Acute Inflammatory Surgical Disease

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KEYWORDS

• Appendicitis • Cholecystitis • Cholangitis • Pancreatitis • Diverticulitis
• Clostridium difficile • Colitis

KEY POINTS

- Computed tomography is the most accurate way to diagnose appendicitis and its complications. Abscesses should be percutaneously drained, phlegmon treated with antibiotics, and appendectomy performed in most other cases.
- Immediate laparoscopic cholecystectomy is standard treatment for acute cholecystitis, though percutaneous cholecystostomy is effective in high risk patients. Cholangitis should be treated with endoscopic retrograde cholangiography and sphincterotomy.
- Infected pancreatic necrosis is the primary indication for intervention in pancreatitis. A "step-up" approach beginning with percutaneous or endoscopic drainage and proceeding to surgical debridement when necessary should be used.
- Diverticulitis without abscess or with small abscess should be treated with antibiotics alone. Large diverticular abscesses should be percutaneously drained. In cases of free perforation with peritonitis mandating surgery, primary anastomosis with or without proximal diversion should be considered.
- Subtotal colectomy with end ileostomy is standard surgical therapy for medically refractory Clostridium difficile colitis. There may be a role for ileostomy with antegrade colonic lavage.

Infectious and inflammatory diseases comprise some of the most common gastrointestinal disorders resulting in hospitalization in the United States. Accordingly, they occupy a significant proportion of the workload of the acute care surgeon.

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APPENDICITIS

Key points

- Young men with a typical clinical presentation do not require imaging.
- Computed tomography with intravenous contrast is the imaging modality of choice when required.
- Perforated appendicitis with abscess should be treated with percutaneous drainage.
- Perforated appendicitis with phlegmon should be treated with antibiotics alone.
- Laparoscopic appendectomy results in fewer surgical infections than open appendectomy.

In 1886, Reginald Fitz of Boston, in his monograph "Diseases of the Vermiform Appendix," correctly identified the appendix as the primary cause of right lower quadrant inflammation and coined the term appendicitis. Appendicitis is the most common problem of the colon, affecting approximately 300,000 patients a year and some estimate 8% of the Western country population will face appendicitis some time in their lives.[1] In the past, reliance on physical examination and laboratory findings have been the mainstay of diagnosis but in the era of computed tomography and ultrasound imaging, studies are increasingly accepted to assess for appendicitis. The standard treatment has traditionally been open appendectomy, but the number of laparoscopic appendectomies has now surpassed the number of open appendectomies in the United States. Even more recently, there has been a growing debate regarding the nonoperative approach to appendicitis, namely treatment with antibiotics. We review the basic diagnostic options and describe treatment options for acute appendicitis, including the treatment of the perforated appendicitis or delayed presentations.

Clinical History and Physical Examination

Appendicitis typically occurs as a result of the obstruction of the appendiceal lumen that subsequently results in ischemia and inflammation. This ischemia and inflammation evolves over several hours and is the cause of early visceral pain that then localizes to the right lower quadrant. The obstruction is typically the result of a fecolith or adenitis.[2] These processes lead to necrosis and perforation of the appendix, which occur usually after at least 48 hours of symptoms. The bacteriology of appendicitis is a mixed enteral flora, including *Escherichia coli*, *Streptococcus viridans*, and *Bacteroides* species.

The clinical history of appendicitis typically includes a 24-hour to 48-hour progression of vague periumbilical pain that migrates and becomes more localized to the right lower quadrant. The tenderness is usually a localized peritonitis with additional manifestations of pain on coughing (Dunphy sign), pain with flexion and internal rotation of the right hip (obturator sign), pain with passive extension of the right hip (psoas sign), or pain in the right lower quadrant during palpation of the left lower quadrant (Rovsing sign). In addition, patients may have tenderness with rectal examination.

The typical laboratory findings include a mild to moderate leukocytosis with a left shift, a urinalysis showing a few white blood cells, and other laboratory findings of inflammation, such as elevated C-reactive protein. The differential diagnosis of right lower quadrant tenderness includes sigmoid diverticulitis (secondary to a redundant sigmoid that reaches across the midline), cecal diverticulitis, retroperitoneal or rectus sheath hematoma, viral enteritis, Crohn disease, perforating colonic carcinoma, and, in women, a number of gynecologic pathologies. A meta-analysis done by Andersen[3]

found that the history of migration of pain, peritoneal irritation, and elevated laboratory findings suggestive of an inflammatory process were the great predictors of appendicitis. Despite the history, physical findings, and laboratory findings, it is clear that there is no single confirmatory test. The use of physical examination, history, and laboratory values has in the past resulted in negative appendectomy rates of about 15%. One study also attributed $740 million in hospital charges in the 1990s to negative appendectomies.[4] As a result, a number of scoring systems have been developed to improve the positive predictive value of a combination of factors.

The most commonly used and referenced is the Alvarado or MANTRELS scoring system (**Table 1**).[5] Although the ability of the score, which is a compilation of multiple signs, symptoms, and laboratory values, is better than any individual piece of data, it does not have the power to reliably rule in or rule out appendicitis by itself. A score of 7 to 10 warrants appendectomy and those less than 7 are observed. Using this scoring system, there remains an 11% negative appendectomy rate, albeit improved from the 15% rate that is typical without using the score.

Radiographic Imaging

The continued evolution of ultrasound and computed tomography (CT) technology has significantly improved the sensitivity and specificity. Ultrasonography in adults has a sensitivity of approximately 83% with a specificity of approximately 93%. CT scan has a sensitivity of approximately 94% with a 94% specificity.[6] Therefore, whether to use either ultrasonography or CT to rule in or rule out the diagnosis is now an important consideration. The downside to CT is the ionizing energy and cost. The current recommendations of the Surgical Infection Society and Infectious Disease Society of America guidelines is to obtain helical CT with intravenous (IV) contrast as the test of choice when imaging is necessary.[7] Oral and rectal contrast are not necessary components of the imaging. The use of CT scanning has reduced negative appendectomy rates further to approximately 2.6%.[8] A proposed diagnostic algorithm is depicted in **Fig. 1**.

Treatment

Once the diagnosis of appendicitis is made, there are a few options for treatment: (1) appendectomy (open vs laparoscopic), (2) antibiotics, and (3) percutaneous drainage and antibiotics. The open appendectomy, first described by McBurney in 1889,[9] is a classic approach to appendicitis but has for the most part been replaced in the United

Table 1
Alvarado score

	Variable	Value
Symptoms	Migration	1
	Anorexia	1
	Nausea-vomiting	1
Signs	Tenderness in right left quadrant	2
	Rebound tenderness	1
	Fever	1
Laboratory Values	White blood cells >10,000/μL	2
	Shift to the left (>75% neutrophils)	1
Total Score		10

Adapted from Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med 1986;15:557–64.

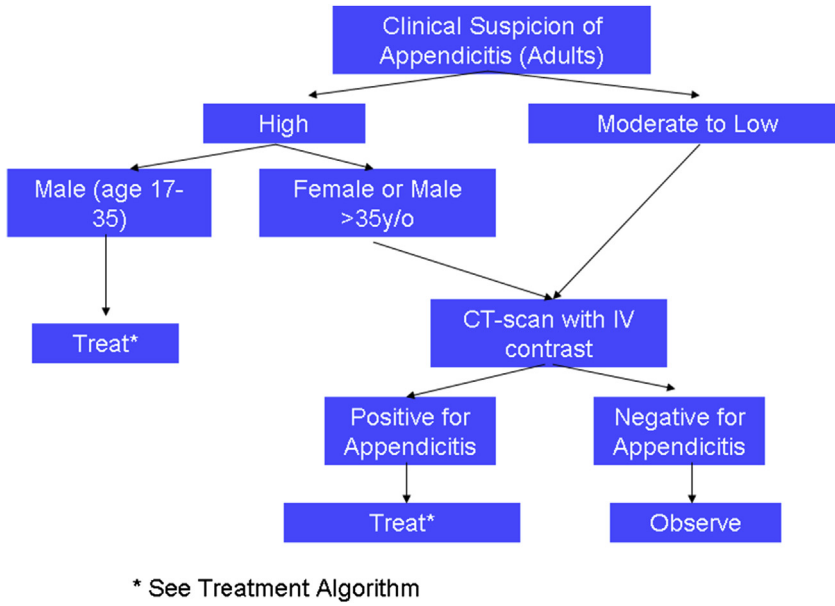

Fig. 1. Algorithm for diagnosis of acute appendicitis. y/o, years old.

States by laparoscopic appendectomy, first described by Semm in 1983.[10] In 2010, Ingraham and others[11] conducted a study using the American College of Surgeons National Surgical Quality Improvement Program across 222 hospitals. This study found that 76.4% of appendectomies were performed laparoscopically. Overall morbidity and surgical site infections were significantly lower in those who underwent laparoscopic surgery. Although this study supported the use of laparoscopic surgery, there were differences among the groups and they were not randomized. There are a number of randomized trials and in 2010 an update of a Cochrane meta-analysis found that the methodology in the randomized trials was moderate to poor but that there was an increased intra-abdominal infection with laparoscopic appendectomy, whereas open appendectomy had an increased risk of incisional infections. Overall, there is a decreased incidence of surgical infections using the laparoscopic approach; however, given the lack of definitive data, the open technique is still a viable option.

Although the surgical dictum since 1889 has been to remove the inflamed appendix, other inflammatory intra-abdominal processes, such as diverticulitis, have been increasingly treated with antibiotics rather than surgery. There is no question that there are complications associated with surgery for appendicitis and that resolution without surgery has been described. This has led some to consider more routine treatment of appendicitis with antibiotics. In 2006, Styrud and colleagues[12] undertook a randomized controlled trial to evaluate antibiotic treatment versus appendectomy. In 6 hospitals in Sweden they randomized 252 male patients to either antibiotic treatment (2 g IV cefotaxime twice a day for 2 days and 0.8 g tinidazole once daily followed by 10 days of oral ofloxacin) versus appendectomy (open or laparoscopic). Of the 128 randomized to antibiotics, 85% were successfully treated without surgery; 18 of the 128 were operated on within 24 hours and all but one had an acute appendicitis. There were no differences in the number of perforated appendicitis between the 2 groups. The rate of recurrence of symptoms was 14% during the 1-year follow-up. Since

then, a follow-up study in Sweden randomized 369 male and female unselected patients to antibiotics versus surgery, which also demonstrated a 14% recurrence rate at 1 year.[13] Efficacy of antibiotic treatment was 90%.

In those patients who present with an appendiceal abscess, the diagnosis is confirmed with CT scan and treatment is typically with a percutaneously placed drain and antibiotics. A number of studies comparing early appendectomy to percutaneous drainage and antibiotic treatment in the setting of appendiceal abscess have favored percutaneous drainage and antibiotics. A treatment algorithm is proposed in **Fig. 2**.

ACUTE CHOLECYSTITIS/CHOLANGITIS

Key points

- Immediate cholecystectomy is the treatment of choice for acute cholecystitis.
- Cholecystostomy tube is a very effective option for poor-risk patients.
- Immediate endoscopic retrograde cholangiopancreatography (ERCP) is the preferred treatment for cholangitis.

Acute cholecystitis is the most common inflammatory process of the biliary tree, occurring in 20% to 30% of patients with symptomatic biliary colic. The inflammatory process may be calculous or acalculous in origin, most commonly calculous. It is estimated that 20 million people are diagnosed with gallstones, with more than a million hospitalizations and 700,000 operative procedures per year.[14] By the age of 70, 15% of men and 24% of women have gallstones, and this number increases to 24% and 35%, respectively, by the age of 90.[15,16] However, two-thirds of those with gallstones are asymptomatic.[17] The risk of becoming symptomatic is approximately 1% to 4% per year.[18] Calculous cholecystitis is caused by the acute obstruction of the cystic duct by a gallstone. Acalculous cholecystitis is an inflammatory process that is related to stasis and dysfunction of the gallbladder and is most commonly associated with a systemic critical illness.

Calculous Acute Cholecystitis

Once the cystic duct is obstructed, patients present with increasing right upper quadrant pain that often migrates from the epigastrium. This pain may be associated with

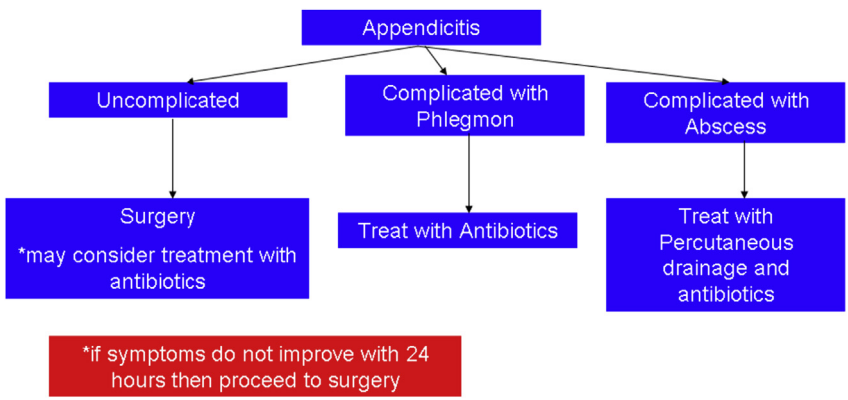

Fig. 2. Algorithm for treatment of acute appendicitis.

nausea and vomiting, fever, and malaise. On physical examination the patient will demonstrate right upper quadrant tenderness, which may include a Murphy sign. The Murphy sign is tenderness on inspiration with palpation overlying the gallbladder that causes the patient to arrest their attempt at a full inspiration. It is uncommon for patients to become jaundiced, but they may present with mild jaundice. Often this mild obstructive pattern is the result of a partial obstruction of the right hepatic duct or common bile duct by the inflamed gallbladder (Mirizzi syndrome).[19] Typical laboratory values include a moderately elevated white blood cell count in the range of 10 to 17 cells/mm^3, mild elevation of total bilirubin, alkaline phosphatase, transaminases, or amylase.[6]

The diagnosis is usually made by the combination of history, physical examination, and laboratory findings; however, imaging provides important additional information. The most helpful initial imaging study is the ultrasound of the right upper quadrant. This study provides the surgeon with evidence of cholelithiasis with a sensitivity and specificity greater than 95%.[5,20] It can also demonstrate ultrasonographic signs of acute cholecystitis, including a thickened gallbladder wall (>4 mm), pericholecystic fluid, and a sonographic Murphy sign (more sensitive than the traditional Murphy sign because the probe can be accurately applied directly to the gallbladder). A positive ultrasonic Murphy sign has a sensitivity and specificity of approximately 85% to 95% for acute cholecystitis. This study also provides information regarding the size of the common bile duct (normal <8 mm), although the sensitivity for gallstones in the common bile duct is low due to overlying duodenal air. A hepatobiliary iminodiacetic acid scan is the use of radiotracer that is excreted in the bile. This study is a functional one and will demonstrate a lack of bile flow into the gallbladder, which is suggestive of an obstructed cystic duct; however, this test is not the first-line test for acute cholecystitis due to lack of wide rapid availability and cost.[21] The role of CT scan is limited but may be used in cases in which the ultrasound, serum tests, history, and physical are equivocal and to assess for other potential causes of abdominal pain when the diagnosis is unclear.

The duration of the obstruction and inflammation is related to the severity of gallbladder wall ischemia. The ischemia leads to the spectrum of disease ranging from inflammation, purulent cholecystitis gallbladder, emphysematous gallbladder, to frank necrosis (**Fig. 3**) and perforation. The gallbladder may become secondarily infected as a result of the stasis of bile with *E coli* and *Klebsiella* being the most common organisms.

Treatment

Treatment of acute calculus cholecystitis is supportive with a nasogastric tube if nausea or vomiting persists, nothing by mouth, IV fluids, antibiotics, and cholecystectomy (laparoscopic or open). The timing of the cholecystectomy has drawn some debate over the years, but a few randomized controlled trials have concluded that cholecystectomy within 24 to 72 hours is advantageous compared with delayed cholecystectomy.[22] The conversion rate from laparoscopic to open is similar in these patients and the complication rate is lower in the immediate cholecystectomy groups. Therefore, it is generally recommended to perform a cholecystectomy within 24 hours of the patient's admission. During this time period, the laparoscopic cholecystectomy is occasionally made easier by planes developed by edema. For patients presenting with 5 or more days of symptoms, some debate still remains whether immediate cholecystectomy is appropriate or is associated with high rates of open conversion and complications. This question has not been directly studied. If the patient is deemed not a surgical candidate, then the gallbladder may be

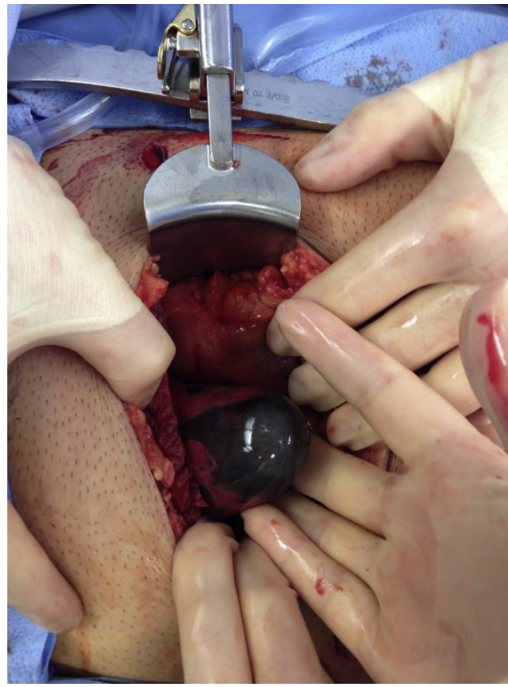

Fig. 3. Necrotizing cholecystitis.

percutaneously drained. Percutaneous drainage is more than 90% effective and patients usually improve within 24 hours after drainage. If improvement has not occurred by 24 hours, then one may consider the possibility of medical failure and may have to revert to cholecystectomy. The role and timing of percutaneous cholecystostomy has not been clearly defined according to a recent meta-analysis.[23] However, it is clear that particularly in the high-risk elderly that it is an effective and at times definitive treatment.[24] The timing of, need for, and optimal technique for interval cholecystectomy after percutaneous cholecystostomy tube placement has not been definitively studied. We typically perform cholecystostomy tube injection 4 to 6 weeks after drainage. If tube injection shows a persistently occluded cystic duct, we recommend cholecystectomy in all but the most medically infirm patients. If the cystic duct is patent, the risks and benefits of cholecystectomy can be determined on a case-by-case basis. A complete algorithm for management of acute cholecystitis is provided in **Fig. 4**.

Acalculous Cholecystitis

Only 5% to 10% of all cases of cholecystitis are acalculous. The symptoms are similar to calculous cholecystitis but usually occur in the face of concomitant critical illness. The illness may be medical or traumatic. An underlying sepsis or state of shock is often associated with acalculous cholecystitis and, therefore, early treatment with antibiotics and an intervention are warranted. Most cases are treated with percutaneous cholecystostomy but cholecystectomy is an option. The mortality rate for this condition may be up to 40% because of the associated comorbid conditions.

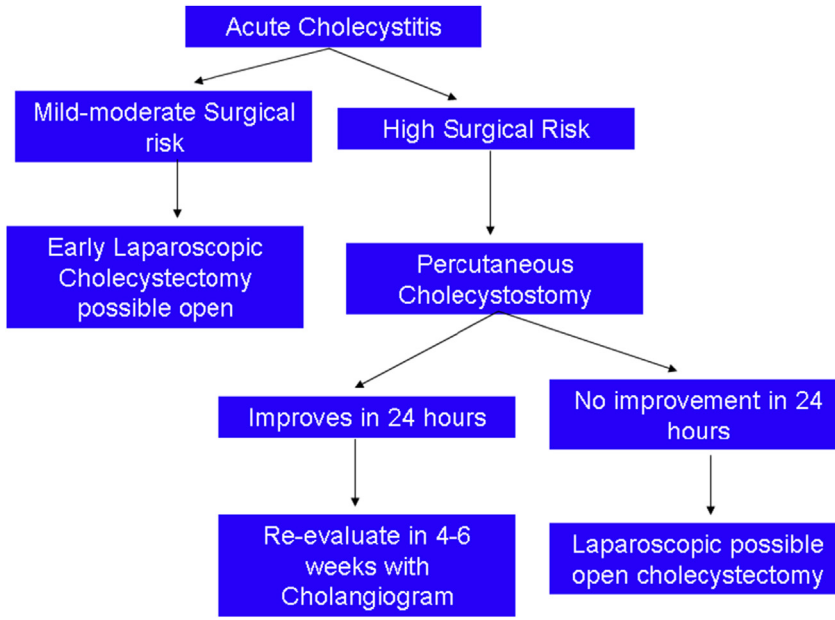

Fig. 4. Algorithm for treatment of acute cholecystitis.

Acute Cholangitis

Acute cholangitis is the result of 2 forces: obstruction and bacterbilia. The bacterbilia is thought be a result of biliary stasis and obstruction. The obstruction causes acute elevations in the biliary pressures leading to rapid bacteremia and sepsis. The 3 typical features of cholangitis (fever, jaundice, and right upper quadrant pain) were described in 1877 by Charcot. The most common cause of obstruction is gallstones; however, benign and malignant strictures, instrumentation, or periampullary cancer have also caused cholangitis.[6]

Patients will present with Charcot triad (described previously); however, severe disease is often accompanied by hypotension and change in mental status with these 5 signs termed Reynold pentad. Fever, often with rigors, is the commonest sign. The laboratory findings are what one might find with a septic patient with an elevated white blood cell count and a left shift. In addition, given the biliary obstruction responsible for the disease, the total bilirubin levels will be elevated with most being direct bilirubinemia along with associated elevations in alkaline phosphatases and transaminases.

Once the diagnosis is made, treatment is initiated immediately with antibiotic administration and fluid resuscitation. An ERCP is performed with stone extraction and sphincterotomy. If the patient presents with severe symptoms, an emergent ERCP is indicated.[25] If the ampulla cannot be cannulated, then a percutaneous transhepatic cholangiocatheter (PTC) may be performed[26] or surgical decompression. ERCP and PTC are less invasive and therefore are the preferred approach in these often unstable patients.[27] Those patients who recover uneventfully should undergo a cholecystectomy if they are not prohibitive surgical candidates. With sphincterotomy, the recurrence rate of biliary complications is decreased from 25% to 5% and therefore may be considered all that is required in patients with multiple other comorbidities.[28,29]

ACUTE PANCREATITIS

Key points

- Imaging is rarely needed to diagnose acute pancreatitis and should not generally be performed at presentation.
- CT scanning with intravenous contrast should be performed to assess for local complications in patients failing to improve.
- Infected necrosis is the most common indication for surgery in acute pancreatitis, but intervention should be delayed for 4 weeks whenever possible.
- Minimally invasive percutaneous or endoscopic drainage should be the first intervention in infected necrotizing pancreatitis.
- If minimally invasive drainage does not resolve the infected necrosis, surgical debridement is needed.

Acute pancreatitis encompasses a wide range of severity, from mild and self-limited to lethal. In its severe forms, the disease tests the judgment, patience, and tenacity of even the most experienced surgeons. This section answers the most common clinical questions related to care of acute pancreatitis, such as which patients should receive antibiotics, what is the best method of nutrition, which patients require surgery, what is the optimal surgical approach, and others.

Epidemiology and Etiology

Acute pancreatitis is the most common gastrointestinal disorder requiring hospitalization in the United States, with an estimated 274,000 hospitalizations in 2009 and its incidence appears to be increasing.[30,31] In the United States, cases are evenly distributed between men and women, although alcohol is more commonly the cause in men and gallstones are more commonly the cause in women. The incidence increases with increasing age, although the greatest number of cases occur in patients in the fifth or sixth decade of life.[30] The most common causes of acute pancreatitis are ethanol ingestion and gallstones. Less frequent causes include instrumentation of the bile or pancreatic ducts (ERCP), medications (especially diuretics, antiepileptics, and protease inhibitors), hypertriglyceridemia, hypercalcemia, congenital anatomic or genetic conditions (eg, pancreas divisum or cystic fibrosis transmembrane conductance regulator mutation), mumps, pancreatic neoplasm, and trauma or hypoperfusion. In 10% to 15% of cases a cause is not identified. The overall mortality is 2% to 4%.[31,32]

Pathophysiology

The pathophysiology of acute pancreatitis is poorly understood. The most common causes of acute pancreatitis can generally be broken down into mechanical (gallstones, ERCP) or systemic (alcohol, medications, hypercalcemia, hypertriglyceridemia). There are 2 suggested mechanisms whereby the mechanical causes result in acute pancreatitis: obstruction of the ampulla, or bile reflux into the pancreatic ductal system. How various systemic agents trigger acute pancreatitis is even less clear.

Most investigators agree that, whatever the inciting mechanism, acute pancreatitis result from activation of trypsin within the pancreatic acinar cells. The pancreas has mechanisms for preventing intracellular trypsin activation and counteracting low levels

of activation, but when these mechanisms are overwhelmed, pancreatic autodigestion ensues, which can progress beyond the gland itself and into the surrounding peripancreatic tissues. This local injury can in turn activate a variety of systemic inflammatory mediators (complement, interleukins, phospholipase A2) that may be responsible for the systemic effects seen in severe acute pancreatitis.[32]

Diagnosis, Classification, and Severity

The diagnosis of acute pancreatitis is based on the identification of 2 of the following 3 criteria: (1) clinical: central upper abdominal pain, often with associated nausea and vomiting, and sometimes radiating to the back, (2) laboratory: serum amylase or lipase greater than 3 times the upper limit of normal, (3) radiographic: imaging (usually CT or magnetic resonance imaging [MRI]) characteristic of acute pancreatitis. Imaging is rarely required to make the diagnosis of acute pancreatitis, which can usually be made on the basis of clinical and biochemical parameters alone. Rather, imaging should be used acutely only when the diagnosis is unclear, and is typically more valuable later in the course of disease to better define local complications (discussed later in this article). The etiology of any episode of pancreatitis should be sought, as it may allow prevention of recurrent episodes. When there is no obvious inciting factor, such as heavy alcohol use or recent ERCP, abdominal ultrasound should be performed to evaluate for gallstones as a potential cause.

Terminology has been a frequent source of confusion in acute pancreatitis over the past 2 decades. An international working group recently presented revised definitions that will hopefully provide more uniformity. The severity definitions effectively stratify patients by morbidity and mortality (**Box 1**). Complex or pancreatitis-specific severity scoring systems (eg, Ranson, Glasgow, Balthazar, APACHE 2) do not perform better than these and need not be calculated. Overall, at least 80% of acute pancreatitis is mild, and 20% is severe or moderately severe.[33]

Initial Medical Management

Fluid resuscitation

Patients with severe or moderately severe pancreatitis often manifest systemic signs of inflammation (SIRS). Fluid resuscitation is required in the acute phase and based on the limited data available the fluid of choice is Ringer lactate.[34] The rate and total amount of

Box 1
Severity classification in acute pancreatitis

Mild Acute Pancreatitis

- No organ failure
- No local or systemic complications

Moderately Severe Acute Pancreatitis

- Organ failure that resolves within 48 hours and/or
- Local or systemic complication (without persistent organ failure)

Severe Acute Pancreatitis

- Persistent organ failure (>48 hours)

Adapted from Sarr MG, Banks PA, Bollen TL, et al. The new revised classification of acute pancreatitis 2012. Surg Clin North Am 2013;93(3):549–62.

fluid used during initial resuscitation can be difficult to calibrate. The consequences of under-resuscitation include end-organ damage and especially renal failure. Over-resuscitation can be complicated by pulmonary edema, respiratory failure, and abdominal compartment syndrome. The "sweet spot" between under-resuscitation and over-resuscitation is difficult to identify. We suggest initial resuscitation with Ringer lactate at 5 to 10 mL/kg/h with continuous reassessment of the end points of resuscitation. Relevant end points include clinical (eg, heart rate, blood pressure, urine output), invasive (eg, stroke volume variation), and biochemical (eg, hematocrit, lactate) parameters.

Nutrition

In mild pancreatitis, oral intake can be resumed as soon as abdominal pain and laboratory parameters are improving, often within the first 24 hours after presentation. Neither needs to be completely resolved before resuming oral intake. Oral intake can be rapidly advanced to a full solid diet. Indeed, one randomized controlled trial showed that initial oral intake can be with a full solid diet.[35,36] In patients with severe pancreatitis requiring nutritional supplementation, enteral feeding should be the primary therapy. No specific formulation or immunonutrition has been shown to improve outcomes. Nasogastric feeding is equivalent to nasojejunal feeding, and can be the first route of administration with nasojejunal feeding reserved for patients who do not tolerate nasogastric feeds. Parenteral nutrition should be used only in patients who cannot reach nutritional goals with enteral nutrition within 5 to 7 days.[37–40]

Antibiotics

Systemic antibiotics should be reserved for the treatment (not the prophylaxis) of infected pancreatic necrosis.[41] When treatment is initiated, carbepenems or a quinolone plus metronidazole comprises the best initial regimen based on evidence of effective pancreatic tissue penetration and an appropriate spectrum of antimicrobial activity.[42] Because fungal infection is not uncommon (25%), patients with persistently worsening clinical condition or with microbiologic evidence for fungal infection should be treated with antifungals. If cultures show *Candida albicans*, fluconazole is appropriate. Although good evidence for the optimal antifungal agents in pancreatitis is lacking, if the indication is severe sepsis we recommend using broader spectrum antifungal agents until definitive culture and sensitivities are available. There is some evidence that prophylactic selective digestive decontamination (SDD) with enteral antibiotics may be effective in reducing the rate of infected pancreatic necrosis, but this is not strong enough to make SDD a standard recommendation.

Imaging

CT is the most common imaging modality used for diagnosis of acute pancreatitis and its complications. As noted previously, CT is rarely needed to make the diagnosis of acute pancreatitis and should not be used routinely at the time of presentation but should be reserved for cases in which there is diagnostic uncertainty or clinical deterioration in spite of appropriate initial treatment.[43–45] Whenever possible, CT should be performed with oral and IV contrast. If CT is performed to assess for local complications and the severity of the pancreatitis, the optimal timing is 72 to 96 hours after presentation, as CT scans performed in the first 72 hours frequently underestimate the degree of pancreatic and peripancreatic necrosis. Even when early CT shows significant abnormalities, follow-up imaging is not recommended unless there is clinical deterioration or lack of improvement. A patient who continues to improve after an episode of acute pancreatitis, even a severe episode with documented necrosis, does not require serial imaging to monitor resolution. MRI can provide most of the

same information as CT. Potential advantages include the lack of ionizing radiation and superiority in delineating liquid and solid components within peripancreatic necrosis. As noted earlier in the Diagnosis section, early ultrasonography should also be used to assess for gallstones as the source of the pancreatitis episode if no other etiology is apparent.

Intervention

Initial medical management for pancreatitis can be easily provided at most hospitals, but intervention requires a facility with a multidisciplinary team including at least surgeons, interventional radiologists, and gastroenterologists experienced in managing the disease.[46] The clearest consensus indication for intervention is infected pancreatic necrosis. Infected necrosis can be diagnosed definitively by the finding of air in an area of pancreatic necrosis on CT scanning or by Gram stain and culture of a fine-needle aspirate (FNA) of the necrosis. However, infected necrosis is a clinical diagnosis, and experienced clinicians are as accurate as invasive testing in detecting it. It is important to remember that FNA is only approximately 65% sensitive for the diagnosis of infection. Thus, patients who are clinically unwell with suspicion for infected necrosis should be treated as if they have infection, as there is no reliable means to exclude it, and the consequences of missing it are grave.

Once the diagnosis of infected necrosis is made, treatment is with the supportive care described previously. When possible, in stable patients intervention should be delayed to 28 days or more from the onset of the pancreatitis episode. This may be impossible if patients are clinically unstable. Whenever the first intervention is undertaken, a minimally invasive percutaneous or endoscopic drainage procedure should be the initial procedure as the first step in a so-called "step-up" approach.[47,48] Between 20% and 45% of patients with infected necrosis can be successfully treated with percutaneous or endoscopic drainage alone, although this may require several repeat drainage procedures. Drains should be placed taking into account the planned strategies for subsequent stages of the step-up approach. When possible, this may involve placing at least one drain into the area of infected necrosis via a retroperitoneal route to allow for video-assisted retroperitoneal debridement (VARD) along the drain tract (**Fig. 5**). VARD involves a small subcostal flank incision, dissection along the drain tract into the necrosis cavity, and blunt debridement of the necrotic and infected fluid and tissue. Long retractors are used to expose the tract and cavity and a standard laparoscope is used to improve visualization of the cavity, although there is no insufflation.[49] For patients with necrosis anatomically amenable to such a "step-up" approach, short-term benefits include the ability to avoid any surgery in a significant subset of the population and less new-onset organ failure. Long-term benefits include reduced incidence of diabetes mellitus and incisional hernia. For patients debrided entirely via an endoscopic route, there also may be a mortality advantage compared with open surgery without any preoperative drainage procedure.[50]

Due to the anatomy of their necrosis, some patients with infected pancreatic necrosis will not be amenable to endoscopic or retroperitoneal debridement, in which case laparotomy or less commonly laparoscopy may be used for transperitoneal debridement. Additionally, it must be noted that although minimally invasive drainage as a first step likely confers significant advantages, when surgery is subsequently required, the evidence is less compelling that any one surgical approach is superior to others. The general principles of delay until 4 weeks after the onset of disease and preoperative drainage of some form should still be applied whatever the approach. Transabdominal debridement should involve removal of all or nearly all infected or necrotic pancreatic and peripancreatic tissue with closed suction drainage of the

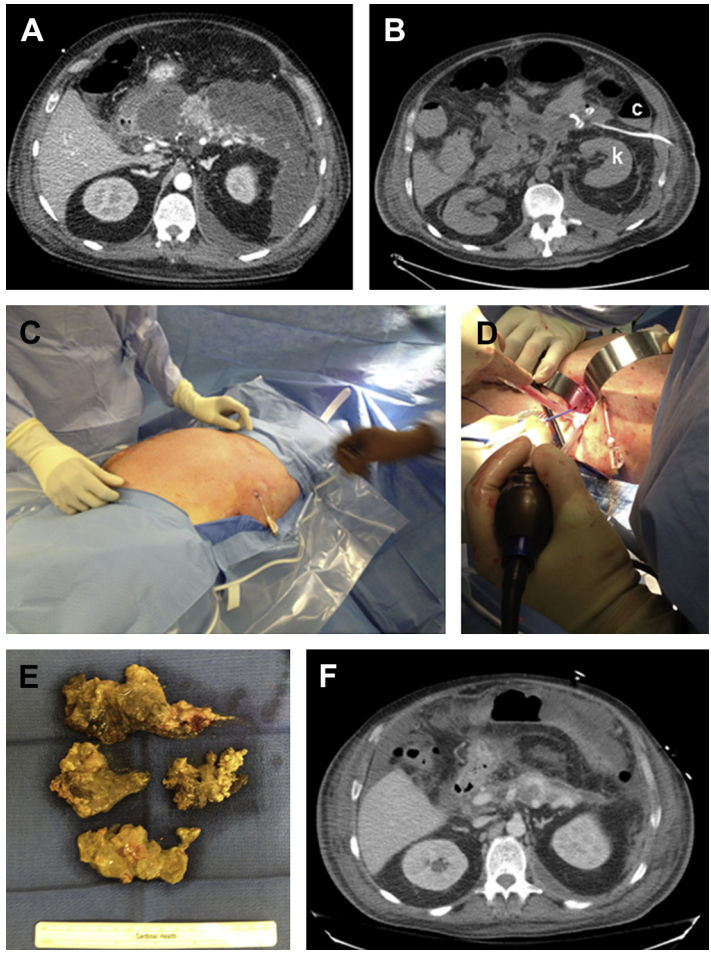

Fig. 5. Video-assisted retroperitoneal pancreatic debridement (VARD). (*A*) CT scan showing walled off pancreatic necrosis amenable to retroperitoneal access. (*B*) Percutaneous drain placed via a retroperitoneal route to guide VARD. C, colon; K, kidney. (*C*) Positioning in the operating room with right side elevated and percutaneous drain prepped into the operative field. (*D*) Dissecting along the percutaneous drain tract into the necrosis cavity. (*E*) Necrotic pancreatic tissue removed by VARD. The ruler is 15 cm long. (*F*) Postoperative CT scan showing resolution of the necrosis cavity.

necrotic cavity. The use of different incisions (midline vs subcostal), approaches to the pancreas (transmesocolic, through the gastrocolic omentum, or retroperitoneal), and drainage (closed packing, closed suction alone, continuous lavage) are at the discretion of the surgeon and acceptable results can be obtained with variable techniques.[51]

Intervention is less often needed for sterile pancreatic necrosis. The most common indication is gastric outlet obstruction. Intervention can often be delayed longer, as this complication will often resolve with time. If patients with presumed sterile necrosis remain persistently unwell, the possibility of occult infection must be considered. Intervention can include surgical debridement or bypass.

Other complications that may prompt intervention in the acute setting include abdominal compartment syndrome (ACS), hemorrhage of a visceral artery (usually splenic artery) pseudoaneurysm, and bowel perforation or fistula. When these complications arise in the acute setting they should, as a rule, be treated by the least invasive methods possible. For ACS, medical treatment should include volume removal (via diuresis or ultrafiltration), and neuromuscular blockade. If there is persistent ACS and significant ascites, percutaneous drainage may be beneficial, and is currently under investigation in a randomized trial.[52] Definitive treatment is decompressive laparotomy.[53] When this is necessary early in the course of disease, the lesser sac should not be entered and pancreatic debridement should be avoided. Bleeding from a visceral artery pseudoaneurysm should be controlled endovascularly by angioembolization whenever possible, as direct surgical control in a region of active or recent pancreatitis is extremely difficult.[54] Intestinal perforation is similarly difficult to manage. Contained perforations or controlled fistulas may be manageable with drainage or diversion. When there is bowel ischemia or uncontrolled enteric spillage, exploratory laparotomy with resection will likely be necessary.

Late Complications

Pancreatic fistulas and pseudocysts result from disruption of the pancreatic duct due to destruction of the surrounding parenchyma. Fistulas may result from severe pancreatitis or as a complication of pancreatic debridement, after which they are common. One advantage of endoscopic transluminal debridement may be that such leaks from the pancreatic duct drain internally, rather than forming external fistulas. Whatever the cause, when the fistula is controlled with percutaneous drains, it will usually close, although it may require many weeks to months. Pancreatic duct stenting, octreotide administration, and restriction of enteral nutrition have all been advocated to aid in fistula closure, but are not routinely helpful. In the special situation of a disconnected distal pancreatic remnant in which a segment of the gland has been completely separated from any route of drainage into the gastrointestinal tract, spontaneous closure is very rare. Such patients may be treated either endoscopically by transluminal stenting to attempt to convert the external fistula into a controlled internal fistula, or may be treated surgically by either roux-en-Y jejunostomy to the distal pancreatic remnant or resection of the disconnected distal segment.

Pseudocysts form when the ductal disruption is walled off by the body into an organized collection of pancreatic juice encased by reactive inflammatory tissue, a process that occurs 4 weeks or more after damage to the pancreatic duct. Asymptomatic pseudocysts do not require intervention. The most common symptoms are early satiety and abdominal pain. Pseudocysts may also cause true gastric outlet obstruction, become infected, or lead to pseudoaneurysm formation. Internal drainage is the treatment of choice for pseudocysts requiring intervention. For pseudocysts closely apposed to the stomach or duodenum, endoscopic pseudocyst-gastrostomy or duodenostomy is the treatment of choice. For very large or endoscopically inaccessible pseudocysts, surgical cyst gastrostomy or roux-en-Y cyst jejunostomy are necessary.[55]

Vascular complications of pancreatitis include arterial pseudoaneurysm and venous thrombosis. These most commonly involve the splenic vessels, but in pancreatitis primarily affecting the head, pseudoaneurysms of the pancreaticoduodenal or gastroduodenal arteries may occur along with thrombosis of the superior mesenteric or portal veins. Pseuodaneurysms result from the action of pancreatic enzymes on the arterial wall. They may be identified incidentally on contrast-enhanced CT or can present with

catastrophic hemorrhage. We recommend intervening even on asymptomatic pseudoaneurysms in most cases, as there is no reliable way to predict hemorrhage. As noted previously, whether addressed electively or emergently they are best treated with angioembolization.[54] Splenic vein thrombosis due to pancreatitis can usually be observed. We occasionally anticoagulate if clot extends into the main portal vein. Even without anticoagulation, the thrombus can resolve. If it does not, the most common late complication is gastric varices. If these result in gastrointestinal bleeding, they can be eliminated by splenectomy.[56]

Efforts should be made to prevent recurrence after an episode of pancreatitis by cessation of ethanol abuse for alcoholic pancreatitis, treatment of the underlying condition in hypercalcemia and hypertriglyceridemia, and cessation of any offending medications in cases of medication-induced pancreatitis. In patients with gallstone pancreatitis, cholecystectomy during the same hospitalization is recommended for mild cases. In pancreatitis with peripancreatic fluid collections, cholecystectomy should be delayed for 6 weeks. In especially poor operative candidates, ERCP with sphincterotomy reduces the risk of recurrent gallstone pancreatitis and can be considered as an alternative to cholecystectomy.

DIVERTICULITIS

Key points

- Colonoscopy should be performed after an episode of diverticulitis unless the patient has had a recent one.
- Diverticular abscess should be treated with percutaneous drainage and antibiotics. Elective laparoscopic colectomy after resolution should usually be undertaken.
- Emergency sigmoid colectomy is rarely required for acute diverticulitis.
- When emergency sigmoid colectomy is required, primary anastomosis with or without diverting ileostomy should be strongly considered.
- The utility and role of laparoscopic lavage has yet to be determined.

The management of sigmoid diverticulitis in all its manifestations has changed considerably in recent years. Indications for elective or emergency surgery, choices of surgical approach, and methods for preventing recurrence are all evolving. This review discusses these issues with a focus on the acute management of complicated diverticulitis.

Epidemiology and Etiology

Diverticulitis is the third most common cause of hospitalization due to gastrointestinal disease in the United States, with an estimated 219,000 visits in 2009, and the incidence is increasing.[30,57] The prevalence of diverticulosis is age dependent and in the United States is approximately 20% by age 40, rising to 60% by age 60. Suggested risk factors for diverticulosis include low dietary fiber intake, obesity, and lack of physical activity. In a recent longitudinal study of patients with incidentally identified diverticulosis, the subsequent risk of developing diverticulitis was approximately 4.3% over 11 years of follow-up.[58] Seasonal and regional variations in hospital admissions for diverticulitis have been noted in the United States, although what drives these variations is unclear. A minority of episodes of diverticulitis require hospital admission, but hospitalized patients younger than 45 are more likely to be men,

whereas women comprise most patients hospitalized in those older than 54.[57] The overall incidence of diverticulitis continues to increase with increasing age. After a first episode of diverticulitis, 20% to 40% of patients develop recurrent diverticulitis, with a similar percentage of those patients going on to develop a third episode.[59] Most patients with complicated diverticular disease (perforation, abscess, fistula, or stricture) have never had prior episodes of acute diverticulitis.[60]

Pathophysiology

The pathophysiology of colonic diverticula formation is incompletely understood. Colonic diverticula are pseudodiverticula composed of mucosal and submucosal layers only. The colon may be anatomically predisposed to formation of these diverticulae because the muscular layers are not circumferential and because of weakness at the site of entrance of the vasa recta. At the microscopic level, collagen cross-linking increases with age and increased elastin deposition has been noted in the colon of patients with diverticulosis. These processes may result in a highly contractile and less distensible colon, which is predisposed to segmentation, the phenomenon when adjacent haustra simultaneously contract creating a short closed segment of colon with very high intraluminal pressure. Low-fiber diets are associated with diverticula formation, although the pathophysiologic link is not completely clear. Less stool bulk may predispose to segmentation and higher intraluminal pressures. Other environmental or genetic predispositions are suggested by the observation that right-sided diverticulosis and diverticulitis is significantly more common in Asia than in Western countries, and by the high prevalence of diverticulosis in patients with certain connective tissue disorders, such as Ehlers-Danlos syndrome. Thus anatomic factors probably interact with functional and environmental factors to form diverticulae.[61,62] Diverticulitis results from acute inflammation of a diverticulum. When this leads to perforation, complicated disease ensues. The factors that initiate inflammation and lead to micro or gross perforation are poorly understood. Diverticular obstruction, colonic stasis, changes in the local bacterial biome, and local ischemia have all been implicated.

Diagnosis, Classification, and Severity

Evaluation of a patient with suspected diverticulitis should include a history focused on localizing pain, eliciting evidence of possible prior episodes, and identifying clinical evidence of complicated disease (obstructive symptoms, pneumaturia, fecaluria, or vaginal discharge). Pain is usually in the lower abdomen and the differential diagnosis includes appendicitis, infectious or ischemic colitis, inflammatory bowel disease, nephrolithiasis, and gynecologic pathology. The abdominal examination usually reveals focal left lower quadrant or suprapubic tenderness. The diagnosis can be made without laboratory testing or radiologic imaging in clinically mild cases, especially in patients with a history of the disease. In patients never previously diagnosed, or those who appear systemically ill, laboratory evaluation should include a complete blood count and urinalysis. CT scanning with oral and IV contrast is by far the most useful diagnostic modality in suspected acute diverticulitis, as it is both sensitive and specific, can evaluate the other diagnostic possibilities, and can identify complications, such as abscess, fistula, or obstruction. CT cannot, however, definitively differentiate between diverticulitis and colonic adenocarcinoma. Because as many as 3% to 5% of cases of clinically diagnosed diverticulitis may turn out to be adenocarcinoma, colonoscopy or other appropriate colorectal cancer screening should be performed after resolution of the acute episode unless patients have had a recent screening evaluation and have a known diagnosis of recurrent diverticulitis.

Surgeons are usually involved in the care of patients with acute diverticulitis when they manifest systemic symptoms, fail to improve with medical therapy, or develop complicated disease. Complicated disease refers to diverticulitis associated with abscess, fistula, perforation, stricture, or obstruction. For cases of perforation, the Hinchey classification is the most commonly used schema (**Box 2**).

Specific Diverticulitis Entities and Their Management

Uncomplicated diverticulitis is typically treated with 7 to 14 days of antibiotics and bowel rest until symptoms improve, at which point the diet is gradually reintroduced starting with liquids. The need for antibiotics in the treatment of acute uncomplicated diverticulitis has recently been challenged by a multicenter randomized controlled trial that showed no difference in hospital stay, the development of complications, or recurrence rates between patients randomized to receive antibiotics and those randomized not to receive them. Only 3% of patients in the no-antibiotic arm crossed over to the antibiotic arm due to worsening pain or fever.[63] Although the necessity of antibiotics in mild diverticulitis will likely continue to be investigated, they are still considered standard in mild disease and are a mainstay of treatment in complicated disease. Antibiotic regimens should cover enteric gram-negative organisms and anaerobes. Ciprofloxacin and metronidazole is the most common regimen; alternatives include a beta-lactam/beta-lactamase combination (amoxicillin/clavulanic acid or piperacillin/tazobactam), substitution of clindamycin for metronidazole, and moxifloxacin or a carbapenem as monotherapy.[7,64] Patients with systemic inflammatory response syndrome or organ failure due to complicated diverticulitis should be resuscitated appropriately, in an intensive care unit if necessary. Even in the setting of free perforation requiring surgery, most septic patients will benefit from at least a brief period of preoperative resuscitation.

The most common complication of diverticulitis is abscess, which is typically diagnosed on CT, and the mainstay of therapy, is percutaneous radiologically guided drainage. The Hinchey classification distinguishes between localized pericolonic abscess and pelvic abscesses. Many Hinchey I and small Hinchey II abscesses can be treated with antibiotics alone. The American Society of Colon and Rectal Surgeons recommends antibiotic therapy alone for abscesses smaller than 2 cm. A retrospective study demonstrated 100% success in the acute treatment of diverticular abscesses smaller than 3 cm, and other studies have called into question the necessity of draining intermediate-sized abscesses (3–5 cm).[65,66] The question of how large an abscess can be before it requires percutaneous drainage is in evolution. A combined evaluation of the patient's clinical condition and the radiographic characteristics of the abscess is the most rational approach to intermediate-sized abscesses at this time. A medium-sized abscess (eg, 4 cm) that is difficult or

Box 2
Hinchey classification for perforated diverticulitis

Stage I: pericolic or mesenteric abscess

Stage II: walled off pelvic abscess

Stage III: generalized purulent peritonitis

Stage IV: generalized fecal peritonitis

Adapted from Hinchey EJ, Schaal PG, Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg 1978;12:85.

dangerous to access percutaneously in a patient who is clinically well should probably be treated initially with antibiotics alone, whereas a similar-sized abscess that is easily accessible in a patient with severe pain or persistent fever should be drained. In patients initially managed with antibiotics alone, drainage should be undertaken if technically feasible in the absence of clinical improvement. The success rate with percutaneous drainage is in the range of 60% to 85%. Drains are typically removed when imaging shows resolution of the abscess cavity and output is low (<10–20 mL/24 hours). The surgical options for failed nonoperative management are discussed as follows.

Diverticular stricture is the second most common cause of large bowel obstruction in the United States. Even when a benign etiology is strongly suggested, it is difficult to definitively rule out malignancy, and so resection is usually required to prevent recurrent obstruction and rule out or treat possible malignancy. Most obstructions due to diverticulitis are incomplete and result from inflammation or edema superimposed on a chronic stricture during an acute flare of diverticulitis. With treatment, the acute obstruction may resolve, allowing decompression and elective single-stage resection. When obstruction is high grade, the options are immediate resection or performance of a procedure to temporarily relieve the obstruction. We favor resection with primary anastomosis whenever possible. On table lavage of the proximal colon has not been shown to have any advantage over manual decompression of the proximal colon; therefore, we do not routinely perform or recommend it.[67] Whether a proximal diverting loop ileostomy is necessary when resection and anastomosis is performed remains a matter of debate. Reports indicate that anastomosis without proximal diversion can be performed safely, but it has not been studied in a controlled fashion and for now can be left to individual surgeon judgment.[68] Patients with metabolic derangement, severe malnutrition, or other reasons not to undergo immediate resection may benefit from a temporizing procedure to relieve the obstruction. Colonic stents have an excellent track record for relief of malignant large bowel obstruction, but are associated with a much higher complication rate when used for diverticular stricture and should be used only very selectively if at all.[69] For the rare patients who are acutely ill from large bowel obstruction or in imminent danger of cecal perforation (cecum >10 cm), a temporary transverse loop colostomy remains a good option; it can be safely performed quickly, even under local anesthesia if needed due to hemodynamic instability, and relieves the obstruction. It can be closed at the time of subsequent resection and primary anastomosis. As mentioned previously, this is rarely necessary and resection with primary anastomosis is usually preferred.

Free perforation is generally associated with diffuse peritonitis on abdominal examination, widespread uncontained pneumoperitoneum and free fluid on CT scan, and signs of severe systemic infection. It is important to note that pneumoperitoneum alone, even large-volume pneumoperitoneum, is not a reliable sign of ongoing free perforation nor is it an indication for surgery. Diverticular perforations will often seal, and patients with pneumoperitoneum who do not otherwise clinically or radiographically manifest ongoing fecal spillage may still be managed nonoperatively.[70] Patients with ongoing free perforation require broad-spectrum antibiotics and fluid resuscitation, as noted previously, but also require surgical intervention. Surgical options include sigmoid colectomy with end colostomy (Hartmann procedure), sigmoid colectomy with primary colorectal anastomosis with or without diverting loop ileostomy, and laparoscopic lavage with primary closure of the perforation. The Hartmann procedure has been less frequently used in recent years, as awareness of the morbidity of colostomy reversal has increased. In general, it

should be used mostly in patients for whom a permanent end colostomy would be acceptable, such as patients with dementia or incontinence, in whom it may actually be a boon. Otherwise, primary anastomosis with diverting loop ileostomy appears to be as safe in the short term, and to be accompanied by much higher rates of stoma closure, a lower rate of serious complications, shorter hospital stay, and lower costs.[71]

The role of laparoscopic lavage in the management of diverticular perforations is unclear. Numerous single-center series report good outcomes. The primary problem with these is the lack of comparative data. Many patients with Hinchey III for whom the procedure is most ardently advocated are likely to improve with medical management alone. Case series beg the question: was any surgery needed at all? There is no definitive data indicating that laparoscopic lavage adds anything to a combination of antibiotic treatment and percutaneous radiologically guided drainage of localized collections. Advocates of the technique differ on whether it is appropriate in patients with Hinchey IV disease, whether ongoing perforation with leakage should be actively sought either preoperatively or intraoperatively, and whether a finding of perforation or stool spillage constitutes a reason to convert to a sigmoid resection or whether a simple laparoscopic repair as part of the lavage procedure is appropriate. Defining the appropriate role for this technique is one of the larger unanswered questions in the current acute surgical management of complicated diverticulitis and would benefit greatly from a randomized trial.[72]

Prevention of Recurrence

We typically recommend colonoscopy 6 weeks after a first episode of acute diverticulitis and in patients who are otherwise due for colorectal cancer screening. In one large series of 319 patients, 89% of patients had the diagnosis of diverticulitis confirmed, and 26% of these had adenomatous polyps identified. Nine patients (2.8%) had an unsuspected colorectal cancer identified.[73] If the episode of diverticulitis is confirmed, patients are often anxious to know what they can do to prevent recurrences. Advice on this topic has been clouded by decades of myth surrounding dietary modifications. Although the ideal diet to prevent recurrent diverticulitis is not known, the avoidance of seeds and nuts, which have been baselessly demonized for decades, is not necessary. Debate remains over whether high-fiber diets can prevent recurrent symptoms, and whether low-residue diets improve symptoms in the setting of an acute flair. This debate can still rage largely unchecked by evidence. High-fiber diets are supported by some evidence, are unlikely to cause harm, and are still recommended in a number of professional society guidelines for prevention of recurrent diverticulitis; we recommend them, but without much enthusiasm.[74] Medical therapy, including intermittent luminal antibiotics, probiotics, and 5-aminosalicylic acid, has been investigated for prevention of recurrent diverticulitis. These remain options for patients with multiply recurrent disease who are poor candidates for or decline surgery (discussed later), but all these interventions require further investigation before they can be routinely recommended. The 5-aminosalycylic acid therapy has the best support in the form of a randomized controlled trial.[75,76]

Guidelines for elective sigmoid resection to prevent recurrent diverticulitis have evolved considerably in the past decade, but are not governed by clear evidence and still recommend making decisions on a case-by-case basis considering the severity of the episode(s) and the medical condition and age of the patient. For patients suffering an episode of complicated diverticulitis requiring percutaneous abscess drainage, the incidence of recurrent severe sepsis may be as high as 41%, and thus interval sigmoid colectomy should usually be planned.[77] This constitutes

one of the clearer indications for elective sigmoid resection, although even in this setting nonoperative management can be considered in elderly or poor-risk patients, in whom recurrence is common, but can typically be managed nonoperatively with minimal morbidity.[78] The number of uncomplicated episodes that should prompt resection is less clear, as is the impact that age should have on decision making. Approximately one-third of patients will suffer recurrence after a single episode of uncomplicated acute diverticulitis, and another third of those develop a third episode. If the first episode was uncomplicated, the subsequent episodes usually are, thus early surgery in this setting is unlikely to prevent complicated and morbid episodes of diverticulitis. We rarely offer colectomy if there have been fewer than 3 episodes. Modifying considerations may include the presence of immunosuppression, chronic renal failure, or collagen vascular disease, all of which confer a significantly increased risk of subsequently developing complicated disease, or the presence of persistent symptoms between acute episodes. We recommend laparoscopic colectomy as the preferred method of resection based on an overall lower morbidity rate in experienced hands.[79]

CLOSTRIDIUM DIFFICILE COLITIS

Key points

- Oral vancomycin is standard treatment for moderate to severe *Clostridium difficile* infection (CDI), and can be supplemented with intravenous metronidazole and vancomycin enemas in severe cases.
- Fidaxomicin reduces recurrent CDI compared with standard therapy.
- Patients developing new or worsening organ failure on appropriate medical therapy need surgery.
- Surgical options include subtotal colectomy with end ileostomy, or loop ileostomy with antegrade colonic lavage.
- Fidaxomicin, tapered intermittent vancomycin, and fecal bacteriotherapy are options for recalcitrant recurrent CDI.

Clostridium difficile infection (CDI) is one of the most common hospital-acquired infections, and is a frequent cause of morbidity and mortality among hospitalized patients. *C difficile* colonizes the intestinal tract after the normal gut flora has been altered by antibiotic therapy. Most CDI is relatively mild, but a minority of patients (3%–12%) can progress to severe disease resulting in systemic toxicity and shock. This subset is the primary concern of the acute care surgeon.

Epidemiology and Etiology

CDI afflicts up to 10% of all hospitalized patients and 20% of such patients receiving antibiotics.[80] A study using the Nationwide Inpatient Sample showed a 109% increase in incidence of *C difficile* infections between 1993 and 2003.[80] More recent national data showed that the rate of *C difficile* hospitalizations per 1000 nonmaternal, adult discharges increased from about 5.6 in 2001 to 12.8 in 2012, with annual costs in the United States estimated in the billions of dollars.[81,82] Two percent to 8% of patients with CDI will develop fulminant disease, defined as CDI with significant systemic toxic effects and shock, resulting in the need for intensive care unit (ICU) admission, colectomy, or death.[80,83,84] Mortality rates for fulminant CDI range between 13.8% and 80.0%.[83,84] These increases in the incidence, prevalence, severity, and

recurrence rates of CDI have been closely linked to the development of the hypervirulent NAP1/BI/027 strain.[85]

Risk factors for CDI include antibiotic exposure, institutionalization (including hospitalization and nursing home residence), advanced age, severe illness, and gastric acid suppression (especially with proton pump inhibitors). The antibiotics most commonly associated with CDI are flouroquinolones, although a very wide array of antibiotics have been implicated and the disease can even occur in the absence of antibiotic exposure.[85,86]

Pathophysiology

C difficile is an anaerobic gram-positive, spore-forming, toxin-producing bacillus. Outside the colon, it survives in spore form and is highly resistant to heat, acid, and antibiotics. This feature is closely linked to its nosocomial spread. Currently, full-contact precautions (gown and gloves) as well as hand washing with soap and water in addition to use of an alcohol-based hand rub (ABHR) are recommended for health care providers contacting patients with *C difficile*. ABHRs alone are inadequate to eradicate spores. Similarly, special precautions are required for cleaning of the health care environment (usually sodium hypochlorite solutions) and potential fomites (such as stethoscopes) which require sporicidal wipes.[87] On reaching the colon, spores convert to the vegetative, toxin-producing forms that result in clinical infection and are susceptible to antimicrobial agents. The vegetative form of *C difficile* releases 2 exotoxins that mediate colitis and diarrhea: toxin A ("enterotoxin") and toxin B ("cytotoxin"). These toxins cause mucosal cell death, resulting in the classic pseudomembranes seen on endoscopy (**Fig. 6**), disrupting the gut barrier, and leading in severe cases to a toxic megacolon picture. Stool toxin levels correlate with disease severity, whereas host antitoxin antibodies are inversely correlated with infection incidence, severity, and recurrence.

Diagnosis, Classification, and Severity

Watery diarrhea is the clinical hallmark of CDI, although clinical manifestations of disease can range from none (asymptomatic carrier status) to fulminant septic shock. CDI

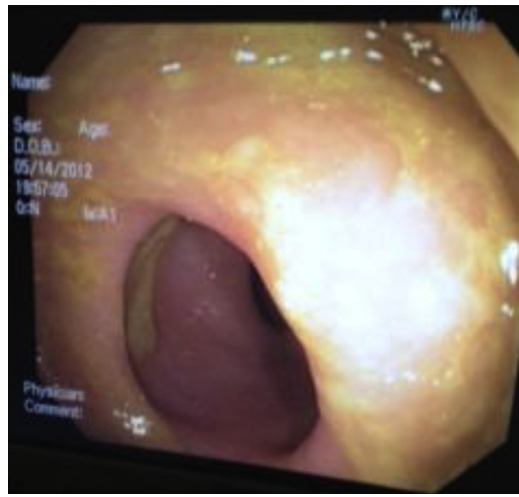

Fig. 6. Pseudomembranous colitis in a patient with *C difficile* infection. Note the edematous mucosa and exudative pseudomembranes.

should be suspected in any hospitalized patient with diarrhea and appropriate testing should be performed to confirm the diagnosis (see later in this article). As awareness of the prevalence of CDI has increased in recent years, infection is probably promptly suspected and diagnosed in most cases with diarrhea. Surgeons caring for hospitalized inpatients will frequently encounter other presentations in which diarrhea is absent, however. These situations can constitute more of a diagnostic challenge. Unexplained leukocytosis, even in the absence of diarrhea should raise suspicion for CDI. Pancolitis seen on imaging performed for other symptoms (such as abdominal pain, nausea, vomiting, or fever) is also an occasional first indicator of colitis and CDI.

When CDI is suspected, the diagnosis should be confirmed by laboratory studies or endoscopy. Laboratory studies performed on stool form the foundation of diagnosis. Most clinical laboratories rely on enzyme immunoassay (EIA) toxin testing due to a combination of rapid turnaround time, low cost, and decent sensitivity and specificity. Because a certain quantity of toxin (100–1000 pg) must be present to allow detection, sensitivity may be as low as 75%, however. This is minimally improved by sending samples on consecutive days, which unearths a new positive test less than 3% of the time. We consider polymerase chain reaction (PCR), which has sensitivities and specificities in the 93% to 97% range, as the best single stool test for CDI. In clinical microbiology laboratories, both PCR and EIA are often used as part of a multistep diagnostic algorithm because of their cost and lack of sensitivity respectively. Clinicians should understand the testing algorithm used at their institution and its performance characteristics.[88]

Colonoscopy or sigmoidoscopy is unnecessary when a patient has diarrhea and a positive stool sample, but may be diagnostically useful in certain situations. These include when suspicion for CDI remains high despite negative laboratory tests, when an immediate diagnosis is necessary, and when the diagnosis is suspected but due to ileus, no stool is available for diagnostic testing. Pseudomembranes are specific for CDI in the proper clinical setting and are a marker for severe disease. The chief drawback to endoscopy is the risk of perforation, which likely increases with the severity of colonic inflammation, although we have never experienced this. In patients with advanced colitis, abdominal CT shows marked colonic thickening in a pancolonic distribution, although *C difficile* colitis is not distinguishable radiographically from other forms of infectious colitis.

There are no established criteria for differentiating “mild to moderate” from “severe” CDI. Different investigators have used slightly different criteria in studies. The distinction is ultimately clinical and based on an assessment of colonic disease severity and systemic effects. Criteria to be considered include the following: number of bowel movements (>10–12, severe); presence of abdominal pain or tenderness, leukocytosis, or leukopenia (white blood cell count >15–20,000 or <4000, severe); fever; elevated serum lactate (>2.2); tachycardia; hypotension or need for vasopressors; respiratory failure; age (>60–70); pseudomembranes on endoscopy, or extensive colonic wall thickening on CT scan. Any patient requiring admission to an ICU for treatment of CDI should be considered to have severe disease and treated accordingly.

Initial Medical Management

A combined algorithm for medical and surgical management used since 2007 as a guideline in the Division of Trauma, Emergency Surgery, and Critical Care at the Massachusetts General Hospital is provided in **Fig. 7**. The criteria used to help determine the need for surgery were chosen because they were highly associated with mortality in a retrospective study from our institution.[83] The first steps in treatment of CDI are cessation of the inciting antibiotic as soon as possible, and standard supportive

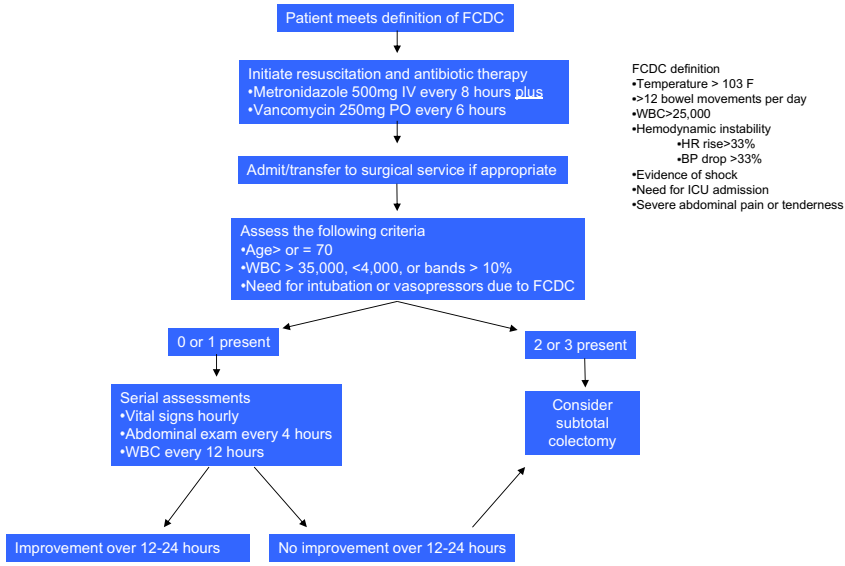

Fig. 7. Suggested algorithm for determining the need for surgery in *C difficile* colitis. *Abbreviations*: FCDC, fulminant *C difficile* colitics; ICU, intensive care unit; IV, intravenous; PO, by mouth; WBC, white blood cell count.

therapy, such as intravascular volume restoration, and correction of electrolyte abnormalities. Enteral feeding should be used whenever possible. Patients with severe disease should be serially examined and moved to monitored settings (ICU or observation unit) as appropriate based on their physiology.

Antibiotics targeted at *C difficile* form the mainstay of medical management. For nonsevere disease, oral metronidazole is the first line agent of choice. The recommended dosage and duration of therapy for nonsevere disease is 500 mg 3 times per day for 10 to 14 days or at least 7 days beyond the cessation of any inciting antibiotics. Oral vancomycin is a standard alternative. Vancomycin 125 mg orally 4 times per day for the same duration is an alternative dose for nonsevere disease. For severe disease, oral vancomycin is first-line therapy. Dosing can be anywhere from 125 mg to 500 mg 4 times per day. There is some evidence that higher colonic vancomycin levels are achieved at higher doses, but no clear evidence of clinical benefit. Severely ill patients with CDI often have ileus with delayed transit of oral vancomycin into the colon. For this reason, we routinely use IV metronidazole (500 mg every 6–8 hours) in conjunction with oral vancomycin when initiating antibiotic therapy in severe CDI. If patients do not show improvement with this regimen, intracolonic vancomycin is an additional option. The ideal method of administration has not been carefully defined, but 500 mg given in 100 mL normal saline every 6 hours as a retention enema is a standard regimen. Fidaxomicin is a relatively new macrocyclic antibiotic with bactericidal activity against *C difficile* (in contrast to vancomycin and metronidazole, which are bacteristatic). It has equal short-term efficacy to oral vancomycin, but results in less recurrent CDI.[89] Its exact role in the antibiotic armamentarium has yet to be defined, but if available, it is a reasonable addition to the standard regimen in the absence of clinical improvement.

Recurrent CDI is a common problem, affecting approximately 25% of patients initially treated successfully. Some authorities recommend treating first recurrences

with the same antibiotic used to treat the index infection. This has the advantage of simplicity, but is associated with a subsequent recurrence rate of approximately 50%.[90] Fidaxomicin has a lower rate of subsequent recurrences when used to treat a first recurrence.[91] For first recurrences that are moderate to severe or for second recurrences, an intermittent tapered vancomycin (125 mg twice daily for 7 days, then once daily for 7 days, then every other day for 7 days, then every third day for 2 weeks) is more effective than standard antimicrobial regimens at preventing subsequent recurrences.[92] Fecal bacteriotherapy in which donor stool is prepared and infused into the gastrointestinal tract of patients with recurrent CDI is also effective in reducing subsequent recurrences, although is not currently widely available.[93]

Surgery

Surgery is necessary for medically refractory CDI that progresses to the systemic inflammatory response syndrome causing multiorgan failure, toxic megacolon, and perforation or impending perforation. The 2 main questions confronting the surgeon are (1) when to operate, and (2) what operation to perform. The timing of surgery in severe *C difficile* colitis remains a difficult clinical judgment. Generally, we favor early surgery in patients with signs of organ failure. A significant number of patients who are hypotensive on initial presentation because of severe volume depletion from diarrhea and who have not yet been treated medically will respond quickly to volume restoration and antibiotic therapy. This should be attempted with careful observation. Those who do not respond, and any patients developing respiratory failure, renal failure, or refractory hypotension should undergo prompt surgery before a prolonged period of organ failure has resulted in an unrecoverable situation. Patients developing new organ failure due to CDI while on appropriate medical therapy should undergo surgery promptly, as there is no other therapy available that can reasonably be expected to turn the tide. Surgery offers the best chance of cure when performed before severe, prolonged, multisystem failure has developed.[83]

Subtotal colectomy (resection of the colon from the ileocecal valve to the rectum at the peritoneal reflection) is the appropriate surgical intervention for severe CDI mandating surgery. Given the indications for surgery (shock, organ failure) anastomosis should not be performed, instead leaving an end ileostomy and a rectal stump. At exploration, the colon is usually extremely boggy and dilated. If surgery is performed promptly, as recommended previously, frank necrosis or perforation is unusual. There is no role for segmental colonic resection in CDI; the infection is a pancolonic process and segmental resection will not adequately relieve the systemic toxin burden. Partial colonic resection has been associated with high mortality rates.[94] After subtotal colectomy, we usually continue IV metronidazole for 7 days to treat residual disease in the rectum. If there is evidence of ongoing proctitis, then vancomycin enemas as described previously are administered into the rectal stump. After resolution of the acute illness, ileorectal anastomosis can be performed to restore gastrointestinal continuity, although given the numerous comorbidities and advanced age of many patients requiring surgery, this is performed in only a minority of patients.

One intriguing approach to the surgical treatment of medically refractory CDI is ileostomy with colonic lavage. In this technique, a loop ileostomy is created in the terminal ileum, either laparoscopically, or using an open technique. Intraoperative antegrade colonic lavage is then performed with polyethylene glycol via a catheter introduced into the distal limb of the ileostomy. Postoperatively, the catheter is left in place, and antegrade enteral vancomycin is administered. In the experience reported to date, this approach is effective in treating colitis and preserving the colon more than 90% of the time with an acceptable mortality (21%) and a high rate of

ileostomy reversal.[95] Despite exciting early results, this technique has not been directly compared with subtotal colectomy in any organized trial and we cannot yet recommend it as standard therapy, although it holds promise for the future. We currently perform it only very selectively outside of an ongoing randomized trial.

Nonstandard Agents: Monoclonal Antibodies, Anion-Binding Resins, Fecal Bacteriotherapy, Intravenous Immunoglobulin

Therapies aimed at the *C difficile* toxin itself have the theoretical advantage of not further disturbing the colonic flora while attenuating the systemic inflammatory response. Monoclonal antibodies directed at toxins A and B have been shown to reduce recurrence compared with vancomycin in a randomized controlled trial, but are not widely clinically available.[96] Anion-binding resins, such as colestipol, cholestyramine, and tolevamer, have not been shown to be as effective as standard antibiotics in treating *C difficile* colitis, but may have an adjunctive role, particularly for treating recurrent *C difficile* colitis. They should be used carefully, as they may also bind enteral vancomycin, thus reducing efficacy, and dosing regimens need to be carefully coordinated. Intravenous immunoglobulin contains *C difficile* antitoxin, and case reports describe benefit in refractory *C difficile* infection. No benefit has been shown in case-controlled studies and no trials have been done. We do not recommend its use.

Since a disruption of normal colonic flora underlies the pathophysiology of *C difficile* infection, efforts to therapeutically alter colonic flora have been made. Probiotic therapy with live bacterial cultures has been disappointing in either preventing or eliminating CDI. Fecal bacteriotherapy, or "stool transplantation" as it is sometime colloquially termed, was discussed previously, and has been shown to be effective for severe and recurrent CDI, although the infrastructure to safely perform this technique is not widely available.

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