation have not been established. There are numerous drug–drug interactions with CYP3A substrates, strong CYP3A/2C8 inducers, and strong CYP2C8 inhibitors. Examples include amiodarone, rifampin, efavirenz, rilpivirine, ethinyl estradiol, fluticasone nasal spray, HIV protease inhibitors, and HMG-CoA reductase inhibitors. Adverse effects include nausea (8%), pruritus (7%), and insomnia (5%). Incidence of adverse effects is higher when coadministered with ribavirin, as expected. A rare but serious side effect is increases in ALT (1%); ALT should be monitored

during the first 4 weeks of treatment. Patients on ethinyl estradiol are at higher risk of this side effect, and, as a result, ethinyl estradiol products are contraindicated. HBV reactivation can occur; screen for HBV at baseline and manage as clinically indicated. Please see the ribavirin section for ribavirin specific information.

Daclatasvir

Daclatasvir is an NS5A inhibitor that was originally approved in 2015. It is indicated for the treatment of HCV genotypes 1 and 3 in combination with sofosbuvir and/or ribavirin. Patients with genotype 1 and compensated liver disease receive daclatasvir 60 mg with sofosbuvir 400 mg once daily. Ribavirin is added for decompensated liver diseases or patients who are post liver transplant. RAS testing for genotype 1a in patients with cirrhosis is recommended because certain mutations (M28, Q30, L31, Y93) are associated with decreased efficacy. In genotype 3, patients without cirrhosis are eligible for daclatasvir and sofosbuvir given for 12 weeks. However, patients with any degree of cirrhosis or those posttransplantation require the addition of ribavirin. Treatment duration is 12 weeks.

Daclatasvir can be administered without regard to food, and metabolism occurs primarily via CYP3A4. Elimination is biliary; no changes in dosing are indicated for renal impairment. Safety and efficacy in pregnancy and lactation have not been established. Dose adjustment is required when administered with strong CYP3A4 inhibitors (reduce dose to 30 mg once daily) and moderate CYP3A4 inducers (increase dose to 90 mg once daily). Daclatasvir is contraindicated with strong CYP3A4 inducers such as rifampin, phenytoin, and carbamazepine. It also may increase serum concentrations of HMG-CoA reductase inhibitors, digoxin, and amiodarone. Rarely, reactivation of HBV leading to fulminant hepatitis, hepatic failure, and death has been reported in patients coinfected with HBV who were not currently receiving HBV therapy. Therefore, it is important to screen for HBV exposure and coinfection prior to initiation of HCV therapy and manage as clinically indicated. Please see the ribavirin section for ribavirin-specific information.

Ribavirin

Ribavirin is a synthetic guanosine analog with numerous proposed mechanisms of action including inhibition of viral RNA synthesis and immunomodulatory effects. Ribavirin has a broad spectrum of activity against RNA viruses, including HCV, RSV, and viral hemorrhagic fevers.

A major use for ribavirin is as combination therapy with against HCV; monotherapy is not effective. Oral ribavirin was initially combined with injected interferon-α and has been shown to produce a sustained virologic response when used either as initial therapy or after relapse in patients previously treated with interferon-α alone. In current practice, ribavirin is typically added to DAA regimens such as LDV/SOF, SOF/VEL, EBR/GZR, and GLE/PIB to improve sustained virologic response in patients with decompensated cirrhosis, genotype 1 or 3, or prior treatment failures. For patients <75 kg, 1,000 mg in two divided doses with food is recommended. In patients weighing ≥75 kg, 1,200 mg in two divided doses with food is recommended. Duration of therapy ranges from 12 to 24 weeks depending on patient-specific factors.

Ribavirin is administered as an aerosol via a specialized nebulizer for confirmed, severe, lower respiratory RSV infection. It is approved for use in infants and children, and used off-label in immunosuppressed adult populations. The mechanism of action against RSV is not completely understood; however, ribavirin has demonstrated in vitro activity against RSV. The FDA-approved dose is 6 g administered over 12 to 18 hours per day. Intermittent aerosolization strategies have also been investigated and used in practice. Ribavirin has also been used for treatment of Lassa fever and Hantaviruses.

Pharmacokinetics

Ribavirin is rapidly absorbed after oral administration, but bioavailability varies based on formulation. It undergoes hepatic metabolism, and its half-life is very long (up to 300 hours at steady state). Dose adjustment begins at CrCl <50 mL/min. Refer to a formulations-specific monograph for further information as pharmacokinetics are formulation-specific. It is contraindicated in pregnancy. Aerosolized ribavirin is absorbed systemically with a plasma half-life of 9.5 hours.

Adverse effects

Ribavirin is teratogenic and embryotoxic and so use in pregnancy is contraindicated. Patient counseling, discussion of contraception options, and close monitoring of women of childbearing potential on ribavirin therapy is recommended. The risk of teratogenicity persists for up to 6 months after completion of ribavirin therapy. Similar precautions should be observed if the male partner is being treated.

Hematologic side effects are common and principally consist of hemolytic anemia, but leukopenia and thrombocytopenia are possible as well. The recommendations for dosage adjustment and discontinuation vary depending on whether the patient has known cardiac disease. If the affected cell line recovers, ribavirin can be reinitiated at a lower dose. Ribavirin by aerosolization may worsen respiratory status, cause bronchospasm, or lead to worsening ventilation.

Drug interactions

It is not recommended to coadminister ribavirin with zidovudine due to increased risk of anemia. Concomitant therapy with azathioprine may lead to increased concentrations of azathioprine's active metabolite and lead to enhanced immunosuppression.

Cytomegalovirus therapies

Ganciclovir and valganciclovir

Ganciclovir, a guanine derivative, is a major antiviral agent used primarily for the treatment of CMV, but it also has activity against acyclovir-resistant HSV and VZV. It is the active form of the oral

prodrug valganciclovir. After preferential cellular uptake in CMV-infected cells, ganciclovir undergoes monophosphorylation via the CMV UL97 kinase. It is subsequently triphosphorylated to its active form by cellular kinases, and ganciclovir trisphosphate competitively inhibits viral DNA polymerase and decreases the rate of DNA chain elongation.

In patients with HIV, valganciclovir and ganciclovir are used primarily in AIDS-associated CMV retinitis. Patients with CD4 counts of <50 cells/mm^3 are at highest risk of CMV disease. Efficacy in patients with AIDS is clearly established because treatment with anti-CMV therapy reduces involvement of the contralateral eye, prevents visceral organ involvement, and improves mortality. Preferred therapy for treatment of sight-threatening retinitis begins with an induction phase of valganciclovir 900 mg orally twice daily for 14 to 21 days in combination with intravitreal ganciclovir or foscarnet. After induction therapy, chronic maintenance therapy continues with valganciclovir 900 mg orally once daily. IV ganciclovir can be used as an alternative for induction and maintenance in patients with impaired oral absorption at a dose of 5 mg/kg IV every 12 hours and 5 mg/kg IV every 24 hours, respectively. Therapy can be discontinued after 3 to 6 months with inactive lesions and CD4 count of >100 cells/mm^3 for 3 to 6 months in response to antiretroviral therapy. Chronic maintenance therapy should be re-introduced if CD4 count falls below 100 cells/mm^3. An intravitreal ganciclovir implant for the treatment of CMV retinitis was available, but has since been discontinued in the United States. A ganciclovir ophthalmic solution is commercially available for treatment of HSV keratitis. Fortunately, the incidence of CMV retinitis has significantly decreased since the development and optimization of antiretroviral therapy. Both agents can also be used for the treatment of invasive CMV colitis and pneumonitis with ganciclovir 5 mg/kg IV every 12 hours or valganciclovir 900 mg orally every 12 hours. Duration of therapy in these syndromes varies depending on patient-specific factors, clinical course, and severity of illness.

Ganciclovir and valganciclovir are used to prevent CMV disease in bone marrow transplant patients. They are either used as prophylaxis or preemptive therapy. Prophylactic therapy is typically reserved for high-risk patients. Preemptive therapy consists of closing monitoring of CMV DNA and initiating therapy if CMV DNA increases significantly. Preemptive therapy uses doses of ganciclovir and valganciclovir similar to those for induction of CMV retinitis. Duration is typically 2 weeks, but may be extended to include maintenance therapy if viremia persists. Maintenance dosing is similar to that for CMV retinitis. The duration of maintenance therapy depends on the intensity of immunosuppression and should be given for at least 100 days after the transplant. In solid organ transplant, a similar approach of either prophylactic or preemptive therapy exists. Duration of therapy varies based on organ transplanted and institutional protocols.

Resistance to ganciclovir and valganciclovir can develop and should be considered in patients who fail to respond to therapy or develop breakthrough viremia. Resistance is typically mediated by changes in the UL97 kinase, which is responsible for the first step in the activation of ganciclovir to ganciclovir triphosphate. Additionally mutations in UL54 gene, which is responsible for encoding the CMV DNA polymerase, can also confer resistance to ganciclovir. Foscarnet and cidofovir maintain activity in strains with UL97-mediated resistance, but cross-resistance can occur with UL54 mutations.

Pharmacokinetics

Similar to oral acyclovir and valacyclovir, oral ganciclovir has poor bioavailability and has been primarily replaced by valganciclovir. Valganciclovir should be administered with food due to 30% lower bioavailability if taken on an empty stomach. After oral administration, valganciclovir is rapidly converted to ganciclovir by hepatic and intestinal esterases. There is minimal plasma protein binding. Ganciclovir is excreted renally as unchanged drug. Dose reductions begin at CrCls of <70 mL/min and 60 mL/min for ganciclovir and valganciclovir, respectively. Half-life ranges from 4 to 6 hours in different populations and is prolonged in patients with renal impairment. No hepatic dose adjustments are required. Both agents carry a warning for birth defects based on animal data, and use in pregnant women should depend on risks and benefits of use.

Adverse effects and drug interactions

The major toxicity of ganciclovir is hematologic and can involve all cell lines, but most commonly causes neutropenia and thrombocytopenia. Incidence varies based on patient population but can be as high as 42% to 58% in bone marrow transplant patients. Neutropenia is typically reversible upon discontinuation. Risk of hematologic toxicity is compounded by use of other agents that affect blood counts such as chemotherapeutic agents, trimethoprim-sulfamethoxazole, dapsone, and zidovudine. Increases in serum creatinine have also been reported, and concomitant nephrotoxins such as amphotericin B and cyclosporine should be prescribed with caution. Probenecid increases ganciclovir drug exposure by 53%.

Cidofovir

Cidofovir is a cytosine analogue with activity against numerous viruses, including adenoviruses, HSV, VZV, and CMV. Cidofovir was designed to minimize the resistance that develops in response to nucleoside analogs that require phosphorylation by viral enzymes, such as acyclovir and ganciclovir. Although cidofovir must be diphosphorylated to become active, it does not require phosphorylation by viral kinases as it bypasses the UL97 kinase. Rather, cidofovir is activated by cellular enzymes alone. Cidofovir is more active against herpesvirus DNA polymerases than cellular DNA polymerases and thus has selective antiviral activity.

Cidofovir is used as an alternative to ganciclovir/valganciclovir for the treatment of CMV retinitis in patients with HIV. Cidofovir has been effective in delaying the progression of CMV retinitis in AIDS patients, including those who have failed ganciclovir or foscarnet therapy. It can also be used topically or systemically for patients with acyclovir-resistant HSV or VZV. Successful treatment of serious adenovirus infections with cidofovir in immunocompromised patients has been reported. Last, it has shown efficacy in BK

virus–associated hemorrhagic cystitis at lower doses or administered intravesicularly.

Ganciclovir-resistant strains of CMV, which carry mutations in the UL97 phosphokinase gene, generally remain susceptible to cidofovir. Cidofovir may be considered in patients failing ganciclovir or those who have developed resistance. However, other ganciclovir-resistant mutants, especially those carrying mutations in the DNA polymerase gene (UL54) may be cross-resistant to cidofovir. CMV strains resistant to ganciclovir, foscarnet, and cidofovir have also been described. Induction therapy with cidofovir is initiated at a dosage of 5 mg/kg once weekly for 2 weeks, followed by the same dose once every 2 weeks as maintenance therapy.

Cidofovir is highly nephrotoxic, which often limits its use in clinical practice. Nephrotoxicity is mediated by high concentrations of cidofovir in the renal tubules. Infrequent dosing due to its long half-life and administration with probenecid, which prevents rapid secretion of the drug by the renal tubules, both attenuate nephrotoxicity. Probenecid is administered as follows: 2 g 3 hours before infusion and 1 g at 2 and 8 hours after infusion. Baseline renal function should be assessed prior to use. A CrCl of <55 mL/min, a serum creatinine of >1.5 mg/dL, or 2+ proteinuria is a contraindication to its use. IV saline prehydration with 1 L of normal saline immediately before cidofovir infusion is mandatory to prevent nephrotoxicity. If possible, an additional liter of saline should be administered with and after cidofovir over a 1- to 3-hour period. In addition, great care should be taken to monitor renal function with both urine and serum measurements, and the importance of taking the probenecid should be emphasized.

Pharmacokinetics

Approximately 70% to 85% of cidofovir is eliminated unchanged by the kidneys. Its plasma half-life is approximately 2.5 hours, but it has a long-lasting antiviral effect due to the long intracellular half-life of the disphophorylated form. There are no hepatic dose adjustments, and cidofovir should not be used in pregnant women unless benefits outweigh risks to the fetus.

Adverse effects

As described previously, the major toxicity of cidofovir is its nephrotoxicity. Cases of Fanconi's syndrome with cidofovir have been reported. Neutropenia has occurred in approximately 20% of cidofovir recipients in clinical trials. Cidofovir requires administration with probenecid, and the adverse effects of probenecid should also be considered.

Drug interactions

The most important drug interactions are those with other nephrotoxic medications. Caution should be exercised with concomitant therapy with nephrotoxins such as vancomycin, aminoglycosides, NSAIDs, and amphotericin B. Probenecid decreases cidofovir clearance through inhibition of renal transporters, but overall attenuates nephrotoxicity by decreasing the rate of renal tubule exposure to cidofovir. Probenecid has the potential to increase systemic concentrations of other drugs such as β-lactams and other anti-HSV agents such as valacyclovir.

Foscarnet

Foscarnet (phosphonoformic acid) binds to pyrophosphate binding sites on CMV DNA polymerase. It does not require phosphorylation, unlike ganciclovir and cidofovir. At therapeutic concentrations, foscarnet does not bind to human DNA polymerases. Foscarnet can be used as alternative therapy to ganciclovir/valganciclovir for treatment of CMV retinitis, treatment of ganciclovir-resistant or cidofovir-resistant CMV, and acyclovir-resistant VZV and HSV. It retains activity in CMV strains with mutations in the UL97 gene, but cross-resistance can occur through mutations in UL54. Induction treatment is given at 60 mg/kg IV every 8 hours for 2 to 3 weeks, followed by maintenance therapy at 90 mg/kg once daily.

Pharmacokinetics

Foscarnet is administered intravenously only and excreted renally. Its half-life is variable and highly dependent on renal function, which is invariably impaired by foscarnet. Thus, close monitoring of renal function with appropriate dosage adjustment is recommended. No hepatic dose adjustment is required, and foscarnet should be avoided in pregnancy unless benefits outweigh risks.

Adverse effects

The major toxicities of foscarnet are impairment of renal function (27%), anemia (33%), and electrolyte abnormalities. Hypocalcemia (15–30%), hypophosphatemia (8–26%), hyperphosphatemia (6%), hypomagnesemia (15–30%), and hypokalemia (16–48%) may occur. Careful assessment of baseline renal function and electrolytes status is required prior to initiation. Aggressive electrolyte monitoring and repletion is recommended.

Drug interactions

Adverse effects of foscarnet may be potentiated with agents with similar toxicity profiles. If possible, avoid concomitant nephrotoxins such as vancomycin and aminoglycosides. Amphotericin B also causes electrolyte derangements, and these effects may be compounded with concomitant foscarnet.

Letermovir

Letermovir was approved as a first-in-class agent in the United States in 2017, as a CMV DNA terminase complex inhibitor for the prophylaxis of CMV in CMV-seropositive allogeneic stem cell transplant patients. Inhibition of this complex prevents cleavage to produce individual viral units. It is dosed as 480 mg orally or intravenously once daily beginning between day 0 and 28 posttransplant and continued through day 100. Approval trials demonstrated letermovir had significantly lower failure rates at week 24 when compared to placebo. Given its unique mechanism of action in inhibiting the DNA terminase complex consisting of UL51, UL56,

and UL89, cross-resistance with other agents is not anticipated. Although not FDA-approved for treatment of CMV, cases of successful treatment of CMV have been reported in the literature and additional studies for treatment are under way. Letermovir-associated resistance mutations have been observed in clinical trials.

Pharmacokinetics

Letermovir is rapidly absorbed and can be administered with or without food. The bioavailability in the target population is 35%, but is increased to 85% if coadministered with cyclosporine. It is highly plasma protein-bound and undergoes metabolism through UGT1A1/1A3. Elimination is primarily as unchanged drug through the hepatobiliary system, with a half-life of 12 hours. Use of letermovir is not recommended in patients with a CrCl of <10 mL/min or with severe hepatic impairment (Child Pugh Class C). There are insufficient data for use in pregnancy and lactation.

Adverse effects

Common adverse events seen in clinical trials included nausea (27%), diarrhea (26%), and vomiting (19%); however, the incidence of adverse effects leading to discontinuation were similar between groups. Nausea was the most common adverse effect that led to discontinuation. Hematologic toxicities were common, but incidence was similar to the placebo group.

Drug interactions

There are numerous drug–drug interactions with letermovir. Letermovir is a substrate of CYP2D6, CYP3A4, P-gp, and OATP1B1/1B3, as well as a moderate inhibitor of CYP3A4. A significant interaction exists with cyclosporine, where the dose of letermovir must be halved to 240 mg once daily. Cyclosporine concentrations should be monitored closely when initiating letermovir. It also has the potential to increase drug exposure of amiodarone, tacrolimus, pimozide, and HMG-CoA reductase inhibitors among others.

Coronavirus disease 2019 therapy

Remdesivir

Remdesivir was initially developed as antiviral agent for the treatment of Ebola, but it failed to provide a significant benefit. Remdesivir is an adenosine analog that undergoes triphosphorylation to inhibit viral RNA-dependent RNA polymerase. During the coronavirus disease 2019 (COVID-19) pandemic, remdesivir was found to have in vitro activity against the causative pathogen SARS-CoV-2. Data regarding efficacy of remdesivir are currently evolving. The dose is 200 mg IV once on day 1 followed by 100 mg IV once daily for patients weighing >40 kg. For patients <40 kg, 5 mg/kg IV on day 1 followed by 2.5 mg/kg IV once daily is indicated. Optimal duration of therapy is unclear. The most common adverse effect is liver toxicity, and close monitoring of hepatic function is prudent. The IV formulation contains sulfobutylether-β-cyclodextrin, which has been associated with nephrotoxicity. Due to the pressing need for antiviral therapy, drug–drug interaction studies were forgone and so there are limited data on this subject.

Suggested reading

AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. August 30, 2020. http://www.hcvguidelines.org

Centers for Disease Control and Prevention (CDC). Influenza antiviral medications. August 30, 2020. https://www.cdc.gov/flu/professionals/antivirals/index.htm

Cunha BA, Torres DC, Cunha CB et al. Antimicrobial drug summaries. In Cunha CB, Cunha BA, eds. *Antibiotic essentials*, 17th ed. New Delhi: Jaypee Publishing; 2020;539–770.

Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560–1599.

Workowski KA, Bolan G. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(3):1–138.

Probiotics: an update

Varsha Gupta and Ritu Garg

Nobel laureate Elie Metchnikoff, in the early 1900s, proposed that the long life of Bulgarian peasants resulted from their consumption of fermented milk products. The term "probiotic" was first used in 1965, by Lilly and Stillwell, to describe substances secreted by one organism which stimulate the growth of another. In 2002, Marteau et al. defined them as "microbial preparations or components of microbial cells that have a beneficial effect on health and well- being."

Humans live in close association with vast numbers of microorganisms present on the skin, in the mouth, and in the gastrointestinal (GI) tract. The GI tract harbors a rich flora of >500 different bacterial species, some of which have important health functions that include stimulating the immune system, protecting the host from invading bacteria and viruses, and aiding digestion.

The use of antibiotics, immunosuppressive therapy, and irradiation, as well as other means of treatment, may cause alterations in the composition and actions of these gut flora. Therefore, the introduction of beneficial bacterial species into the GI tract may be a very attractive option to reestablish microbial equilibrium and prevent disease.

The term "probiotics" was derived from the Greek meaning "for life." The Food and Agriculture Organization/World Health Organization (FAO/WHO) later defined probiotic as "live microorganisms," which, when administered in adequate amounts, confer a health benefit on the host.

Bacterial products, in the absence of viable organisms, may have similar effects on signaling pathways and barrier functions. These bacterial products are broadly characterized as *postbiotics* and can be defined as nonviable bacterial products or metabolic by-products from probiotic microorganisms that have biologic activity in the host. Generally, postbiotics include bacterial metabolic by-products, such as bacteriocin, organic acids, ethanol, diacetyl, acetaldehydes, and hydrogen peroxide; it has been also found that certain heat-killed probiotics can also retain important bacterial structures that may exert biological activity in the host. Research shows that these metabolic products have a broad inhibitory property toward pathogenic microbes and therefore can be used as an alternative to antibiotics. Because these are nonviable bacterial products or metabolic by-products from probiotics, postbiotics are nontoxic, nonpathogenic, and resistant to hydrolysis by mammalian enzymes. In some instances, postbiotics can also enhance barrier function against species like *Saccharomyces boulardii*, and they have been shown to improve angiogenesis in vitro and in vivo in epithelial cells by activation of $\alpha 2\beta 1$ integrin collagen receptors.

A *prebiotic* is a nondigestible food ingredient that confers benefits on the host by selectively stimulating the growth and/or activity of one bacterium species or a group of bacteria species in the colon and thus improving host health. Prebiotics are dietary carbohydrates that escape digestion in the upper GI tract and alter the bacterial composition of the gut by changing the type of substrate provided to the existing microbial population in the gut; these carbohydrates include fructo oligosaccharides, gluco oligosaccharides, and inulin.

Both probiotics and prebiotics are together called as *synbiotics*. They improve the survival of bacteria in the GI tract and thus enhance their effect. The synergistic benefits are more efficiently promoted when both probiotics and prebiotics work together in the living system.

The characteristics of an ideal probiotic preparation include:

- High cell viability, thus resistant to low pH and acids
- The ability to persist in the intestine, even if the probiotic strain cannot colonize the gut
- Adhesive to the gut epithelium so that it can cancel the flushing effects of peristalsis
- Able to interact or send signals to immune cells associated with the gut and influence local metabolic activity
- Of human origin
- Nonpathogenic, nontoxic, free of serious side effects
- Resistant to processing and be present in the product in adequate numbers of viable cells to confer a health benefit

Numerous microorganisms are used as probiotics. The following lists those microbes being used in probiotic preparations.

- Lactobacillus: *L. acidophilus, L. casei, L. fermentum, L. gasseri, L. johnsonii, L. lactis, L. paracasei, L. plantarum, L. reuteri, L. rhamnosus GG, L. salivarius, L. bulgaricus, L. sporogenes, L. delbrueckii, L. brevis, L. cellobiosus, L. helveticus, L. crispatus, L. delbrueckii subsp. lactis, L. salivarius subsp. salicinius.*
- Bifidobacterium: *B. bifidum, B. breve, B. lactis, B. longum, B. infantis, B. thermophilum, B. animalis, B. adolescentis*
- Streptococcus: *S. thermophilus, S. salivarius, S. lactis, S. cremoris, S. intermedius*
- Saccharomyces: *S. boulardii, S. cerevisiae*
- Others: *Bacillus cereus, Escherichia coli, Enterococcus faecalis, Enterococcus faecium, Propionibacterium, Bacteroides uniformis, Peptostreptococcus, Leuconostoc, Pediococcus, Akkermansia, Aspergillus niger, Aspergillus oryzae, Candida pintolopesii.*

Sources of probiotics are shown in Figure 209.1.

Mechanism of action

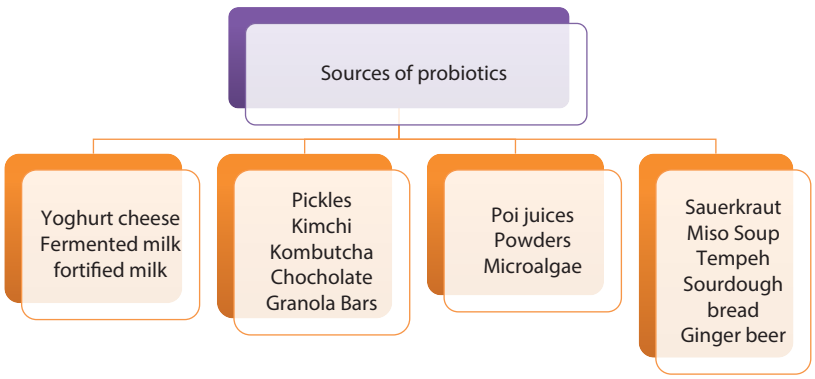
The beneficial actions of intestinal microflora, also referred to as "colonization resistance" or the "barrier effect," is an important mechanism used by the indigenous (autochthonous) gut bacteria to maintain their presence and confer niche protection against freshly ingested microorganisms, including pathogens. Probiotics are also known to demonstrate promising results by adding to the gut flora's unique ability to compete with pathogenic microbiota for adhesion to the gut and improve their colonization. Probiotics also stimulate, modulate, and regulate the host's immune response by initiating the activation of specific genes within localized host cells. They even modulate GI hormone release and regulate brain behavior through bidirectional neuronal signaling as part of the gut–brain axis. Probiotics also play a significant role in inducing intestinal angiogenesis by vascular endothelial growth factor receptor (VEGFR) signaling that, in turn, regulates the acute and chronic inflammation in intestinal mucosal tissue caused by the progression of inflammatory bowel disease (IBD). Because probiotics have physiological functions that contribute to the health of the host environment by regulating microbes they are also helpful in combating overweight and obesity.

Clinical significance of probiotics and potential applications

The use of probiotics for clinical health benefits is a fascinating area of research because probiotics have been shown to be effective in varied clinical conditions ranging from infantile diarrhea, necrotizing enterocolitis (NE), antibiotic-associated diarrhea, relapsing *Clostridium difficile* colitis, *Helicobacter pylori* infections, and inflammatory bowel disease to cancer, female urogenital infections, and surgical infections.

necrotizing enterocolitis

NE is one devastating intestinal disorder that a preterm infant may face in a neonatal intensive care unit (NICU). Low-birthweight preterm infants delivered by caesarean section often require intensive care and are breastfed only after several days. The normal process by which microorganisms such as lactobacilli are ingested via vaginal birth and propagated by the mother's milk does not take place in these infants. A human trial with 2.5×10^8 colony-forming units (CFUs) of live *Lactobacillus acidophilus* and 2.5×10^8 CFU of live *Bifidobacterium infantis* given to 1,237 newborns in Colombia resulted in a 60% reduction in NE and overall mortality.



Diarrhea

Probiotics can prevent or ameliorate diarrhea through their effects on the immune system. Moreover, probiotics might prevent infection because they compete with pathogenic viruses or bacteria for binding sites on epithelial cells. Anti-pathogenic activity is regarded as one of the most beneficial effects of probiotics because, unlike classic antibiotics, disturbance or alteration in the composition of the complex population of the gut microbiota is inhibited. Probiotics might also inhibit the growth of pathogenic bacteria by producing *bacteriocin*, which is mostly involved in increasing the membrane permeability of target cells, which leads to the depolarization of the membrane potential and, ultimately, cell death.

The use of probiotics reduces the duration of diarrhea, although the size of the effect varied considerably between studies. Probiotics have preventive as well as curative effects on several types of diarrhea of different etiologies. There is ample evidence that probiotics reduce the duration and severity of rotavirus diarrhea, antibiotic-associated diarrhea, radiation-induced diarrhea, and traveler's diarrhea.

Helicobacter pylori infection

H. pylori is a major cause of chronic gastritis and peptic ulcers and is a risk factor for gastric malignancies. Antibiotics directed toward *H. pylori* eradication are 90% effective. However, these treatments are expensive and can cause side effects as well as with antibiotic resistance. Probiotic treatment can reduce the side effects associated with *H. pylori* therapy.

Constipation

In adults, data suggest a favorable effect of treatment with *Bifidobacterium lactis* DN-173 010, *Lactobacillus casei* Shirota, and *E. coli* Nissle 1917 on the frequency of defecation and stool consistency.

Lactose intolerance

Lactose intolerance results from insufficient activity in the lactose-cleaving enzyme lactase (β-galactosidase) in the small intestine. The health effect associated with the consumption of fermented milk products is an enhancement of lactose digestion and avoidance of intolerance symptoms in lactose malabsorbers. Yogurt commonly made from *Lactobacillus bulgaricus* and *Streptococcus salivarius subsp. thermophilus* is usually effective.

Inflammatory bowel disease

IBD classically includes ulcerative colitis, Crohn's disease, and chronic pouchitis, representing different patterns of chronic inflammation within the GI tract. Research has shown that an imbalance in the gut microbiota plays an important pathophysiological role in the regulation of IBD. It is also understood that the disorder could possibly be altered by supplementation with probiotics, prebiotics, and both. IBD has been associated with impaired production of short-chain fatty acids (SCFAs), particularly acetate, butyrate, and propionate. Moreover, these SCFAs are known to play a key role in maintaining colonic homeostasis. They also possess anti-inflammatory effects and improve the propulsive colonic function. Therefore, supplementation with indigestible carbohydrates and fiber (prebiotic) alone or in combination with probiotics to increase the production of SCFAs could be a useful therapeutic approach. Presently, progress in the field is mostly concerned with developing genetically engineered probiotic bacterial strains that are able to produce and discharge immunomodulators such as interleukin-10 or lipoteichoic acids that can impact the host immune system and restore the level of protective commensal bacterial species.

Urogenital tract infections

According to the US Centers for Disease Control and Prevention (CDC), >1 billion women around the world suffer from non–sexually transmitted urogenital infections, such as bacterial vaginosis (BV), urinary tract infection (UTI), and several other yeast infections. Sexually transmitted diseases (STDs) are also a significant cause of morbidity worldwide. The two most commonly documented bacterial STIs in some developed countries are *Gonorrhoea* and *Chlamydia*, which are caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis,* respectively. As the pathogenic organisms responsible for these conditions are concurrently becoming resistant to existing medications, it may be that instead of developing new medicines, our present focus should be on developing new live supplements, like nonpathogenic microbes that act against these pathogens. There is an association between abnormal vaginal microbial flora and an increased incidence of UTI. There are about 50 different species of microorganisms inhabiting the vagina that are regarded as the main regulators of the vaginal micro-environment. Imbalance in the microbial composition greatly influences the health of the vaginal microenvironment, potentially leading to the compromised states of BV and UTI. These compromised states can be restored by balancing the number of *Lactobacillus* spp. present via supplementation with probiotics.

Cancers

Cancer is a dreadful disease affecting peoples all over the globe. More than 70% of the global cancer deaths are from the Asian, African, and American continents. Currently, many new drugs with powerful therapeutic properties have been discovered, but tolerance to their burden of side effect has been a major limitation to effective treatment. Natural sources that confer anticarcinogenic effects, such as probiotics, have been receiving prime focus in recent years. In vitro studies have demonstrated that probiotic strains *Lactobacillus fermentum* NCIMB-5221 and -8829 are highly potent in suppressing colorectal cancer cells and promoting normal epithelial colon cell growth through the production of SCFAs (ferulic acid). This ability was also compared with other probiotics, namely *L. acidophilus* ATCC 314 and *L. rhamnosus* ATCC 51303, both of which were previously characterized as having tumorigenic activity. And, two other probiotic strains, *L. acidophilus* LA102 and *L. casei* LC232, have also been found to show pronounced cytotoxic activities, with in vitro anti-proliferative activity against two colorectal

cancer cell lines (Caco-2 and HRT-18). Although probiotics could play a significant role in neutralizing cancer, research is limited only to in vitro tests. Hence, the anti-cancer potential of probiotics must be proved in in vivo models and then proceed toward animal and clinical trials.

Allergy

The increasing prevalence of allergic diseases caused by immune disorders is a serious economic and social burden worldwide. Recently, the beneficial role of probiotics in the prevention and management of allergic diseases has advanced the understanding of their cause and prevention. In vitro studies of certain probiotics, such as *Lactobacillus plantarum* L67, have shown the potential of these substances to prevent allergy-associated disorders through the production of interleukin-12 and interferon-γ in their host. In another study, *L. plantarum* 06CC2 significantly alleviated allergic symptoms and reduced the levels of total immunoglobulin E, ovalbumin-specific immunoglobulin E, and histamine in the sera of ovalbumin-sensitized mice. In the spleen cells of mice, *L. plantarum* 06CC2 is known to significantly enhance the secretions of interferon- γ and interleukin-4, which are responsible for alleviating allergic symptoms. Further work may be helpful in evaluating the anti-allergic activity of probiotics and their mode of action.

Serum cholesterol

Large dietary intake of yogurt was found to lower dietary cholesterolemia, and the findings suggested that yogurt contains a factor that inhibits the synthesis of cholesterol from acetate.

Diabetes

According to the International Diabetes Federation (IDF) of Southeast Asia, 425 million people have diabetes worldwide, including 78 million people in the Southeast Asian region. The management of this disorder includes multiple medications although there is no definitive cure for diabetes. Based on large-scale 16 S rRNA gene sequencing, quantitative real-time polymerase chain reaction (PCR), and fluorescent in situ hybridization, a connection between the composition of the intestinal microbiota and metabolic diseases like obesity and diabetes has been postulated by Larsen et al. Gram-negative Bacteroidetes and the gram-positive Firmicutes are two specific bacterial phyla that dominant the gut microenvironment. More specifically, patients with type 2 diabetes have significantly reduced numbers of Firmicutes species, and, as the Bacteroidetes/Firmicutes ratio increases, this positively correlates with plasma glucose concentration. A similar pattern has been implicated in the development of autoimmune diseases such as type 1 diabetes. Management of type 2 diabetes by modulating gut hormones, such as gastric inhibitory polypeptide and glucagon-like peptide-1, via probiotic and prebiotic interventions is another convincing strategy. Hormones play a role in glucose homeostasis so that improving the gut microbiome could result in neutralizing this disorder caused by peripheral insulin resistance or failure of β cells to produce insulin. Current research is focused on generating new prebiotics, such as arabinoxylane and arabinoxylane oligosaccharides, which show promising results in neutralizing metabolic disorders because both carbohydrates have been linked to adiposity reduction.

Obesity

Weight loss is facilitated by thermogenic and lipolytic responses through stimulating the sympathetic nervous system. Probiotic strains of *Lactobacillus gasseri* BNR17 have been shown to possess properties that inhibit the increases in adipocyte tissue that are the main source of leptin and adiponectin and thereby limit leptin secretion. Other probiotic microbes such as *L. casei, Lactobacillus acidophilus,* and *Bifidobacterium longum* have also been reported to have hypocholesterolemic effects.

Oral medicine and dentistry

Particular species of *Lactobacillus* and *Bifidobacterium* may exert beneficial effects in the oral cavity by inhibiting carcinogenic streptococci and various species of *Candida. Lactobacillus reuteri* was efficacious in reducing both gingivitis and plaque in patients with moderate to severe gingivitis.

Brain and central nervous system

In recent years, many studies have been devoted to elucidating the influence of gut microbiota on the central nervous system (CNS). The "microbiota-gut-brain axis" is an interactive, bidirectional communication established by the exchange of regulatory signals between the GI tract and the CNS. The effect of probiotics on the CNS has been mainly studied in clinical trials, where it has been evident that gut microbiota influence human brain development function. In children with autism spectrum disorder, a daily dose of *L. plantarum* WCFS1 ($4.5X10^{10}$ CFU/d) led to an improvement in their school records and attitude toward food. In a randomized trial involving healthy volunteers, there was reduced psychological distress when participants were treated with oral administration of *Lactobacillus helveticus* R0052 and *B. longum* R0175. Another clinical trial showed a decrease in anxiety symptoms by administration of *L. casei strain Shirota* to patients suffering from chronic fatigue syndrome, and reduced anxiety was thought to be due to improved bowel function. Human intestine–derived strains of *L. brevis* DPC6108 and *Bifidobacterium dentium* were reported to produce large amounts of γ-aminobutyric acid, a brain neurotransmitter that helps humans to suppress anxiety and depression. Oral intake of *L. acidophilus* has been shown to assist people in regulating their mood in respect to rewards and addictive behavior.

Bones

Several studies in humans have shown positive effects of nondigestible oligosaccharides (NDO) on mineral absorption and metabolism and on bone composition and architecture. Synbiotics (i.e., a combination of probiotics and prebiotics) can induce additional effects. Proposed future applications include the treatment of

rheumatoid arthritis, prevention of ethanol-induced liver disease, and prevention or treatment of graft-versus-host disease.

Next-generation probiotics

Probiotics are thought to improve the microbiotic balance in the host, prevent disturbances, and decrease the risk of pathogen colonization. They have been referred to as "functional foods" or "beneficial bacteria," and they have been considered for the prevention and treatment of *C. difficile*–associated diarrhea. Furthermore, findings from randomized control trials (RCTs) and meta-analyses suggest that there is moderate evidence for the ability of probiotics to prevent primary *C. difficile* infection (CDI) in those people at risk, but there is not enough evidence to suggest that probiotics can prevent secondary CDI (recurrent CDI; rCDI). There are still some evidence gaps for the use of probiotics in the prevention of CDI concerning the interaction between specific classes of antibiotics with the probiotics used on CDI risk, the bacterial taxa that provides the best efficacy in the prevention of CDI, and the use of probiotics in immunocompromised or critically ill patients.

Overall, classical probiotics show limited effects on the human gut microbiota, thus the need for a better selection and formulation of bacterial strains. Results from previous studies show promising outcomes in the treatment or prevention of diverse metabolic and inflammatory diseases by specific bacteria. Those probiotics encompass species different from *Lactobacillus* and *Bifidobacterium*. The FAO definition of probiotics is broad, allowing flexibility in terms of the phylogenetic origin of probiotics. Information generated from previous studies assisted in the selection of next-generation probiotics, which include members from *Clostridium* clusters IV, XIVa and XVIII; *F. prausnitzii*; *Akkermansia muciniphila*; *Bacteroides uniformis*; *Bacteroides fragilis*; and *Eubacterium hallii*. These next-generation probiotics were evaluated in preclinical trials and yielded positive outcomes for inflammatory and metabolic disorders. In addition, new techniques are required for the development of new probiotic products containing strains of human origin. These strains must come from the major groups of the intestinal microbiota and must be safe and proved to have potential beneficial effects.

Fecal microbiota transplant therapy

Fecal microbiota transplant (FMT) or fecal bacteriotherapy is an alternative strategy successfully used for the treatment of CDI. FMT can resolve both CDI and rCDI with a success rate of 90% when further antibiotic treatments fail. Given the success of FMT, it is now being considered as potential treatment for disorders such as ulcerative colitis, IBS, and metabolic syndrome. The complexity of the fecal sample can be the key factor behind the positive shift in microbiota composition generated by FMT. Thus, diversity of the donor microbiome may be crucial. Indeed, some patients do not respond to FMT, probably because only specific bacterial phylotypes can be therapeutic when effectively transferred. Adverse effects after FMT include nausea, vomiting, fever, abdominal pain, and diarrhea. The uncharacterized nature of FMT may result in undetected or unmonitored risk factors such as viruses, pathogens, or even allergens being passed to the FMT recipient, causing disease. To overcome this problem, Petrof et al. (2013) developed a synthetic bacterial cocktail with characterized nature. The authors of the study suggested that using a synthetic stool substitute may be an effective method to replace the use of FMT for treating rCDI, and thus, the concept of "RePOOPulating" the gut microbiome was coined. In addition, patient safety can be guaranteed because the bacterial mixture can be rendered pathogen- and virus-free. These data suggest that a multispecies community such as that in the RePOOPulate study can be more effective than single-strain probiotics or mixed cultures of probiotic species. This may be because the RePOOPulate community preserves its structure and thus successfully colonized a new environment. Moreover, RePOOPulate consisted of a more phylogenetically diverse community including strains with beneficial health effects that can be candidates for next-generation probiotics.

Safety

To establish safety guidelines for probiotic organisms, the FAO and the WHO recommended that probiotic strains should be characterized through a series of tests to determine, at a minimum, antibiotic resistance patterns, metabolic activity, toxin production, hemolytic activity, infectivity in immunocompromised animal models, side effects, and adverse incidents in consumers.

Conclusion

The evidence suggests that probiotics have a considerable role to play in the prevention and treatment of certain conditions related to the GI and urogenital tracts, and the contribution of probiotics in preventing and treatment of diabetes, obesity, and cancer is an exciting and rapidly advancing research ground. For that reason, current research focus is on evaluating new strains of probiotics and their applicability in biomedical/clinical research, thus paving a new direction for exploration and exploitation of probiotics aimed at improving human health.

Suggested reading

Food and Agriculture Organization of the United Nations and World Health Organizations. *Regulatory and clinical aspects of dairy probiotics.* Food and Agriculture Organization of the United Nations

and World Health Organization expert consultation report. Geneva: Food and Agriculture Organization of the United Nations and World Health Organization; 2001. Working group Report (online). https://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf

Gupta V, Garg G. Probiotics in antimicrobial therapy: General considerations. In Schlossberg D ed., *Clinical infectious disease*, 2nd ed. New York: Cambridge University Press; 2015: 1366–1370.

Gupta V, Garg R. Probiotics. *Indian J Med Microbiol*. 2009;27(3):202–209.

Gupta V, Nag D, Garg P. Recurrent urinary tract infections in women: How promising is the use of probiotics? *Indian J Med Microbiol*. 2017;35:347–354.

Hage RE, Sanabria EM, De-Wiele TV. Emerging trends in "smart probiotics": Functional consideration for the development of novel health and Industrial applications. *Front Microbiol*. 2017;8:1–11.

Kerry RG, Patra JK, Gouda S, Park Y, Shin HS, Das G. Benefaction of probiotics for human health: A review. *J Food Drug Anal*. 2018;26:927–939.

Petrof, EO, Gloor GB, Vanner SJ, et al. Stool substitute transplant therapy for the eradication of Clostridium difficile infection: "RePOOPulating" the gut. *Microbiome*. 2013;1:3. doi:10.1186/2049-2618-1-3.

Sanders ME, Merenstein D, Merrifield CA, Hutkins R. Probiotics for human use. *Nutrition Bull*. 2018;43:212–225.

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Hypersensitivity to antibiotics

Santiago Alvarez-Arango and N. Franklin Adkinson, Jr.

Adverse drug reactions (ADRs) are usefully separated into type A reactions (predictable from known pharmacologic properties and largely dose related), which make up 85% to 90% of all ADRs, and type B reactions (unpredictable and restricted to a vulnerable subpopulation). Type B reactions comprise 10% to 15% and include *immunologic drug reactions, drug intolerance* (e.g., tinnitus after single aspirin tablet), and *idiosyncratic reactions*, some of which are pseudoallergies (e.g., aspirin-induced reactions, vancomycin-induced red man syndrome).

ADRs can be subdivided based on time of appearance of symptoms (e.g., immediate vs. delayed ADRs), mode of action of the drugs, or on immunologic mechanism. Immune mechanisms are thought to be involved in 6% to 10% of all ADRs. Allergenic drugs can induce the entire spectrum of immunopathologic reactions, which are clinically indistinguishable from reactions elicited by foreign macromolecules (Table 210.1). *Gell and Coombs type I reactions* are caused by drug/antigen-specific immunoglobulin E (IgE) that binds to high-affinity Fc-IgE receptors on mast cells and basophils. Cross-linking of these receptors leads to the release of vasoactive mediators such as histamine and cysteinyl leukotrienes. Typical syndromes include urticaria, anaphylaxis, rhinitis, and bronchoconstriction, which can occur immediately in a previously sensitized individual. *Type II cytolytic reactions* are generally confined to rapidly haptenating drugs such as penicillins and are based on immunoglobulin G (IgG)-mediated cytotoxic mechanisms, resulting mainly in blood cell cytopenias. *Type III reactions* are immune complex–mediated and may involve complement activation and stimulation of Fc-α receptor-activated inflammatory cells. Drug-specific immune complexes result from high-dose, prolonged therapy and may produce drug fever, a classic serum sickness syndrome, and various forms of cutaneous vasculitis. *Type IV reactions* are mediated by T lymphocytes and cause "delayed hypersensitivity reactions," the most typical examples being delayed maculopapular exanthem and contact dermatitis from topically applied drugs. Many drug-induced hypersensitivity reactions such as bullous, pustular, and some morbilliform skin eruptions that are presumed to have an immune etiology did not seem to fit into the older Gell and Coombs classification. Recent studies of T-cell subsets and functions in the pathogenesis of delayed-onset immune reactions have suggested subcategories of type IV reactions, as shown in Table 210.1.

However, some drug reactions resemble allergic syndromes but are not immunologic in origin. These nonimmune hypersensitivity reactions are also known as "pseudoallergic reactions." Most pseudoallergic reactions mimic type 1 IgE-mediated reactions such as urticaria, angioedema, bronchospasm, and anaphylaxis (Table 210.2). In such cases, basophils and mast cells are activated by nonimmune mechanisms, and vasoactive mediators are released.

In this chapter, we review type B ADRs to antibiotics with a focus on current concepts in the diagnosis and management of allergies to β-lactam antibiotics, the prototype of immunologic drug allergies. Moreover, we address the current issue regarding overdiagnosis of β-lactam allergy and its impact on clinical practice and healthcare utilization. Last, we also address the management of multiple antibiotic sensitivity syndromes.

TABLE 210.1 **FEATURES OF IMMUNOPATHOLOGIC REACTIONS TO ANTIBIOTICS AND MANAGEMENT STRATEGIES**

Reaction category	Clinical manifestation	common examples for antibiotics	Timing for sensitization with the first use of the drug	Onset after re-exposure to the drug	Skin tests	In vitro tests	Readministration of the drug (DPT/ desensitization)
Type I (IgE)	Urticaria, angioedema, rhinitis, bronchospasm, anaphylaxis	B-lactam antibiotics Sulfamethoxazole	Required: 1–2 wk	Usually within 1 h (rarely after hours)	Immediate (wheal/ flare)[a] Intradermal tests	RAST (serum IgE) Serum mast cell tryptase level Basophil activation	Desensitization if skin test þ
Type II (IgG and complement)	Hemolytic anemia, drug-induced nephritis, thrombocytopenia, Neutropenia	Penicillins Cephalosporins Sulfonamides	Required: 1–2 wk	Many days or weeks	None	Complete blood count Coombs tests	Cautious DPT
Type III (IgG immune complexes)	Serum sickness, fever, vasculitis	Penicillins Cephalosporins Sulfonamides Streptomycin	Required: 10–21 d	Usually days to weeks	None	ESR CRP Immune complex Serum complement levels	Cautious DPT
Type IVa (Th1 lymphocytes)	Allergic contact dermatitis	Penicillins Neomycin Bactrim	Required: 1–3 wk	8–120 h	Patch tests Intradermal tests (delayed response at 48–72 h)	Lymphocyte transformation tests	Likely contraindicated
Type IVb (Th2 lymphocytes)	Maculopapular eruptions	Penicillins, especially diaminopenicillins like amoxicillin and ampicillin Sulfonamides	Required: 4–14 d		Patch tests Intradermal tests (delayed response at 48–72 h)	Lymphocyte transformation tests[b]	DPT useful
Type IVc cytotoxic lymph. (perforin/ granzyme B)	Contact dermatitis, maculopapular and bullous exanthema, hepatitis, SJS, TEN	Sulfonamides Penicillins Macrolides	Required: 1–2 wk		Patch tests Intradermal tests (delayed response at 48–72 h)	Lymphocyte transformation tests[b]	Contraindicated (for bullous exanthem and SJS/TEN)

Abbreviations: CRP = C-reactive protein, ESR = erythrocyte sedimentation rate.

TABLE 210.2 **FEATURES OF NONIMMUNE HYPERSENSITIVITY REACTIONS TO ANTIBIOTICS AND MANAGEMENT STRATEGIES**

Reaction category	Clinical manifestation	common examples for antibiotics	Timing for sensitization with the first use of the drug	Onset after re-exposure to the drug	Skin tests	In vitro tests	Readministration of the drug (DPT/ desensitization)
Nonimmunologic	Urticaria, angioedema, rhinitis, erythema bronchospasm	Vancomycin (red man syndrome)	Not required Reaction may occur with first dose	Within minutes, infusion rate dependent	None	None	Slow infusion Use premedication

Abbrevations: DPT = drug provocation tests; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; RAST ¼ radioallergosorbent test; IgE = immunoglobulin E; IgG = immunoglobulin G; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis.
[a] Only validated for penicillin skin testing, which has high negative predictive value. Positivity may be helpful with certain antibiotics; however, negative skin tests do not exclude the diagnosis for many immediate reactions to antibiotics.
[b] Clinically, false positivity may occur.
According to Gell and Coombs, as modified.

Epidemiology of antibiotic allergy

β-Lactams and sulfonamides are the most prevalent causes of antibiotic hypersensitivity. In a cross-sectional survey of a general population from Porto, Portugal, history of hypersensitivity to penicillin and other β-lactam antibiotics was found in 4.5% of adults. In the United States, in recent large healthcare insurance database studies, history of hypersensitivity to penicillin was recorded in about 10% of patients. Data from developing countries are limited but suggest that penicillin allergy is the most commonly reported antibiotic allergy. History of hypersensitivity to sulfonamides has been reported to occur in 2% to 4% of populations but is increased among AIDS patients to 40% to 80%. Immunologic reactions to the newer classes of antibiotics are often rare and poorly documented. The perceived relative risk of immunologic drug reactions with commonly used antibiotics is given in Table 210.3.

Burden of antibiotic allergy

β-Lactams are among the most commonly prescribed antibiotics for the treatment of many types of bacterial infections. However, recent data show a significant decrease in β-lactam prescriptions, in part due to a rising prevalence of histories of allergy, which can exceed 30% in intensive care environments. Emergence of bacterial resistance as well as the introduction of newer antibiotics have also contributed to this trend. Penicillin allergy is reported by 10% of the US population, which is equivalent to >32.7 million people. Prescriptions of quinolones and macrolides as alternative antibiotics for common infections have been increasing, as has the use of vancomycin in patients with histories of penicillin allergy. Yet only 10% to 15% of the subjects with a history of acute, IgE-dependent penicillin reactions have a currently positive penicillin type I skin tests. Unevaluated histories of antibiotic allergies may lead to the substitution of often less effective or more toxic—and more expensive—alternative drugs, which can result in high medical and economic burdens on healthcare. Studies from the United States, Europe, and Australia have shown that penicillin-allergic patients have higher antibiotic costs, longer hospital stays, and are more likely to receive a broader spectrum antibiotic such as cephalosporins, macrolides, and quinolones, leading to increased frequency of drug-resistant microbes. In addition, hospitalizations with registration of penicillin allergy are associated with increased length of stay, economic costs, and frequency of infections by drug-resistant agents. At the Mayo Clinic, prophylactic vancomycin use in patients with a history of penicillin or cephalosporin allergy undergoing elective orthopedic surgery was substantially reduced by targeted allergy consultation and penicillin allergy skin testing. Similar benefits are likely to occur in patients with histories of other antibiotic allergies who are appropriately evaluated before alternative antibiotics are selected.

Clinical features

The presentation of antibiotic allergies is similar to known hypersensitivity reactions, and the clinical features are variable depending on the type and severity of the reaction and the organ systems affected (Table 210.1 and Table 210.2). Many factors, such as the immunologic profile of the antibiotic; treatment factors, including dosage, administration route, and frequency; host factors such as immune status and comorbidities; and the inflammatory milieu in which antibiotics are used, can influence the frequency and characteristics of hypersensitivity reactions.

The skin is the most common organ involved in antibiotic reactions, and it is involved in up to 90% of anaphylactic episodes. Maculopapular eruptions (MPEs), urticaria, and pruritus are the most common presentations that typically occur after hours, days, or even weeks of antibiotic exposure but can also be part of an acute allergic reaction. Immunologic drug reactions require a sensitization period, whereas a nonimmunologic mast cell release can occur on first exposure in susceptible patients (e.g., vancomycin-induced red man syndrome).

TABLE 210.3 **RELATIVE RISKS OF IMMUNOLOGIC REACTIONS TO COMMONLY USED ANTIBIOTICS**

Risk of inducing an immunologic reaction[a]	Antibiotic (or its class)
Common (>2%)	Penicillins
	Antimicrobial sulfonamides
	Nitrofurantoin
Intermediate (0.1–2%)	Bacitracin
	Cephalosporins
	Penems
	Itraconazole
	Quinolones
	Minocycline
Rare (0.1%)	Monobactam (aztreonam)
	Aminoglycosides
	Amphotericin B
	Chloramphenicol
	Clindamycin
	Fluconazole
	Griseofulvin
	Ketoconazole
	Macrolide antibiotics
	Vancomycin
	Tetracyclines
	Polymyxin
	Metronidazole
	Linezolid
	Daptomycin

[a] Among patients receiving multiple courses of therapy.

Antibiotics can also cause severe but rare exfoliative skin syndromes such as toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS). Other targeted organ manifestations, such as interstitial pneumonitis and immune cytopenias, are rare. Life-threatening reactions such as anaphylaxis are also rare. However, fatalities in Australia due to anaphylaxis during a 9-year study period revealed an increase of approximately 150% in drug-induced anaphylaxis admissions and an increase of approximately 300% in drug-induced anaphylaxis deaths. Although β-lactams are the most common antibiotic class inducing anaphylaxis, IgE antibody responses have also been documented for sulfonamides; those now in use are given in Table 210.4.

Clinical assessment

Drug allergy syndromes are recognized by the constellation of signs and symptoms identified with a particular mechanism of immunopathology (Table 210.1 and Table 210.2). Appropriate diagnosis of these cases depends largely on careful history taking, with attention to prior drug experience and the chronology of the reaction, supplemented by compatible physical and laboratory findings and knowledge of drug allergenicity profiles (Table 210.3). For atypical or discordant reactions, skepticism is appropriate to avoid labeling the patient as "drug allergic" incorrectly.

Step 1: Initial evaluation

History-taking

A detailed history is essential for the initial evaluation of patients with suspected drug allergies. The history guides a decision about performing further diagnostic testing and other evaluation strategies. It is also possible to make a reasonable decision about the risks of reintroducing the suspected drug by using historical detail. Medical records that describe previous reactions and treatment can be very helpful, especially in patients with vague histories or altered mental status. Occasionally, information provided by a relative or friend who witnessed the event can also be very helpful in differential diagnosis. Nevertheless, it is crucial to document in detail a witnessed drug allergy reaction and update medical records and allergy labels to accurately reflect the signs and symptoms as well as the timing of a suspected antibiotic allergy.

The clinical history of suspected drug allergy should be focused on both medication-related and patient-related factors. The medication(s) implicated, clinical features of the reaction(s), and the previous exposure and reaction to each drug and related compounds, as well as patient comorbid disorders, should be recorded. For example, patients with chronic urticaria often attribute cutaneous reactions to drugs and foods. Similarly, symptoms of chest tightness or pain, dyspnea, and tachycardia after use of a drug can be a sign of underlying cardiovascular disease. Other patient comorbidities include the high frequency of amoxicillin-induced morbilliform rashes in patients with mononucleosis and frequent trimethoprim-sulfamethoxazole reactions in AIDS patients. Another example is that patients with cystic fibrosis have a higher risk for immune reactions to antibiotics, probably because of frequent reexposure.

History-taking provides information helpful in assessing the likelihood of immune mediation. Immunologic reactions require a sensitization period, so putatively allergic patients should have a history of prior use of either the drug itself or a structurally related compound. For first drug exposure, an immunologic reaction may be seen after 3 to 10 days, which can be sufficient for primary sensitization. Reexposure will lead to a Type I reaction, which classically begins within 1 hour of the first administered dose.

Nonimmunologic reactions do not require sensitization, and reactions may be seen even after the first dose. Pseudoallergic reactions can often be distinguished from IgE-mediated reactions with similar clinical manifestations by reliable histories of previous drug use. Based on clinical features and the chronology of the reaction, conclusions can be drawn about whether a reaction is immunologically mediated (Table 210.1). However, in certain situations, immunologic and nonimmunologic reactions may be clinically indistinguishable.

TABLE 210.4 **CLINICAL FEATURES OF HYPERSENSITIVITY REACTIONS**

Antibiotic	Common	Less common/rare
β-lactams	Urticaria, MPE	Exfoliative dermatitis, TEN, SJS, serum sickness syndrome, vasculitis, cytopenias, anaphylaxis, nephritis
Sulfonamide	Fixed drug eruption HIV(+): delayed MPE + fever, urticaria, angioedema	Erythema multiforme, SJS, TEN Anaphylactic reactions
Quinolones	Urticaria, FDE, photoallergic reactions	Acute interstitial nephritis, acute hepatitis, serum sickness, SJS, TEN, MPE, acute pancreatitis, anemia; thrombocytopenia
Macrolides	Urticaria, angioedema, FDE, and MPE	TEN, vasculitis
Vancomycin	"Red man syndrome," lineary IgA bullous dermatosis	MPE, FDE, vasculitis, thrombocytopenia, erythema multiforme, and urticaria anaphylaxis

Abbrevations: FDE = fixed drug eruptions; MPE = maculopapular eruption; TEN = toxic epidermal necrolysis; SJS = Stevens–Johnson syndrome; IgA = immunoglobulin A; HIV = human immunodeficiency virus.

Physical examination

Direct observation of patients undergoing presumed drug reactions can be useful for both differential diagnosis and objective assessment of severity, which can often be exaggerated in retrospective patient accounts. A complete physical examination is desirable because many organ systems have the potential for involvement. For skin reactions occurring with drug use, a detailed dermatologic examination is often helpful. Viral exanthems are easily confused with maculopapular drug eruptions. Fever and coryza or pharyngitis can help to identify the former.

Step 2: Decision about application of further diagnostic testing

History alone is often not sufficient for establishing current drug sensitivity. Only 10% to 15% of subjects with a convincing history of IgE-dependent penicillin allergy will be positive by validated skin testing, indicating a very low diagnostic accuracy of history alone for current sensitivity. Data with other drugs are similar, suggesting that sensitivity may wane with time. Approximately 80% of patients with IgE-mediated penicillin allergy have lost the sensitivity by skin testing after 10 years. Thus, patients with recent reactions are more likely to be allergic than are patients with remote reactions.

Drug provocation tests that are the gold standard for the diagnosis of current drug allergy have a similarly low positivity rate in patients with a history of drug allergy. These data indicate that diagnosis of current sensitivity based on history alone is often not advisable. Further diagnostic tests for definite diagnosis may be needed. Unfortunately, many in vivo and in vitro diagnostic tests for allergy have shown limited value in the diagnosis of allergy to haptenic (small molecular weight) drugs.

Although skin testing provides valuable information for the diagnosis of immediate reactions to penicillins and in some cases to other β-lactams, the validity of skin tests with other antibiotics is limited because the antigenic determinants are not adequately known. In vitro tests for drug-specific IgE to antibiotics are of limited value because they are less sensitive than intradermal tests. A positive result, however, is usually reliable and corresponds to skin test results. If there is no contraindication, drug provocation testing with the offending drug is the most reliable test for diagnosis of current antibiotic hypersensitivity for many haptenic drug allergies. Because such testing carries some risk for the patient, its use is usually restricted to cases where alternative antibiotics are unacceptable or there are multiple antibiotic sensitivities. A stepwise approach to the diagnosis of antibiotic allergy is given in Figure 210.1. Diagnostic testing can be pursued based on likely immunopathology as given in Table 210.1 and Table 210.2.

Evaluation of immediate-type sensitivities

Skin testing for β-lactam antibiotics

Intradermal skin testing with a 15- to 20-minute readout of wheal and flare has been validated for detecting drug-specific IgE antibodies to penicillins and other β-lactam antibiotics. A major determinant analog (*penicilloyl-polylysine*) and minor determinants (*benzylpenicilloate, benzylpenilloate*, and *benzylpenicillin* isomers of penicillin) are used for skin test evaluation for IgE-dependent penicillin allergy. IgE antibodies to minor determinants are clinically associated with anaphylactic reactions and can predict the risk of more severe reactions. IgE antibodies to the major penicilloyl determinant correlate loosely with risk for urticarial reactions.

Testing is undertaken with two or more reagents, usually penicilloyl-polylysine (Pre-Pen) antigen and either penicillin alone (10,000 IU/mL) or a mixture of minor antigens, including at least benzylpenicillin and benzylpenicilloate (10 mM each). Of these minor determinants, only benzylpenicillin is available commercially in the United States. Skin prick testing with full-strength reagents is done first, and, if these tests are negative at 15 minutes, they are followed by intracutaneous testing, raising an initial bleb of 2 to 3 mm. A wheal diameter of least 3 mm greater than negative control is considered positive. In some centers, elective testing is followed by the administration of one to three doses of oral penicillin and a period of observation to confirm that the drug is tolerated. For

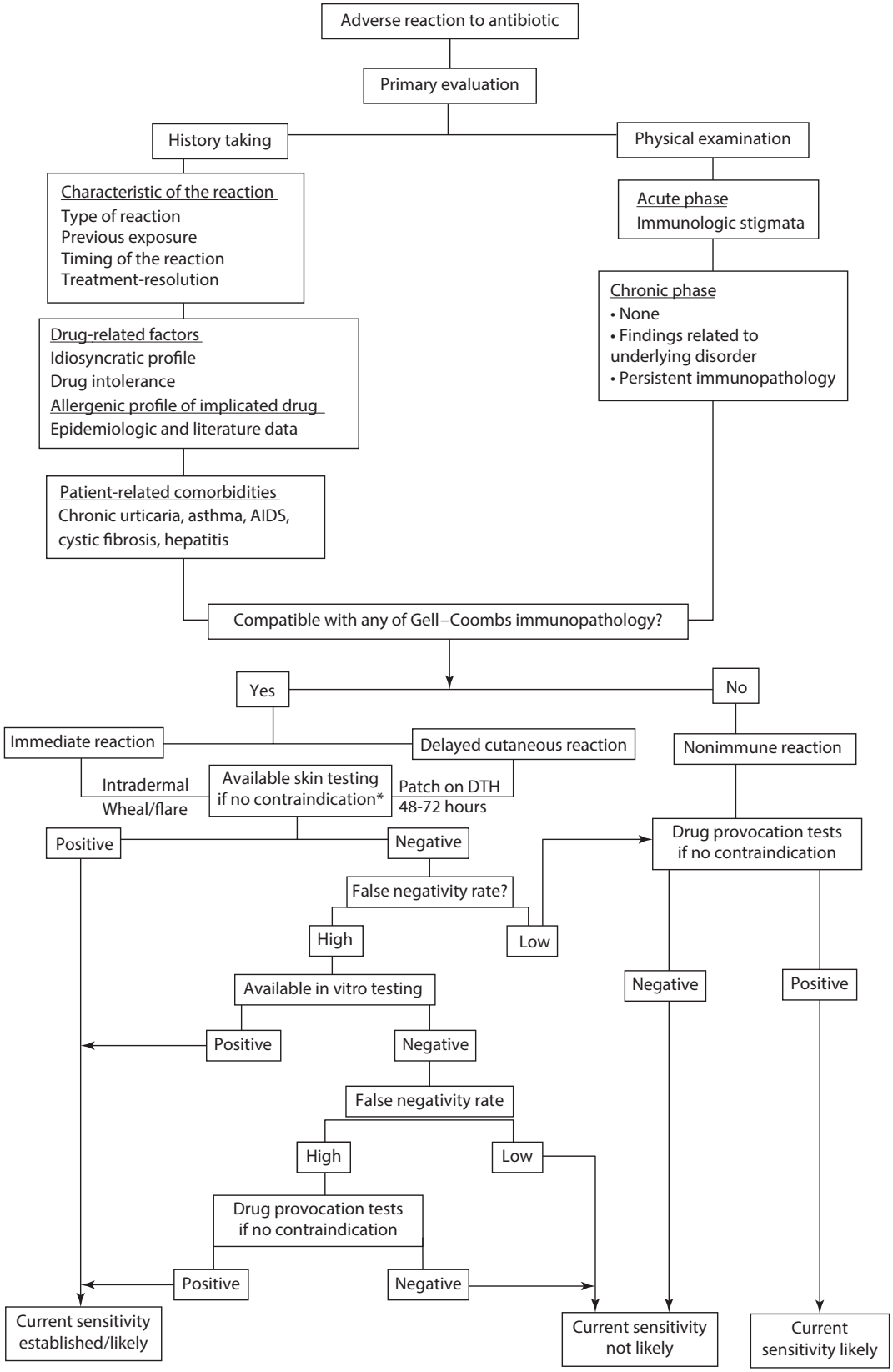

FIGURE 210.1 A diagnostic algorithm for evaluation of putative immunologic reactions to antibiotics. *Contraindications for skin immunoglobulin E testing are extensive skin lesion, recent antihistamine use, and history of serious immediate systemic reaction with allergen exposure. AIDS, acquired immunodeficiency syndrome; DTH, delayed-type hypersensitivity.

hospitalized patients with serious infection, a rapid dose escalation of the intravenous antibiotic of choice is judiciously employed. Late-occurring maculopapular rashes are not easily predictable by skin testing and oral challenge and may occur at a frequency of 3% to 10% for penicillin antibiotics.

Falsely negative penicillin skin testing for IgE is rare, and all reports are of mild, self-limited, and/or transient reactions. About 85% to 90% of patients with histories compatible with IgE-dependent reactions will have currently negative penicillin testing, allowing a large majority of such patients to be retreated safely. Despite this substantial diagnostic power, it has been difficult to maintain persistent commercial sources for these reagents in the United States and Europe. Some academic centers have produced the reagents for their own use, but concerns persist about access to these orphan drug products.

Recent studies show promising results with cephalosporin skin tests. Concentrations of 2 to 3 mg/mL of a parenteral cephalosporin preparation are reported to be usually nonirritating, but each cephalosporin requires concurrent evaluation for its irritant potential in nonallergic subjects. Although a positive cephalosporin skin test implies the presence of drug-specific IgE antibodies, a negative test does not exclude immediate hypersensitivity.

Commercial cephalosporin skin test reagents are not currently available in the United States. Positive intradermal skin tests have been reported for imipenem and other β-lactams, but validated skin testing protocols have not been developed.

In vitro tests

Specific IgE tests have been established for a wide variety of immediate-type drug allergies. Only with penicillin allergy have in vitro test results been systematically compared with skin tests. The consistent finding has been diagnostic sensitivity for penicilloyl-IgE by radioallergosorbent test (RAST) of 65% to 85% compared with penicilloyl-polylysine skin tests and 32% to 50% compared with a combination of skin testing and challenge. Minor determinant penicillin IgE antibodies are not reliably detected by available immunoassays. In recent years, flow cytometry has been increasingly used in the diagnosis of allergy. Assessment of basophil activation by means of increase in surface markers such as CD63 and CD203c have been investigated in penicillin allergy. However, the sensitivity of the basophil activation test has been highly variable, and, in the case of β-lactam antibiotics, sensitivity ranged from 44% to 63% when compared with a diagnosis confirmed by skin testing. As with unvalidated skin tests, a clearly positive result is of greater clinical value than a negative result, thus in vitro basophil activation tests remain investigational.

Evaluation of nonimmediate reactions

Skin testing

European studies suggest that both patch tests and intradermal tests with delayed cutaneous readouts (at 48 and 72 hours) are useful in evaluating non-immediate reactions to aminopenicillins and certain β-lactams and that both can reliably predict the results of rechallenge. Additional studies are required to confirm and extend these results to other drug allergies and to define more precisely the clinical correlation and predictive value for retreatment.

Other tests

Drug-specific T lymphocytes, which are involved in some cutaneous hypersensitivity reactions, may be detected with the use of in vitro lymphocyte transformation tests, which are utilized in Europe but not approved for diagnostic use in the United States. However, sensitization may be found after recent treatment even in the absence of any clinical reactivity, and positive test results have been demonstrated after both immediate and delayed antibiotic-induced reactions caused by β-lactam antibiotics, sulfonamides, and quinolones. Cytokine detection assays are also available to evaluate delayed-type hypersensitivity drug reactions but are still investigational.

Use of drug provocation tests

Definitive diagnosis of drug allergy involves provocation testing as the last step, during which gradually increasing doses of the offending drug are given. Provocation testing may be necessary to accurately identify the responsible agent when multiple drugs are given simultaneously and a reaction occurs. It is particularly important not to incorrectly label a patient allergic to a β-lactam antibiotic because it leads to the use of more-expensive and less-effective drugs and may result in adverse consequences, including but not limited to, a longer length of hospital stay and increased risk of infection.

Studies indicate that only a small minority of history-positive subjects have positive drug challenges. Drug provocation tests should be considered only after evaluating the risk–benefit ratio for an individual patient and should be performed by experienced personnel in an appropriate environment. Informed consent of the patient should be obtained prior to the procedure.

Management of antibiotic allergy

Alternatives for drug-allergic patients

Three alternative approaches are available to provide acceptable pharmacotherapy for infection in antibiotic-allergic patients (Figure 210.2). The physician may choose to use an unrelated antibiotic, or a potentially cross-reactive alternative, or to readminister the implicated antibiotic after an induction of a drug tolerance procedure, also commonly known as *drug desensitization*. A structurally unrelated antibiotic is usually chosen if the tradeoffs of safety, efficacy, and cost are acceptable. If there is no acceptable alternative to the offending drug class, a potentially cross-reacting member of the same antibiotic family may be administered using rapid dose escalation under careful

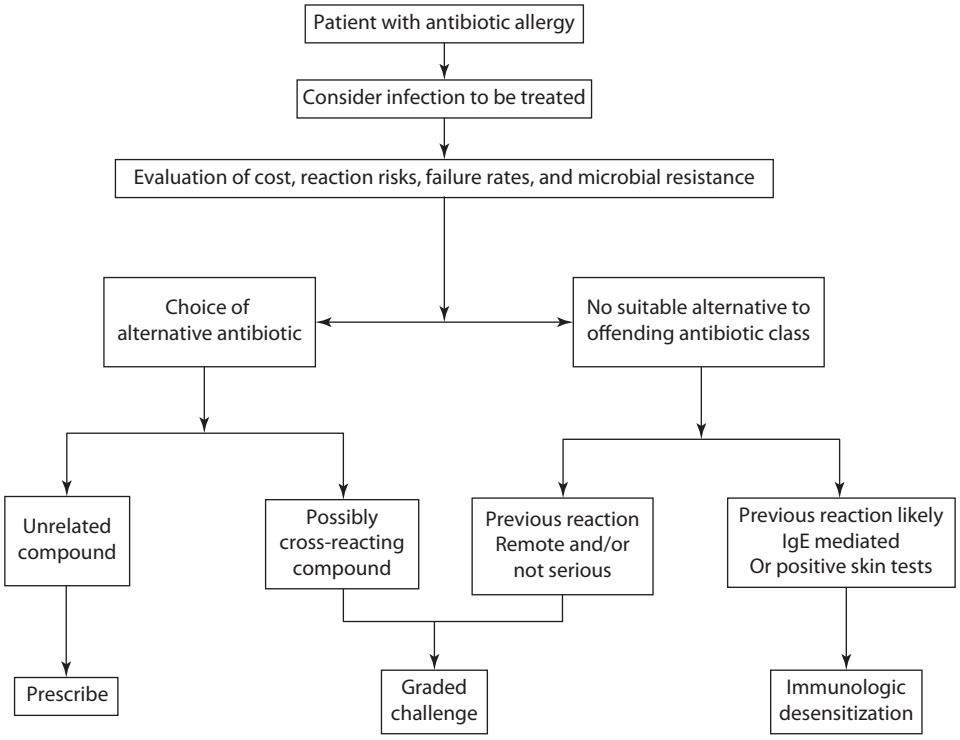

FIGURE 210.2 An approach to treating patients with antibiotic allergy.

observation. If a reaction occurs during graded challenge, then an induction of drug tolerance protocol is warranted. Classical induction of drug tolerance is applied only for IgE-dependent allergy in patients with demonstrable or presumed IgE antibody responses. Induction of drug challenge protocols have been used for non–IgE-mediated reactions; however, neither the effectiveness of the procedure nor a clear mechanism of action has been demonstrated. The procedure aims to induce a temporary state of drug tolerance.

Induction of drug tolerance procedures usually start at 1/10,000 of the full dose with a 2- to 2.5-fold dose increment every 30 to 60 minutes. The procedure entails risk of acute allergic reactions, which occur in mild form in 30% to 80% of penicillin-allergic patients undergoing desensitization. Reactions are generally confined to local and mild systemic reactions during the procedure and, occasionally, late-occurring reactions during therapy, including urticaria or serum sickness and hemolytic anemia if prolonged high-dose therapy is used. The protocol should usually be performed in a hospital setting where experienced personnel and emergency treatment are available. Induction of drug tolerance is an active and reversible process dependent on the continuous presence of the drug. After drug discontinuation, the tolerized state dissipates over days to weeks, and the induction of tolerance procedure would need to be repeated for subsequent treatment courses. Both oral and parenteral routes can be used to initiate drug tolerance, and both appear equally effective in inducing clinical tolerance. The oral approach is arguably safer, although not always feasible.

A variety of protocols have been used for reintroducing β-lactams, trimethoprim-sulfamethoxazole, vancomycin, and other antimicrobials. Table 210.4 shows an illustrative published protocol for penicillin.

Management of β-lactam allergy

β-Lactam antibiotics are the most commonly prescribed class of antibiotics and the most frequent cause of antibiotic allergy. It is the only group of antibiotics for which skin tests have been validated. This group includes penicillins, cephalosporins, carbapenems, and monobactams, all of which share a β-lactam ring but otherwise vary in nuclear structure and side chains.

If skin testing reagents are available, then therapy may be dispensed according to the results of skin tests. When reagents or consultants are not available, an approach is outlined in Figure 210.3. Patients with histories of a reaction to a β-lactam class other than penicillin should first be skin tested with the benzylpenicillin reagents and, if negative, with the diluted β-lactam chosen for use. Yet multiple studies have shown that most patients with penicillin IgE responses can be safely treated with third- and fourth-generation cephalosporins, carbapenems, and monobactams.

Cross-reactivity among β-lactam antibiotics

Cross-reactivity within the penicillin class is virtually complete. A patient who is allergic to any penicillin is likely to react to all penicillins. However, some data suggest that there are patients who are selectively allergic to amoxicillin or ampicillin while tolerating other penicillins. Immunologic cross-reactivity between cephalosporins and penicillins is readily demonstrated in vitro

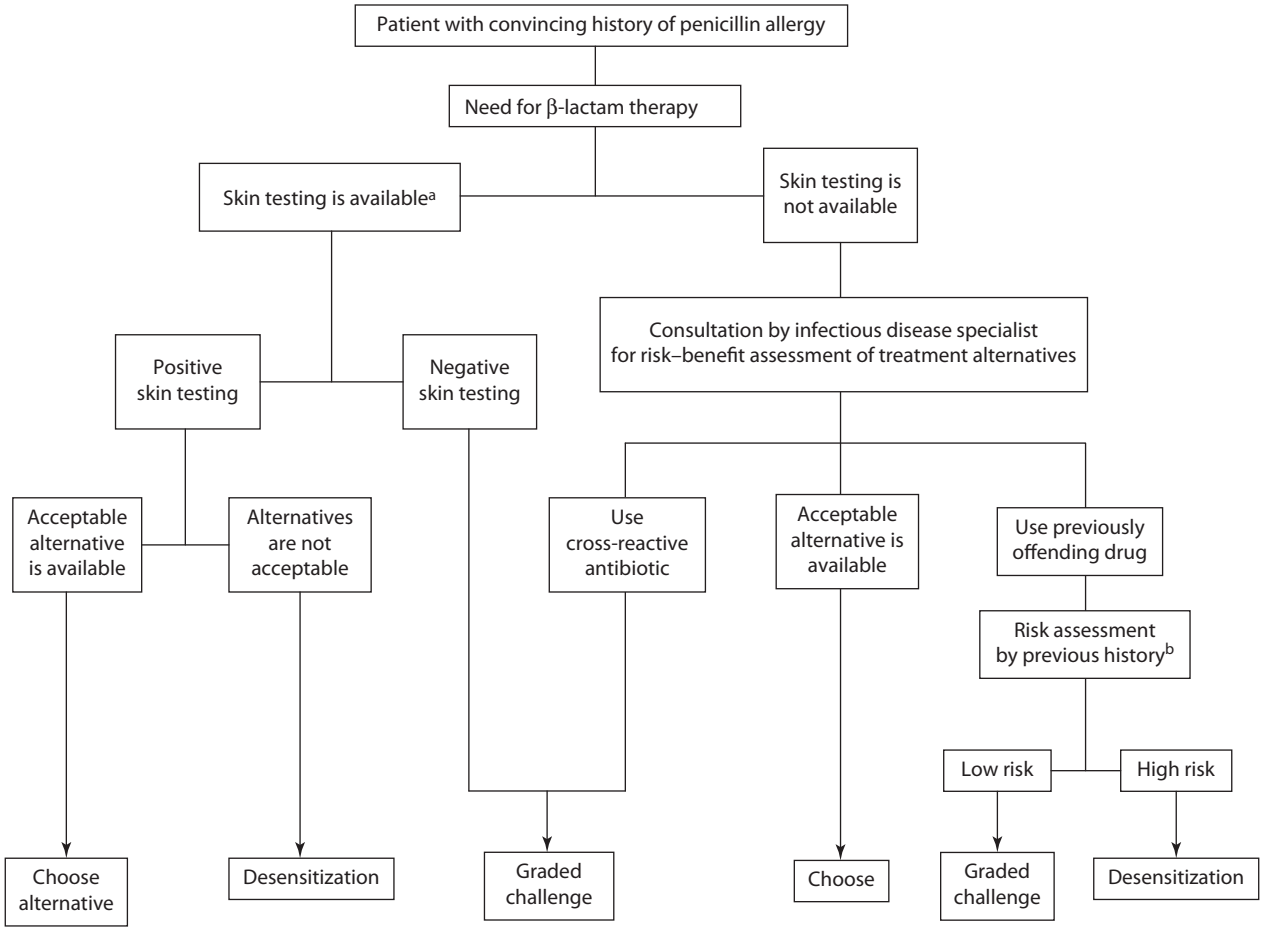

FIGURE 210.3 Diagnostic evaluation of patients with histories of penicillin allergy. (A) Intradermal skin tests should include penicilloyl-polylysine (Pre-Pen) as a major determinant analog, plus one or more minor determinants (especially benzylpenicillin, benzylpenicilloate); the previously offending antibiotic if known and/or the currently desired antibiotic choice may be usefully included, especially in evaluating non-penicillin β-lactams. (B) Risk assessment by previous history: *High risk*: Histories of bronchospasm, angioedema, hypotension, shock that occurred within 30 minutes of penicillin administration in the last year. *Low risk*: History of isolated urticaria or maculopapular rash occurring after days of treatment remotely (>5 years in the past).

and by skin testing, yet multiple studies have shown that most patients with penicillin IgE responses can be safely treated with cephalosporins, especially those of the third and fourth generations. Still, penicillin allergy conveys an odds ratio of 4.8 for acute reactions to first-generation cephalosporin in a meta-analysis, and in one series, a majority of cases of fatal anaphylactic reactions to cephalosporins involved penicillin-allergic patients. Because of this, administration of cephalosporins to penicillin-allergic patients should be undertaken cautiously, especially for patients with previous life-threatening reactions to β-lactam antibiotics of any class.

Penicillin-allergic patients can be given the monobactam aztreonam with little risk because clinically significant cross-reactivity between penicillin and monobactams has not been demonstrated. In contrast, cross-reactions between aztreonam and ceftazidime have been reported, presumably due to identical side chains. The carbapenem antibiotics (imipenem, meropenem, and ertapenem) will induce positive skin tests in about half of penicillin-allergic patients. However, a clinical report from Europe found that 100% of 110 patients with positive penicillin skin tests tolerated imipenem. A more recent study found a cross-reactivity rate of 0.8% between penicillin and imipenem in 124 children. These data suggest that cautious cross-treatment may be reasonably attempted.

Sulfonamide antimicrobials (sulfamethoxazole, sulfadiazine, sulfisoxazole, and sulfacetamide) are extensively cross-reactive and also cross-react with dapsone. Sulfonamide antimicrobial agents differ from other sulfonamide-containing medications by having an aromatic amine group at the N4 position and a substituted ring at the N1 position that are not found in non-antibiotic sulfonamide-containing drugs. Patients allergic to sulfonamide antibiotics tolerate thiazide diuretics, oral hypoglycemic agents, and other SO_2-containing drugs and vice versa.

Other antibiotics

Immunologic reactions to quinolones and macrolides are very rare. These antibiotics mostly evoke maculopapular eruptions and occasionally urticaria and angioedema (Table 210.4). As there are no validated skin or in vitro tests, drug provocation tests are the only available diagnostic methods for these classes of antibiotics.

TABLE 210.5 **PARENTERAL DESENSITIZATION PROTOCOL**

Infection number	Benzylpenicillin concentration (U/mL)	Volume/route (mL)
1	100	0.1 ID
2	100	0.2 SC
3	100	0.4 SC
4	100	0.8 SC
5	1,000	0.1 ID
6	1,000	0.3 SC
7	1,000	0.6 SC
8	10,000	0.1 ID
9	10,000	0.2 SC
10	10,000	0.4 SC
11	10,000	0.8 SC
12	100,000	0.1 ID
13	100,000	0.3 SC
14	100,000	0.6 SC
15	1,000,000	0.1 ID
16	1,000,000	0.2 SC
17	1,000,000	0.2 IM
18	1,000,000	0.4 IM
19	Continuous IV infusion (1,000,000 U/h)	

Doses are administered at 20-minute intervals. Observe skin wheal and flare response to intradermal doses.
Abbreviations: ID = intradermal; SC = subcutaneous; IM = intramuscular; IV = intravenous.
Adapted from Wesis ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clinical Allergy*. 1988;18:515–540.

Vancomycin is associated with two main types of hypersensitivity reactions; namely, a nonallergic hypersensitivity reaction (pseudoallergic reaction) known as "red man syndrome" and anaphylaxis. Skin testing with vancomycin at concentrations of 1 μg/mL or lower is presumptive for the presence of IgE antibodies that can be elicited by multiple courses of therapy.

Topical antibiotics such as bacitracin and neomycin usually cause delayed-type skin reactions. Although immediate-type reactions are rarely reported, repeated usage of bacitracin has been associated with near fatal anaphylaxis in a few cases. Hypersensitivity reactions to metronidazole are infrequently reported. Fixed drug eruptions and delayed-type skin reactions are the most common clinical presentations.

The general approach to antibiotic allergy, as depicted in Figure 210.1, is also useful for management of adverse reactions to non–β-lactam antibiotics.

Multiple antibiotic allergy syndromes

Some patients show a marked propensity to react to several chemically unrelated antibiotics and sometimes to non-antibiotic drugs. This condition has been termed the multiple drug allergy syndrome (MDAS). In most cases, MDAS presents clinically as acute urticaria +/− angioedema after ingestion of multiple doses of offending drugs. However, other variants including non-urticarial rashes, including SJS, anaphylaxis, serum sickness-like reactions, and immune cytopenias, have also been described. Mechanisms underlying multiple drug reactivity are still unclear. Published studies have suggested a high propensity to MDAS among patients with a history of allergy to β-lactams or any other antimicrobial drug. Whether MDAS results from a facilitated ability to make immune responses to drug haptens or an increased vulnerability to drug-induced immunopathology has yet to be determined. Some cases of MDAS are "pseudoallergic" and reflect classically conditioned responses that can readily be misinterpreted as anaphylaxis.

Clinical management of MDAS is similar to that in patients with single antibiotic allergy. Avoidance of unnecessary use of drugs should be the first step. Preferential use of low-risk antibiotics such as macrolides and quinolones may be helpful. With testing (e.g., validated skin or in vitro tests) or full allergy consultations, readministration of previously implicated drugs, especially β-lactams, can be justified.

Conclusion

Patients relating a history of immune or nonimmune reactions to antibiotics are not rare in medical practice. Because history alone has low diagnostic value, it is desirable that the history-positive patient should be evaluated by diagnostic tests when validated or by drug provocation tests when the index of suspicion is low. Although alternative antimicrobials can often be identified, they can have higher costs and treatment failures or greater toxicity. For the truly drug-allergic patient, management approaches include cautious administration of cross-reactive antimicrobials from the same class or drug desensitization. When approached systematically, almost all antibiotic-sensitive patients can be safely and effectively treated.

Suggested reading

Blumenthal KG, Shenoy ES, Varughese CA, Hurwitz S, Hooper DC, Banerji A. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. *Ann Allergy Asthma Immunol.* 2015 Oct 1;115(4):294.

Celik GE, Pichler WJ, Adkinson NF Jr. Drug allergy. In Adkinson NF Jr, Bochner BS, Burks W, et al. *Middleton's allergy: Principles and practice*, 8th ed. Philadelphia, PA: Mosby/Elsevier; 2014: 1274–1295.

Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014 Apr;69(4):420–437.

Gruchalla RS, Pirmohamed M. Antibiotic allergy. *N Engl J Med.* 2006;354:601–609.

Khan D, Solensky R. Drug allergy. *J Allergy Clin Immunol*. 2010;125: S126–S137.

Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. *J Allergy Clin Immunol*. 2014 Mar 1;133(3): 790–796.

Macy E, Ho N. Multiple drug intolerance syndrome: Prevalence, clinical characteristics, and management. *Ann Allergy Asthma Immunol*. 2012;108:88–93.

Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: A meta-analysis. *Otolaryngol Head Neck Surg*. 2007;136:340–347.

Solensky R, Khan D. The Joint Task Force on Practice Parameters: American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: An updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105(4): 259–227.

Sousa-Pinto B, Cardoso-Fernandes A, Araújo L, Fonseca JA, Freitas A, Delgado L. Clinical and economic burden of hospitalizations with registration of penicillin allergy. *Ann Allergy Asthma Immunol*. 2018 Feb 1;120(2):190–194.

Unger N, Gauthier T, Cheung LW. Penicillin skin testing: potential implications for antimicrobial stewardship. *Pharmacotherapy*. 2013;33(8):856–867.

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Antimicrobial agent tables

Diane Parente and Cheston B. Cunha

TABLE 211.1 **ANTIMICROBIAL AGENTS**

Name		Usual dose		Change in absorption with food	Adult dose interval
Generic	**Brand**	**Adult[a,c]**	**Pediatric[a,d]**		**>50**
Amikacin[e]	Amikin	IV: 15–20 mg/kg/d divided q8–24h; IT: 5–50 mg/d q24h	15–30 mg/kg/d divided q8–24h	n.a.	Usual
Amoxicillin	Amoxil	IR tablets: 500 mg–1 g PO q8–12h; XR tablets: 775 mg PO q24h	≤3 months: 25–50 mg/kg/d divided q8h; ≥3 months: 25–50 mg/kg/d divided q8h (max dose: 500 mg/dose)	IR: Unchanged; XR: Decreased	Usual
Amoxicillin–clavulanate	Augmentin	IR tablets: 500 mg PO q8–12h; 875 mg PO q12h; XR tablets: 2 g PO q12h	20–90 mg of amoxicillin/kg/d PO divided q8–12h[f]	Increased	Usual
Ampicillin	Ampen, Omnipen	Oral: 250–500 mg PO q6h; IV/IM: 1–2 g q4–6h	Oral: 50–100 mg/kg/d divided q6h (max 2 g/d); IV:50–400 mg/kg/d divided q4–6h (max 12 g/d)	Decreased	Usual
Ampicillin–sulbactam[g]	Unasyn	1.5–3 g IV q6h	100–400 mg ampicillin/kg/d divided q4–6h	n.a.	q6–8h
Azithromycin	Zithromax	250–500 mg IV/PO q24h	5–12 mg/kg/dose IV/PO q24h	Decreased	Usual
Azlocillin	Alocilin	2–4 g IV q4–6h	75 mg/kg IV q6h	n.a.	Usual
Aztreonam	Azactam	1–2 g IV q6–8h	90–120 mg/kg/d divided q6–8h	n.a.	Usual
Bacampicillin	Spectrobid	0.4–0.8 g PO q12h	12.5–25 mg/kg PO q12h	None	Usual
Carbenicillin indanyl sodium	Geocillin	1–2 0.382–g tabs PO q6h	7.5–12.5 mg/kg PO q6h	Increased	[b]
Cefaclor	Ceclor	IR: 250–500 mg PO q8h; XR: 500 mg PO q12h	20–40 mg/kg/d PO divided q8–12h	Unchanged	Usual
Cefadroxil	Duricef	500 mg–1 g PO q12–24h	15 mg/kg/dose PO q12h	Unchanged	Usual
Cefamandole	Mandol	2 g IV q6h	50–150 mg/kg/d divided q4–8h IV	n.a.	Usual
Cefazolin	Ancef, Kefzol	1–2 g IV q8h	25–150 mg/kg/d IV divided q6–8h	n.a.	Usual
Cefdinir	Omnicef	300 mg PO q12h	14 mg/kg/d PO divided q12–24h	Unchanged	Usual
Cefditoren	Spectracef	400 mg PO q12h	400 mg PO q12h	Increased	Usual
Cefepime	Maxipime	1–2 g IV q8–12h	50 mg/kg/dose IV q8–12h	n.a.	Usual
Cefiderocol	Fetroja	2 g IV q8h	[b]	n.a.	Usual
Cefixime	Suprax	400 mg PO q12–24h	8 mg/kg/d PO divided q12–24h	Unchanged	Usual
Cefmetazole	Zefazone	2 g IV q6–12h	[b]	n.a.	Usual

adjustment for reduced CrCl		Dosing in dialysis		Major toxicity
10–50	≤10	HD	PD	
q12–48h	>48h	2.5–3.75 mg/kg pHD	2.5 mg/kg/d IV or 3–4 mg/2 L dialysate removed	Renal toxicity, vestibular or auditory toxicity, CNS reactions, neuromuscular blockade (rare)
q8–12h	q12–24h	250–500 mg q12–24h, pHD on HD days	250–500 mg q12h	Allergic reactions (rare: anaphylactic), rash, diarrhea, nausea, vomiting
q8–12h	q12–24h	250–500 mg q12–24h, pHD on HD days	250–500 mg q12h	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting, cholestatic hepatitis
q6–12h	q12–24h	1–2 g IV q12–24h, pHD on HD days	1–2 g IV q12–24h	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
q8–12h	q24h	1.5–3 g IV q24h	1.5 g IV q12h or 3 g IV q24h	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
Usual	Usual	Usual	Usual	GI disturbance, QT prolongation and ventricular arrhythmias
q8h	q12h	3 g pHD	[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
q8–12h	q24h	q24h, pHD on HD days	q24h	Neutropenia, elevated serum transaminases
Usual	[b]	[b]	[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
[b]	[b]	[b]	[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
Usual	Usual	Usual	[b]	Allergic reactions, GI disturbance, arthritis, serum sickness
500 mg q12–24h	250 mg q36h	500 mg–1 g	[b]	Allergic reactions, GI disturbance
1 g q6h	1 g q12h	1 g	[b]	Thrombophlebitis with IV infusion, allergic reactions, GI disturbance
0.5–1 g q8–12h	0.5–1 g q24h	0.5–1 g q24h	500 mg q12h	Allergic reactions, GI disturbance, diarrhea
q24h	q24h	Every other day	[b]	Diarrhea, nausea, headache, rash
200 mg q12h	200 mg/d	[b]	[b]	GI disturbance, vulvovaginal candidiasis, leukopenia, neutropenia, thrombocytopenia
q12–24h	1 g q24h	0.5–1 g q24h	1 g q24h	Nausea, diarrhea, vomiting, rash, phlebitis, seizures
1–1.5 g q8h	750 mg q12h	750 mg q12h	[b]	Encephalopathy, constipation, diarrhea, headache, hypokalemia, elevated AST/ALT
260 mg q24h	176 mg q24h	260 mg q24h	176 mg q24h	Thrombophlebitis, allergic reactions, GI disturbance
q16–24h	q48h	[b]	[b]	Thrombophlebitis, allergic reactions, GI disturbance

(*continued*)

TABLE 211.1 CONTINUED

Name		Usual dose		Change in absorption with food	Adult dose interval
Generic	Brand	Adult[a,c]	Pediatric[a,d]		>50
Cefonicid	Monocid	0.5–2 g IV q24h	[b]	n.a.	Usual
Cefoperazone	Cefobid	2 g IV q12h	25–100 mg/kg IV q12h	n.a.	q6–12h
Cefotaxime	Claforan	1–2 g IV q4–8h	50–200 mg/kg/d IV divided q6–8h	n.a.	q6h
Cefotetan	Cefotan	1–2 g IV/IM q12h	20–50 mg/kg/dose IV/IM q12h	n.a.	Usual
Cefoxitin	Mefoxin	1–2 g IV q6–8h	80–160 mg/kg/d IV divided q4–8h	n.a.	Usual
Cefpodoxime	Vantin	100–400 mg PO q12h	5 mg/kg/dose PO q12h	Increased	Usual
Cefprozil	Cefzil	250–500 mg PO q12–24h	7.5–15 mg/kg/dose PO q12h	Unchanged	Usual
Ceftaroline	Teflaro	600 mg IV q12h	<2 months: 6 mg/kg/dose IV q8h; ≥2 months to <2 years: 8 mg/kg/dose IV q8h; ≥2 years and ≤33 kg: 12 mg/kg/dose IV q8h; ≥2 years and >33 kg: 400 mg IV q8h or 600 mg q12h	n.a.	Usual
Ceftazidime	Fortaz, Tazicef, Tazidime	1–2 g IV q8h	90–300 mg/kg/d IV divided q8h	n.a.	Usual
Ceftazidime-avibactam[h]	Avycaz	2.5 g IV q8h	≥3 months to <6 months: 40 mg/kg/dose IV q8h; ≥6 months to <18 years: 50 mg/kg/dose IV q8h	n.a.	Usual
Ceftibuten	Cedax	400 mg PO q24h	9 mg/kg/dose PO q24h	Decreased	Usual
Ceftizoxime	Cefizox	1–4 g IV q8h	≥6 months: 50 mg/kg/dose IV q6–8h	n.a.	Usual
Ceftobiprole	Zevtera, Mabelio	500 mg IV q8h	[b]	n.a.	Usual
Ceftolozone-tazobactam	Zerbaxa	1.5–3 g IV q8h	[b]	n.a.	Usual
Ceftriaxone	Rocephin	1–2 g IV q24h; Meningitis: 2 g IV q12h	50–100 mg/kg/d IV divided q12–24h	n.a.	Usual
Cefuroxime	Zinacef, Kefurox	1.5 g IV q8h	50–100 mg/kg/dose IV divided q6–8h	n.a.	Usual

adjustment for reduced CrCl		Dosing in dialysis		Major toxicity
10–50	≤10	HD	PD	
4–15 mg/kg q24–48h	3–15 mg/kg q3–5 days	None	[b]	Allergic reactions, GI disturbance, hypoprothrombinemia or hemorrhage
q6–12h	q6–12h	Dose after HD	[b]	Thrombophlebitis, allergic reactions, GI disturbance
q6–12h	q24h	q24h, pHD on HD days	1 g q24h	Thrombophlebitis, allergic reactions, GI disturbance
q24h	q48h	25% dose nonHD days, 50% on HD days, q24h	1 g q24h	Thrombophlebitis, allergic reactions, GI disturbance
q12–24h	500 mg–1 g q12–24h	1–2 g pHD	[b]	Thrombophlebitis, allergic reactions, GI disturbance
q12–24h	q24h	Dose 3 times/week pHD	[b]	Allergic reactions, GI disturbance, vaginal infection
CrCl <30–50% dose q12–24h	50% dose q12–24h	Dose pHD	[b]	Allergic reactions, GI disturbance
300–400 mg q12h	200 mg q12h	200 mg q12h	[b]	Allergic reactions, GI disturbance, direct Coombs seroconversion, headache
q12–24h	500 mg–1 g q24h	500 mg–1 g q24h	1 g q24h	GI disturbance, increased lactate dehydrogenase, increased γ-glutamyl transferase, eosinophilia, increased ALT/AST/serum alkaline phosphatase, neurotoxicity
CrCl 31–50: 1.25 g q8h; CrCl 16–30: 0.94 g q12h	CrCl 6–15: 0.94 g q24h; CrCl ≤5: 0.94 g q48h	0.94 g q24–48h, pHD on HD days	[b]	GI disturbance, phlebitis, positive direct Coombs test; neurotoxicity
100–200 mg q24h	100 mg q24h	400 mg pHD	[b]	GI disturbance, headache
250 mg–1 g q12h	500 mg q24h	Dose pHD	3 g q48h	Thrombophlebitis, allergic reactions, increased liver enzymes
CrCl 30–<50: 500 mg q12h	CrCl <30: 250 mg q12h	250 mg q24h	[b]	Hyponatremia, headache, GI disturbance, increased serum creatinine, allergic reactions
CrCl 30–50: 750 mg–1.5 g q8h; CrCl 15–29: 375–750 mg q8h	[b]	Load 750 mg then 150 mg q8h OR Load 2.25 g then 450 mg q8h	[b]	Increased liver enzymes, headache, intracranial hemorrhage, insomnia, hypokalemia, GI disturbance, fever
q12–24h	q12–24h	q12–24h	[b]	Thrombophlebitis, allergic reactions, GI disturbance, cholelithiasis
q8–12h	q24h	Administer additional dose at end of HD	q24h	Thrombophlebitis, allergic reactions, GI disturbance, vaginitis, decreased hematocrit, decreased hemoglobin, eosinophilia, increased liver enzymes, Jarisch-Herxheimer reaction

(*continued*)

TABLE 211.1 **CONTINUED**

Name		Usual dose		Change in absorption with food	Adult dose interval
Generic	**Brand**	**Adult[a,c]**	**Pediatric[a,d]**		**>50**
Cefuroxime axetil	Ceftin	250–500 mg PO q12h	10–30 mg/kg/d PO divided q12h	Increased	Usual
Cephalexin	Keflex, Biocef, Keftab	250 mg–1 g PO q6h	25–100 mg/kg/d divided PO q6–12h	Unchanged	Usual
Cephalothin		500 mg–2 g IV q4–6h	80–160 mg/kg/d IV divided q4–6h	n.a.	Usual
Cephapirin		500 mg–2 g IV q4–6h	40–80 mg/kg/d IV divided q6h	n.a.	Usual
Cephradine		Oral: 250 mg–1 g q6–12h; IV: 500 mg–2 g q4–6h	Oral: 25–100 mg/kg/d divided q6–12h IV: 50–100 mg/kg/d divided q6h	Decreased	Usual
Chloramphenicol	Chloromycetin	50 to 100 mg/kg/d IV divided q6h	12.5–25 mg/kg/dose IV q6h	n.a.	Usual
Cinoxacin		250 mg PO q6h or 500 mg PO q12h	[b]	Unchanged	Usual
Ciprofloxacin	Cipro	Oral: 250–750 mg q12h; IV: 400 mg q12h	N.R.	Decreased	Usual
Clarithromycin	Biaxin	IR: 250–500 mg PO q12h; XR: 1 g PO q24h	IR: 15 mg/kg/d PO divided q12h	IR: Unchanged XR: Increased	Usual
Clindamycin	Cleocin	Oral: 300–450 mg PO q6–8h IV: 600–900 mg q6–8h	Oral: 10–40 mg/kg/d divided q6–8h; IV: 20–40 mg/kg/d divided q6–8h	Unchanged	Usual
Cloxacillin	Cloxi	Oral: 250–500 mg q6h; IV: 250–500 mg q6h	12.5–25 mg/kg PO q6h	Decreased	Usual
Colistin[i]	Coly-mycin	Loading dose: 300 mg CBA (~9 million IU); Maintenance dose: 300–360 mg CBA (~9–10.9 million IU) divided q12h; infuse over 0.5–1 h	2.5–5 mg CBA/kg/d IV divided q6–12h	n.a.	245–360 mg CBA (7.4–10.9 million IU) q12h
Dalbavancin	Dalvance, Xydalba	1.5 g IV once OR 1 g once then 500 mg once 1 week later	≥3 months to <6 years: 22.5 mg/kg IV as a single dose; ≥6 years to <18 years: 18 mg/kg IV as a single dose OR ≥3 months to <6 years: 15 mg/kg IV as a single dose on day 1 then 7.5 mg/kg as a single dose on day 8; ≥6 years to <18 years: 12 mg/kg IV as a single dose on day 1 then 6 mg/kg as a single dose on day 8	n.a.	Usual

adjustment for reduced CrCl		Dosing in dialysis		Major toxicity
10–50	≤10	HD	PD	
q12–24h	q48h	Administer additional dose at end of HD	[b]	Thrombophlebitis, allergic reactions, GI disturbance, vaginitis, decreased hematocrit, decreased hemoglobin, eosinophilia, increased liver enzymes, Jarisch-Herxheimer reaction
250 mg q8–12h	250 mg q24–48h	250–500 mg q12–24h, pHD on HD days	250–500 mg q12–24h	Allergic reactions, GI disturbance
1–1.5 g q6h	0.5 g q6h	500 mg–2 g	Add up to 6 mg/kg to dialysate	Thrombophlebitis with IV infusion, allergic reactions, GI disturbance
q6–8h	q12h	7.5–15 mg/kg pHD then q12h	[b]	Thrombophlebitis, allergic reactions, GI disturbance
50% of dose at normal interval	25% of usual dose at normal interval	250 mg before HD, then 12, 36, and 48 h pHD	500 mg q6h	Allergic reactions, GI disturbance
q6h	q6h	Dose pHD	q6h	Blood dyscrasias, gray baby syndrome, GI disturbance, hepatotoxicity
250 mg q12h	250 mg q24h	[b]	[b]	GI disturbance, dizziness, headache, tremors, confusion, photosensitivity
250–500 mg PO q12h, IV q12–24h	500 mg PO q24h; 200–400 mg IV q24h	250–500 mg PO q24h; 200–400 mg q24h	250–500 mg PO q24h; 200–400 mg q24h	GI disturbance, dizziness, headache, tremors, confusion, QT prolongation, aortic aneurysm, dysglycemia, photosensitivity, tendon rupture/tendinitis, peripheral neuropathy, seizures, psychiatric reactions
q12h	Decrease dose by 50%	Dose pHD	[b]	GI disturbance, abnormal taste, headache; QT prolongation, increased liver function tests, hepatitis, candidiasis (oral)
Usual	Usual	Usual	Usual	Diarrhea, including pseudomembranous colitis, allergic reactions
Usual	Usual	Usual	Usual	Allergic reactions, GI disturbance
160–220 mg CBA (4.85–6.65 million IU) q12h	145 mg CBA (4.4 million IU) q12h	Non-HD day: 130 mg CBA (3.95 million IU), on HD day 40 mg CBA (1.2 million IU)	[b]	Nephrotoxicity, neurotoxicity including dizziness, oral paresthesia, paresthesia, peripheral paresthesia, seizures, slurred speech, vertigo
CrCl <30 1.125 g once OR 750 mg once then 375 mg once 1 week later	CrCl <30 1.125 g once OR 750 mg once then 375 mg once 1 week later	Usual	[b]	Increased liver enzymes, Red-Man syndrome, headache, GI disturbance

(*continued*)

TABLE 211.1 CONTINUED

Name		Usual dose		Change in absorption with food	Adult dose interval
Generic	Brand	Adult[a,c]	Pediatric[a,d]		>50
Dapsone		50–100 mg PO q12–24h; 200 mg PO weekly dependent on indication	1–2 mg/kg/d divided q24h	Unchanged	Usual
Daptomycin	Cubicin	4–12 mg/kg IV q24h	1–5 years: 10 mg/kg IV q24h; 6–11 years: 7 mg/kg IV q24h; ≥12–17 years: 4–6 mg/kg IV q24h	n.a.	Usual
Delafloxacin	Baxdela	Oral: 450 mg PO q12h; IV: 300 mg q12h	[b]	n.a.	Usual
Dicloxacillin	Dynapen	250–500 mg PO q6h	12–50 mg/kg/d PO divided q6h	Decreased	Usual
Doripenem	Doribax	500 mg IV q8h	[b]	n.a.	Usual
Doxycycline	Vibramycin	100 mg PO/IV q12h	2.2 mg/kg/d PO/IV; divided q12h	Decreased	Usual
Eravacycline	Xerava	1 mg/kg IV q12h	[b]	n.a.	Usual
Ertapenem	Invanz	1 g IV/IM q24h	50 mg/kg/dose IV/IM divided q12h	n.a.	Usual
Erythromycin base		250–500 mg PO q6–12h	30–50 mg/kg/d PO divided q6–8h	Decreased	Usual
Erythromycin estolate	Ilosone	0.25–0.5 g PO q6h	3–50 mg/kg/d divided q6h	Decreased	Usual
Erythromycin ethyl succinate	EES, EryPed	400–800 mg PO q6–12h	30–50 mg/kg/d PO divided q8h	Increased	Usual
Erythromycin lactobionate		15–20 mg/kg/d IV divided q6h	15–20 mg/kg/d divided IV q6h	n.a.	Usual
Fidaxomicin	Dificid	200 mg PO q12h	≥6 months: 16 mg/kg/dose PO q12h (max 200 mg/dose)	Unchanged	Usual
Fosfomycin	Monurol	Oral: 3 g once or q2–3d; IV: 12–24 g/d divided q6–8h	Oral: <12 years: 2 g once; IV: <10 kg: 200–300 mg/kg/d divided q6h; 10–40 kg: 200–400 mg/kg/d divided q6–8h; >40 kg 12–24 g/d divided q6–8h	Unchanged	IV: Usual
Gatifloxacin	Zymaxid, Zymar	400 mg PO/IV q24h	[b]	None	Usual

adjustment for reduced CrCl		Dosing in dialysis		Major toxicity
10–50	≤10	HD	PD	
Usual	Usual	[b]	[b]	Blood dyscrasias, dermatologic reactions (toxic erythema multiforme), hyperbilirubinemia, hepatitis, peripheral neuropathy, headache, GI irritation, infectious mono-like syndrome
q24–48h	q48h	q48h, pHD on HD days	q48h	Eosinophilic pneumonia, myopathy, rhabdomyolysis, peripheral neuropathy, GI disturbance, increased creatine phosphokinase, insomnia, headache
oral:450 mg q12h; IV: 200 mg q12h	N.R.	N.R.	q12h	GI disturbance, dizziness, headache, tremors, confusion, QT prolongation, aortic aneurysm, dysglycemia, photosensitivity, tendon rupture/tendinitis, peripheral neuropathy, seizures, psychiatric reactions
Usual	Usual	Usual	Usual	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
250 mg q8h	250 mg q12h	250–500 mg q24h	[b]	Anaphylaxis, hypersensitivity, GI disturbance, seizures, headache
Usual	Usual	Usual	Usual	GI disturbance, photosensitivity reactions, hepatic toxicity, esophageal ulcers
Usual	Usual	Usual	Usual	abnormal LFTs, photosensitivity reactions
CrCl ≤30: 500 mg q24h	CrCl ≤30: 500 mg q24h	500 mg q24h, give supplemented dose of 150 mg pHD	[b]	Thrombocytopenia, increased LFTs, allergic reactions; seizures, GI disturbance
Usual	Usual	Usual	Usual	GI disturbance; rare: allergic reactions, hepatic dysfunction, hearing loss
Usual	Usual	Usual	Usual	Cholestatic hepatitis, hearing loss or tinnitus, GI disturbance, hypersensitivity reactions
Usual	Usual	Usual	Usual	GI disturbance; rare: allergic reactions, hepatic dysfunction
Usual	Usual	Usual	Usual	GI disturbance; rare: allergic reactions, hepatic dysfunction, hearing loss
Usual	Usual	Usual	Usual	Nausea, vomiting, hypersensitivity reaction, fever
20–70% of dose q8–12h	20% of dose q12–24h	2 g pHD	[b]	Electrolyte abnormalities, hepatic abnormalities, headache, GI disturbance, vaginitis
400 mg ×1 then 50% q24h	[b]	[b]	[b]	Hyperglycemia, hypoglycemia, QT prolongation, tendon rupture

(*continued*)

TABLE 211.1 CONTINUED

Name		Usual dose		Change in absorption with food	Adult dose interval
Generic	Brand	Adult[a,c]	Pediatric[a,d]		>50
Gentamicin[e]	Garamycin	IV: 3–5 mg/kg/d divided q8h or 5–7 mg/kg IV q24h; IT: 4–8 mg/d	2–2.5 mg/kg IV q8h or 4.5–7.5 m/kg IV q24h	n.a.	Usual
Grepafloxacin		400–600 mg q24h	[b]	No change	Usual
Imipenem-cilastatin	Primaxin	500 mg IV q6h or 1 g IV q8h	60–100 mg/kg/d IV divided q6h	n.a.	Usual
Imipenem-cilastatin-relebactam	Recarbrio	1.25 g IV q6h	[b]	n.a.	CrCl 60–89: 1 g q6h
Kanamycin[e]	Kantrex	15 mg/kg/d divided IV q8–12h	15 mg/kg/d divided IV q8–12h (newborn: 0–7 d, 15–20 mg/kg/d q12h; 1–4 wk, 15 mg/kg/d q8–12h)	n.a.	Usual
Lefamulin	Xenleta	Oral: 600 mg q12h; IV: 150 mg IV q12h	[b]	Decreased	Usual
Levofloxacin	Levaquin	250–750 mg PO/IV q24h	N.R.	Unchanged	Usual
Lincomycin	Lincocin	600 mg–1 g IV q8–12h	10–20 mg/kg/d IV divided q8–12	n.a.	q8–12h
Linezolid	Zyvox	600 mg PO/IV q12h	<12 years: 10 mg/kg/dose IV/PO q8h; ≥12 years: 600 mg IV/PO q12h	Unchanged	Usual
Lomefloxacin	Maxaquin, Uniquin, Okacyn	400 mg PO q24h	N.R.	Decrease	Usual
Loracarbef	Lorabid	400 mg PO q12h	15–30 mg/kg/d PO divided q12h	Decreased	Usual
Meropenem	Merrem	500 mg - 2 g IV q8h	20–40 mg/kg/dose IV q8h	n.a.	Usual
Meropenem-vaborbactam	Vabomere	4 g IV q8h	[b]	n.a.	Usual
Metronidazole	Flagyl	Oral: 250 mg–1 g q6–12h; IV: 500–1 g q6–12h	Oral: 15–50 mg/kg/d divided q8h; IV: 22.5–40 mg/kg/d divided q6–8h	Unchanged	Usual
Mezlocillin		3–4 g IV q4–6h	50 mg/kg IV q4–6h	n.a.	Usual
Minocycline	Minocin, Dynacin	200 mg IV/PO once, then 100 mg IV/PO q12h	4 mg/kg (max 200 mg) IV/PO once, then 2 mg/kg/dose q12h (max 100 mg)	Unchanged	Usual

adjustment for reduced CrCl		Dosing in dialysis		Major toxicity
10–50	≤10	HD	PD	
q12–48h	>48 h	1–2 mg/kg q48–72h	1 mg/2 L dialysate removed	Renal toxicity, vestibular and auditory toxicity, CNS reactions, neuromuscular blockade (rare)
Usual	Usual	Usual	Usual	Phototoxicity, QT prolongation, tendon rupture
200–300 mg q6h or 500 mg q8–12h	N.R.	250–500 mg pHD then q12h	[b]	Fever, rash, nausea, vomiting, diarrhea, seizures (rare)
CrCl 30–59 L 750 mg q6h; CrCl 15–29: 500 mg q6h	N.R.	500 mg IV q6h	N.R.	Fever, headache, diarrhea, vomiting, increased liver enzymes, seizures (rare)
q12–48h	>48 h	4–5 mg/kg pHD	3.75 mg/kg/d	Cranial nerve VIII and renal damage
Usual	Usual	Usual	Usual	QT prolongation, hypokalemia, GI disturbance, increased liver enzymes, headache, insomnia
250 mg q24h or 500 mg q48h	250–500 mg q48h	250–500 mg q48h	250–500 mg q48h	GI disturbance, dizziness, headache, tremors, confusion, QT prolongation, aortic aneurysm, dysglycemia, photosensitivity, tendon rupture/tendinitis, peripheral neuropathy, seizures, psychiatric reactions
q8–12h	q8–12h	[b]	[b]	Diarrhea, including pseudomembranous colitis
Usual	Usual	Usual	Usual	Myelosuppression (primarily thrombocytopenia), lactic acidosis, peripheral neuropathy, optic neuropathy, serotonin syndrome
0.2 g q24h	0.2 g q24h	0.4 g load, then 0.2 g q24h	[b]	Nausea, vomiting, dizziness, headache, tremors, confusion, photosensitivity
200 mg q24h	200 mg q72h	400 mg pHD	[b]	Allergic reactions, GI disturbance
q12h	500 mg–1 g q24h	500 mg–1 g q24h	500 mg–1 g q24h	Seizures, rash, headache, GI disturbance
2 g q8–12h	1 g q12h	[b]	[b]	Thrombocytopenia, seizures, headache, diarrhea
q6–12h	q6–12h	q6–12h	q6–12h	Headache, nausea, vaginitis, metallic taste, GI disturbance
CrCl 10–30: 1.5–3 g q6–8h	1.5–2 g q8h	3–4 g pHD then q12h	3 g q12h	Hypokalemia
Usual	Usual	Usual	Usual	GI disturbance, photosensitivity, hepatic toxicity, esophageal ulcers, vestibular toxicity; tooth discoloration

(*continued*)

TABLE 211.1 CONTINUED

Name		Usual dose		Change in absorption with food	Adult dose interval
Generic	Brand	Adult[a,c]	Pediatric[a,d]		>50
Moxifloxacin	Avelox	400 mg PO/IV q24h	N.R.	Unchanged	Usual
Nafcillin	Nallpen, Unipen	1–2 g IV q4h	Birth–7 days: 75 mg/kg/d IV divided q8–12h; 8–28 days: 100–150 mg/kg/d IV divided q6–8h; >28 days: 200 mg/kg/d IV divided q6h	n.a.	Usual
Neomycin	Neo-tabs	4–12 g/d PO divided q4–6h	–	Unchanged	[b]
Netilmicin[c]		4–6 mg/kg/d IV/IM divided q8–24h	0–1 week: 3 mg/kg IV/IM q12h; >1 week 2.5 mg/kg IV/IM q8h	n.a.	q8–12h
Nitrofurantoin macrocrystals	Furadantin, Macrodantin	50–100 mg PO q6h;	5–7 mg/kg/d PO divided q6h	Increased	Usual
Nitrofurantoin monohydrate/macrocrystals	Macrobid	100 mg PO q12h	Adolescents: 100 mg PO q12h	Increased	Usual
Norfloxacin	Noroxin	400 mg PO q12h	N.R.	Decreased	Usual
Ofloxacin	Floxin	200 mg PO q12h or 400 mg PO q24h	N.R.	Unchanged	Usual
Omadacycline	Nuzyra	Oral: 450 mg q24h on days 1 and 2, then 300 mg q24h; IV: 200 mg once, then 100 mg q24h	[b]	Decreased	Usual
Oritavancin	Orbactive	1.2 g IV once	[b]	n.a.	CrCl ≥30: Usual
Oxacillin	Bactocil	1–3 g IV q4–6h	100–200 mg/kg/d IV divided q4–6h (max 12 g/d)	n.a.	Usual
Penicillin V	Pen–VeeK, Pen–V	125–500 mg PO q6–8h	25–75 mg/kg/d PO divided q6h (max 2 g/d)	Decreased	Usual

adjustment for reduced CrCl		Dosing in dialysis		Major toxicity
10–50	≤10	HD	PD	
Usual	Usual	Usual	Usual	GI disturbance, dizziness, headache, tremors, confusion, QT prolongation, aortic aneurysm, dysglycemia, photosensitivity, tendon rupture/tendinitis, peripheral neuropathy, seizures, psychiatric reactions
Usual	Usual	Usual	Usual	Allergic reactions (rare: anaphylactic), diarrhea, bone marrow suppression agranulocytosis, interstitial nephritis, hypokalemia
[b]	[b]	[b]	[b]	Cranial nerve VIII and renal damage
q12–48h	>48 h	2 mg/kg pHD	[b]	Renal toxicity, vestibular and auditory toxicity, CNS reactions, neuromuscular blockade (rare)
Avoid CrCl <30	N.R.	N.R.	N.R.	Headache, increased serum phosphate, increased LFT, decreased hemoglobin, eosinophilia
Avoid CrCl <30	N.R.	N.R.	N.R.	Headache, increased serum phosphate, increased LFT, decreased hemoglobin, eosinophilia
CrCl ≤30: q24h	q24h	[b]	[b]	GI disturbance, dizziness, headache, tremors, confusion, QT prolongation, aortic aneurysm, dysglycemia, photosensitivity, tendon rupture/tendinitis, peripheral neuropathy, seizures, psychiatric reactions
q24h	100–200 mg q24h	100–200 mg pHD	200 mg q24h	GI disturbance, dizziness, headache, tremors, confusion, QT prolongation, aortic aneurysm, dysglycemia, photosensitivity, tendon rupture/tendinitis, peripheral neuropathy, seizures, psychiatric reactions, visual disturbance
Usual	Usual	Usual	Usual	GI disturbance, headache, hypertension, insomnia, increased LFT
[b]	[b]	[b]	[b]	GI disturbance, headache, increased LFT
Usual	Usual	Usual	Usual	Allergic reactions (rare: anaphylactic), diarrhea, acute interstitial nephritis, acute renal tubular disease
Usual	Usual	Usual	[b]	Allergic reactions (rare: anaphylactic), melanoglossia, GI disturbance, oral candidiasis

(*continued*)

TABLE 211.1 CONTINUED

Name		Usual dose		Change in absorption with food	Adult dose interval
Generic	Brand	Adult[a,c]	Pediatric[a,d]		>50
Penicillin G benzathine	Bicillin L-A	1.2–2.4 million units IM once	≤27 kg: 600,000 units IM once; >27 kg: 1.2 million units IM once	n.a.	Usual
Penicillin G	various	2–4 million U IV q4–6h	25,000–90,000 U/kg/d divided q4–8h PO 25,000–400,000 U/kg/d divided IV q4–6h (neonate: 0–7 d, 50,000–150,000 U/kg/d q8–12h; 1–4 wk, 75,000–200,000 U/kg/d q6–8h)	Decreased	Usual
Piperacillin		6–18 g/d IV divided q6–12h	≥12 years: refer to adult dosing	n.a.	Usual
Piperacillin–tazobactam	Zosyn	3.375–4.5 g IV q6–8h	≥2 months: 240–300 mg piperacillin/kg/d divided q6–8h (max 16 g/d)	n.a.	Usual
Plazomicin[j]	Zemdri	15 mg/kg IV q24h	[b]	n.a.	CrCl 30-<60:10 mg/kg q24h
Polymyxin B	Aerosporin, Neosporin	Loading dose: 2–2.5 mg/kg (20,000–25,000 IU/kg); Maintenance dose: 1.25–1.5 mg/kg (12,500–15,000 IU/kg) IV q12h; infused over 1 h	2.5–4 mg/kg/d (25,000–40,000 IU/kg/d) IV divided q4–6h	n.a.	Usual
Procaine penicillin G	Wycillin	600,000–2.4 million units IM q12–24h	50,000 units/kg/d IM divided q12–24h	n.a.	Usual
Quinupristin–dalfopristin	Synercid	7.5 mg/kg IV q8h	[b]	n.a.	Usual
Rifaximin	Xifaxan	200–400 mg PO TID	100–550 mg PO q6–8h, dosing specific to indication and age	Unchanged	[b]
Sparfloxacin		400 mg PO once, then 200 mg PO q24h	[b]	Unchanged	Usual
Spectinomycin	Spectam, Trobicin	2 g IM x1 dose	[b]	n.a.	Usual
Streptomycin[e]		7.5–15 mg/kg IV/IM q12–24h	15–40 mg/kg/d IV/IM divided q6–12h (max 2 g/d)	n.a.	Usual
Sulfadiazine	Microsulfon	500 mg–1.5 g PO q6h	120–150 mg/kg/d PO divided q4–6h (max 6 g/d)	Unchanged	[b]

adjustment for reduced CrCl		Dosing in dialysis		Major toxicity
10–50	≤10	HD	PD	
Usual	Usual	Usual	Usual	Allergic reactions (rare: anaphylactic), GI disturbance, Jarisch-Herxheimer reaction
1–2 million U IV q4h	1 million U IV q8h	500,000 U	[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
3–4 g q8h	3–4 g q12h	1 g pHD, then 2 g IV q8h	[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting; platelet dysfunction with high doses
2.25–3.375 g q6h or 4.5 g q8h	2.25 g q6–8h or 4.5 g q12h	4.5 g q12h or 2.25 g q8h	4.5 g q12h or 2.25 g q8h	Allergic reactions (rare: anaphylactic), GI disturbance
CrCl 15-<30: 10 mg/kg q48h	[b]	[b]	[b]	Nephrotoxicity, ototoxicity
Usual	Usual	Usual	[b]	Nephrotoxicity, flushing, neurotoxicity: ataxia, blurred vision, drowsiness, irritability, numbness of extremities, oral paresthesia, dizziness
Usual	Usual	[b]	[b]	Allergic reactions (rare: anaphylactic), diarrhea, nausea, vomiting
Usual	Usual	[b]	[b]	Pain at infusion site, thrombophlebitis, arthralgia, myalgia, hyperbilirubinemia
[b]	[b]	[b]	[b]	Peripheral edema, dizziness, fatigue, ascites, nausea, headache, depression, pruritus, skin rash, GI disturbance, anemia, muscle spasm, arthralgia, fever
400 mg once, then 200 mg q48h	400 mg once, then 200 mg q48h	[b]	[b]	Photosensitivity, diarrhea, nausea, headaches, cardiac arrhythmias in patients taking antiarrhythmic drugs
Usual	Usual	[b]	[b]	Pain at injection site, nausea, allergic reactions
q24–72h	q72–96h	50% of dose pHD on HD days	[b]	Cranial nerve VIII damage, paresthesias, rash, fever, nephrotoxicity, neuromuscular blockade, optic neuritis, ototoxicity
[b]	[b]	[b]	[b]	GI disturbance, rash, pruritus, bone marrow suppression, serum sickness, drug fever, crystalluria, photosensitivity, hepatitis

(*continued*)

TABLE 211.1 CONTINUED

Name		Usual dose		Change in absorption with food	Adult dose interval
Generic	Brand	Adult[a,c]	Pediatric[a,d]		>50
Sulfisoxazole	Pediazole	Oral: 0.5–1 g PO q6h: IV: 25 mg/kg IV q6h	120–150 mg/kg/d divided PO q4–6h	Decreased	Usual
Tedizolid	Sivextro	200 mg IV/PO q24h	≥12 years: 200 mg IV/PO q24h	Unchanged	Usual
Teichoplanin	various	0.2–0.4 g IV q24h	10 mg/kg IV q24h	n.a.	Usual
Telavancin	Vibativ	10 mg/kg IV q24h	[b]	n.a.	Usual
Telithromycin	Ketek	800 mg PO q24h	[b]	Unchanged	Usual
Tetracycline	Achromycin	250–500 mg PO q6h	6.25–12.5 mg/kg/dose PO q6h (max 3 g/d)	Decreased	Usual
Ticarcillin	Ticar	3 g IV q6h	≥3 months: <60 kg, 50 mg/kg IV q4–6h (max 3 g/dose); ≥60 kg: 3 g IV q4–6h	n.a.	Usual
Ticarcillin–clavulanate potassium[l]	Timentin	3.1 g IV q4–6h	200–300 mg ticarcillin/kg/d IV divided q4–6h	n.a.	Usual
Tigecycline[o]	Tygacil	Package insert: 100 mg IV once, then 50 mg q12h; High dose therapy (for serious systemic infections) dosing: loading dose 200–400 mg IV once, then maintenance dose of 100–200 (50% of load) mg IV q24h	8–11 years: 1.2–2 mg/kg/dose IV q12h (max 50 mg/dose); ≥12–17 years: 1.5 mg/kg/dose IV once (max 100 mg/dose), then 1 mg/kg/dose q12h (max 50 mg/dose)	n.a.	Usual
Tinidazole	Tindamax	1–2 g PO q24h	≥3 years: 50 mg/kg/dose PO q24h (max 2 g/dose)	Unchanged	Usual
Tobramycin[c]	Nebcin	IV: 3–5 mg/kg/d divided q8h or 5–7 mg/kg IV q24h; IT: 5–20 mg/d	3–6 mg/kg/d divided IV q8h (newborn: 0–7 d, ≤4 mg/kg/d q12h; 1–4 wk, 3–5 mg/kg/d q8h)	n.a.	Usual
Trimethoprim–sulfamethoxazole[m]	Bactrim, Septra	Oral: 1–2 DS PO q8–12h; IV: 8–20 mg/kg/d divided q6–12h	≥2 months: 6–12 mg TMP/kg/d IV/PO divided q6–12h (max 160 mg TMP/dose)	Unchanged	Usual
Trimethoprim	Proloprim	100 mg PO q12h	≥6 months–11 years: 2–5 mg/kg/dose PO q12h	Unchanged	Usual

adjustment for reduced CrCl		Dosing in dialysis		Major toxicity
10–50	≤10	HD	PD	
q8–12h	q12–24h	[b]	[b]	Rash, photosensitivity, drug fever
Usual	Usual	Usual	Usual	GI disturbance, thrombocytopenia, optic neuropathy
q48h	q72h	[b]	[b]	Ototoxicity
CrCl 30–50: 7.5 mg/kg q24h; CrCl 10–30: 10 mg/kg q48h	[b]	[b]	[b]	Nephrotoxicity, QT prolongation, metallic taste, GI disturbance
CrCl <30: 600 mg q24h	CrCl <30: 600 mg q24hk	600 mg q24h, dose pHD on HD days	[b]	GI disturbance, headache, dizziness, thrombocytopenia, increased LFTs, reversible diplopia (females <40 years)
Use doxycycline	Use doxycycline	Use doxycycline	[b]	GI disturbance, photosensitivity, hepatic toxicity, esophageal ulcers, candidiasis (thrush and vaginitis)
2 g q8h	2 g q12h	3 g pHD; then 2 g q12h	3 g q12h	Allergic reactions (rare: anaphylactic), GI disturbance, Jarisch-Herxheimer reaction (with syphilis or other spirochetal infections), increased LFTs
q6–8h	2 g q12h	3.1 g pHD; then 2 g q12h	3.1 g q12h	Allergic reactions (rare: anaphylactic), GI disturbance, Jarisch-Herxheimer reaction (with syphilis or other spirochetal infections), increased LFTs
Usual	Usual	Usual	Usual	GI disturbance (nausea/vomiting), increased LFTs, electrolyte abnormalities.
Usual	Usual	Administer pHD on HD days	[b]	Metallic taste, GI disturbance
q12–48h	>48 h	1–2 mg/kg q48–72h	1 mg/2 L dialysate removed	Renal toxicity, vestibular and auditory toxicity, CNS reactions, neuromuscular blockade (rare)
CrCl 15–30: 50% of usual dose; Oral: q12–24h; IV: q6–24h	CrCl <15: 25% of usual dose; Oral: q12–24h; IV: 24–48h	Follow dosing for CrCl <15: administer pHD on HD days	CrCl <15: 25% of usual dose; q24–48h	GI disturbance (dose dependent), rash, pseudoelevation in serum creatinine, reversible hyperkalemia (dose dependent), bone marrow suppression
q12–18h	q24h	q24h	q24–48h	GI disturbance, reversible hyperkalemia (dose dependent), bone marrow suppression

(*continued*)

TABLE 211.1 **CONTINUED**

Name		Usual dose		Change in absorption with food	Adult dose interval
Generic	**Brand**	**Adult**[a,c]	**Pediatric**[a,d]		**>50**
Trovafloxacin	Bactocil	300 mg IV load; 200 mg IV/PO q24h	[b]	Unchanged	Usual
Vancomycin	Vancocin	Oral: 125 mg q6h (*C. difficile* infection) or 500 mg q6h (fulminant *C. difficile* infection); IV: 15–20 mg/kg IV q8h	40 mg/kg/d divided PO q6–8h 40 mg/kg/d divided IV q6–12h (newborn: 0–7 d, 15 mg/kg load, then 10 mg/kg q12h; 1–4 wk, 10 mg/kg q8h)	Not absorbed	CrCl >90: q8h, CrCl 60–89: q12h

[a] Dosing weight, actual body weight (kg) unless indicated otherwise
[b] Insufficient information available to make a recommendation.
[c] Specific dosing is dependent on indication
[d] Pediatric dosing may be specific to age, weight (kg), and/or indication
[e] In underweight (less than IBW), ABW is used. In normal-weight, IBW is used. In overweight patients (ABW >20% ideal weight), AdjBW is used. Aminoglycoside dosing may be
[f] Dosing based on amoxicillin component; formulations are not interchangeable
[g] Dosing based on ampicillin component
[h] Dosing based on ceftazidime component
[i] Use AdjBW to estimate CrCl; CBA= colistin base activity; CMS= colistin methanesulfonate
[j] Use ABW in non-obese patients, for patients with ABW > IBW by ≥25% use AdjBW
[k] CrCl <30 ute and concomitant hepatic impairment: 400 mg once daily
[l] Dosing based on Ticarcillin component
[m] Weight-based dosing recommendations are based on the TMP component. Each double-strength tablet contains TMP 160 mg and SMX 800 mg. Each single-strength tablet

Abbreviations: q = every; h = hour; IV= intravenous; PO = by mouth; IM = intramuscular; IT = intrathecal; CrCl = creatinine clearance (); HD = hemodialysis; PD = peritoneal body weight (kg); AdjBW = adjusted body weight (kg); TBW= total body weight (kg); IR = immediate release; XR = extended release; pHD =post-hemodialysis; n.a.=not

adjustment for reduced CrCl		Dosing in dialysis		Major toxicity
10–50	≤10	HD	PD	
Usual	Usual	Usual	Usual	Hepatotoxicity, including severe liver failure, dizziness, nausea, headache, photosensitivity, insomnia
CrCl 30–59: q24h	CrCl <30: dose by vancomycin level	Dose by level	Dose by level	Red-man syndrome, nephrotoxicity, thrombocytopenia, ototoxicity, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), IgA dermatitis

modified after obtaining serum levels.

contains TMP 80 mg and SMX 400 mg. CrCl <15, HD, PD - avoid if possible

dialysis; CNS = central nervous system; GI =gastrointestinal; TEN = toxic epidermal necrolysis; p = post; LFTs = liver function tests; IBW= ideal body weight (kg); ABW = actual applicable; AST =aspartate aminotransferase; ALT =alanine aminotransferase; N.R.=not recommended; TMP= trimethoprim; SMX=sulfamethoxazole

TABLE 211.2

Name		Usual dose		Change in absorption with food
Generic	**Brand**	**Adult[a,c]**	**Pediatric[a,d]**	
Bedaquiline	Sirturo	Weeks 1–2: 400 mg PO q24h Weeks 3–24: 200 mg 3 times weekly	≥5 years: 15 to <30 kg: Weeks 1–2: 200 mg PO q24h Weeks 3–24: 100 mg 3 times weekly ≥30 kg: use adult dosing	Increased
Capreomycin	Capastat	15 mg/kg IV/IM q24h or 25 mg/kg IV/IM 3 times weekly	<15 years: ≤40 kg: 15–20 mg/kg IV/IM q24h or 25 mg/kg/dose 2 times weekly (max 1 g/dose) >40 kg or ≥15 years: use adult dosing	N.A.
Clofazimine		100 mg PO q24h	[b]	Increased
Cycloserine	Seromycin	10–50 mg/kg/d (max 1 g/d) PO, divided q12–24h	15–20 mg/kg/d (max 1 g/d) PO, divided q12–24h	Unchanged
Ethambutol[e]	Myambutol	15–25 mg/kg (max 1.6 g) PO q24h	15–25 mg/kg PO q24h	Unchanged
Ethionamide	Trecator	15–20 mg/kg/d (max 1 g/d) PO; divided q12–24h	15–20 mg/kg/d PO divided q8–12h	Unchanged
INH + RIF + PZA	Rifater	6 tablets PO q24h	[b]	Decreased
INH + RIF	Rifamate	2 capsules PO q24h	[b]	Decreased
Isoniazid		300 mg PO q24h or 900 mg PO 1–3 times weekly	<15 years and ≤40 kg: 10–15 mg/kg/dose (max 300 mg/dose) PO q24h; >40 kg or ≥15 years: use adult dosing	Decreased
Para-amino salicylic acid		150 mg/kg q6–12h	150–360 mg/kg/d divided q6–8h	Decreased
Pyrazinamide	Tebrazid	25 mg/kg (max 2 g) PO q24h	35 mg/kg/dose (max 2 g) PO q24h	Unchanged
Rifabutin (ansamycin)	Mycobutin	300 mg PO q24h	10–20 mg/kg/d (max 300 mg/d) PO q24h or 3 times weekly	Unchanged
Rifampin	Rifadin, Rimactane	600 mg IV/PO q24h	10–20 mg/kg/d IV/PO max 600 mg/d); divided q12–24h	Decreased
Rifapentine	Priftin	Active TB: 600 mg PO 2 times weekly for 2 months, then 600 mg once weekly for 4 months; Latent TB: 600–900 mg PO once weekly	≥12 years: use adult dosing	Increased
Streptomycin[f]		15 mg/kg IV/IM q24h or 25 mg/kg IV/IM 3 times weekly	15–40 mg/kg/d IV/IM q24h (max 1 g/dose)	N.A.

[a] Dosing weight, actual body weight (kg) unless indicated otherwise.
[b] Insufficient information available to make a recommendation.
[c] Specific dosing is dependent on indication.
[d] Pediatric dosing may be specific to age, weight (kg), and/or indication.
[e] Use lean body weight.
[f] In underweight (less than IBW), ABW is used. In normal weight, IBW is used. In overweight patients (ABW >20% ideal weight), AdjBW is used. Aminoglycoside dosing may be
CNS, central nervous system; CrCl, creatinine clearance mL/min; GI, gastrointestinal; HD, hemodialysis; INH, isoniazid; IT, intrathecal; N.A., not applicable; N.R., not

Adult dose reduced interval adjustment CrCl for			Dosing in dialysis		Major toxicity
>50	10–50	≤10	HD	PD	
Usual	Usual	Use with caution	[b]	[b]	QT prolongation, increased LFTs, hepatotoxicity, headache, arthralgia, rash, hyperuricemia, peripheral neuropathy, anemia, otovestibular toxicity
q24h	7.5 mg/kg q24–48h	7.5 mg/kg 2×/wk	15 mg/kg/dose 2–3 times weekly	[b]	Nephrotoxicity, ototoxicity, electrolyte abnormalities, pain at injection site
q24h	q24h	q24h	Use with caution	Use with Caution	Hyperpigmentation, ichthyosis, dry eyes, GI disturbance
q12h	250 mg q24h	N.R.	500 mg 3 times weekly	[b]	Anxiety, depression, confusion, hallucinations, headache, peripheral neuropathy (associated with peaks >35 mcg/mL), seizure (dose dependent)
q24h	q24–36h	q48h	15 mg/kg/d pHD	q48h	Optic neuritis, allergic reactions, GI disturbance, acute gout
q12h	CrCl ≥30: q12h	CrCl <30: 250–500 mg/d	CrCl <30: 250–500 mg/d	[b]	GI disturbance, liver toxicity, CNS disturbance, yellow staining of eyes or skin, dizziness, ototoxicity, Goiter, gynecomastia, hypoglycemia, hypothyroidism, menstrual disease, pellagra
q24h	q24h	[b]	[b]	[b]	As with individual drugs
q24h	q24h	[b]	[b]	[b]	As with individual drugs
q24h	q24h	150 mg q24h in slow acetylators	5 mg/kg pHD	Daily dose pPD	Peripheral neuropathy, liver toxicity (possibly fatal), glossitis, GI disturbance, fever
[b]	[b]	[b]	[b]	[b]	GI disturbance
q24h	q24h	CrCl <30: 25–35 mg/kg/dose 3 times weekly	[b]	[b]	Arthralgia, hyperuricemia, liver toxicity, GI disturbance, rash, gouty arthritis
q24h	q24h	CrCl <30: 150 mg q24h	[b]	[b]	Uveitis, orange discoloration of urine, sweat, tears; liver toxicity, GI disturbance, myalgia, arthralgia
q24h	q24h	300 mg q24h	300–600 mg q24h	300–600 mg q24h	Orange discoloration of urine, sweat, tears; liver toxicity, GI disturbance, flu-like syndrome
[b]	[b]	[b]	[b]	[b]	Similar to rifampin
q24h	q24–72h	q72–96h	50% of dose pHD on HD days	[b]	Cranial nerve VIII damage, paresthesias, rash, fever, nephrotoxicity, neuromuscular blockade, optic neuritis, ototoxicity

modified after obtaining serum levels.
recommended; PD, peritoneal dialysis; pHD, post hemodialysis; pPD, post peritoneal dialysis.; PZA, pyrazinamide; RIF, rifampin.

TABLE 211.3

Name		Usual dose		Change in absorption with food
Generic	**Brand**	**Adult[a,c]**	**Pediatric[a,d]**	
Amphotericin B (conventional)	Fungizone	0.25–1 mg/kg IV q24h	0.25–1 mg/kg IV q24–48h	N.A.
Amphotericin B lipid complex	Abelcet	5 mg/kg IV q24h	5 mg/kg IV q24h	N.A.
Amphotericin B liposomal	AmBisome	3–5 mg/kg IV q24h	3–5 mg/kg IV q24h	N.A.
Amphotericin B cholesteryl sulfate complex		3–4 mg/kg q24h	3–4 mg/kg q24h	N.A.
Anidulafungin	Eraxis	200 mg IV once, then 100 mg IV q24h	N.A.	N.A.
Caspofungin	Cancidas	75 mg IV once, then 50 mg IV q12h	≥3 months to <18 years:70 mg IV once, then 50 mg IV q24h	N.A.
Clotrimazole	Mycelex	10 mg PO 3–5 times daily	≥3 years: 10 mg PO 5 time daily	Unchanged
Fluconazole	Diflucan	150–800 mg IV/PO q24h	6 to 12 mg/kg/dose IV/PO, followed by 3 to 12 mg/kg/dose IV/PO q24h	Unchanged
Flucytosine	Ancobon	25 mg/kg PO q6h	25 mg/kg PO q6h	Decreased
Griseofulvin	Grisactin, Grifulvin, Fulvicin	500 mg–1 g PO q24h	>2 years: 15 mg/kg PO q24h	Increased
Isavuconazonium Sulfate	Cresemba	IV/PO Load: 372 mg q8h for 6 doses; Maintenance: 372 mg q24h; start 12–24 h last loading dose	[b]	Unchanged
Itraconazole[e]	Sporanox	200 mg PO q12–24h; can load 200 mg PO q8h for 3 days	2.5–5 mg/kg/dose (max 200 mg) PO q8h for 3 days, then 5–10 mg/kg/dose (max 400 mg) PO q12–24h	Capsule: Increased; Solution: Decreased
Ketoconazole	Nizoral	200–400 mg PO q24h	≥2 years: 3.3–6.6 mg/kg PO q24h (max 400 mg/d)	Increased
Micafungin	Mycamine	100–150 mg IV q24h	≤40 kg: 2–6 mg/kg IV q24h	N.A.
Miconazole		50 mg PO q24h	[b]	N.A.
Nystatin	Mycostatin	400,000–600,000 units q6h	200,000–600,000 units q6h	Not absorbed
Posaconazole[e]	Noxafil	Delayed release tablet or IV: 300 mg q12h x 2 doses, then 300 mg q24h; Oral suspension: 200 mg q6h	Oral Suspension: 200–300 mg q8h	Increased
Voriconazole[e]	Vfend	Oral: 200 mg PO q12h; IV: 6 mg/kg q12h for 2 doses, then 4 mg/kg q12h	2–<15 years: Oral suspension: 9 mg/kg q12h (max 350 mg/dose); IV: 6–9 mg/kg q12h for 2 doses, then 3–8 mg/kg q12h	Oral: Decreased; IV: N.A.

[a] Dosing weight, actual body weight (kg) unless indicated otherwise.
[b] Insufficient information available to make a recommendation.
[c] Specific dosing is dependent on indication.
[d] Pediatric dosing may be specific to age, weight (kg), and/or indication.
[e] Formulations are not interchangeable.
CrCl, creatinine clearance mL/min; GI, gastrointestinal; HD, hemodialysis; N.A., not applicable; PD, peritoneal dialysis; pHD, post hemodialysis; SLE, systemic lupus erythematosus.

Adult dose interval adjustment for reduced CrCl			Dosing in dialysis		Major toxicity
>50	10–50	≤10	HD	PD	
q24h	q24h	q24h	Usual	Usual	Fever, chills, nausea with infusion, renal insufficiency, anemia, hypokalemia, hypomagnesemia, flushing, hypertension
Usual	[b]	[b]	[b]	[b]	Fever, chills, nausea with infusion, renal insufficiency (less than amphotericin B conventional), anemia, hypokalemia, hypomagnesemia, flushing, hypertension
Usual	[b]	[b]	[b]	[b]	Fever, chills, nausea with infusion, renal insufficiency (less than amphotericin B conventional), anemia, hypokalemia, hypomagnesemia, flushing, hypertension
Usual	[b]	[b]	[b]	[b]	Fever, chills, nausea with infusion, renal insufficiency (less than amphotericin B conventional), anemia, hypokalemia, hypomagnesemia, flushing, hypertension
Usual	Usual	Usual	Usual	Usual	Infusion site reaction, hypokalemia, hypomagnesemia, GI disturbance, drug fever
Usual	Usual	Usual	Usual	Usual	Infusion site reaction, hypokalemia, hypomagnesemia, GI disturbance, drug fever
Usual	Usual	Usual	Usual	Usual	Elevated LFTs, nausea, taste disturbance
q24h	50% dose q24h	50% dose q24h	Usual dose 3 times weekly pHD on HD days	50% dose q24h	Headache, GI upset, hepatitis, elevated LFTs
q6h	q12–24h	q48h	q48–72h	[b]	Bone marrow suppression, hypoglycemia, hypokalemia, agranulocytosis, elevated LFTs
Usual	Usual	Usual	[b]	[b]	GI disturbance, allergic and photosensitivity reactions, blood dyscrasias, liver toxicity, exacerbation of SLE and leprosy
Usual	Usual	Usual	Usual	Usual	Peripheral edema, headache, fatigue, insomnia, hypokalemia, GI disturbance, elevated LFTs, dyspnea
Usual	Usual	Usual	Usual	Usual	Nausea, rash, headache, edema, hypokalemia, hepatotoxicity
Usual	Usual	Usual	Usual	Usual	Nausea, vomiting, gynecomastia, decreased testosterone synthesis, rash, hepatotoxicity, adrenal insufficiency
Usual	Usual	Usual	Usual	[b]	Thrombophlebitis, GI disturbance, abnormal LFTs, fever, rash, hyperkalemia, hypoglycemia, headache
Usual	Usual	Usual	Usual	Usual	Headache, GI disturbance
Usual	Usual	Usual	Usual	Usual	GI disturbance
Usual	Usual	Usual	[b]	[b]	GI disturbance, headache, hypokalemia, prolonged QT interval, hepatotoxicity
Usual	Usual; PO preferred due to accumulation of cyclodextrin	Usual; PO preferred due to accumulation of cyclodextrin	[b]	[b]	Photopsia, hepatotoxicity, CNS neurotoxicity (hallucinations), alopecia, and photosensitivity associated with later squamous cell carcinoma and melanoma (with prolonged use)

TABLE 211.4

Name		Usual dose		
Generic	**Brand**	**Adult**	**Child**	**Change in absorption with food**
Abacavir	Ziagen	0.3 g PO q12h	8 mg/kg PO q12h	Unchanged
Abacavir/ lamivudine	Epzicom	1 daily	[b]	Unchanged
Acyclovir	Zovirax	0.2–0.8 g PO 2–5×/d 5–12 mg/kg IV q8h	0.2 g 5×/d (HSV) PO 20 mg/kg PO q6h, max 800 mg q6h (VZV) 25–50 mg/kg/d IV q8h	Unchanged
Amantadine	Symmetrel	0.1 g PO q12h	2.2–4.4 mg/kg PO q12h	No data
Amprenavir		1.2 g PO q12h	[b]	Decreased with high-fat meal
Atazanavir	Reyataz	300–400 mg PO qd	[b]	Increased
Boceprevir	Victrelis	800 mg PO TID	[b]	Increased
Cidofovir	Vistide	5 mg/kg IV qwk ×2 wk, then 5 mg/kg q2wk	[b]	n/a
Darunavir	Prezista	600 mg PO BID with 100 mg PO ritonavir	[b]	Increased
Didanosine	Videx	0.167–0.2 g PO q12h	0.143–0.248 mg/m2 divided PO q12h	Decreased
Efavirenz	Sustiva	0.6 g PO qhs	[b]	Unchanged
Emtricitabine	Emtriva	200 mg PO qd	6 mg/kg PO sol qd (3 mo–17 yr)	Unchanged
Enfuvirtide	Fuzeon	90 mg SC BID	2 mg/kg SC BID	n/a
Entecavir	Baraclude	0.5–1 mg PO qd	>16 yr, 0.5–1 mg PO qd	Decreased
Etravirine	Intelence	200 mg PO BID	>6 yr, based on weight	Increased
Famciclovir	Famvir	0.125 g PO q12h (HSV) 0.5 g PO q8h (VZV)	[b]	Unchanged
Fosamprenavir	Lexiva	700–1,400 mg PO BID	[b]	Unchanged
Foscarnet	Foscavir	60 mg/kg IV q8h ×14–21 d; then 90 mg/kg/d	[b]	n/a
Ganciclovir	Cytovene	5 mg/kg IV q12h ×14–21 d; then 5 mg/kg/d	5 mg/kg IV q12h	IV: n/a
Indinavir	Crixivan	800 mg PO q8h	[b]	Decreased
Lamivudine	Epivir	150 mg PO q12h	4 mg/kg PO q12h	Unchanged

	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		
Pregnancy class[a]	>50	10–50	≤10	HD	PD	Major toxicity
C	Usual	Usual	[b]	[b]	[b]	Nausea, hypersensitivity reaction with myalgias, fever, rash; anaphylaxis
C	Usual	[b]	N.R.	N.R.	N.R.	See individual drugs
C	2–5×/d PO IV q8h	2–5×/d PO IV q12–24h	0.2–0.8 g PO q24h 2.5–6 mg/kg IV q24h	0.5 g PO pHD	2–5 mg/kg/d	Headache, rash, renal toxicity, CNS symptoms (rare)
C	q12h	0.1–0.2 g 2–3×/wk	0.1–0.2 g qwk	[b]	[b]	Livedo reticularis, edema, insomnia, dizziness, lethargy
[b]	Usual	Usual	Usual	No supplement	No supplement	Nausea, diarrhea, rash
B	Usual	Usual	Usual	No supplement	No supplement	Hyperbilirubinemia, rash
B	Usual	Usual	Usual	No supplement	No supplement	Anemia, neutropenia, hypersensitivity reactions, nausea, dysgeusia
C	Check prescribing information	Check prescribing information	Check prescribing information	[b]	[b]	Proteinuria, renal insufficiency, neutropenia
B	Usual	Usual	Usual	No supplement	No supplement	Erythema multiforme, neutropenia
B	q12h	q12–24h	100 mg PO q24h	Dose pHD	[b]	Diarrhea, nausea, vomiting, pancreatitis, peripheral neuropathy
D	Usual	Usual	Usual	Usual	Usual	Drowsiness, CNS side effects, rash
B	Usual	q48–72h	q96h	Give dose after dialysis session on HD days	[b]	Lactic acidosis, hepatotoxicity, neutropenia
B	Usual	Usual	[b]	[b]	[b]	Injection site reactions, hypersensitivity reaction
C	Usual	0.25 mg–0.15 mg PO qd	0.05 mg PO qd	0.05 mg pHD	0.05 mg P capd	Lactic acidosis, elevated transaminases
B	Usual	Usual	Usual	No supplement	No supplement	Skin, hypersensitivity reactions
B	0.5 g q8h; 0.125 g q12h	0.5 g q12–24h; 0.125 g q12–24h	0.25 g q48h; 0.125 g q48h	Dose pHD	[b]	Headache, nausea
C	[b]	[b]	[b]	[b]	[b]	Diarrhea, rash, nausea, hemolytic anemia (rare)
C	63–90 mg/kg/d maintenance	78–63 mg/kg/d maintenance	[b]	[b]	[b]	Renal dysfunction, anemia, nausea, disturbances of calcium, magnesium, phosphorus, potassium metabolism
C	q12h	2.5 mg/kg q24h	1.25 mg/kg q24h	1.25 mg/kg pHD	[b]	Neutropenia, thrombocytopenia
C	[b]	[b]	[b]	[b]	[b]	Nephrolithiasis, nausea, headache
C	150 mg PO q12h	100–150 g PO qd	25–50 mg PO qd	[b]	[b]	Headache, nausea, neutropenia, increased AST, and ALT

(*continued*)

TABLE 211.4 CONTINUED

Name		Usual dose		
Generic	**Brand**	**Adult**	**Child**	**Change in absorption with food**
Lopinavir/ritonavir	Kaletra	400/100 mg PO BID	12 mg/3 mg/kg PO BID 6 mo–12 yr	Increased
Maraviroc	Selzentry	150–600 mg PO BID	[b]	Unchanged
Nelfinavir	Viracept	0.75 g PO TID or 1.25 g PO q12h	0.2–0.3 mg/kg q8h	Increased
Nevirapine	Viramune	200 mg PO q24h ×14 d, then 200 mg PO q12h	[b]	Unchanged
Oseltamivir	Tamiflu	75 mg PO BID ×5 d	>1 yr, weight based. See prescribing information	Unchanged
Raltegravir	Isentress	400 mg PO BID	>2 yr, weight based. See prescribing information	Unchanged
Ribavirin	Copegus, Rebetol, Virazole	12–18 h/d ×3 d via aerosol, 0.4–0.6 g PO q12h, IV investigational	12–22 h/d × 6 d via aerosol	[b]
Rimantadine	Flumadine	0.1 g PO q12h	[b]	Unchanged
Rilpivirine	Edurant	25 mg PO daily	[b]	Increased
Ritonavir	Norvir	600 mg PO q12h	[b]	Unchanged
Saquinavir hard gel	Invirase	1.0 g PO q12h with 0.2 g PO ritonavir		Increased
Saquinavir soft gel		1.2 g PO TID		Increased
Stavudine	Zerit	0.04 g PO q12h	[b]	Unchanged
Telaprevir	Incivek	750 mg PO TID	[b]	Increased
Telbivudine	Tyzeka	600 mg PO qd	>16 yr 600 mg PO qd	Unchanged
Tenofovir	Viread	300 mg PO qd	[b]	Increased
Tenofovir/emtricitabine	Truvada	1 daily	[b]	Increased
Tenofovir/emtricitabine/efavirenz	Atripla	1 daily	[b]	Increased
Tenofovir/emtricitabine/elvitegravir/cobicistat	Stribild	1 daily	[b]	Increased
Tenofovir/emtricitabine/rilpivirine	Complera	1 daily	[b]	Increased

	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		
Pregnancy class[a]	>50	10–50	≤10	HD	PD	Major toxicity
C	[b]	[b]	[b]	[b]	[b]	Diarrhea, dyslipidemia, LFT elevation
B	Usual	Usual	[b]	[b]	[b]	Skin, hypersensitivity reactions, hepatotoxicity
B	Usual	Usual	Usual	Usual	Usual	Diarrhea, nausea
B	[b]	[b]	[b]	[b]	[b]	Rash, including Stevens–Johnson syndrome; hepatotoxicity
C	Usual	qd CrCl 10–30	[b]	[b]	[b]	Nausea, vomiting, headache
C	Usual	Usual	Usual	Usual	Usual	Insomnia, nausea, headache, fatigue
X	[b]	[b]	[b]	[b]	[b]	Anemia, headache, hyperbilirubinemia, bronchospasm
C	q12h	q12h	q12h	[b]	[b]	Fewer CNS side effects than amantadine
B	Usual	Usual	Use caution	Usual	Usual	Depressive disorders, elevated transaminases
B	Usual	Usual	Usual	Usual	Usual	Nausea, vomiting, diarrhea
B	Usual	Usual	Usual	Usual	Usual	Diarrhea, nausea
B	Usual	Usual	Usual	Usual	Usual	Diarrhea, nausea, headache
C	[b]	[b]	[b]	[b]	[b]	Peripheral neuropathy, liver toxicity
B	Usual	Usual	[b]	[b]	[b]	Skin reactions, hypersensitivity, anemia, nausea
B	Usual	q48h	q72h	q96h: give after the end the dialysis session on dialysis days	[b]	Lactic acidosis, myopathy, elevated CPK, elevated LFTs
B	Usual	q48h	Twice weekly	[b]	pHD q7d	Lactic acidosis, nephrotoxicity
B	Usual	N.R.	N.R.	N.R.	N.R.	See individual drugs
D	Usual	N.R.	N.R.	N.R.	N.R.	See individual drugs
B	Usual	N.R.	N.R.	N.R.	N.R.	Renal insufficiency, do not initiate if CrCl <70. Lactic acidosis
B	Usual	N.R.	N.R.	N.R.	N.R.	See individual drugs

(*continued*)

TABLE 211.4 CONTINUED

Name		Usual dose		
Generic	**Brand**	**Adult**	**Child**	**Change in absorption with food**
Tipranavir	Aptivus	500 mg PO BID with 200 mg PO ritonavir	[b]	Unchanged
Valacyclovir	Valtrex	1 g PO TID (VZV); 0.5 g PO BID (HSV)	Unchanged	No effect
Valganciclovir	Valcyte	900 mg PO q12h × 21 d, then 900 mg PO q24h	[b]	Increased
Vidarabine		10–15 mg/kg/d IV over 12 h	10–15 mg/kg/d IV over 12 h	n/a
Zalcitabine		0.375–0.75 g PO q8h	0.75 g PO q8h (children >13 yr)	Decreased
Zanamivir	Relenza	10 mg BID by inhaler × 5d	5 mg BID by inhaler × 5 d, >6 yr	No change
Zidovudine	Retrovir	0.1 g PO q4h or 0.2 g PO q8h 1–2 mg/kg IV q4h	180 mg/m^2 PO q6h	Decreased

[a] Food and Drug Administration pregnancy categories: A = adequate studies in pregnant women, no risk; B = animal studies no risk, human studies inadequate, or animal toxicity, abnormalities in humans, risk exceeds benefit.
[b] Insufficient information available to make a recommendation.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; AWP, average wholesale price; capd, continuous ambulatory peritoneal dialysis; CNS, central nervous system; approved; N.R., not recommended; P, post; PD, peritoneal dialysis; pHD, post hemodialysis; VZV, varicella-zoster virus.
Unit price is per dose.
From 2013 Red Book Online.

	Dose interval adjustment for reduced CrCl			Supplemental dose in dialysis		
Pregnancy class[a]	>50	10–50	≤10	HD	PD	Major toxicity
C	Usual	Usual	Usual	Usual	[b]	Diarrhea, hepatotoxicity, hyperlipidemia, bleeding
B	Usual	q12–24h	0.5 g q24h	0.5 g q24h	0.5 g q24h	Nausea, headache; thrombotic thrombocytopenic purpura in immunocompromised patients
C	Usual	0.45 g q12–48h	N.R.	N.R.	N.R.	Neutropenia, thrombocytopenia
Not established	Usual	Usual	10 mg/kg/d over 12 h	Usual dose pHD	[b]	GI disturbance, nausea, vomiting, thrombophlebitis
C	q8h	q12h	q24h	[b]	[b]	Peripheral neuropathy, stomatitis, esophageal ulcers, pancreatitis
C	Usual	Usual	Usual	Usual	Usual	Bronchospasm, nasal and throat discomfort
C	q4h	q6h	q6–12h	100 mg pHD	100 mg q6–12h	Anemia, granulocytopenia, headache, nausea, insomnia, nail pigment changes

human studies no risk; C = animal studies show toxicity, human studies inadequate but benefit may exceed risk; D = evidence of human risk, benefit may outweigh risk; X = fetal

CPK, creatine phosphokinase; CrCl, creatinine clearance mL/min; GI, gastrointestinal; HD, hemodialysis; HSV, herpes simplex virus; LFT, liver function test; N.A., not

TABLE 211.5

Name		Usual dose		Change in absorption with food
Generic	**Brand**	**Adult**[a,c]	**Pediatric**[a,d]	
Albendazole	Albenza	400 mg PO q12–24h	>2 years: 400 mg PO q12–24h	Increased
Artemether–lumefantrine	Coartem	400 mg PO, repeat in 8 h then twice daily for 48 h	Weight-based, see full prescribing information	Increased
Artemisinine		10 mg/kg/d ×5 d	Same as adult	[b]
Atovaquone	Mepron	750 mg PO q12h	1–3 months: 30 mg/kg PO q24h; 4–24 months: 45 mg/kg PO q24h; >24 months: 30 mg/kg PO q24h; (max: 1,500 mg/d)	Increased
Benznidazole[e]		5–7 mg/kg/d PO divided q12h (max 300 mg/d)	5–8 mg/kg PO q12h	Unchanged
Bithionol[f]	Bitin	30–50 mg/kg on alternate days ×10–15 d	Same as adult	[b]
Chloroquine phosphate	Aralen phosphate	1 g (600 mg base) PO on day 1, followed by 500 mg (300 mg base) 6h, 24h, and 48h following first dose	16.6 mg/kg chloroquine phosphate (max dose: 1 g) PO; followed by 8.3 mg/kg chloroquine phosphate (max: 500 mg/dose) PO at 6h, 24h, and 48h following first dose	Unchanged
Dehydroemetine[f]		1 mg/kg/d (max 60 mg/d) IM for 4–6 days	1 mg/kg/d IM for max of 5 days	n.a
Diethyl carbamazine[f]	Hetrazan	Day 1: 50 mg PO Day 2: 50 mg PO q8h Day 3: 100 mg PO q8h Days 4–14: 6 mg/kg/d divided q8h	Day 1: 1 mg/kg PO Day 2: 1 mg/kg PO q8h Day 3: 1–2 mg/kg PO q8h Days 4–21: 2 mg/kg PO q8h	Increased
Diloxanide furoate[e]	Furamide	500 mg PO q8h for 10 days	[b]	[b]
Eflornithine[e]	Ornidyl	400 mg/kg/d IV divided QID × 14 d, then 300 mg/kg/d PO ×3–4 wk	[b]	[b]
Furazolidone	Furoxone	100 mg PO q6h for 7–10 days	1.25–1.5 mg/kg PO q6h for 5–10 days	[b]
Halofantrine	Halfan	500 mg PO q6h for 3 doses, repeat in 1 wk	<37 kg: 8 mg/kg q6h for 3 doses; repeat in 1 week; ≥37 kg: use adult dosing	Increased
Hydroxychloroquine sulfate salt	Plaquenil	800 mg once, followed by 400 mg at 6h, 24h, and 48h following first dose (total dose: 2 g)	12.9 mg/kg hydroxychloroquine (max dose: 800 mg); followed by 6.5 mg/kg at 6h, 24h, and 48h following first dose; (max: 400 mg/dose)	Increased

Dose interval adjustment for reduced CrCl			Dosing in dialysis		
>50	10–50	≤10	HD	PD	Major toxicity
Usual	Usual	Usual	Usual	[b]	Diarrhea, abdominal discomfort, elevated AST, ALT and bone marrow suppression, alopecia with high dose
Usual	Usual	[b]	[b]	[b]	Headache, anorexia, fever, QT prolongation
Usual	[b]	[b]	[b]	[b]	Transient heart block, elevated AST and ALT, neutropenia, decreased reticulocyte count, abdominal pain, diarrhea, fever
Usual	Usual	Usual	Usual	Usual	Rash, GI disturbance, fever, headache, insomnia, myalgia, flu-like symptoms
[b]	[b]	[b]	[b]	[b]	Peripheral neuropathy, rash, bone marrow suppression, weight loss, GI disturbance
[b]	[b]	[b]	[b]	[b]	Hypotension, wheezing, angioedema, rash, hyperthermia, diarrhea, anorexia, nausea, vomiting, dizziness, headache
Usual	Usual	No Adjustment with Short-term Use	No Adjustment with Short-term Use	No Adjustment with Short-term Use	Blurred vision (retinopathy with prolonged use), GI effects, pruritus, hemolysis in patients with G6PD deficiency, hypoglycemia,
[b]	[b]	[b]	[b]	[b]	Arrhythmias, precordial pain, pain at injection site, muscle weakness, GI disturbance, neuropathy, heart failure, headache
Usual	[b]	[b]	[b]	[b]	Headache, malaise, arthralgia, nausea, vomiting, anorexia, pruritus, fever, hypotension, lymphadenitis, encephalopathy
[b]	[b]	[b]	[b]	[b]	Flatulence
Usual	[b]	[b]	[b]	[b]	Anemia, thrombocytopenia, leukopenia, nausea, vomiting, diarrhea, transient hearing loss
[b]	[b]	[b]	[b]	[b]	GI disturbance, yellow-brown discoloration of urine, rash, fever, headache, hemolysis in patients with G6PD deficiency
Usual	[b]	[b]	[b]	[b]	Abdominal pain, vomiting, diarrhea, headache, pruritus, rash
Usual	[b]	[b]	[b]	[b]	Blurred vision, GI disturbance, pruritus, rash, headache, QTc prolongation, abnormal LFTs, cardiomyopathy (rare), hypoglycemia, bone marrow suppression, neuromuscular effects (long-term use)

(*continued*)

TABLE 211.5 CONTINUED

Name		Usual dose		Change in absorption with food
Generic	Brand	Adult[a,c]	Pediatric[a,d]	
Iodoquinol	Yodoxin, Diquinol	650 mg PO q8h	40 mg/kg/d PO divided q8h	Unchanged
Ivermectin	Stromectol	150–200 mcg/kg/dose PO	≥15 kg: 150–200 mcg/kg/dose PO	Decreased
Mebendazole	Vermox	100–200 mg PO q12h	Same as adults	Unchanged
Mefloquine	Lariam	750 mg PO once, followed by 500 mg PO 6–12 hrs after first dose	15 mg/kg PO once (maximum: 750 mg/dose) followed by 10 mg/kg PO 6–12 hrs after first dose	Increased
Meglumine antimonate[e]	Glucantine	20 mg/kg IV ×2 d (850 mg/d limit)	[b]	n.a
Melarsoprol B[f]	Mel B, Arsobal	2.2 mg/kg/d IV for 10 days	2.2 mg/kg/d IV for 10 days	n.a
Niclosamide	Niclocide	2 g PO q24h	50 mg/kg PO q24h	N.A.
Nifurtimox[f]	Lampit	8–15 mg/kg/d PO divided q6–8h	1–10 years: 15–20 mg/kg/d PO; 11–16 years: 12.5–15 mg/kg/d PO; ≥17 years: 8–10 mg/kg/d PO divided q6–8h	[b]
Niridazole[e]	Ambilhar	[b]	[b]	[b]
Oxamniquine[e]	Vansil	15 mg/kg PO q12–24h once	10–15 mg/kg/dose PO q12h	Increased
Paromomycin	Humatin	25–35 mg/kg/d PO divided q8h	25 to 35 mg/kg/d PO divided q6–12h	Unchanged
Pentamidine	Pentam, Nebupent	3–4 mg/kg IV q24h	3–4 mg/kg IV q24h	n/a
Piperazine citrate[e]	Antepar	2–3.5 g/d PO for 2–7 days	75 mg/kg/d (max: 3.5 g) PO for 2 days	[b]
Praziquantel	Biltricide	40–75 mg/kg/d PO divided q8–12h	25 mg/kg PO q8h	Increased
Primaquine phosphate		30 mg (base) PO q24h	0.5 mg/kg (base) PO q24h	Unchanged
Proguanil HCl/atovaquone	Malarone	400/1,000 mg PO q24h (treatment)	31.25/12.5 mg–1,000/400 mg PO q24h (depending on weight) (treatment)	Increased
Pyrantel pamoate	Antiminth, Pin-X	11 mg base/kg (max 1 g/d) PO once	≥2 years: 11 mg/kg/d PO once	Unchanged

Dose interval adjustment for reduced CrCl			Dosing in dialysis		
>50	10–50	≤10	HD	PD	Major toxicity
Usual	[b]	[b]	[b]	[b]	Optic neuritis, peripheral neuropathy, GI disturbance, skin eruptions, vertigo, fever, chills
Usual	[b]	[b]	[b]	[b]	Mazzotti reaction, fever, lymphadenitis, arthralgia
Usual	[b]	[b]	[b]	[b]	Diarrhea, nausea, vomiting, abdominal pain, fever, headache, neutropenia, thrombocytopenia, hepatitis
Usual	Usual	Usual	Usual	[b]	Vertigo, nightmares, insomnia, GI disturbance, sinus bradycardia, visual disturbance
Usual	[b]	[b]	[b]	[b]	Bradycardia, hypotension, rashes, facial edema, injection site pain, pancreatitis, leukopenia, nephrotoxicity
Usual	[b]	[b]	[b]	[b]	Encephalopathy, phlebitis, peripheral neuropathy, Jarisch-Herxheimer-like reaction, hepatic dysfunction, hypertension, arthralgia, GI disturbance, fever, hemolysis in patients with G6PD deficiency
Usual	Usual	Usual	Usual	Usual	Nausea, abdominal discomfort, diarrhea, drowsiness, dizziness, headache
Usual	[b]	[b]	[b]	[b]	GI disturbance, weight loss, restlessness, insomnia, paresthesias, seizures, rash, neutropenia, hepatitis, hemolysis in patients with G6PD deficiency
Usual	[b]	[b]	[b]	[b]	Seizures, hallucinations
Usual	[b]	[b]	[b]	[b]	Dizziness, drowsiness, headache, nausea, vomiting, abdominal pain, orange-red discoloration of urine, fever, hepatitis, EEG changes, hallucinations
Usual	Usual	Usual, Monitor for ototoxicity	Usual, Monitor for ototoxicity	Usual, Monitor for ototoxicity	GI disturbance, rash, headaches, vertigo, nephrotoxicity, ototoxicity
Usual	Usual	4 mg/kg q48h	[b]	[b]	Nephrotoxicity, hypotension, sterile abscess with IM injection, hypoglycemia or hyperglycemia, nausea, vomiting, abdominal pain, pancreatitis, hypocalcemia, cough and bronchospasm with inhalation, QTc prolongation, bone marrow suppression, increased LFTs
Usual	N.R.	N.R.	[b]	[b]	GI disturbance, headache, dizziness, rash, hemolytic anemia, ataxia
Usual	Usual	Usual	Usual	[b]	Malaise, bitter taste, headache, dizziness, sedation, GI disturbance, fever, sweating, fatigue, pruritus, rash
Usual	Usual	Usual	[b]	[b]	Hemolytic anemia in patients with G6PD deficiency (must screen prior to start), methemoglobinemia, leukopenia, neutropenia, GI disturbance, blurred vision, pruritus
Usual	CrCl ≤30 mL/min N.R.	N.R.	N.R.	N.R.	Pruritus, GI Disturbance, increased LFTs, hepatitis, asthenia, headache, neutropenia, pancytopenia
Usual	[b]	[b]	[b]	[b]	GI disturbance, dizziness, drowsiness, headache

(*continued*)

TABLE 211.5 CONTINUED

Name		Usual dose		Change in absorption with food
Generic	Brand	Adult[a,c]	Pediatric[a,d]	
Pyrimethamine	Daraprim	25–75 mg PO q24h	1–2 mg/kg PO q24h (max 50 mg/d)	[b]
Pyrimethamine/sulfadoxine	Fansidar	2–3 tablets PO once	>2years: 5–10 kg: ½ tab PO once 11–20 kg: 1 tab PO once 21–30 kg:1½ tabs PO once 31–45 kg: 2 tabs PO once >45 kg: 3 tablets PO once	[b]
Quinacrine Hcl[e]	Atabrine	100 mg PO q8h	2 mg/kg (max dose: 100 mg) PO q8h for 5 days	[b]
Quinidine gluconate	Quinaglute	6.25 mg base/kg IV over 1–2 hrs, then 0.0125 mg base/kg/min	Same as adult	Increased
Quinine sulfate	Legatrin Quinamm	650 mg PO q6–8h	10 mg/kg PO q8h	Increased
Spiramycin[e]	Rovamycine	1 g (3 million units) PO q8h	[b]	Unchanged
Stibogluconate	Pentostam	20 mg/kg IV q24h	20 mg/kg IV q24h	n.a
Suramin[f]	Germanin	1 g IV qwk ×5 wk (100-mg test dose)	[b]	n/a
Thiabendazole	Mintezol	50 mg/kg/d PO divided q12–24h	25 mg/kg (max 1.5 g) PO q12h	[b]
Trimetrexate	Neutrexin	45 mg/m2/d with leucovorin 20 mg/m2 q6h; continue leucovorin at least 72 h after last dose	[b]	n/a

[a] Dosing weight, actual body weight (kg) unless indicated otherwise.
[b] Insufficient information available to make a recommendation.
[c] Specific dosing is dependent on indication.
[d] Pediatric dosing may be specific to age, weight (kg), and/or indication.
[e] Not available in the United States.
[f] Available from the Centers for Disease Control and Prevention drug service.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance mL/min; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; HD, he-

Dose interval adjustment for reduced CrCl			Dosing in dialysis		
>50	10–50	≤10	HD	PD	Major toxicity
Usual	Usual	Usual	Usual	[b]	Reversible bone marrow suppression with high doses, megaloblastic anemia, folate deficiency, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, GI disturbance, headache, dizziness
Usual	[b]	[b]	[b]	[b]	Folic acid deficiency (leading to megaloblastic anemia and pancytopenia, hemolytic anemia, leukopenia, thrombocytopenia), elevated LFTs, GI disturbance, headache, dizziness, insomnia, Stevens-Johnson Syndrome, toxic epidermal necrolysis, interstitial nephritis, crystalluria, hypersensitivity pneumonitis, jaundice, hepatitis, polyneuritis, atrophic glossitis
Usual	[b]	[b]	[b]	[b]	Bitter taste, dizziness, headache, GI disturbance, yellow discoloration of skin/urine (dose dependent), acute psychosis, restlessness, insomnia, rash
Usual	Usual	Usual loading dose, reduce maintenance by 50–75% on 3rd day	[b]	[b]	Cardiac toxicity (close monitoring required), tachycardia, QTc prolongation, flattening t-wave, ventricular arrhythmias, hypoglycemia, hypotension, hemolytic anemia (G6PD deficiency), tinnitus, thrombocytopenia, elevated LFTs, rash, torsades de pointes
Usual	Usual	650 mg q24h	[b]	[b]	Cardiac toxicity, flushing, pruritus, rash, fever, tinnitus, headache, nausea, thrombocytopenia, hemolysis in patients with G6PD deficiency, hypoglycemia, hepatitis
Usual	[b]	[b]	[b]	[b]	QT interval prolongation, vasculitis, rash, diarrhea, increased LFTs, leukopenia, thrombocytopenia, cholestatic hepatitis, dizziness, dry mouth
Usual	[b]	[b]	[b]	[b]	Abdominal pain, nausea, vomiting, malaise, headache, elevated AST and ALT, nephrotoxicity, myalgia, arthralgia, fever, rash, cough, prolonged QTc
Usual	[b]	[b]	[b]	[b]	Nausea, vomiting, shock, loss of consciousness, death during administration; fever, rash, exfoliative dermatitis, paresthesia, photophobia, renal insufficiency, diarrhea
Usual	[b]	[b]	[b]	[b]	GI disturbance, asthenia, disorientation, vertigo, drowsiness, rash, headache, leukopenia, olfactory disturbance, hepatotoxicity, Stevens-Johnson syndrome, toxic epidermal necrolysis
Usual	[b]	[b]	[b]	[b]	Neutropenia (must be given with leucovorin); rash; elevated AST and ALT; reversible peripheral neuropathy

modialysis; LFT, liver function tests; N.A., not approved; N.R., not recommended; PD, peritoneal dialysis.

New Drugs

Artesunate Anti-malarial

Suggested reading

Cunha BA, Torres DC, Cunha CB et al. Antimicrobial drug summaries. In Cunha CB, Cunha BA, eds. *Antibiotic essentials*, 17th ed. New Delhi: Jaypee Publishing; 2020.

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