Section I

Acute Pancreatitis

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Acute Pancreatitis

An Overview

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Introduction

Acute pancreatitis (AP) is a common problem worldwide. Its spectrum of disease varies from mild, so-called interstitial acute pancreatitis, to severe necrotizing pancreatitis. Overall, its mortality rate is increased in patients older than age 65 years [1]. AP is among the most common gastroenterological causes of hospitalizations [2]. Roberts et al. [3] investigated regional and national patterns in the incidence and etiology of AP across Europe and found that the incidence of AP ranged from 4.6 to 100 per 100 000 population. Overall there was a median increase of 3.4% per annum over time and incidence was usually highest in eastern or northern Europe. Similarly, in the United States the rate of hospitalizations related to AP has increased from 2002 to 2013 [3,4] but overall mortality decreased [5]. In the 2012 Burden of Gastrointestinal Disease in the United States, AP was reported as the most common reason for hospitalization [6].

Causes

Table 1.1 lists the causes of acute pancreatitis. However, biliary disease and alcohol are the two most common causes, together accounting for approximately two-thirds of cases [7]. Biliary diseases include cholelithiasis, choledocholithiasis, microlithiasis (stones <5 mm), and biliary sludge, and are likely the most common cause of AP. Microlithiasis is more frequently detected by endoscopic ultrasound (EUS) than by transabdominal ultrasound [8]. It is also the most common diagnosis by EUS in patients with idiopathic AP [9].

Biliary causes should be evaluated in all patients who present with AP. The initial test is surface ultrasonography, which allows excellent visualization of the gallbladder but limited views of the common bile duct and pancreas, especially in obese patients and those with ileus.

Cholelithiasis is felt to be the most common cause of AP. Our goal is to determine its presence with the least mortality. The role of endoscopic retrograde cholangiopancreatography (ERCP) has changed from a diagnostic to a therapeutic modality for two reasons: first, because of its associated morbidity (4–7%) and mortality (0.06–0.33%) (although these figures include therapeutic and not simply diagnostic ERCP) [10,11]; and second because of the development and widespread availability of magnetic resonance cholangiopancreatography (MRCP) and EUS as diagnostic modalities. In patients with AP, the primary role of early ERCP (<48 hours) is in patients with acute cholangitis, where ERCP with endoscopic sphincterotomy (ES) reduces mortality and systemic and local adverse events [12].

In patients with AP and suspected biliary obstruction that is manifested by a dilated common bile duct and elevated liver function tests, MRCP or EUS is used to confirm these findings and establish a diagnosis [12]. EUS or MRCP has comparable accuracy to diagnostic ERCP and therefore a negative study obviates the need for ERCP. A systematic review of randomized controlled trials and clinical trials by De Lisi et al. [13] found that EUS had a lower failure rate than ERCP and that ERCP was avoided in 71% of patients. In the patient with suspected biliary AP and negative surface ultrasound, the question is whether MRCP or EUS should be utilized. The advantage of MRCP is that no contrast agent, anesthesia, or radiation is required. In a study by Makary et al. [14], magnetic resonance cholangiography accurately identified 57 of 62 (94%) of patients with gallstones and correctly identified choledocholithiasis in 94%. In a meta-analysis, Wan et al. [15] compared EUS with MRCP in patients with idiopathic AP and found a diagnostic yield of 64% for EUS and 34% for MRCP.

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Table 1.1 ABC causes of acute pancreatitis.

A	Alcohol, autoimmune
B	Biliary, including gallstones, microlithiasis and sludge
C	Congenital: pancreas divisum; Crohn's disease via inflammation, or ampullary or duodenal obstruction
D	Drugs, toxins (including, smoking, tobacco and marijuana use)
E	Post-ERCP pancreatitis, eosinophilic pancreatitis
F	Formations: primary cancers (pancreatic ductal adenocarcinoma, especially in patients >50 years), lymphomas, carcinoids, metastatic cancers, small cell lung cancers, renal cancers, melanoma
G	Genetic mutations and polymorphisms: cystic fibrosis, transmembrane conductance regulator (*CFTR*), cationic trypsinogen (*PRSS1*), serine protease inhibitor Kayal type 1 (*SPINK1*), and claudin-2 (*CTRC*)
H	Hypertriglyceridemia and hypercalcemia: hypertriglyceridemia may be associated with metabolic pancreatitis (i.e. elevated glucose, obesity); hypercalcemia associated with hyperthyroidism or iatrogenic infusion
I	Infection: viruses such as cytomegalovirus, mumps and Epstein–Barr virus; ascariasis and *Clonorchis sinensis*; bacterial tuberculosis
J	Juxta-ampullary diverticula: likely mechanism is obstruction
K	Kinetic injury and other trauma, including seat belt injuries

ERCP, endoscopic retrograde cholangiopancreatography.
Source: adapted from Barkin et al. [7].

The improved detection rate of EUS over MRCP should not be unexpected as EUS has high resolution (0.1 mm), which accounts for its ability to detect small stones (<5 mm), so-called microlithiasis that is difficult to detect by MRCP [13]. These small stones are considered to be the cause of unexplained pancreatitis in 75% of patients with an intact gallbladder [16]. The clinical question in patients with AP and elevated liver function tests is whether a common bile stone is present. Kondo et al. [17] compared EUS, MRCP, and computed tomography (CT) for detecting common duct stones and found 100% using EUS compared with 88% using either MRCP or CT. The false negatives for MRCP and CT were stones under 5 mm, which EUS would be expected to visualize, as it did [17]. In summary we should utilize a low-risk diagnostic test to evaluate AP patients with unexplained biliary obstruction. If MRCP is negative, EUS is utilized to determine anatomy and need for simultaneous ERCP if a stone is detected [18].

Metabolic AP represents the association of hyperlipidemia, obesity, and diabetes and is being increasingly recognized and described [19]. Obesity increases the risk of developing more severe AP, with a higher risk of both local and systemic complications and of in-hospital mortality compared with lean subjects [20]. A body mass index (BMI) over 25 increases the risk of severe AP while BMI over 30 increases risk of mortality [21]. Larger visceral adiposity is a strong predictor of severe pancreatitis [22]. Higher BMI increases the risk of both gallstone-related AP and non-gallstone-related AP [23].

Type 2 diabetes mellitus and obesity are related. Approximately two-thirds of individuals with non-insulin-dependent diabetes mellitus (NIDDM) are obese, which increases their risk of AP [24]. In addition, hypertriglyceridemia (HTG) has been found to be an independent risk factor for AP in patients with type 2 diabetes mellitus [25]. Triglyceride (TG) levels provide the most direct evidence of HTG-induced AP and should be measured on admission in patients with AP, as TG levels can rapidly decrease with fasting. HTG is frequently unrecognized or unappreciated as a cause of AP as TG levels are measured later in the course of the disease. Amylase level may be normal in patients with AP due to high TG concentration (>500 mg/dl) [26] and therefore lipase levels should be used as these are unaffected by TG level [27].

HTG may be primary or secondary to medications or conditions such as alcohol abuse, pregnancy, and hyperthyroidism. There is a group of drugs that cause AP by elevating serum TGs. These drugs have been reviewed by Elkouly et al. [28] and commonly include clomifene, estrogen products, nadolol, tamoxifen, furosemide, and propofol among others [28]. In addition, HTG is part of so-called metabolic pancreatitis, comprising obesity, diabetes, and HTG; obesity predisposes to gallstones and thus patients with HTG must be evaluated for cholelithiasis. The level of TG causing AP has been thought to be 1000 mg/dl or greater. However, a prospective cohort study by Pedersen et al. [29] showed that nonfasting mild to moderate HTG (TG ≥177 mg/dl or 2 mmol/l) is associated with a high risk of AP. HTG is associated not only with an increased risk for AP [30] but also with worse prognosis of AP, with significantly increased renal and respiratory failure and shock [31]. These authors also found an increased incidence of systemic inflammatory response syndrome (SIRS) in TG-associated AP. TG levels in patients who developed organ failure were found to be initially much higher than in patients who did not develop organ failure [32]. HTG-associated AP accompanied by another etiology (e.g. alcoholism) was found to have a significantly higher frequency of persistent organ failure than with HTG alone. Thus, cofactors may induce and increase the severity of AP. In addition, the rate of persistent organ failure increases proportionally with increasing levels of HTG [33].

Recurrent AP occurs in approximately one-third of patients with HTG-associated AP. The goal of therapy is twofold: (i) lowering of the TG level and (ii) removal of precipitating events or coexistent disease. The precipitating events include alcohol abuse, obesity, uncontrolled diabetes

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mellitus, and pregnancy. Precipitating medication that may increase TG levels (i.e. birth control) should be discontinued. Vipperla et al. [30] found that a precipitating cause was present in 78% of patients with HTG-associated AP. Peak TG levels exceeding 3000 mg/dl independently predict recurrence of AP, while lower rates of recurrent AP are associated with reduced serum TG levels [34]. An attempt should be made to normalize TG levels in all patients with HTG in order to decrease their risk of recurrent AP. Statins reduce the risk of AP in patients with normal or mildly increased levels of TGs [35].

Genetic mutations, with or without the presence of an environmental factor, can cause AP. The most common mutations involve *PRSS-1*, *CFTR*, *SPINK-1*, and *CTRC*, which control trypsin activity in the pancreas. We are finding new mutations in the genes that can result in AP and have learned that some mutations require an environmental cofactor to cause AP [36]. A genetic cause of idiopathic (unexplained) AP should be sought in patients aged below 35 years and in those with acute recurrent idiopathic pancreatitis (ARIP) [37]. In the past, genetic searches were limited to patients who had a family history of pancreatitis, but Jalaly et al. [37] found that a positive family history of pancreatitis did not predict pathogenic genetic variation testing. This is likely explained by the fact that pancreatitis in the family members included in this study was caused by the usual factors (i.e. alcohol, biliary disease). It is important to identify a genetic cause of AP in order to counsel the patient about avoidance of other triggers of AP (e.g. smoking) and to initiate surveillance for the development of exocrine and endocrine insufficiency and pancreatic cancer [36], as well as considering family planning issues (Table 1.2).

Cystic fibrosis occurs in 1 in 2500 persons of northern European descent [38]. Genetic mutations in the *CFTR* gene, the cause of cystic fibrosis, are increased in patients with idiopathic acute and chronic pancreatitis as well patients with recurrent acute pancreatitis compared with a control group. Gastroenterologists see adult patients with so-called atypical cystic fibrosis. This group presents with unexplained acute or chronic pancreatitis and/or exocrine pancreatic insufficiency (EPI). Clinical clues to the presence of atypical cystic fibrosis are the presence of asthma, inability to conceive (due to congenital absence of the vas deferens), and/or chronic sinusitis. Cystic fibrosis risk factors for chronic pancreatitis include other genetic abnormalities predisposing to pancreatitis and pancreas divisum. Genetic testing in adult patients in the twenty-first century is in a state of flux as many new genetic mutations are being found to be associated with AP [39].

Table 1.2 Indications for genetic testing in patients with acute pancreatitis.

Idiopathic acute pancreatitis in patients aged <35 years
Acute recurrent idiopathic pancreatitis
Family history of idiopathic chronic pancreatitis or recurrent acute pancreatitis
Individuals whose families have an identified gene mutation associated with hereditary pancreatitis

Source: adapted from Hasan et al. [38].

Up to 22% of patients with AP, after extensive evaluation, have an unidentified cause of their AP. In these patients with so-called idiopathic pancreatitis, we must explore all possible causes of AP as they have an increased propensity to develop recurrent pancreatitis and possibly chronic pancreatitis and pancreatic cancer. In addition, once a cause is identified, invasive diagnostic testing can be limited. Genetic abnormalities are frequently not sought in these patients. Jalaly et al. [37] evaluated 197 patients with ARIP, including 134 who underwent genetic testing, and found 88 pathogenic genetic variants in 64 (48%). Pathogenic genetic variants were identified in 58% of patients with ARIP and in 63% of patients with unexplained first episode of AP aged below 35 years. These were independently associated with pathogenic genetic variants in their adjusted analyses [37]. In addition, the authors found that a family history of pancreatitis did not predict pathogenic variants on genetic testing as these patients may have contracted AP from the usual causes.

Current smoking compared with lifelong nonsmoking is associated with AP (relative risk, RR, 2.14) after adjustment for age, sex, BMI, and alcohol consumption. This association is stronger (RR 3.19) in heavy smokers (20–30 cigarettes/day). This association was independent of alcohol consumption [40]. Barkin et al. [7] reported that cannabis use is a likely cause of AP, and that abstinence eliminates recurrent episodes.

Drug-induced AP must be considered in all patients with idiopathic AP. We have information on very few drugs where patients have undergone positive rechallenge, even more so on drugs with consistent latency. Most of our information is from case series and reports [41]. It is estimated that up to 5% of AP is caused by drugs [42]. The drug may be a single etiology or a cofactor (i.e. acting with a gene or another drug). Unfortunately, there are no clues except history to drug-induced AP as it is not accompanied by evidence of a drug reaction (i.e. rash, lymphadenopathy and/or eosinophilia) [42]. Table 1.3 lists the drugs most likely to cause AP; however, multiple other drugs have been associated with AP [43].

Pancreatic neoplasms, both primary and metastatic, can present with AP. The relationship between an underlying pancreatic cancer and AP is well recognized [44]. This association has been found both in western and eastern populations [45]. The risk of an underlying

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Table 1.3 Drugs commonly associated with acute pancreatitis.

6-Mercaptopurine
Azathioprine
Valproic acid
Didanosine
Angiotensin-converting enzyme inhibitors
Furosemide
Isoniazid
Metronidazole
Sulindac
Tetracycline
Amiodarone
Lynesterol/methoxyethinylestradiol
Norethindronate/mestranol
Trans-retinoic acid
Interferon-alpha

Source: adapted from Tenner [42].

pancreatic cancer is greatest in the first year after AP and then decreases, and such a cancer should be sought in patients aged over 40 years who have AP [44]. On imaging, the appearance of AP may obscure the small underlying pancreatic cancer, or the method itself may be insufficiently sensitive. A clue to the existence of an underlying pancreatic cancer is the presence of pancreatic duct dilation. In a systematic review, Wan et al. [15] compared EUS with MRCP in patients with idiopathic acute pancreatitis and showed that EUS had a diagnostic yield of 64% compared with 34% for MRCP. Therefore, EUS is the recommended method when screening for an underlying neoplasm in patients aged over 50 years, even if a likely cause of their AP is present (i.e. alcohol and gallstones). To quote Munigala et al. [44]: "It is usually inappropriate to assume a causative correlation between any metabolic disorder or drug with the first episode of AP." To cast blame on alcohol or gallstones for AP in patients with an underlying pancreatic cancer results in delayed diagnosis. This is also applicable to patients who present with a pseudocyst [46].

Laboratory Diagnosis

The diagnosis of AP is based on the presence of a chief complaint of epigastric abdominal pain in an appropriate individual who has a propensity for an etiology of AP and the finding of a laboratory test greater than threefold the upper limit of normal. Early imaging on admission or in the emergency room using CT is only indicated if diagnostic criteria are not fulfilled or there are findings that call the diagnosis of AP into question. Unfortunately, upper abdominal pain and tenderness is a frequent presentation of a plethora of disease states. Abdominal tenderness from AP may, in addition to epigastric location, also be present in the right upper quadrant. Findings of an acute abdomen may be present and, if so, CT imaging should be considered. The pain may radiate into the back and be associated with nausea and vomiting as well as fever [47]. The second consideration should be whether the patient has a potential etiology for AP (e.g. biliary disease, alcohol, trauma; see Table 1.1). Its presence increases our diagnostic certainty.

The laboratory diagnosis for AP has changed from determination of amylase to determination of lipase but the criterion is still a threefold increase. Lipase has several advantages over serum amylase: sensitivity is higher (82–100% vs. 67–100% for total amylase) and a slightly better specificity (82–100% vs. 85–98% for amylase) [47]. In addition, lipase offers a larger diagnostic window than amylase as it remains elevated for a longer period: amylase elevation lasts for only three to five days [48] whereas lipase shows persistent elevation for up to two weeks. Other causes of elevated lipase in patients with abdominal pain include trauma, appendicitis, diabetic ketoacidosis, small bowel disease, inflammatory bowel disease, ischemia, obstruction, cirrhosis, renal failure, and upper gastrointestinal malignancies (esophagus, stomach). It is questionable whether HTG may produce falsely low lipase levels [27]. There is no advantage of ordering amylase together with lipase. Unfortunately, laboratory tests are not diagnostic of AP and levels do not predict severity of AP. There is no benefit in monitoring laboratory diagnostic tests (i.e. amylase/lipase) during the course of AP [48].

Imaging

The initial imaging of a patient with suspected AP should include chest X-ray and flat and upright abdominal radiographs. Their usefulness is to exclude other causes of abdominal pain, and occasionally to visualize findings suggestive of AP (i.e. sentinel loop, colon cutoff sign, and left pleural effusions) [47]. Abdominal surface ultrasound should follow radiological imaging. Its best role is for gallbladder visualization with determination of the presence of cholelithiasis. It can visualize the pancreas in approximately two-thirds of patients, revealing peripancreatic changes of inflammation; however, this is markedly decreased when the individual is obese and or if an ileus is present.

CT is the gold standard for pancreatic imaging. However, when possible, it should not be performed until the patient has been rehydrated. This delay will prevent renal injury from contrast and allow the clinician to decide if CT is needed. The primary reason for early CT scan (<72 hours)

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is diagnostic uncertainty. Early CT does not improve clinical outcome or influence treatment nor does it improve prediction of severe disease over clinical scoring. Optimal timing for initial CT assessment is 72–96 hours after onset of symptoms [49], which also allows time for necrosis to occur. The advantages of CT over magnetic resonance imaging (MRI) is its increased availability and decreased cost. It has increased sensitivity for definition of small air bubbles and calcification within the pancreas [50].

MRI may be equivalent to CT for evaluating severity of disease. MRCP is especially useful for depicting 3–5 mm choledocholithiasis. If biliary stone disease remains a consideration after MRCP, EUS is the next procedure and it has up to an 80% success rate. In addition, MRCP can visualize disruption (partial or complete) of the main pancreatic duct [51].

Risk Stratification

Use of a severity index should allow prediction of the small group of patients who are going to develop severe disease, characterized by organ system failure, pancreatic necrosis with or without infection, and increased mortality. Overall mortality for AP is 2% but this increases to 30% in those with severe disease [52,53]. However, Di et al. [53] found that the test characteristics and clinical utility of these AP severity scores remain uncertain. They did not find studies that directly assessed influence of these models on patient management.

Predicting severity of AP should be simple and allow prediction early in the patient's course. This is best accomplished by the Bedside Index for Severity in Acute Pancreatitis (BISAP) or SIRS, which can predict severity within the first 24 hours. The BISAP includes blood urea nitrogen (BUN) greater than 25 mg/dl, impaired mental status (Glasgow Coma Scale score <15), SIRS score 2 or above, age over 60 years, and pleural effusion. One point is given for each and a score of more than 3 indicates an increased risk of death [54]. A follow-up evaluation by Singh et al. [55] on the BISAP score reported that a score of 3 or more was associated with an increased risk of developing organ failure, persistent organ failure, and pancreatic necrosis.

SIRS is defined by the presence of two or more of heart rate above 90 bpm, respiratory rate above 20 breaths per minute or $PaCO_2$ below 32 mmHg (4.3 kPa), body temperature below 36 or above 38°C, and leukocyte count less than 4×10^9/l or more than 12×10^9/l. Its presence during the first 24 hours of admission has high sensitivity for predicting severe disease (85%). However, persistent SIRS predicted the development of persistent organ failure in only a minority of patients [56].

On admission, hematocrit above 44% and rise in BUN at 24 hours may be optional predictive tools. Reducing BUN and hematocrit should be utilized to guide fluid resuscitation over the first 12–24 hours and are an accurate predictor of death [57]. We agree with Forsmark and Yadav [58] that monitoring serum BUN and hematocrit along with SIRS over the first 48 hours is simple and an effective scoring system for predicting severe AP.

Classification

The revised Atlanta Classification of Acute Pancreatitis classifies severity into mild, moderately severe and severe using both clinical and radiographic criteria (Table 1.4) [59]. In mild AP, patients usually improve rapidly with supportive care (fluid resuscitation) and mortality is rare, except in patients with severe comorbidity [60]. Patients with acute mild pancreatitis by definition do not have local complications such as peripancreatic collection, sterile pancreatic necrosis, and exacerbation of a comorbidity, and they do not have a modified Marshall score of 2 or more that defines the presence of organ failure (respiratory, renal, cardiovascular) [59].

Moderately severe AP is defined as the presence of transitory organ system failure (<48 hours) and/or local or systemic complications exacerbating comorbid disease without persistent organ failure [59]. Severe AP is characterized by single or multiple organ failure for longer than 48 hours, determined by analysis of the respiratory, renal and/or cardiovascular systems using the modified Marshall scoring system. Patients with persistent SIRS for longer than 48 hours, or with infected necrosis, are usually in this category, although infected necrosis can be present without organ failure. (Table 1.5).

Table 1.4 Classification of acute pancreatitis.

	Mild	Moderate	Severe
Organ failure	None	Transient (resolves within 48 hours)	Persistent organ failure (>48 hours) of one or more organs
Local complications	None	Yes, without persistent organ failure	
Systemic complications	None	Yes, without persistent organ failure	

Source: adapted from Banks et al. [59].

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Table 1.5 Predictors of severe acute pancreatitis.

Patient	Age, obesity (BMI >30), altered mental status, numerous and severe comorbidities including coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, chronic liver disease, long history of alcohol abuse
SIRS	Present and persists >48 hours
Laboratory	Hematocrit >44% and no decrease with hydration
	Urea nitrogen >20 mg/dl (>7.1 mmol/l) rising and/or no decrease with hydration, and/or elevated creatinine >1.8 mg/dl (>159 mmol/l)
Imaging	Pleural effusion or infiltrates

Source: adapted from Forsmark et al. [52].

Treatment

The foundation for therapy of patients with AP is fluid restoration, as the major effect of pancreatic inflammation is fluid sequestration. The goals of fluid therapy are to replenish the lost circulatory fluids to maintain organ system perfusion and oxygenation including the pancreas. Unfortunately, our recommendations are not based on conclusive scientific information [61]. Sinha et al. [62] reported variables that independently predicted increased fluid sequestration within the first 48 hours after hospital admission; these included younger age (<40 years), alcohol etiology, hemoconcentration, and SIRS. Increasing volumes of fluid sequestration were associated with longer hospitalizations, persistent SIRS, and persistent organ system failure [63]. Buxbaum et al. [64] reported a randomized trial of patients with nonsevere AP to aggressive (20 ml/kg bolus followed by 3 ml/kg per hour vs. standard therapy with 10 ml/kg bolus followed by 1.5 ml/kg per hour) hydration with Ringer's lactate solution. They found that a significantly higher proportion of patients treated with aggressive compared with standard hydration showed clinical improvement. In addition to higher volumes of fluid, early fluid resuscitation reduces morbidity among patients with AP. Warndorf et al. [65] reported that early resuscitation, defined as the administration of one-third or more of the total 72-hour fluid volume within 24 hours of presentation, was associated with decreased SIRS as well as reduced organ failure, lower rate of admissions to the intensive care unit (ICU), and reduced length of hospitalization; the fluid of choice is Ringer's lactate [65]. The clinical goals of fluid replacement therapy are to achieve hemodynamic stability. Clinically, we follow the parameters of heart rate, urine output, and blood pressure; in addition, we follow the laboratory markers BUN and hematocrit. Thus, the volumes infused are based on the patient's vital signs, incorporating blood pressure, pulse and respiratory rates, age, cardiac and renal disease, laboratory values (BUN, creatinine and hematocrit), and the presence of SIRS. This so-called goal-directed therapy for fluid management is defined as titration of intravenous fluids to specific clinical and biochemical targets of perfusion [66].

Table 1.6 Fluid therapy for patients with moderately severe or severe acute pancreatitis.

1) Bolus of Ringer's lactate: administer 1 liter in the emergency room
2) Infusion of Ringer's lactate at 5–10 ml/kg per hour until clinical hemodynamic stability and laboratory parameters are reached
3) Change intravenous fluid rate to 3 ml/kg per hour once parameters are reached

Source: adapted from DiMagno MJ. Clinical update on fluid therapy and nutritional support in acute pancreatitis. *Pancreatology* 2015;15(6):583–588.

Fluid therapy is most effective if given early in the course of AP. This was shown by an international multicenter study which found that early moderate (>500–1000 ml) compared to nonaggressive (<500 ml) fluid volume administration in the emergency room was associated with lower rates of local complications; indeed, the groups who received aggressive therapy (>1000 ml) also had a significantly lower need for intervention [67]. We utilize a combination of initial bolus and high-volume intravenous infusion and assess our goal-directed therapy using the patient's vital signs, hourly urine output, and measurement of BUN, creatinine and hematocrit every six to eight hours. When hemodynamic stability is achieved and laboratory values are normal (BUN <20 mg/dl and hematocrit <35%), we decrease rates of infusion (Table 1.6).

Prophylactic Antibiotics

The basis for administration of prophylactic antibiotics in patients with AP is to prevent infection in those who develop necrotizing AP. The mortality in patients with necrosis is up to 20% compared with 5% mortality in those with edematous or interstitial AP [68]. Once infection complicates necrosis, mortality increases to 30–40%. Therefore, prophylactic antibiotics would appear to be a reasonable therapeutic approach. However, it has been shown to be ineffective in a Cochrane Database systematic review by Villatoro et al. [69], who found that there was no benefit to antibiotics for preventing pancreatic necrosis infection or decreasing mortality.

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 to patients early in the course of AP who have suspected biliary sepsis or show evidence of

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extrapancreatic 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 (one to two weeks) after onset of disease. The role of antibiotics in this phase is to allow the organization of the necrosis as well as delaying surgery, usually until four weeks, as this is associated with decreased mortality compared with early intervention. In addition, delay and use of antibiotics may allow for application of less invasive drainage procedures. In addition, antibiotic therapy alone can effectively treat a subgroup of patients with infected necrosis [70,71]. An initial report by Runzi et al. [71] of nonsurgical treatment of 16 patients with severe AP with infected pancreatic necrosis (IPN), treated only with an antibiotic regimen adapted to bacteriology and nonsurgical therapy, reported a 12% (2 of 16 patients) mortality rate. Six recovered without further complications and 10 patients developed single or multiple organ failure. This study placed a wedge in the concept that all patients with IPN needed immediate open pancreatic surgical drainage. The currently accepted management of patients with IPN is that early in their course they 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 less invasively.

Nutrition

One of our goals in treating patients with AP is early oral feeding. This should commence as soon as the patient is hungry and ideally when they are not vomiting and have improving nausea and abdominal pain. Oral feeding is a critical foundation of our therapeutic regimen. It maintains small bowel integrity thereby decreasing bacterial translocation. Early enteral nasogastric tube feeding does not reduce infection or death compared with oral feeding at 72 hours. In studies by Bakker et al. [72] and Cote [73], over two-thirds of the patients tolerated an oral diet after its initiation at 72 hours after randomization, showing that starting an oral diet at 72 hours is not harmful to the patient. In patients with moderate or severe AP, early oral refeeding (defined as when patients are hungry and initiated when clinical and laboratory parameters resolve) is safe and may shorten hospitalization compared to conventional oral refeeding [74]. Vaughn et al. [75] in a systematic review of early (<48 hours) versus delayed (>48 hours) feeding in patients with AP found that adverse events secondary to early feeding did not increase. In these patients with mild to moderate AP, it may also reduce the length of hospital stay [75]. Their early nutrition group included oral as well as tube feeding.

Oral feeding intolerance, defined as relapse of symptoms following oral feeding, occurs in one of six patients with AP [76]. Predictors are complicated or severe disease reflected by presence of pleural effusion and/or (peri)pancreatic collections. If patients have oral feeding intolerance, enteral nutrition (EN) can be initiated with either nasogastric or nasojejunal feeding, as they have similar safety and efficacy. This should start early (<48 hours) in the course of severe AP, but should be delayed for 72 hours in patients with mild to moderate AP to determine if they can tolerate oral feeding. Infusion is with polymeric formula. Low rates of infusion possibly decrease bowel permeability but our goal should aim to meet patients' caloric demands. EN should be started prior to 48 hours in patients with severe pancreatitis, especially those who are intubated. Khalid et al. [77] showed that the benefits of early feeding were more evident in the sickest (treated with multiple vasopressors) ICU patients.

Bakker et al. [78] reported a meta-analysis of 165 individuals from eight randomized trials. The cohort was divided into those who received EN within 24 hours of admission and those who received EN after 24 hours of admission. Those receiving EN within 24 hours of admission had decreased organ failure (42% vs. 16%; odds ratio 0.42) and reduction in the complications of IPN and/or organ failure. There was no difference in mortality, and therefore the earlier the initiation of EN, the better for the patient with severe AP. However, the benefits of EN begun within three days could reduce the risk of secondary infection and improve the nutritional status of patients with AP [78].

Overall, EN should be utilized over parenteral nutrition in patients with AP. EN has a multitude of advantages over parenteral nutrition, including avoidance of catheter-related sepsis, lower cost, maintenance of gut barrier function, and decreased bacterial translocation, a critical mechanism in developing infections in AP patients. EN, compared with parenteral nutrition, results in reduction in the risk of total and pancreatic infectious complications and risk of death [79,80].

Post-discharge Cholecystectomy

In addition to treating the acute episode of pancreatitis, we need to focus on decreasing the possibility of the patient's readmission, shown by Munigala et al. [81] to be 14%. The factors that have been associated with increased readmission are shown in Table 1.7. Symptoms upon discharge that have been shown to be associated with increased rate of readmission include inability to tolerate a regular diet and need for pain medications [82]. Cholecystectomy on index admission for acute biliary pancreatitis reduces rates of readmission [82].

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Table 1.7 Factors associated with increased readmission rates.

Patient: alcohol and substance abuse
Increased comorbidities (increasing Charlson comorbidity index)
Severe pancreatitis: association with pseudocyst, necrotizing pancreatitis
Discharge to extended care facility (not home discharge)
Biliary pancreatitis not undergoing cholecystectomy on initial admission: note that cholecystectomy on index admission for acute biliary pancreatitis reduces rates of readmission

Source: adapted from Munigala et al. [81].

The Dutch Pancreatitis Study Group followed more than 600 patients after an episode of AP and found that recurrent pancreatitis developed in 117 (17%). This was more common in those with alcoholic or idiopathic or other etiologies compared with biliary disease. In addition, recurrent pancreatitis was more common in smokers and those who had experienced necrotizing pancreatitis. They reported that smoking was the most important factor for recurrent acute pancreatitis (RAP) [83]. The severity of recurrent compared with initial episodes of AP was reported by Lee et al. [84] and Mallick et al. [85]. Lee et al. found that RAP was associated with zero mortality compared with 4.7% mortality in initial episodes. Prior AP episodes had a decreased risk of severe disease (i.e. multisystem organ failure) [84]. This observation may be due to destruction of acinar cells with their replacement by pancreatic fibrosis. Mallick et al. confirmed these observations in a group of 632 patients with an initial episode of AP. Severe pancreatitis, surgical intervention, and mortality were less in patients with RAP compared to patients with an initial episode of AP [85].

Biliary disease is the leading cause of AP in Western countries, and therefore cholecystectomy is the optimal therapy. However, the timing of laparoscopic cholecystectomy in patients with acute biliary pancreatitis has been a contentious issue. The concern of performing same-admission, so-called early, cholecystectomy is safety and prolonged length of stay. Conversely, issues associated with delayed laparoscopic cholecystectomy include when it should be performed post AP and determining the risks of recurrent AP and the occurrence of biliary events (i.e. colic, cholecystitis) in the interim. In addition, this timing issue only applies in patients with mild and possibly moderate AP as it is felt that patients with severe disease should undergo cholecystectomy once they recover from their organ failure. There is no consensus about the timing of cholecystectomy in patients with pancreatic necrosis with or without infection. Da Costa et al. [86] reported a randomized controlled trial comparing same admission versus delayed (so-called interval) cholecystectomy for patients with mild gallstone pancreatitis. The risk of recurrent gallstone-related complications occurred more frequently (17% in the delayed group vs. 5% in the early group). A systematic review by Lyu et al. [87] of 1833 patients found that gallstone-related complications occurred in 25% of patients during the waiting period in the delayed cholecystectomy group.

The goal of cholecystectomy is prevention of recurrent AP and biliary events. Multiple societies have recommended cholecystectomy be performed during the initial admission rather than after discharge to prevent occurrence of these events [61]. Bilal et al. [88] reported the trends of same-admission cholecystectomy in the United States and found a decrease in use of the procedure, from 48.7% in 2004 to 45% in 2014. Delayed cholecystectomy was found to be more common in patients with severe pancreatitis, sepsis, three or more Elixhauser comorbidities, and admission to small or rural hospitals [89] and in older patients [90]. Delayed cholecystectomy in these patients was likely related to the presence of severe pancreatitis with severe comorbidities. In these patients, as always, we must balance risks and benefits of early cholecystectomy.

A concern of early cholecystectomy is whether it is associated with increased operative complications (i.e. conversion of laparoscopy cholecystectomy to open cholecystectomy). Van Baal et al. [91] from the Dutch Pancreatic Group reported a systematic review and found no differences in operative complications, conversion to open cholecystectomy, or mortality between early (index) cholecystectomy and interval cholecystectomy. A follow-up question in patients with mild acute biliary pancreatitis who are not undergoing early cholecystectomy is whether they should undergo ERCP with ES to prevent readmissions from RAP and biliary events. Ridtitid et al. [92] found that ERCP/ES performed in a delayed cholecystectomy group of AP patients was associated with a significantly lower rate of acute recurrent biliary pancreatitis (4% vs. 36% of those patients not undergoing ERCP/ES). ERCP/ES was associated with the occurrence of mild pancreatitis (4%) and with post-sphincterotomy bleeding (5%). Bakker et al. [93] reported similar findings: in patients with mild biliary pancreatitis who did not have index cholecystectomy but underwent ERCP/ES, the procedure significantly decreased the occurrence of interval biliary events to 7.4% (compared with 18.4% in those who did not undergo ERCP/ES). This was primarily due to a reduced risk of biliary pancreatitis. Thus, ES is a temporizing measure in patients who are unfit for surgery. ES does not protect totally against biliary colic or acute cholecystitis [93]. The next issue is whether the patients who undergo ERCP/ES should subsequently undergo cholecystectomy, which could further decrease this 7.4% rate of biliary events. Zargar et al. [94] reported a randomized trial of cholecystectomy versus expectant management in patients with biliary AP who had undergone ERCP/ES and found

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that cholecystectomy significantly reduced the biliary complications in these high-risk patients. Similar findings were reported by Khan et al. [95] in a systematic review and meta-analysis that compared early cholecystectomy versus a "wait-and-watch" strategy after ES in high-risk patients. They recommended that patients undergo laparoscopic cholecystectomy because it is associated with lower rates of subsequent recurrent cholecystitis, cholangitis, and biliary colic.

Long-term Sequelae

The morbidity of a bout of AP persists in some patients after recovery. Long-term assessment is addressed in Table 1.8. An episode of AP increases a patient's risk of developing diabetes mellitus, progressing to chronic pancreatitis with EPI, and is associated with an increased risk of harboring or developing pancreatic cancer. Ventre et al. [96] reported that patients who had severe AP that required critical care were found to have a high risk for developing new-onset diabetes mellitus. In addition, as expected, greater pre-hospitalization comorbidity, as determined by the Charlson score, negatively influenced survival. Das et al. [97] conducted a systematic review of diabetes mellitus prevalence after AP and found pre-diabetes mellitus in 16%; this is important, as 40% of patients with pre-diabetes progress to diabetes over 5–10 years. Diabetes mellitus was found in 23% and requirement for insulin treatment in 15%. Newly diagnosed diabetes (so-called type 3c diabetes) developed in 15% within 12 months after the first episode of AP. Interestingly, they found that there was no effect of disease severity on the risk of developing diabetes mellitus. Conversely, in a study of patients who had severe pancreatitis, of whom almost three-quarters underwent open necrosectomy, new-onset diabetes mellitus was found in 45%, and pancreatic insufficiency requiring pancreatic enzyme replacement was found in 25% [98].

Shen et al. [99] reported a cohort study that included almost 3000 patients with their first attack of AP and approximately 12 000 individually matched controls. The incidence of developing diabetes within the first three months after AP was 60.8 per 1000 person-years in the AP group compared with 8.0 per 1000 person-years in the control group (hazard ratio, HR, 5.9). The adjusted HR was 2.54 for developing diabetes mellitus beyond three months. Similar to other studies, the results for patients with mild AP were similar to those for all AP groups. We should therefore be aware that after AP of all severities, the risk of developing diabetes mellitus is increased, so-called "diabetes of the exocrine pancreas" [100].

Table 1.8 Long-term sequelae after resolution of acute pancreatitis.

Chronic pancreatitis
Exocrine pancreatic insufficiency
Diabetes mellitus
Pancreatic ductal adenocarcinoma
Decreased quality of life

Hollemans et al. [101] reported on the follow-up of almost 1500 patients with AP at 36 months. They found a pooled prevalence of EPI of 27%. Using fecal elastase levels, EPI occurred significantly more often in patients with alcoholic pancreatitis than in those with other etiologies. EPI was significantly more common in patients with severe than mild AP [101]. The presence of pre-diabetes and/or diabetes mellitus in patients after AP should necessitate a search for coexistent EPI. In patients after AP, Das et al. [102] found a prevalence of concomitant EPI of 40% in patients with newly diagnosed pre-diabetes or diabetes.

Machicado et al. [103] reported the long-term deleterious effect on physical health-related quality of life using a physical- and mental health-related quality of life telephone survey. Individuals who had experienced AP had a significantly lower physical component survey (PCS) score than did controls and this was associated with the presence of multisystem organ failure during hospitalization, which is similar to other ICU survivors. In addition, at time of follow-up lower PCS scores were associated with abdominal pain, analgesic use, disability, and cigarette use. Thus, support to discontinue smoking and alcohol use and to control pain on discharge should be a focus of ongoing care.

The long-term (median of 10.5 years) follow-up of pancreatic function after the first episode of acute alcoholic pancreatitis was reported by Nikkola et al. [104]. As expected, 35% had one or more recurrent episodes of AP during a maximum follow-up of 13 years. New pancreatogenic diabetes developed in 19%, all of which had recurrent AP. Exocrine pancreatic dysfunction occurred in 77 (24%) patients, which was associated with abnormal endocrine function [104]. In alcoholic patients with RAP, progression to chronic pancreatitis occurred in 19% [104] and in 38% mainly in alcoholics as reported by Lankisch et al. [105].

The risk of pancreatic cancer after a primary episode of AP was reported by Rijkers et al. [106] in 731 patients who were followed for a median of 55 months. Pancreatic cancer incidence rate (per 1000 patient-years) in the group who progressed to chronic pancreatitis was 9.0 compared with 1.1 in those did not progress to chronic pancreatitis. The median time to developing pancreatic cancer was 47 months in those with chronic pancreatitis and 12 months in those who did not have chronic pancreatitis. One wonders if the AP was secondary to the underlying pancreatic cancer in this group without chronic pancreatitis. No comparative group was utilized in this study [106].

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Sadr-Azodi et al. [107] performed a population-based cohort study including all Swedish residents diagnosed with AP in order to determine the relationship between AP and pancreatic cancer. Approximately 70% of patients with pancreatic cancer had a history of AP. The risk of pancreatic cancer was increased during the first few years after the episode of AP and then gradually declined. The risk of pancreatic cancer between two months and two years after hospitalization for AP was highest in individuals aged 60 and above without gallstone-related pancreatitis but with diabetes mellitus. Those cancers diagnosed within six months of AP were more likely to be localized [107].

A follow-up, nationwide, matched cohort study from Denmark by Kirkegard et al. [108] found that patients with AP had increased risk of pancreatic cancer. Their risk for developing pancreatic cancer decreased with time but was still elevated at two and five years post episode and this included a three-year washout period to reduce the likelihood of including prevalent cases of pancreatic cancer. Thus, we must continue to follow up and search for an underlying neoplasm in patients with AP who are older than 40 years of age, irrespective of the presumed cause of their AP. The reason(s) for this association may be similar etiologies, including alcohol, smoking, diet, diabetes, and obesity [109].

Thus, patients with a history of AP regardless of cause should likely undergo screening for pancreatic cancer in the five years after their initial episode.

References

1 Gapp J, Hall AG, Walters RW, et al. Trends and outcomes of hospitalizations related to acute pancreatitis. Epidemiology from 2001 to 2014 in the United States. *Pancreas* 2019;48(4):548–554.

2 Afghani E, Pandol SJ, Shimosegawa T, et al. Acute pancreatitis: progress and challenges. A report on an international symposium. *Pancreas* 2015;44:1195–1210.

3 Roberts SE, Morrison-Rees S, John A, et al. The incidence and etiology of acute pancreatitis across Europe. *Pancreatology* 2017;17:155–165.

4 Brindise E, Elkhatib I, Kuruvilla A, Silva R. Temporal trends in incidence and outcomes of acute pancreatitis in hospitalized patients in the United States. *Pancreas* 2019;48:169–175.

5 Krishna SG, Kamboj AK, Hart PA, et al. The changing epidemiology of acute pancreatitis hospitalizations: a decade of trends and the impact of chronic pancreatitis. *Pancreas* 2017;46:482–488.

6 Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver and pancreatic diseases in the United States: Update 2018. *Gastroenterology* 2019;156:254–272.

7 Barkin JA, Nemeth Z, Saluja AK, Barkin JS. Cannabis-induced acute pancreatitis: a systematic review. *Pancreas* 2017;46:1035–1038.

8 Ardengh JC, Malheiros CA, Rahl F, et al. Microlithiasis of the gallbladder: role of endoscopic ultrasonography in patients with idiopathic pancreatitis. *Rev Assoc Med Bras* 2010;56(1):27–31.

9 Vila JJ. Endoscopic ultrasonography and idiopathic acute pancreatitis. *World J Gastrointest Endosc* 2010;2:107–111.

10 Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007;102:1781–1788.

11 Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc* 2009;70:80–88.

12 Buxbaum JL, Abbas Fehmi SM, Sultan S, et al. ASGE guideline on the role of endoscopy in the evaluation and management of choledocholithiasis. *Gastrointest Endosc* 2019;89(6):1075–1105.e15.

13 De Lisi S, Leandro G, Buscarini E. Endoscopic ultrasonography versus endoscopic retrograde cholangiopancreatography in acute biliary pancreatitis: a systematic review. *Eur J Gastroenterol Hepatol* 2011;23:367–374.

14 Makary MA, Duncan MD, Harmon JW, et al. The role of magnetic resonance cholangiography in the management of patients with gallstone pancreatitis. *Ann Surg* 2005;241:119–124

15 Wan J, Ouyang Y, Yu C, et al. Comparison of EUS with MRCP in idiopathic acute pancreatitis: a systematic review and meta-analysis. *Gastrointest Endosc* 2018;87:1180–1188.

16 Wilcox CM, Varadarajulu S, Eloubeidi M. Role of endoscopic evaluation in idiopathic pancreatitis: a systematic review. *Gastrointest Endosc* 2006;63:1037–1045.

17 Kondo S, Isayama H, Akahane M, et al. Detection of bile duct stones: comparison between endoscopic ultrasonography, magnetic resonance cholangiography and helical-computed-tomography cholangiography. *Eur J Radiol* 2005;54:271–275.

18 Savides TJ. EUS-guided ERCP for patients with intermediate probability for choledocholithiasis: is it

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time for all of us to start doing this? *Gastrointest Endosc* 2008;67:669–672.

19 Khatua B, El Kurdi B, Singh VP. Obesity and pancreatitis. *Curr Opinion Gastroenterol* 2017;33:374–382.

20 Camilleri M, Malhi H, Acosta A. Gastrointestinal complications of obesity. *Gastroenterology* 2017;152(7):1656–1670.

21 Dobszai D, Mátrai, Erőss B, et al. Body-mass index correlates with severity and mortality in acute pancreatitis: a meta-analysis. *World J Gastroenterol* 2019;25:729–743.

22 Natu A, Stevens T, Kang L, et al. Visceral adiposity predicts severity of acute pancreatitis. *Pancreas* 2017;46:776–781.

23 Choi JS, Yi S-W, Park JW, et al. Body mass index and the risk of acute pancreatitis by etiology: a prospective analysis of Korean National Screening Cohort. *J Gastroenterol Hepatol* 2019;34(3):603–611.

24 Molitch ME. Diabetes mellitus. In: Walker HK, Hall WD, Hurst JW (eds) *Clinical Methods: The History, Physical and Laboratory Examinations*, 3rd edn. Boston: Butterworths, 1990, chapter 136.

25 Albai O, Roman D, Frandes M, et al. Hyperglyceridemia, an important and independent risk factor for acute pancreatitis in patients with type 2 diabetes mellitus. *Ther Clin Risk Manag* 2017;13:515–522.

26 Garg R, Rustagi T. Management of hypertriglyceridemia-induced acute pancreatitis. *BioMed Res Int* 2018;2018:4721357.

27 Yin G, Cang X, Yu G, et al. Different clinical presentations of hyperlipidemic acute pancreatitis: a prospective study. *Pancreas* 2015;44:1105–1110.

28 Elkouly MA, Salazar MJ, Simons-Linares R. Hypertriglyceridemia-associated drug-induced acute pancreatitis. *Pancreas* 2019;48(1):22–35.

29 Pedersen SB, Langsted A, Nordestgaard BG. Non-fasting mild-to-moderate hyperglyceridemia and risk of acute pancreatitis. *JAMA Intern Med* 2016;176(12):1834–1842.

30 Vipperla K, Sommerville C, Furlan A et al. Clinical profile and natural course in a large cohort of patients with hypertriglyceridemia and pancreatitis. *J Clin Gastroenterol* 2017;51:77–85.

31 Wang Q, Wang G, Qiu Z, et al. Elevated serum triglycerides in the prognostic assessment of acute pancreatitis. A systematic review and meta-analysis of observational studies. *J Clin Gastroenterol* 2017;51:586–593

32 Sue LY, Batech M, Yadav D, et al. Effect of serum triglycerides on clinical outcomes in acute pancreatitis: findings from a regional integrated health care system. *Pancreas* 2017;46:874–879.

33 Nawaz H, Koutroumpakis E, Easler J, et al. Elevated serum triglycerides are independently associated with persistent organ failure in acute pancreatitis. *Am J Gastroenterol* 2015;110:1497–1503.

34 Zafrir B, Saliba W, Jubran A, et al. Severe hypertriglyceridemia-related pancreatitis: characteristics and predictors of recurrence. *Pancreas* 2019;48:182–186.

35 Preiss D, Tikkanen, MJ, Welsh P. et al. Lipid-modifying therapies and risk of pancreatitis. *JAMA* 2012;308(8):804–811.

36 Raphael KL, Wellingham FF. Hereditary pancreatitis: current perspectives. *Clin Exp Gastroenterol* 2016;9:197–207.

37 Jalaly NY, Moran RA, Fargahi F, et al. An evaluation of factors associated with pathogenic PRSS1, SPINK1, CTFR, and/or CTRC genetic variants in patients with idiopathic pancreatitis. *Am J Gastroenterol* 2017;112:1320–1329.

38 Hasan A, Moscoso DI, Kastrinos F. The role of genetics in pancreatitis. *Gastrointest Endosc Clin North Am* 2018;28:587–603.

39 Weiss FU, Hasselbarth N, Párniczky, et al. Common variants in the CLDN2-MORC4 and PRSS1-PRSS2 loci confer susceptibility to acute pancreatitis. *Pancreatology* 2018;18:477–481.

40 Lindkvist B, Appelros S, Manjer J, et al. A prospective cohort study of smoking in acute pancreatitis. *Pancreatology* 2008;8(1):63–70.

41 Talukdar R, Vege SS. Recent developments in acute pancreatitis. *Clin Gastroenterol Hepatol* 2009;7 (11 Suppl):S3–S9.

42 Tenner S. Drug-induced acute pancreatitis: does it exist? *World J Gastroenterol* 2014;20(44):16529–16534.

43 Meczker A, Miko A, Gede N et al. Retrospective matched-cohort analysis of acute pancreatitis induced by 5-aminosalicylic acid-derived drugs. *Pancreas* 2019;48:488–495.

44 Munigala S, Kanwai F, Xian H, et al. Increased risk of pancreatic adenocarcinoma after acute pancreatitis. *Clin Gastroenterol Hepatol* 2014;12:1143–1150.

45 Chung S-D, Chen K-Y, Xirasagar S, et al. More than 9-times increased risk for pancreatic cancer among patients with acute pancreatitis in Chinese population. *Pancreas* 2012;41:142–146.

46 Diaz LI, Li Y, Barkin JS. Natural history of spontaneous rupture of a pancreatic pseudocyst into the peritoneal cavity and its minimal noninvasive management. *Pancreas* 2019;48(4):e20–e21.

47 Kiriyama S, Gabata T, Takada T, et al. New diagnostic criteria of acute pancreatitis. *J Hepatobiliary Pancreat Sci* 2010;17:24–36.

48 Ismail OZ, Bhayana V. Lipase or amylase for the diagnosis of acute pancreatitis? *Clin Biochem* 2017;50:1275–1280.

10.1002/9781119570097.ch1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/9781119570097.ch1 by Columbia University Libraries, Wiley Online Library on [20/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

49 Working Group IAP/APA Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013;13(4 Suppl 2): e1–e15.

50 Türkvatan A, Erden A, Türkoglu et al. Imaging of acute pancreatitis and its complications. Part 1: Acute pancreatitis. *Diagn Interv Imaging* 2015;96:151–163.

51 Jang JW, Kim M-H, Oh D, et al. Factors and outcomes associated with pancreatic duct disruption in patients with acute necrotizing pancreatitis. *Pancreatology* 2016;16:958–965.

52 Forsmark CE, Vege SS, Wilcox CM. Acute pancreatitis. *N Engl J Med* 2016;375:1972–1981.

53 Di M-Y, Liu H, Yang Z-Yet al. Prediction models of mortality in acute pancreatitis in adults. *Ann Intern Med* 2016;165:482–490.

54 Wu BU. Prognosis in acute pancreatitis. *Can Med Assoc J* 2011;183:673–677.

55 Singh V, Wu B, Bollen T, et al. A prospective evaluation of the bedside Index Severity in acute pancreatitis score in assessing mortality and intermediate markers of severity in acute pancreatitis. *Am J Gastroenterol* 2009;104:966–971.

56 Singh VK, Wu BU, Bollen TL et al. Early systemic inflammatory response syndrome is associated with severe acute pancreatitis. *Clin Gastroenterol Hepatol* 2009;7:1247–1251.

57 Koutroumpakis E, Wu BU, Bakker OJ, et al. Admission hematocrit and rise in blood urea nitrogen at 24 h outperform other laboratory markers in predicting persistent organ failure and pancreatic necrosis in acute pancreatitis: a post hoc analysis of three larger prospective databases. *Am J Gastroenterol* 2015;110:1707–1716.

58 Forsmark CE, Yadav D. Predicting the prognosis of acute pancreatitis. *Ann Intern Med* 2016;165(7):523–524.

59 Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis, 2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;62:102–111.

60 Singh VK, Bollen TL, Bechien U et al. An assessment of the severity of interstitial pancreatitis. *Clin Gastroenterol Hepatol* 2011;9:1098–1103.

61 Vege SS, DiMagno MJ, Forsmark CE, et al. Initial medical treatment of acute pancreatitis: American Gastroenterological Association Institute Technical Review. *Gastroenterology* 2018;154:1103–1139.

62 Sinha A, Vazquez NQ, Faghih M, et al. Early predictors of fluid sequestration in acute pancreatitis. A validation study. *Pancreas* 2016;45:306–310.

63 De-Madaria E, Banks PA, Moya-Hoyo N. Early factors associated with fluid sequestration and outcomes of patients with acute pancreatitis. *Clin Gastroenterol Hepatol* 2014;12:997–1002.

64 Buxbaum JL, Quezada M, Da B, et al. Early aggressive hydration hastens clinical improvement in mild acute pancreatitis. *Am J Gastroenterol* 2017;112:797–803.

65 Warndorf MG, Kurtzman JT, Bartel MJ, et al. Early fluid resuscitation reduces morbidity among patients with acute pancreatitis. *Clin Gastroentrol Hepatol* 2011;9:705–709.

66 Crockett SD, Wani S, Gardner TB. AGA Guidelines on initial management of acute pancreatitis. *Gastroenterology* 2018;154:1096–1101.

67 Singh VK, Gardner TB, Papachristou GI, et al. An international multicenter study of early intravenous fluid administration and outcomes in acute pancreatitis. *United Eur Gastroenterol J* 2017;5(4):491–498.

68 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.

69 Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev* 2010;(5):CD002941.

70 Adler DG, Chari ST, Dahl TJ, et al. Conservative management of infected necrosis complicating severe acute pancreatitis. *Am J Gastroenterol* 2003;98:98–102.

71 Runzi M, Niebel W, Goebell H, et al. Severe acute pancreatitis: nonsurgical treatment of infected necroses. *Pancreas* 2005;30:195–199.

72 Bakker OJ, van Brunschot HC, van Santvoort MG, et al. Early versus on-demand naso-enteric tube feeding in acute pancreatitis. *N Engl J Med* 2014;371:1983–1993.

73 Cote GA. Early enteral feeding does not improve outcomes in patients with predicted severe acute pancreatitis. *Gastroenterology* 2015;148:1476–1478.

74 Zhao X, Zhu SF, Xue GJ, et al. Early oral refeeding based on hunger in moderate and severe acute pancreatitis: a prospective controlled, randomized clinical trial. *Nutrition* 2015;31:171–175.

75 Vaughn VM, Shuster D, Rogers MAM, et al. Early versus delayed feeding in patients with acute pancreatitis. A systematic review. *Ann Intern Med* 2017;166:883–892.

76 Bevan MG, Asrani VM, Bharmal et al. Incidence and predictors of oral feeding intolerance in acute pancreatitis: a systematic review, meta-analysis and meta regression. *Clin Nutr* 2017;36:722–729.

77 Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *Crit Care* 2010;19:261–268.

78 Bakker OJ, van Brunschot S, Farre A, et al. Timing of enteral nutrition in acute pancreatitis: meta-analysis of individuals using a single-arm of randomized trials. *Pancreatology* 2014;14:340–346.

79 Jin M, Zhang H, Lu B, et al. The optimal timing of enteral nutrition and its effect on the prognosis of acute

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pancreatitis: a propensity score matched cohort study. *Pancreatology* 2017;17:651–657.

80 Petrov MS, van Santvoort HC, Besselink MGH, et al. Enteral nutrition and the risk of mortality and infectious complications in patients with severe acute pancreatitis. *Arch Surg* 2008;143(11):1111–1117.

81 Munigala S, Subramaniam D, Subramaniam DP, et al. Predictors for early readmission in acute pancreatitis in the United States: a nationwide population-based study. *Pancreatology* 2017;17:534–542.

82 Garg SK, Campbell JP, Anugwom C, et al. Incidence and predictors of readmissions in acute pancreatitis. *Pancreas* 2018;47:46–54.

83 Ali UA, Issa Y, Hagenaars JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after first episode of acute pancreatitis. *Clin Gastroenterol Hepatol* 2016;14:738–746.

84 Lee PJW, Bhatt A, Holmes J, et al. Decreased severity in recurrent vs. initial episodes of acute pancreatitis. *Pancreas* 2015;44:896–900.

85 Mallick B, Sharma DJ, Dhaka N et al. Differences between the outcome of recurrent acute pancreatitis and pancreatitis. *JGH Open* 2018;2(4):134–138.

86 Da Costa DW, Bouwense SA, Schepers NJ, et al. Same-admission vs. interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multi-center randomized controlled study. *Lancet* 2015;386:1261–1268.

87 Lyu Y-X, Cheng Y-X, Jin H-F, et al. Same-admission vs. delayed cholecystectomy for mild acute biliary pancreatitis: a systematic review and meta-analysis. *BMC Surg* 2018;18:111.

88 Bilal M, Kline KT, Trieu J,A et al. Trends in same-admission cholecystectomy and endoscopic retrograde cholangiopancreatography for acute gallstone pancreatitis: A nationwide analysis across a decade. *Pancreatology* 2019;19(4):524–530.

89 Krishna SG, Kruger AJ, Patel N, et al. Cholecystectomy during index admission for acute biliary pancreatitis lowers 30-day readmission rates. *Pancreas* 2018;47:996–1002.

90 Trust MD, Sheffield KM, Boyd CA, et al. Gallstone pancreatitis in older patients: are we operating enough. *Surgery* 2011;150:515–525.

91 van Baal MC, Besselink MG, Bakker OJ, et al. Timing of cholecystectomy after mild biliary pancreatitis. A systematic review. *Ann Surg* 2012;255:860–866.

92 Ridtitid W, Kulpatcharapong S, Piyachaturawat P, et al. The impact of empiric endoscopic biliary sphincterotomy on future gallstone-related complications in patients with non-severe acute biliary pancreatitis whose cholecystectomy was deferred or not performed. *Surg Endosc* 2019;33(10):3325–3333.

93 Bakker OJ, van Santvoort HC, Hagenaars JC, et al. Timing of cholecystectomy after mild biliary pancreatitis. *Br J Surg* 2011;98:1446–1454.

94 Zargar SA, Mushtag M, Beg MA, et al. Wait-and-see policy vs. cholecystectomy after endoscopic sphincterotomy for bile-duct stones in high-risk patients with co-existing gallbladder stones: a prospective randomized trial. *Arab J Gastroenterol* 2014;15:24–26.

95 Khan MA, Khan Z, Tombazzi CR, et al. Role of cholecystectomy after endoscopic sphincterotomy in the management of choledocholithiasis in high-risk patients. A systematic review and meta-analysis. *J Clin Gastroenterol* 2018;52:579–589.

96 Ventre C, Nowell S, Graham C, et al. Open survival and new-onset morbidity after critical admission for acute pancreatitis in Scotland: a national electronic healthcare record linkage cohort study. *BMJ Open* 2018;8(12):e023853.

97 Das SLM, Singh PP, Phillips ARJ, et al. Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. *Gut* 2014;63:818–831

98 Umapathy C, Raina A, Saligram S, et al. Natural history after acute necrotizing pancreatitis: a large US tertiary care experience. *J Gastrointest Surg* 2016;20:1844–1853.

99 Shen H-N, Yang C-C, Chang Y-H. Risk of diabetes mellitus after first-attack acute pancreatitis: a national population-based study. *Am J Gastroenterol* 2015;110:1698–1706.

100 Petrov MS. Diabetes of the exocrine pancreas: American Diabetes Association-compliant lexicon. *Pancreatology* 2017;17:523–526.

101 Hollemans RA, Hallensleben NDL, Mager DJ, et al for the Dutch Pancreatitis Study group. Pancreatic exocrine insufficiency following acute pancreatitis: systematic review and study level meta-analysis. *Pancreatology* 2018;18:253–262.

102 Das SLM, Kennedy JIC, Murphy R, et al. Relationship between the exocrine and endocrine pancreas after acute pancreatitis. *World J Gastroenterol* 2014;20:17196–17205.

103 Machicado JD, Gougol A, Stello K, et al. Acute pancreatitis has a long-term deleterious effect on physical health-related quality of life. *Clin Gastroenterol Hepatol* 2017;15:1435–1443.

104 Nikkola J, Laukkarinen J, Lahtela J, et al. The long-term prospective follow-up of pancreatic function after first episode of acute alcoholic pancreatitis. Recurrence predisposes one to pancreatic dysfunction and pancreatogenic diabetes. *J Clin Gastroenterol* 2017;51:183–190.

105 Lankisch PG, Breuer N, Bruns A, et al. Natural history of acute pancreatitis: a long-term population-based study. *Am J Gastroenterol* 2009;104:2797–2805.

10.1002/9781119570097.ch1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/9781119570097.ch1 by Columbia University Libraries, Wiley Online Library on [20/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

106 Rijkers AP, Bakker OJ, Ali UA, et al. Risk of pancreatic cancer after a primary episode of acute pancreatitis. *Pancreas* 2017;46;1018–1022.

107 Sadr-Azodi O, Oskarsson V, Discacciati A, et al. Pancreatic cancer following acute pancreatitis: a population-based matched cohort study. *Am J Gastroenterol* 2018;113:1711–1719.

108 Kirkegard J, Cronin-Fenton D, Heide-Jorgensen U, Mortensen FV. Acute pancreatitis and pancreatic cancer risk: a nationwide matched-cohort study in Denmark. *Gastroenterology* 2018;154:1729–1736.

109 Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013;144:1252–1261.

10.1002/9781119570097.ch1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/9781119570097.ch1 by Columbia University Libraries, Wiley Online Library on [20/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License