CME

American College of Gastroenterology Guidelines: Management of Acute Pancreatitis

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Acute pancreatitis (AP), defined as acute inflammation of the pancreas, is one of the most common diseases of the gastrointestinal tract leading to hospital admission in the United States. It is important for clinicians to appreciate that AP is heterogenous, progressing differently among patients and is often unpredictable. While most patients experience symptoms lasting a few days, almost one-fifth of patients will go on to experience complications, including pancreatic necrosis and/or organ failure, at times requiring prolonged hospitalization, intensive care, and radiologic, surgical, and/or endoscopic intervention. Early management is essential to identify and treat patients with AP to prevent complications. Patients with biliary pancreatitis typically will require surgery to prevent recurrent disease and may need early endoscopic retrograde cholangiopancreatography if the disease is complicated by cholangitis. Nutrition plays an important role in treating patients with AP. The safety of early refeeding and importance in preventing complications from AP are addressed. This guideline will provide an evidence-based practical approach to the management of patients with AP.

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INTRODUCTION

Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract and leads to a tremendous emotional, physical, and financial burden for the patient. In the United States, there are almost 300,000 admissions annually for AP, resulting in more than 1 million patient days in the hospital at a cost over 2.5 billion dollars (1). The incidence of AP has been increasing by 2%–5% per year and varies between 3.4 and 73.4 cases per 100,000 worldwide (1,2). Although the case fatality rate has decreased over time, the overall population mortality rate has remained unchanged with 5,000–9,000 deaths reported annually (1). Advancements in the management of AP over the past decade have been associated with a decrease in mortality (3). In this context, a group of experts within the American College of Gastroenterology (ACG) were tasked to complete a systematic review of the literature concerning AP and develop guidelines for the membership. In these guidelines, we first discuss the diagnosis, etiology, and severity of AP. We then focus on the early medical management of AP followed by a discussion of the management of complicated disease, most notably pancreatic necrosis. The evolving issues of antibiotics, nutrition, endoscopic, radiologic, and surgical interventions are also addressed.

METHODOLOGY

A health science librarian was contracted to assist in the completion of a MEDLINE search through the OVID interface using the MeSH term acute pancreatitis limited to all clinical trials and meta-analysis for years 1966–2022 limited to the English language literature. A review of clinical trials and reviews known to the authors was also performed for preparation of this document. Similar to prior ACG guidelines, this guideline is structured in sections, each with recommendations or key concepts and summaries of the evidence based on the PICO question. PICO is an acronym that includes the following: P = population/problem, I = intervention, C = comparison, and O = outcome. PICO questions were developed by the consensus of the authors and served as the basis for each recommendation and key concepts (Table 1). PICO questions were primarily used for the management of AP. For the diagnosis, etiology, and severity of AP, the PICO format was not used. Recommendations were made based on the assessment of the quality of evidence by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process (4) (Table 2).

The GRADE system result used to evaluate the quality of the supporting evidence for each recommendation is listed in Table 2, following each recommendation. A strong recommendation is made when the benefits clearly outweigh the negatives and/or the result of no action. Conditional is used when uncertainty remains about the balance of benefits and potential harms. Statements with a strong recommendation are stated with we recommend, whereas conditional recommendations are stated with we suggest. The quality of evidence is classified from high to very low. High-quality evidence indicates that further research is not likely to change the authors' confidence in the estimate of the effect. Moderate-quality evidence is associated with moderate confidence in the effect estimate, although further research would be likely to have an impact on the confidence of the estimate. Low-quality evidence indicates that further study would have an

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Table 1. PICO questions that served as the basis for recommendations and key concepts

At admission
1. In patients with AP complicated by the SIRS and/or organ dysfunction, does admission to a monitored/ICU bed decrease mortality, the development of severe disease, and/or decrease the LOS?
2. In patients with AP, will making patients NPO compared with allowing patients to eat and drink as tolerated result in a decreased risk of complications, prevent recurrent disease, or decrease the length of stay?
3. In patients with mild AP who begin to receive oral feeding, does a liquid diet compared with a regular diet prevent complications, recurrent disease, or decrease the length of stay?
4. In patients with AP, does early aggressive intravenous hydration compared with standard hydration result in a decreased risk of developing severe disease, pancreatic necrosis, and mortality?
5. In patients with AP, does early frequent monitoring of BUN and/or HCT decrease the risk of developing severe disease, necrosis, LOS, and/or mortality?
6. In patients with AP, is there a benefit to early routine imaging (US and/or CT) compared with case specific, as needed imaging?
After admission
7. In patients with acute biliary pancreatitis, does early ERCP (before 24 and 72 hr) compared with maximal medical therapy decrease morbidity and mortality?
8. In patients with AP who do not improve after the first 72 hr, does early cross-sectional imaging to identify the presence of necrosis or other anatomic complications compared with a conservative approach decrease morbidity or mortality?
AP complicated by necrosis
9. In patients with AP complicated by pancreatic necrosis, does enteral (nasogastric or nasojejunal) feeding compared with early oral feeding result in a difference in infectious complications, LOS, and mortality?
10. In patients with AP complicated by pancreatic necrosis, do prophylactic antibiotics compared with as-need antibiotic therapy decrease the incidence of infectious complications, infected pancreatic necrosis, LOS, and mortality?
11. In patients with suspected infected pancreatic necrosis, does a CT fine-needle aspiration compared with immediate antibiotic therapy result in better outcomes, decreased infectious complications, sepsis, LOS, and mortality?
Preventing AP and recurrence
12. In patients with idiopathic pancreatitis, will additional imaging (e.g., EUS, MRCP, and ERCP) compared with a conservative approach result in decreased recurrent attacks of AP?
13. In patients undergoing ERCP, do patients who receive rectal indomethacin suppositories compared with patients who do not receive this therapy have a decreased incidence of AP and severe AP?
14. In patients undergoing ERCP, do patients who receive intravenous hydration before the procedure compared with those who do not have extra hydration have a decreased incidence of AP and severe AP?
15. In patients undergoing complex ERCP, does a pancreatic duct stent prevent AP compared with those who receive only rectal indomethacin suppositories?
16. In patients with idiopathic AP, does therapy directed at biliary disease, sphincterotomy, cholecystectomy, or oral ursodiol compared with conservative management result in decreased recurrence of AP?

AP, acute pancreatitis; BUN, blood urea nitrogen; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; HCT, hematocrit; ICU, intensive care unit; LOS, length of stay; MRCP, magnetic retrograde cholangiopancreatography; NPO, nothing by mouth; SIRS, systemic inflammatory response syndrome.

important impact on the confidence in the estimate and would likely affect the conclusions. Very low-quality evidence indicates very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate effect.

Key concepts are statements that are not amenable to the GRADE process or when there are limitations in the available evidence from the literature but may be valuable to clinicians caring for patients with AP. In some instances, key concepts are derived using a combination of extrapolation from the literature and expert opinion. Key concepts are listed in Table 3.

DIAGNOSIS

Key concepts

1. We suggest that early/at admission routine computed tomography (CT) not be performed for the purpose of determining severity in AP and should be reserved for patients in whom the diagnosis is unclear or who fail to improve clinically within the first 48–72 hours after hospital admission and intravenous hydration.

Summary of evidence

The diagnosis of AP most often is established by identification of 2 of the 3 following criteria: (i) abdominal pain consistent with the disease, (ii) serum amylase and/or lipase greater than 3 times the upper limit of normal, and/or (iii) characteristic findings from abdominal imaging (5). Patients with AP typically present with epigastric or left upper quadrant pain. The pain is usually described as constant with radiation to the back, chest, or flanks, but this description is nonspecific. The intensity of the pain is usually described as severe but can be variable. The intensity and location of the pain do not correlate with severity. Pain described as dull, colicky, or located in the lower abdominal region is not consistent with AP and suggests an alternative etiology. Abdominal imaging is often helpful to determine the diagnosis of AP in patients with atypical presentations. While the laboratory diagnosis of AP has historically relied on elevations of the amylase and lipase, many patients with AP are not correctly diagnosed (6). Due to limitations on sensitivity and negative predictive value, serum amylase alone cannot be used reliably for the diagnosis of AP, and serum lipase is preferred.

Amylase in patients with AP generally rises within a few hours after the onset of symptoms and returns to normal values

Table 2. Recommendations on the management of AP

Etiology	
1. We suggest transabdominal ultrasound in patients with AP to evaluate for biliary pancreatitis and a repeat ultrasound if the initial examination is inconclusive	Conditional recommendation, very low quality of evidence
2. In patients with IAP, we suggest additional diagnostic evaluation with repeat abdominal ultrasound, MRI, and or endoscopic ultrasound	Conditional recommendation; very low quality of evidence
Initial management	
3. We suggest moderately aggressive fluid resuscitation for patients with AP. Additional boluses will be needed if there is evidence of hypovolemia	Conditional recommendation, low quality of evidence
4. We suggest using lactated Ringer solution over normal saline for intravenous resuscitation in AP	Conditional recommendation, low quality of evidence
ERCP in AP	
5. We suggest medical therapy over early (within the first 72 hr) ERCP in acute biliary pancreatitis without cholangitis	Conditional recommendation, low quality of evidence
Preventing PEP	
6. We recommend rectal indomethacin to prevent PEP in individuals considered to be at high risk of post-ERCP pancreatitis	Strong recommendation, moderate quality of evidence
7. We suggest placement of a pancreatic duct stent in patients at high risk for PEP who are receiving rectal indomethacin	Conditional recommendation, low quality of evidence
The role of antibiotics in AP	
8. We suggest against prophylactic antibiotics in patients with severe AP	Conditional recommendation, very low quality of evidence
9. We suggest against FNA in patients with suspected infected pancreatic necrosis	Conditional recommendation, very low quality of evidence
Nutrition in AP	
10. In patients with mild AP, we suggest early oral feeding (within 24–48 hr) as tolerated by the patient compared with the traditional NPO approach	Conditional recommendation, low quality of evidence
11. In patients with mild AP, we suggest initial oral feeding with low-fat solid diet rather than a stepwise liquid to solid approach	Conditional recommendation, low quality of evidence

AP, acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; FNA, fine-needle aspiration; IAP, idiopathic AP; NPO, nothing by mouth; PEP, post-ERCP pancreatitis.

within 3–5 days; however, it may remain within the normal range on admission in as many as one-fifth of patients (7,8). Compared with lipase, serum amylase returns more quickly to values below the upper limit of normal. Serum amylase concentrations may be normal in alcohol-induced AP and hypertriglyceridemia. The serum amylase may be falsely elevated in conditions that cause hyperamylasemia other than AP; for example, in macroamylasemia, a syndrome characterized by the formation of large molecular complexes between amylase and abnormal immunoglobulins, in patients with a decreased glomerular filtration rate, in diseases of salivary glands, and in extrapancreatic abdominal diseases associated with inflammation, including acute appendicitis, cholecystitis, intestinal obstruction or ischemia, peptic ulcer, and gynecological diseases (9).

Serum lipase seems to be more specific and remains elevated longer than amylase following disease presentation. Despite recommendations of recent classifications and guidelines (5,10) that emphasize the advantage of serum lipase, similar problems with the predictive value remain in certain patient populations. Lipase is also found to be elevated in a variety of nonpancreatic diseases. For example, an upper limit of normal greater than 3–5 times may be needed, especially in some patient groups such as diabetic patients (11,12). A Japanese consensus conference to determine appropriate cutoff values for amylase and lipase could not reach consensus on appropriate upper limits of normal (13). Assays of many other pancreatic enzymes have been assessed during the past 15 years, but none seem to offer better diagnostic value than those of serum amylase and lipase (14). Although most studies show a diagnostic efficacy of greater than 3–5 times the upper limit of normal, clinicians must consider the clinical condition of the patient when evaluating amylase and lipase elevations. When doubt about the diagnosis of AP exists, abdominal imaging may assist. Once the diagnosis of AP is established, there is no reason to follow the serum amylase or lipase because there is no relationship to severity, prognosis, or impact on a decision to refeed or discharge the patient (15). While the diagnosis of AP is readily established with characteristic pain, symptoms, and elevations of amylase and lipase greater than 3× normal, some patients without AP will have elevated amylase and/lipase, sometimes greater than 3× normal. In the absence of abdominal pain consistent with the disease, elevations of amylase and lipase do not predict the development of AP.

Abdominal imaging may prove useful to confirm the diagnosis of AP. Contrast-enhanced CT provides more than 90% sensitivity and specificity for the diagnosis of AP (16). Routine use of abdominal CT in patients with AP is unwarranted because the diagnosis is apparent in most patients and most have a mild uncomplicated course. However, in a patient failing to improve after 48–72 hours (e.g., persistent pain, fever, nausea, and unable to begin oral feeding), CT or magnetic resonance imaging (MRI) is recommended to assess local complications such as pancreatic necrosis (17–19). CT and MRI are comparable in the early assessment of AP (20). MRI, while more expensive, time-consuming, and challenging in claustrophobic patients, has advantages in those with contrast allergy and renal insufficiency (can diagnose necrosis on nongadolinium T2-weighted images) and can more accurately detect stones in common bile duct (CBD) and pancreatic duct disruption. Newer techniques such as subtraction CT and perfusion CT are reported to detect necrosis earlier than conventional CT, but the techniques have not yet found wide acceptance.

Table 3. Key concepts in AP

Key concepts
Diagnosis
1. We suggest that early/at admission routine CT not be performed for the purpose of determining severity in AP and should be reserved for patients in whom the diagnosis is unclear or who fail to improve clinically within the first 48–72 hr after hospital admission
Etiology
2. In the absence of gallstones and/or significant history of alcohol use, serum triglyceride should be obtained and considered the etiology, preferably if greater than 1,000 mg/dL
3. In patients older than 40 years in whom an etiology is not established, a pancreatic tumor should be considered as a possible cause of AP
4. Following a second episode of AP with no identifiable cause, in patients fit for surgery, we suggest performing a cholecystectomy to reduce the risk of recurrent episodes of AP
Initial assessment and risk stratification
5. Hemodynamic status and risk assessment should be performed to stratify patients into higher-risk and lower-risk categories to assist consideration of admission to a nonmonitored bed or monitored bed setting, including the intensive care setting
6. Patients with organ failure and/or the SIRS should preferably be admitted to a monitored bed setting
7. Scoring systems and imaging alone are not accurate in determining which patients with AP will develop moderately severe or severe AP
8. In patients with mild disease, clinicians should remain vigilant for the development of severe disease and organ failure during the initial 48 hr from admission
9. Risk factors for the development of severe disease (Table 4) include elevated BUN, HCT, the presence of obesity, comorbidities, and the presence of SIRS
Initial management
10. While we suggest all patients with AP receive moderately aggressive intravenous hydration of isotonic crystalloid, caution is needed if a cardiovascular and/or renal comorbidity exists. Patients should be monitored for volume overload
11. Fluid resuscitation in patients with AP is likely more important early in the course of the disease (within the first 24 hr)
12. Fluid volumes need to be reassessed at frequent intervals within 6 hr of presentation and for the next 24–48 hr with a goal to decrease the BUN
ERCP in AP
13. In patients with AP complicated by cholangitis, early ERCP within the first 24 hr has been shown to decrease morbidity and mortality
14. In the absence of cholangitis and/or jaundice, if a common bile duct stone is suspected, MRCP or EUS should be used to screen for the presence of common bile duct stones before the use of ERCP, and diagnostic ERCP should be avoided
The role of antibiotics in AP
15. While antibiotics should not be used in patients with sterile necrosis, antibiotics are an important part of treatment in infected necrosis along with debridement/necrosectomy
16. In patients with infected necrosis, antibiotics known to penetrate pancreatic necrosis should be used largely to delay surgical, endoscopic, and radiologic drainage beyond 4 wk. Some patients may avoid drainage altogether because the infection may completely resolve with antibiotics
17. Routine administration of antifungal agents along with prophylactic or therapeutic antibiotics is not needed
Nutrition in AP
18. Enteral nutrition in patients with moderately severe or severe AP seems to prevent infectious complications
19. Parenteral nutrition should be avoided, unless the enteral route is not possible, not tolerated, or not meeting the caloric needs
20. Using a nasogastric rather than nasojejunal route for delivery of enteral feeding is preferred because of comparable safety and efficacy
The role of surgery in AP
21. Patients with mild acute biliary pancreatitis should undergo cholecystectomy early, preferably before discharge
22. Minimally invasive methods are preferred to open surgery for debridement and necrosectomy in stable patients with symptomatic pancreatic necrosis
23. We suggest delaying any intervention (surgical, radiological, and/or endoscopic) in stable patients with pancreatic necrosis, preferably 4 wk, to allow for the wall of collection to mature

AP, acute pancreatitis; BUN, blood urea nitrogen; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; HCT, hematocrit; MRCP, magnetic retrograde cholangiopancreatography; SIRS, systemic inflammatory response syndrome.

ETIOLOGY OF AP

Recommendations

1. We suggest transabdominal ultrasound in patients with AP to evaluate for biliary pancreatitis and a repeat US if the initial examination is inconclusive (conditional recommendation, very low quality of evidence).
2. In patients with idiopathic AP (IAP), we recommend additional diagnostic evaluation with repeat abdominal ultrasound, MRI, and/or endoscopic ultrasound (EUS) (conditional recommendation; very low quality of evidence).

Key concepts

2. In the absence of gallstones and/or a significant history of alcohol use, serum triglyceride (TG) should be obtained and considered the etiology, preferably if greater than 1,000 mg/dL.
3. In patients older than 40 years in whom an etiology is not established, a pancreatic tumor should be considered as a possible cause of AP.
4. Following a second episode of AP with no identifiable cause, in patients fit for surgery, we suggest performing a cholecystectomy to reduce the risk of recurrent episodes of AP.

Summary of evidence

Gallstones and alcohol. The etiology of AP can be readily established in most patients. The most common causes include gallstones (40%–70%) and alcohol (25%–35%) (21–23). Due to its commonality and importance of preventing a recurrent attack, abdominal ultrasound to evaluate for cholelithiasis should be performed on all patients with AP (24). A large retrospective study confirmed the high accuracy and sensitivity of ultrasound to diagnose a biliary etiology for AP and found that accuracy was even higher when a second ultrasound was repeated 1 week after the initial study if the initial study was inconclusive (25). Identification of gallstones as the etiology should prompt referral for cholecystectomy to prevent recurrent attacks and potential biliary sepsis (26,27). Gallstone pancreatitis is usually an acute event and cured when the stone is removed or passes. Depending on age and comorbidities, patients who have undergone a biliary sphincterotomy should also be referred for cholecystectomy because they remain at risk of recurrent disease (28).

Alcohol-induced pancreatitis often manifests as a spectrum, ranging from discrete episodes of AP to chronic irreversible changes. The diagnosis should not be entertained unless a person has consumed over 5 years moderate or heavy alcohol consumption (29). "Heavy" alcohol consumption is generally considered to be greater than 50 g per day, but is likely much higher. Clinically evident AP occurs in only up to 5% of heavy drinkers; thus, there are likely other factors that sensitize individuals to the effects of alcohol, such as genetic factors (30) and tobacco use (23,27,31).

Other etiologies of AP. In the absence of alcohol or gallstones, caution must be exercised when attributing a possible etiology for AP to another agent or condition. Medications, infectious agents, and metabolic causes such as hypercalcemia and hypertriglyceridemia are rare causes, more often falsely attributed to causing AP (32,33). Whereas some drugs, such as 6-mercaptopurine, azathioprine, and didanosine clearly can cause AP, there are limited data supporting most medications as causative agents. A novel classification system recently published can assist clinicians in determining the level of evidence that a particular drug causes AP (34).

Primary and secondary hypertriglyceridemia can cause AP; however, these account for only 5% of all cases of AP, although may be higher and in up to 56% of AP in pregnancy (35). Serum TG should rise above 1,000 mg/dL to be considered the cause of AP (36,37). There is little information about the risk of AP due to high TG at a population level. A sophisticated analysis suggested that the risk of AP increased by 4% for every 100 mg/dL of TG above the normal limit, even higher when TG levels are above 500 mg/dL (38). A lactescent serum has been observed in as many as 20% of patients with AP; therefore, a fasting TG level should be re-evaluated 1 month after discharge when hypertriglyceridemia is suspected (39).

A benign or malignant mass that obstructs the main pancreatic or biliary ducts can result in AP. It has been estimated that 5%–14% of patients with benign or malignant pancreatobiliary tumors present with acute idiopathic pancreatitis (40–42). Pancreatic cancer should be suspected in any patient older than 40 years with idiopathic pancreatitis, especially with a prolonged or recurrent course (43). A recent review reported that approximately 1% of AP was due to pancreatic cancer (44). Thus, a contrast-enhanced CT scan with thin slices or MRI/magnetic retrograde cholangiopancreatography (MRCP) is needed in these patients. A more extensive evaluation including EUS and/or MRCP may be indicated initially or after a recurrent episode of IAP (45,46).

Idiopathic and recurrent AP. IAP is defined as pancreatitis with no etiology established after initial laboratory (including lipid and calcium levels) and imaging tests (transabdominal ultrasound and MRCP in the appropriate patient) (47,48). In many patients, an etiology may eventually be found, yet in some, no definite cause is ever established. Patients with no obvious etiology should be referred for a repeat ultrasound and TG level as an outpatient because initial hospital evaluation often fails to identify gallstones and/or elevated TG level (26,47). While EUS may be helpful in identifying an underlying etiology, routine endoscopic retrograde cholangiopancreatography (ERCP) should not be performed because of the increased risks of causing pancreatitis.

EUS has been widely studied as a modality for elucidating the etiology of IAP. In patients with recurrent IAP, EUS identifies the etiology in most patients (49). In a prospective study evaluating the role of EUS in AP, Yusoff et al (49) identified the etiology in almost a third of patients after an initial attack of idiopathic pancreatitis. When evaluating 34 studies evaluating the efficacy of EUS and MRCP, despite the superiority of EUS, the addition of MRCP seems complementary in the evaluation of IAP (50).

Even with a diagnosis established, a recurrent attack of AP is seen in approximately 20%–29% patients after an initial attack of AP (27). Recurrent pancreatitis occurs more often in male individuals, smokers, and those with alcohol with an etiology (51). Recurrence of alcoholic AP is likely due to ongoing alcohol abuse. Treatment has been shown to decrease recurrent disease and the development of chronic pancreatitis (27,29). In addition, failure to treat a biliary etiology, such as gallstones, is a common cause of recurrent AP (52). It is important that clinicians treat these underlying etiologies to prevent recurrent disease and the development of chronic pancreatitis.

There is growing evidence that gallstones or tiny gallstones (microlithiasis and sludge) are the cause of IAP in most of whom

the etiology has not been identified (53,54). Despite extensive evaluation, many patients with IAP will have no objective evidence of gallstones, even microlithiasis (55). Stevens et al (54) retrospectively followed up 2,236 patients with IAP who did and did not undergo cholecystectomy. They found a significant reduction in recurrent pancreatitis in those patients with normal gallbladders who underwent cholecystectomy. In a small randomized prospective trial in patients with idiopathic pancreatitis, laparoscopic cholecystectomy was found to be highly effective in preventing recurrent AP with a number needed to treat to prevent 1 attack being 5 persons (56). Patients with IAP who have abnormal LFT on the first day of their presentation may be more likely to benefit (57). A recent meta-analysis in patients with IAP after extensive testing including EUS and ERCP found significantly fewer recurrences of AP after cholecystectomy, 11% vs 39% (58). Based on the available evidence, we conclude that following an episode of AP with no identifiable cause, in patients who are surgical candidates, cholecystectomy should be performed to reduce the risk of recurrent episodes of pancreatitis.

Anatomic and physiologic anomalies of the pancreas occur in 10%–15% of the population, including pancreas divisum and sphincter of Oddi dysfunction (SOD) (59). It remains unclear whether these disorders cause AP (60). Endoscopic therapy, focusing on treating pancreas divisum and/or SOD, carries a significant risk of precipitating AP and should be performed only in specialized units (61). The landmark EPISOD trial ruled out the role of endoscopic sphincterotomy in SOD type 2 and SOD type 3 (62).

While the role of genetic defects contributing to this disorder has become increasingly recognized and may be a contributory cause in patients with anatomic anomalies (63), it is not clear how this can be used effectively in most patients with idiopathic pancreatitis. Genetic testing may be useful in patients with more than 1 family member with pancreatic disease (64). Patients with true recurrent IAP should be evaluated at centers of excellence focusing on pancreatic disease, providing advanced endoscopy, genetic testing, and a combined multidisciplinary approach.

INITIAL ASSESSMENT AND RISK STRATIFICATION

Key concepts

5. Hemodynamic status and risk assessment should be performed to stratify patients into higher-risk and lower-risk categories to assist consideration of admission to a nonmonitored bed or monitored bed setting, including the intensive care setting.
6. Patients with organ failure and/or the systemic inflammatory response syndrome (SIRS) should preferably be admitted to a monitored bed setting.
7. Scoring systems and imaging alone are not accurate in determining which patients with AP will develop moderately severe or severe AP.
8. In patients with mild disease, clinicians should remain vigilant for the development of severe disease and organ failure during the initial 48 hours from admission.
9. Risk factors of the development of severe disease (Table 4) include elevated blood urea nitrogen (BUN), hematocrit (HCT), the presence of obesity, comorbidities, and the presence of the SIRS.

Summary of evidence

Definition of severe AP. Almost a third of patients with AP will develop severe disease or moderately severe disease (65). Severe AP is defined by the presence of persistent organ failure (fails to resolve within 48 hours) and/or death (5). Organ failure is defined in simple clinical terms as shock (systolic blood pressure less than 90 mm Hg), pulmonary insufficiency (PaO_2 less than 60 mm Hg), renal failure (creatinine >2 mg/dL after rehydration), and/or gastrointestinal bleeding (>500 mL/24 hours) or modified Marshall score of 2 or more in the 3 accepted organ systems (5).

Moderately severe disease is defined as transient organ failure (resolves within 48 hours) and/or the development of local complications (acute pancreatic and/or peripancreatic fluid collections, acute necrotic collections, pseudocyst or walled-off pancreatic necrosis). While the above is a severity classification, the morphologic classification describes necrotizing AP (usually synonymous with moderately severe and severe disease) vs interstitial/edematous AP (usually mild in severity). Pancreatic necrosis is defined as diffuse or focal areas of nonviable pancreatic parenchyma greater than 3 cm in size or greater than 30% of the pancreas (66). Necrotizing pancreatitis includes pure peripancreatic necrosis (approximately 45%), pancreatic and peripancreatic necrosis (approximately 45%), and rarely pure pancreatic necrosis (approximately 5%). Pancreatic necrosis can be sterile or infected (discussed further). In the absence of pancreatic necrosis and/or organ failure, in mild disease, the edematous pancreas is defined as interstitial pancreatitis. Although there is some correlation between pancreatic necrosis, hospital length of stay, and organ failure, patients with sterile necrosis and infected necrosis are as likely to have organ failure (67,68).

Most episodes of AP are mild and self-limiting, needing only brief hospitalization. However, 20% of patients develop a moderately severe or severe disease requiring a prolonged hospitalization (69). Most patients with severe disease present to the emergency department with no organ failure or pancreatic necrosis. The fact that most patients who develop a complicated course initially present to the emergency department appearing to have mild disease, without organ failure or necrosis, has led clinical scientists to recommend intensive early supportive care with aggressive or moderately aggressive intravenous hydration (70,71).

Predicting severe disease. Moderately severe and severe AP constitute approximately 15%–25% of all cases of AP and practically account for all the morbidity and mortality of this disease. While a small proportion of patients with AP can be diagnosed as moderately severe AP during the first 24 hours based on the presence of any organ failure by accepted criteria and or (peri) necrotizing pancreatitis on CT scan, a substantial proportion of patients cannot be reliably classified into mild, moderate, or severe during the first 24–48 hours and sometimes up to 72 or 96 hours. This is the basis for several years of description of numerous clinical markers, laboratory markers, and or scoring systems to predict the future development of 1 of the 3 types during the initial 24–48 hours. The main purpose of predicting or identifying those with increasing morbidity and mortality is to triage them into high-level care and select them for newer interventional trials such as drug trials (sparing patients with mild AP, who may not require such agents with the attendant side effects). However, the main problem with all the predicting markers and systems is the inability to predict moderately severe and severe types with high degree of accuracy. At best, 50% of the

Table 4. Clinical findings associated with a severe course for initial risk assessment[a]

Patient characteristics
Age >55 (69,213)
Obesity (BMI >30 kg/m^2) (93)
Altered mental status (79,95)
Comorbid disease (69)
The systemic inflammatory response syndrome (99,100)
Defined by the presence of >2 of the following criteria:
Pulse >90 beats per minute
Respirations >20 per minute or $PaCO_2$ <32 mm Hg
Temperature >38 °C or >36 °C
WBC count >12,000 or <4,000 cells/mm^3 or >10% immature neutrophils (bands)
Laboratory findings
BUN >20 (79,92)
Rising BUN (79,92)
HCT >44 (83)
Rising HCT (83)
Elevated creatinine (214)
Radiology findings
Pleural effusions (94)
Pulmonary infiltrates (69)
Multiple or extensive extrapancreatic collections (16)

AP, acute pancreatitis; BMI, body mass index; BUN, blood urea nitrogen; HCT, hematocrit; WBC, white blood cell.
[a]The presence of organ failure and/or pancreatic necrosis defines severe AP.

cases predicted to be moderately severe or severe by any predicting system turn out to be such cases, while the prediction for mild AP is highly reliable and only approximately 3% progress to moderately severe or severe. Hence, currently, the systems are only useful to predict the mild type, which helps in earlier discharge of such patients. These limitations of all different type of predictors have been highlighted for the past few years (72,73). Novel pathogenesis markers, next-generation genetic tests identifying polymorphisms, and artificial intelligence analysis of large repositories of data may identify effective predictors (74). An expert review suggested that expert clinician judgment and simple SIRS score is as good as any complex scoring system or any other predictor (75). In a recent editorial, there was a plea to stop looking for more predictors and instead focus on the etiology and pathogenesis of severe AP with a view to develop specific treatments for AP (76).

There have been no studies that looked at applying any of the predictors resulting in a clinical impact compared with routine care. The reason for this is mainly 2-fold: the inability of accurate prediction and the lack of specific treatment, besides supportive care, to prevent severe disease. A recent technical review found no studies using severity prediction tools to demonstrate an impact on the clinical outcomes of AP using severity prediction tools (77). The review recommended for future clinical trials there is a need for measuring clinical outcomes in groups with and without the use of accurate predicting tools, but such a study will be clinically pertinent only if a drug or other specific therapy is available to treat AP.

Elevated HCT (≥44), BUN (≥20 mg/dL), C-reactive protein (≥150 mg/dL), and creatinine (≥2 mg/dL) have been reported in numerous studies to have a significant predictive value for determining moderately severe and severe disease. Such elevated values are based on the hemoconcentration, which occurs due to multiple causes such as nausea and or vomiting, third-space losses, and others. There is one report of decreased hospital stay when a paging system alert and a web-based instrument was available to the clinicians to treat AP, when compared with the outcomes from a historical control (78). In another study, a BUN ≤22 mg/dL or falling BUN called for reducing the intravenous fluids to 1.5 mL/kg per hour from 3 mL/kg per hour and if no such reduction is observed, to re-bolus. The presence of organ failure, SIRS, or Bedside Index for Severity Scoring System score of 3 or more suggested to the treating physicians to consider intensive care unit (ICU) treatment (79). While the study showed a reduction in the length of stay with this intervention, no effect on other important outcomes was noted. In addition, it was also difficult to assess which of the components of the intervention contributed to the clinical outcome.

In a systematic review of randomized controlled trials (RCT) on goal-directed intravenous hydration in AP, there was found to be insufficient evidence to state that goal-directed therapy, using various parameters to guide fluid administration, reduces the risk of persistent single or multiple organ system failure, infected pancreatic necrosis, or mortality from AP (77). The various parameters that were described in those studies for goal-directed intravenous hydration included HCT, creatinine, BUN, and others. Similarly, another systematic review found scant high-quality evidence for the numerous goal-directed methods or combinations (80).

AP is an unpredictable disease early in its course. Clinicians must recognize the inability to predict the development of severe disease in patients presenting with AP within the first 24–48 hours after admission. Despite intense research, severity scoring systems are cumbersome, typically require 48 hours to become accurate, and when predictive of severity, the patient's condition is obvious regardless of the score. This is especially true for the Ranson, Imrie, and APACHE scoring systems. The Bedside Index for Severity Scoring System score, which includes BUN and the presence of SIRS, has been consistently shown to be superior but may be no more accurate than simply monitoring patients for both BUN and/or the development of SIRS (81,82).

Although numerous laboratory tests have been studied to predict severity in patients with AP (83–85), no single laboratory test is consistently accurate to predict severity in patients with AP (86–88). Several investigators have found a rise in HCT and/or rising BUN at 24 hours to be a reliable test in predicting mortality and persisting multiorgan failure in patients with AP (83,84,89). A rising BUN within the first 24 hours has been shown to be associated with increased morbidity and mortality in patients with AP (84). This is likely due to its indirect correlation with decreased intravascular volume and decreased perfusion of the pancreas.

While many studies, especially from Europe, have used the acute-phase reactant C-reactive protein to determine severity, it is not practical because it takes 48–72 hours to become accurate in predicting necrosis and/or death (90). By that time, most patients

have already developed obvious mild or severe disease. CT and/or MRI also cannot reliably determine severity early in the course of AP because necrosis usually is not present on admission and may develop after 24–48 hours (20,91). Thus, close examination to assess early fluid losses, hypovolemic shock, and symptoms suggestive of organ dysfunction is crucial.

Rather than depending on a single laboratory test or scoring system to predict the severity of AP, clinicians need to be aware of the multiple risk factors of severe disease (Table 3). These include the following: the presence of SIRS (92), signs of hypovolemia, such as an elevated BUN (84) and an elevated HCT (83), obesity (93), presence of pleural effusions and/or infiltrates (94), and altered mental status (95). The presence of SIRS at admission has been found to be highly predictive of the development of organ failure/severe disease (96).

During the early phase of the disease (within the first week), death occurs because of the development, persistence, and progressive nature of organ dysfunction (97,98). The development of organ failure seems to be related to the development and persistence of SIRS. The reversal of SIRS and early organ failure has been shown to be important in preventing morbidity and mortality in patients with AP (99–102). While the presence of SIRS during the initial 24 hours has a high sensitivity for predicting organ failure (85%) and mortality (100%), this finding lacks specificity for severe disease (41%). Clinicians need to recognize that the presence at admission or early development of SIRS in a patient with AP warrants aggressive hydration, support, and monitoring. For this reason, such patients should be admitted to a monitored bed or, if organ failure is already present, the ICU as the outcome appears improved (103).

INITIAL MANAGEMENT

Recommendations

3. We suggest moderately aggressive fluid resuscitation for patients with AP. Additional boluses will be needed if there is evidence of hypovolemia (conditional recommendation, low quality of evidence).
4. We suggest using lactated Ringer solution over normal saline for intravenous resuscitation in AP (conditional recommendation, low quality of evidence).

Key concepts

10. While we suggest all patients with AP receive moderately aggressive intravenous hydration of isotonic crystalloid, caution is needed if a cardiovascular and/or renal comorbidity exists. Patients should be monitored for volume overload.
11. Fluid resuscitation in patients with AP is likely more important early in the course of the disease (within the first 24 hours).
12. Fluid volumes need to be reassessed at frequent intervals within 6 hours of presentation and for the next 24–48 hours with a goal to decrease the BUN.

Summary of evidence

The initial treatment of AP depends on intravenous hydration. This recommendation is based on expert opinion (10,104), laboratory experiments (105,106), clinical indirect evidence (83,84,107–109) epidemiologic studies (79), and both retrospective and prospective clinical trials (3,53,92,110). While there has been controversy over the timing, type, and degree of the benefit of early hydration, there is a general consensus that treating a patient with mild disease early in the course of the disease with early aggressive or moderately aggressive hydration is beneficial (71,111).

Patients with AP have marked systemic endothelial injury and increased vascular permeability leading to fluid shifts into the interstitial space and peritoneum (112). This leads to decreased intravascular volume. In addition to these third-space losses, patients presenting with AP are also hypovolemic due to vomiting, reduced oral intake, increased respiratory losses, and diaphoresis. Direct evidence of hypoperfusion of the pancreas leading to cell death and necrosis has been shown (113). The rationale for early intravenous hydration is based on the hypothesis that clinicians can reverse the decreased perfusion of the pancreas from third-space losses and microangiopathic effects. Intravenous hydration can promote blood flow preventing pancreatic cellular death, necrosis, and the ongoing release of pancreatic enzymes activating the numerous cascades characteristic of pancreatic sepsis. In addition, intravenous hydration prevents the ongoing inflammation that leads to a cycle of increased vascular permeability leading to increased third-space fluid losses and worsening the pancreatic hypoperfusion that leads to pancreatic necrosis (Figure 1).

While there is no marker for decreasing pancreatic perfusion, the rise in BUN reflects decreased renal perfusion. This can be interpreted as a marker for decreased pancreatic perfusion. In addition, as the intravascular fluid leaks to the peritoneum, the HCT rises as hemoconcentration develops. Early intravenous resuscitation is essential in correcting hypovolemia, supporting the macrocirculation and microcirculation of the pancreas to prevent serious complications such as pancreatic necrosis (114).

On an initial review of clinical trials, conflicting conclusions may be found regarding the benefit of early aggressive intravenous hydration. However, profound differences in study design explain the findings. The negative studies typically enrolled only patients with severe disease and/or well beyond the time where early aggressive intravenous hydration would have been effective (115–117). While these studies raise concerns about the continuous use of aggressive hydration beyond 48 hours, and in patients with severe disease, the role of early hydration (within the first 6–12 hours) was not addressed in these negative studies. In general, the human studies that enrolled patients with mild disease and provided early aggressive intravenous hydration within the first 24 hours have shown a benefit, decreasing both morbidity and mortality (3,110,118,119). When a benefit was not appreciated, there were too few patients included (low power) in the study and/or there was not a significant difference in the amount of fluids provided to the 2 groups during the first 24 hours (92,120).

Lactated Ringer solution is preferred to normal saline in the resuscitation and early aggressive hydration of patients with AP. The benefit of using lactated Ringer solution in large-volume resuscitation has been shown in other disease states, leading to better electrolyte balance and outcomes (121,122). Khatua et al (123) found that lactated Ringer solution early benefits in systemic inflammation are by providing calcium that binds ionically with nonesterified fatty acids that are associated with severe disease in AP. Lactate has also been shown to reduce pancreatic injury in AP by decreasing inflammation (124). There are additional theoretical benefits to using the more pH-balanced lactated

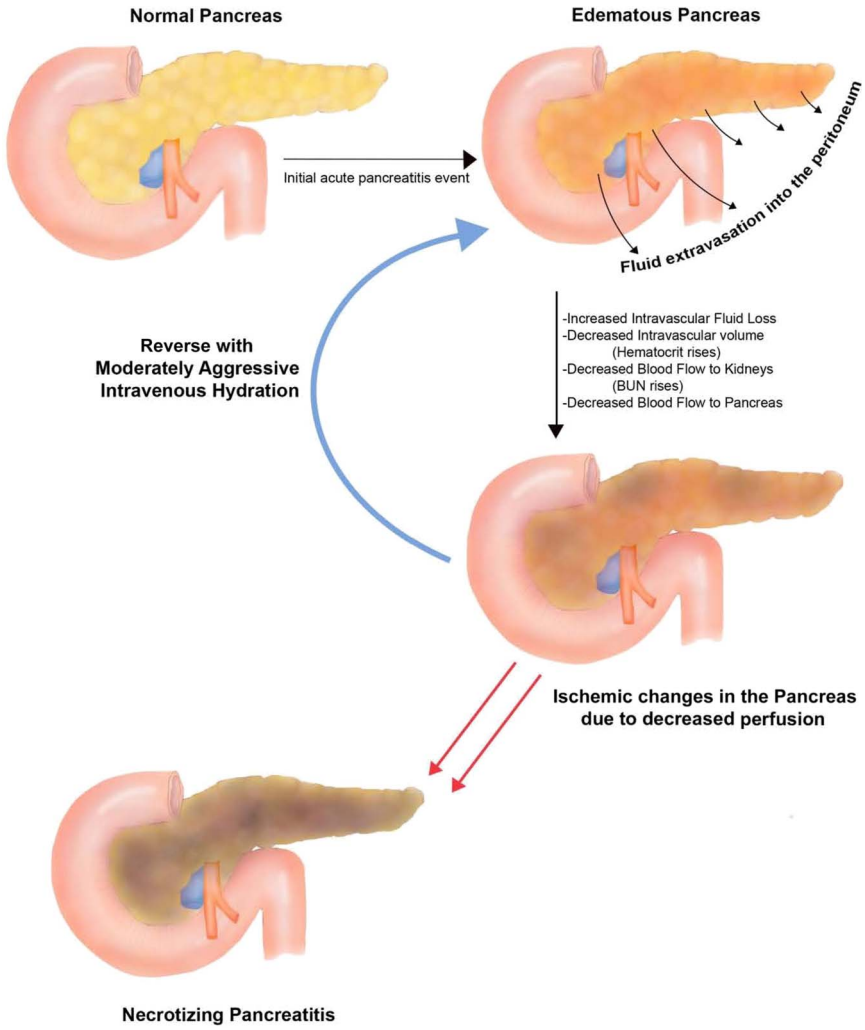

Figure 1. Role of moderately aggressive intravenous hydration in acute pancreatitis. Figure designed by Jasmine Saini, MD. BUN, blood urea nitrogen.

Ringer solution for fluid resuscitation compared with normal saline. Although both are isotonic crystalloid solutions, normal saline is more acidic with a pH of 5.5 and is associated with the development of a nonanion gap hyperchloremic metabolic acidosis and renal injury when large volumes are given (125). This has relevance in AP where the process is premature trypsinogen activation that also requires a low pH. In addition, infusion of large volumes of normal saline has been associated with abdominal discomfort in healthy volunteers. Thus, normal saline may exacerbate the symptoms of abdominal pain associated with AP.

In 3 well-designed prospective randomized trials, lactated Ringer solution has been shown to be more beneficial than normal saline (53,92,119). Wu et al (92) found patients were less likely to develop SIRS, a predictor of severe disease in patients treated with lactated Ringer solution compared with those treated with normal saline. Lee et al (53) showed that patients who were given lactated Ringer solution were less likely to be admitted to the critical care unit and had a shorter hospitalization compared with patients with AP given normal saline. In patients who are in the emergency department for a long period and inadequately treated with early aggressive hydration, the benefit may not exist and may be harmful when transferred to the floor or ICU (126).

Monitoring patients with early aggressive intravenous hydration depends on observation of clinical parameters such as heart rate, blood pressure, and urine output. In general, intravenous hydration providing for a decrease in the HCT (hemodilution) and/or decreased BUN (increased renal perfusion) have been shown to be associated with decreased morbidity and mortality (83,84). Although the precise timing of laboratory testing and numbers for which the HCT and BUN should decrease have not been established, the latest evaluation should be 6–8 hours after admission (111). If an adjustment is to be made to the rate of hydration, it will need to be determined within this time frame to assure the patient the benefit.

A recent, elegant-designed, randomized prospective study by de-Madiera et al (116) has shown that moderate intravenous hydration the first 24–48 hours may be equally effective as aggressive hydration. In this study, moderate hydration was less likely to cause volume overload when compared with early aggressive intravenous hydration. From this study, we can conclude that in patients with no evidence of hypovolemia, an initial resuscitation rate of no more than 1.5 mL/kg of body weight per hour should be administered. However, in patients with hypovolemia, clinicians should administer a bolus of 10 mL/kg (71). While the presence of hypovolemia

might demand higher amounts and rates of hydration, most patients with AP will likely benefit from 3–4 L the first 24 hours, depending on body mass index. Close observation is ultimately the key in managing patients with AP early in the course of the disease.

It is important to recognize that certain groups of patients, such as the older individuals and those with a history of cardiac and/or renal disease, will need caution when applying hydration. Close monitoring for reported complications such as volume overload, pulmonary edema, and abdominal compartment syndrome is needed (126,127). Use of central venous pressure measurement through a centrally placed catheter is commonly used to determine volume status in this clinical setting. However, recent data indicate that the intrathoracic blood volume index may have a better correlation with cardiac index than central venous pressure, allowing more accurate assessment of volume status for patients managed in the ICU.

Once a patient has severe disease, there seems to be no benefit of early aggressive hydration (115). Intravenous hydration in patients with AP has been shown to be most effective early in the course of the disease (110). When severe disease develops and/or after 24 hours, aggressive hydration may actually be harmful (111,116,126,128). While other experts and guidelines have advocated for using a term goal-directed hydration, clinicians often miss the goal failing to provide adequate hydration during the initial 24 hours when the moderately aggressive intravenous hydration is most important (10,110). Keeping in mind that most patients with AP seem to have mild disease, clinicians often do not appreciate the need to treat AP with early hydration because the patients do not appear ill, often having normal HCT and BUN. The goal in these patients seems to have been met. The problem is that AP results in an early extravasation of intravascular fluid into the peritoneum averaging 2–4 L over the first 48 hours (109). If early moderately aggressive intravenous hydration is not provided to these patients with initially appearing mild AP and the disease progresses, because the BUN and/or HCT rise during the first 24–36 hours, the goal is missed, and the risk of necrosis and/or organ failure increase (108,109). Rather than goal-directed therapy, the role of intravenous hydration is better thought of as do not miss the goal therapy, that is, do not allow the BUN and HCT to rise within the first 24–48 hours and do not let SIRS and/or renal insufficiency to develop. Because once these develop, the goal of hydration was missed, and mild disease may be progressing to severe disease.

ERCP IN AP

Recommendations

5. We suggest medical therapy over early (within the first 72 hours) ERCP in acute biliary pancreatitis without cholangitis (conditional recommendation, low quality of evidence).

Key concepts

13. In patients with AP complicated by cholangitis, early ERCP within the first 24 hours has been shown to decrease morbidity and mortality.
14. In the absence of cholangitis and/or jaundice, if a CBD stone is suspected, MRCP or EUS should be used to screen for the presence of CBD stones before the use of ERCP, and diagnostic ERCP should be avoided.

Summary of evidence

The role of ERCP. The pathophysiology of gallstone pancreatitis involves the obstruction of the pancreatic duct by a gallstone that passes from the bile duct into the common channel as it opens into the duodenum. A persistent CBD stone (choledocholithiasis) can lead to persistent pancreatic duct and/or biliary tree obstruction, leading to necrosis and/or cholangitis (129). Although intuitively, removal of obstructing gallstones from the biliary tree in patients with AP should reduce the complications, most gallstones readily pass to the duodenum and are lost in the stool (130). Most patients with gallstone pancreatitis will not benefit from ERCP, including early ERCP.

Schepers et al (131) performed a multicenter trial to determine whether patients with gallstone pancreatitis and predicted severe AP (APACHE >8, Imrie >3, or C-reactive protein >150 mg/dL) would benefit from early (within 24 hours) ERCP. Early ERCP was not found to decrease complications, including mortality in these patients. Yet, patients who underwent urgent ERCP were less likely to be readmitted for subsequent AP or cholangitis. The authors concluded that urgent ERCP is indicated in this situation only for cholangitis or progressive cholestasis defined by a rising bilirubin in the setting of severe or moderately severe AP (bilirubin >3–5 mg/dL).

PREVENTING POST-ERCP PANCREATITIS

Recommendations

6. We recommend rectal indomethacin to prevent post-ERCP pancreatitis (PEP) in individuals considered to be at high risk of PEP (strong recommendation, moderate quality of evidence).
7. We suggest placement of a pancreatic duct stent in patients at high risk for PEP who are receiving rectal indomethacin (conditional recommendation, low quality of evidence).

Summary of evidence

AP remains the most common complication of ERCP. The incidence of AP varies widely 1%–30%, depending on a variety of factors, including patient demographics, intraendoscopy procedures performed, and whether the patient has received prophylaxis (132–134). Although most patients with PEP have mild disease, some patients have severe disease and a complicated course, including death. There has been significant interest in identifying interventions that can reduce PEP.

In general, diagnostic ERCP should be avoided in most patients and, if needed, should be performed in Centers of Excellence. Clinicians must recognize that the risk of PEP is greater in the patient with a normal caliber CBD and normal bilirubin (odds ratio 3.4) when compared with a patient who is jaundiced with a dilated CBD (odds ratio 0.2) (135). In these patients, noninvasive MRCP or less-invasive EUS should be used because these methods of evaluating the CBD are as accurate and pose no risk of pancreatitis (136).

Interventions shown to prevent PEP include the following: (i) guidewire cannulation compared with contrast-guided cannulation, (ii) pancreatic duct stents in the appropriate patient, (iii) rectal indomethacin suppositories, and (iv) preprocedure intravenous hydration (137). Guidewire cannulation, in which the bile duct and pancreatic duct are cannulated by a guidewire inserted through a catheter (e.g., a sphincterotome), has been shown to decrease the risk of pancreatitis (138). This is likely by avoiding hydrostatic

injury, but other factors may be involved. Providing clarity, in a recent systematic review involving 15 trials, avoiding cannulation with radiocontrast agents decreased the risk of AP in most trials. The use of guidewire cannulation compared with contrast-guided cannulation also seems to decrease the risk of severe AP and other complications, including bleeding and perforation (139).

In the appropriate patients undergoing ERCP, such as those with an ampullary tumor undergoing snare resection and those undergoing endoscopic sphincterotomy, the use of a pancreatic duct stent has been shown to decrease the risk of severe PEP. Prophylactic pancreatic duct stenting is a cost-effective strategy for the prevention of PEP for high-risk patients (140); higher incidence of severe pancreatitis has been reported in patients with failed pancreatic duct stenting (141). Yet, it is recognized that pancreatic duct stenting is not always technically feasible with reported failure rate ranging from 4% to 10% (141). In addition, these studies supporting stent placement were unblinded and performed by highly skilled therapeutic endoscopist, thus introducing bias in favor of stenting into the results. Of more importance, these studies were performed before the widespread use of rectal indomethacin (see further).

Multiple studies have shown that a single dose of 100 mg of rectal indomethacin before or immediately after ERCP will prevent PEP in patients at high risk (134,142,143). However, in a consecutive series of high-risk and low-risk patients at a single center, no benefit to periprocedural rectal indomethacin suppositories was observed (144). While the benefit may not have been observed because of the inclusion of many patients at low risk, the number needed to treat low-risk patients to prevent AP and severe AP may be still within the cost-effective range. Thus, rectal indomethacin suppositories (100 mg) should be used in all patients undergoing ERCP, unless contraindicated (137).

In addition to rectal indomethacin, the use of a periprocedural hydration with lactated Ringer solution has been shown to prevent AP (145–147). Buxbaum (147) found that no patients developed PEP when provided lactated Ringer solution at 3 mL/kg/hr during the ERCP, a 20 mL/kg bolus after the procedure, followed by an 8-hour infusion at 3 mL/kg/hr. Similarly, 2 other randomized controlled clinical trials showed a benefit to periprocedural intravenous hydration. Park et al (148) in a prospective randomized multicenter clinical trial showed that lactated Ringer solution at rate of 3 mL/mg during the procedure and then 20 mL/kg bolus after the procedure significantly decreased the risk of PEP in average-risk to high-risk patients. Similarly, Choi et al (149) found vigorous periprocedural intravenous hydration with lactated Ringer solution reduced the incidence and severity of PEP in average-risk and high-risk cases.

While these studies show a benefit to periprocedural infusion of lactated Ringer solution, the timing and additional benefit of rectal indomethacin remains controversial. Mok et al (142) conducted a randomized, double-blinded, placebo-controlled trial on patients at high risk of PEP, the use of a liter of intravenous lactated Ringer solution pre-procedure with 100 mg of rectal indomethacin led to a significant decrease in postprocedure pancreatitis. However, a larger volume of fluid and ongoing aggressive hydration post-ERCP has been shown to be not effective in reducing PEP when rectal indomethacin suppositories are also used (150). Despite the evidence of the benefit of using rectal indomethacin suppositories, in a large study of more than 30,000 patients, only one-third of patients were provided this method of prophylaxis (151). When considering the costs, risks, and potential benefits in light of the published literature, rectal indomethacin and periprocedural hydration should be used in all patients before ERCP (137).

Patients undergoing ERCP who are at high risk for PEP will likely benefit from both rectal indomethacin and a pancreatic duct stent. While a large-scale multicenter RCT showed that patients who received rectal indomethacin alone were less likely to develop pancreatitis following ERCP than patients who received both rectal indomethacin in combination with a pancreatic duct stent (152), a well-designed NIH-sponsored multicenter trial recently showed the opposite results (153). In this large trial conducted at 20 centers in the USA and Canada, 1950 patients at high risk for PEP were randomly assigned to receive rectal indomethacin alone or in combination with a pancreatic duct stent. Patients at high risk were less likely to have PEP when provided both rectal indomethacin and a pancreatic duct stent. Therefore, prophylactic pancreatic duct stent placement is generally recommended in addition to rectal indomethacin in select patients at high risk for PEP. However, recognizing that this study was performed at tertiary care centers of expertise, clinicians need to recognize the possible difficulty of placing a pancreatic duct stent in all patients at high risk for PEP. A case by case approach is needed.

THE ROLE OF ANTIBIOTICS IN AP

Recommendations

8. We suggest against prophylactic antibiotics in patients with severe AP (conditional recommendation, very low quality of evidence).
9. We suggest against fine-needle aspiration (FNA) in patients with suspected infected pancreatic necrosis (conditional recommendation, very low quality of evidence).

Key concepts

15. While antibiotics should not be used in patients with sterile necrosis, antibiotics are an important part of treatment in infected necrosis along with debridement/necrosectomy.
16. In patients with infected necrosis, antibiotics known to penetrate pancreatic necrosis should be used largely to delay surgical, endoscopic, and radiologic drainage beyond 4 weeks. Some patients may avoid drainage altogether because the infection may completely resolve with antibiotics.
17. Routine administration of antifungal agents along with prophylactic or therapeutic antibiotics is not needed.

Summary of evidence

Infectious complications. Infectious complications are a major cause of morbidity and mortality in patients with AP, including cholangitis (154), urinary tract infections (155), infected pseudocysts (abscesses), fluid collections (156), and infected pancreatic necrosis. SIRS that develops early in the course of AP may be indistinguishable from sepsis because of fever, tachycardia, tachypnea, and leukocytosis. When an infection is suspected, antibiotics should be given while the source of the infection is being confirmed. However, once blood and other cultures are found to be negative, when no source of infection is identified, antibiotics should be discontinued.

Sterile necrosis. The paradigm shift and controversy of using antibiotics in AP has centered on pancreatic necrosis. When compared with patients with sterile necrosis, patients with infected pancreatic necrosis have a higher mortality rate (mean

30%, range 14%–69%) (69). For this reason, preventing infection of pancreatic necrosis is important. While some investigators found that infection is rare in the first week after the onset of AP (157), others have found that as many as 25% of all patients with infected necrosis developed the infection in the first week (158). Hypotension, early in the course of AP, has been believed to lead to ischemia of the bowel and allow bacterial translocation from the colon leading to infection of necrosis (159). Alternatively, line infections occurring after the first week have also been shown to lead to infection of necrosis (160).

Although early unblinded trials suggested a benefit in providing antibiotics to patients with sterile necrosis by preventing infectious complications (155,161,162), subsequent better-designed trials have consistently failed to show a benefit (163–166). There have been 11 prospective randomized trials of evaluating the use of prophylactic antibiotics in severe AP, with rigorous study design, participants, and outcome measures since 1993. Similarly, there were 10 meta-analyses reported since 2006 describing the abovementioned RCT, although the number of RCT in each meta-analysis varied depending on the year of publication of meta-analysis and the selection criteria used for choosing the RCT in each meta-analysis. Of interest, earlier meta-analyses and RCT reported a benefit with prophylactic antibiotic use in terms of mortality, infection of pancreatic necrosis, and extrapancreatic infections; however, all the 3 placebo-controlled, double-blind RCT, 5 of the 9 meta-analyses published after 2006, and 2 of the recent guidelines (British Society of Gastroenterology and ACG guidelines) (104,167) did not recommend the use of prophylactic antibiotics because of lack of benefit in the abovementioned outcomes.

Infected necrosis. The role of antibiotics in patients with necrotizing AP now focuses on the presence of infection. The concept that infected pancreatic necrosis requires prompt surgical debridement has also been challenged by multiple reports and case series showing that antibiotics alone can lead to resolution of infection and, in select patients, avoid surgery altogether (168–170). Pooling 11 studies that include 1,136 patients, there is a significant correlation between the timing of surgery and mortality. In general, in clinically stable patients, it seems that postponing necrosectomy in stable patients with antibiotics until 30 days after initial hospital admission is associated with a decreased mortality.

Current consensus is that surgery should be performed on clinically unstable patients with infected necrosis. However, in most patients, those clinically stable, the initial management of infected necrosis should be a 30-day course of antibiotics before surgery to allow the inflammatory reaction to become better organized (171). At this time, for a necrotic collection with a well-defined wall and liquefied material within, the decision and method of drainage can be considered, including endoscopic, radiologic, and/or surgical intervention. If there is no response to such antibiotics in a short time or if the clinical situation deteriorates, necrosectomy/debridement should be performed. The concept that urgent surgery is required in all patients found to have infected necrosis is no longer valid.

The role of CT-guided FNA. The technique of CT-guided FNA (CT-FNA) has proven to be safe, effective, and accurate in distinguishing infected and sterile necrosis (172,173). Because patients with infected necrosis and sterile necrosis may appear similar with leukocytosis and fever and organ failure (67,68) it is impossible to separate these entities without CT-FNA. Because the role of antibiotics is best established in clinically proven infection, CT-FNA should be considered when pancreatic or extrapancreatic infection is suspected. An immediate review of the Gram stain will often establish a diagnosis. However, it may be prudent to begin antibiotics while awaiting microbiologic confirmation. If culture reports are negative, the antibiotics can be discontinued.

There is some controversy as to whether a CT-FNA is necessary in all patients. In many patients, the CT-FNA would not influence the management of a patient (174). Many patients with sterile or infected necrosis either improve quickly or become unstable, and decisions on surgical intervention will not be influenced by the results of the aspiration. In addition, antibiotics can be started for suspected infection on clinical grounds even without the FNA of the pancreatic necrosis because a negative aspiration would still make the antibiotic use necessary due to clinical suspicion (175). In proven infection by blood or other body fluid cultures or by the presence of gas in the pancreatic necrosis, the need for antibiotics is clear. Because the infection will likely seed the necrosis, and the necrosis will be difficult to penetrate, antibiotics chosen should be known to penetrate the necrosis, such as carbapenems, quinolones, cephalosporins, and metronidazole (67,155,160,161). Routine administration of antifungal agents along with prophylactic or therapeutic antibiotics is also not needed.

NUTRITION IN AP

Recommendations

10. In patients with mild AP, we suggest early oral feeding (within 24–48 hours) as tolerated by the patient compared with the traditional nothing-by-mouth approach (conditional recommendation, low quality of evidence).
11. In patients with mild AP, we suggest initial oral feeding with low-fat solid diet rather than a stepwise liquid to solid approach (conditional recommendation, low quality of evidence).

Key concepts

18. Enteral nutrition in patients with moderately severe or severe AP seems to prevent infectious complications.
19. Parenteral nutrition should be avoided, unless the enteral route is not possible, not tolerated, or not meeting the caloric needs.
20. Using a nasogastric rather than nasojejunal route for delivery of enteral feeding is preferred because of comparable safety and efficacy.

Summary of evidence

Nutrition in mild AP. The long-held opinion that patients with AP should be nothing by mouth was based on the experience from other acute abdominal conditions. The idea was to avoid food-induced stimulation of pancreatic exocrine function, to decrease inflammation and hasten recovery, and to place the pancreas at rest. The historical practice was to wait until pain is minimal and enzymes normalize or trend downward before oral feeding can be started. Oral feeding was gradually increased from clear liquid diet to soft and then to low-fat solid diet before discharge. It has been subsequently recognized that oral feeding maintains gut mucosal integrity and prevents translocation of bacteria from the gut lumen into the inflamed/necrosed pancreatic tissue, predisposing to the serious complication of infected pancreatic necrosis. This led to the concept of gut rousing as opposed to gut resting (176).

Interest developed in early oral feeding (immediate or within 24, 48, or 72 hours after admission) without waiting for the pain

and pancreatic enzymes to normalize (177–183). While most of these studies were conducted in patients when the treating team allowed the patients to start oral feeding, some studies applied a novel approach of starting the feeds based on hunger experienced by patients. The results of this approach seem identical (181,184,185). For such early feeding, it is important to have bowel sounds present and no significant nausea, vomiting, or ileus. While most of these studies were performed in cases with mild AP, there were some studies performed in both cases with moderately severe and severe types of disease showing a benefit to early oral feeding (181,185,186).

Systematic reviews and meta-analyses of RCT have highlighted the benefit of early oral feeding in patients with mild, moderately severe, and severe types of AP, without the need to advance the diet slowly from clear liquids to solids (187,188). The universal finding in these studies demonstrate the safety of initiating early oral feeding in mild and moderately severe AP without any increase in important clinical outcomes, such as the development of necrosis, organ failure, and/or other local complications. Such an approach is beneficial by reducing the time to initiate solid feedings, thus reducing the hospital stay and costs. In mild AP, oral intake should, in general, be restored quickly. A low-fat solid diet has been shown to be safe compared with clear liquids, providing more calories (178). Similarly, in other randomized trials, oral feeding with a soft diet has been found to be safe compared with clear liquids and shorten the hospital stay (189,190). A desire for food, simple hunger, can help guide clinicians' decision when to start feedings (185). Based on these studies, oral feedings introduced in patients with mild AP do not need to begin with clear liquids and increase in a stepwise manner but may begin as a low-residue, low-fat, soft diet. However, clinicians should be aware that discharging a patient with persistent nausea despite early eating can result in readmission for recurrent AP (191).

Nutrition in those with moderately severe and severe AP. There is compelling data that patients with sepsis, in general, benefit from early refeeding (192). In general, parenteral nutrition should be avoided. There have been multiple randomized trials showing that TPN is associated with infectious and other line-related complications (69). Because enteral feeding maintains and prevents disruption of the gut mucosal barrier, prevents disruption, and prevents the translocation of bacteria that seed pancreatic necrosis, enteral nutrition should be begun in patients with severe AP, especially pancreatic necrosis (175,193). A meta-analysis of 8 randomized controlled clinical trials involving 381 patients found a decrease in infectious complications, organ failure, and mortality in patients with severe AP provided enteral nutrition compared with those given TPN (193). If enteral nutrition is administered by tube feeds, continuous infusion is preferred over cyclic or bolus administration (192). In addition, a small peptide-based medium-chain TG oil formula may improve tolerance (193).

Although the use of a nasojejunal route was preferred to avoid the gastric phase of stimulation, nasogastric enteral nutrition seems safe. A systematic review describing 92 patients from 4 studies on nasogastric tube feeding found that nasogastric feeding was safe and well tolerated in patients with predicted severe AP (194). There have been some reports of a slight increase in the risk of aspiration with nasogastric feeding. These patients should be placed in a more upright position and be placed on aspiration precautions. Evaluating for residuals, retained volume in the stomach, is not likely to be helpful. Compared with nasojejunal feeding, nasogastric tube placement is far easier, which is important in patients with AP, especially in the intensive care setting. Nasojejunal tube placement requires interventional radiology or endoscopy and thus can be expensive. For these reasons, nasogastric tube feeding maybe preferred (195).

The timing of initiating enteral feeding in patients with severe disease is controversial. While studies initially suggested a benefit in preventing infectious complications, more recent studies suggest that early (within the first 24 hours) initiation of enteral feeding is not beneficial. Bakker et al performed a large randomized trial in patients with predicted severe AP (196) and found that early enteral tube feeding within 24 hours did not reduce the rate of infection (25% vs 26%) when compared with on-demand feeding. In addition, early enteral tube feeding did not reduce mortality (11% vs 7%).

THE ROLE OF SURGERY IN AP

Key concepts

21. Patients with mild acute biliary pancreatitis should undergo cholecystectomy early, preferably before discharge.
22. Minimally invasive methods are preferred to open surgery for debridement and necrosectomy in stable patients with symptomatic pancreatic necrosis.
23. We suggest delaying any intervention (surgical, radiological, and/or endoscopic) in stable patients with pancreatic necrosis, preferably 4 weeks, to allow for the wall of collection to mature.

Summary of evidence

Cholecystectomy. In patients with mild gallstone pancreatitis, same-admission cholecystectomy has been shown to decrease recurrent gallstone-related complications, with a very low risk of cholecystectomy-related complications (198). When evaluating the literature, including 8 cohort studies and 1 randomized trial describing 998 patients who were discharged rather than undergo cholecystectomy compared with early cholecystectomy, 95 (18%) were readmitted for recurrent biliary events (18% vs 0%, $P < 0.0001$), including recurrent biliary pancreatitis (n = 43, 8%) (197). Many of these patients experienced severe disease. In addition to a benefit in morbidity, same-admission cholecystectomy results in substantial cost savings to the health care system (199).

Patients with pancreatic necrosis complicating biliary pancreatitis will require complex decision-making between the surgeon and gastroenterologist. In these patients, cholecystectomy is typically delayed to a later course in the typically prolonged hospitalization, as part of the management of the pancreatic necrosis if present and/or to a later date after discharge (200).

In most patients with gallstone pancreatitis, the CBD stone passes to the duodenum. Routine ERCP is not appropriate unless there is a high suspicion of a persistent CBD stone, manifested by an elevation in the bilirubin (201,202). Patients with mild AP, whose bilirubin is normal, can undergo laparoscopic cholecystectomy with intraoperative cholangiography, and any remaining bile duct stones can be dealt with by postoperative or intraoperative ERCP. In patients with low to moderate risk, MRCP can be used preoperatively; however, routine use of MRCP is unnecessary. In patients with mild AP who cannot undergo surgery, such as older individuals and/or those with severe comorbid disease, biliary sphincterotomy has been shown to be effective to prevent recurrent biliary AP (69).

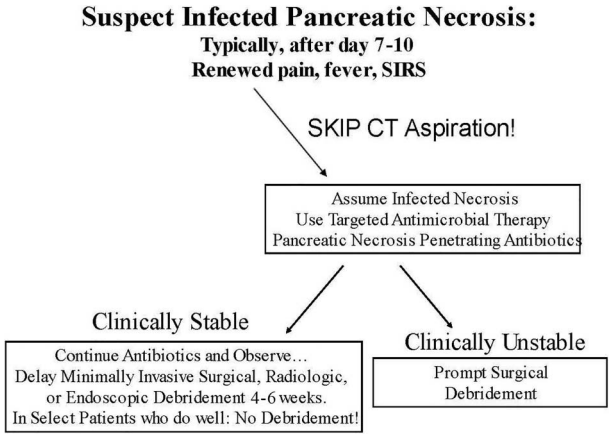

Figure 2. Late management of patients with AP. AP, acute pancreatitis; CT, computed tomography; SIRS, systemic inflammatory response syndrome.

Debridement of necrosis. Historically, open necrosectomy/debridement was the choice of treatment for infected necrosis and symptomatic sterile necrosis. Decades ago, patients with sterile necrosis underwent early debridement resulting in increased mortality. For this reason, early open debridement for sterile necrosis was abandoned (87). For patients with infected necrosis, it was falsely believed that mortality of infected necrosis was nearly 100% if debridement was not performed urgently (69,203). In a retrospective review of 53 patients where the median time to surgery was 28 days, when necrosectomy for infected necrosis was delayed, mortality decreased 22% (157). After reviewing 11 studies that included 1,136 patients, the authors also found a significant correlation between the timing of surgery and mortality. It seems that postponing necrosectomy in stable patients with antibiotics until 30 days after initial hospital admission is associated with a decreased mortality (168).

The concept that infected pancreatic necrosis requires prompt surgical debridement has also been challenged by multiple reports and case series showing that antibiotics alone can lead to resolution of infection and, in select patients, avoid surgery altogether (204,205). In one report (170), of 28 patients given antibiotics for the management of infected pancreatic necrosis, 16 patients avoided surgery. There were 2 deaths in the patients who underwent surgery and 2 deaths in the patients who were treated with antibiotics alone. Thus, in this report, more than half the patients were successfully treated with antibiotics, and the mortality rates in both the surgical and nonsurgical groups were similar.

Current consensus is that the initial management of infected necrosis for patients who are clinically stable should be a 2- to 4-week course of antibiotics before surgery to allow the inflammatory reaction to become better organized (171). At this time, in a collection with a well-defined wall and liquefied material within, the decision and method of drainage can be considered. For patients with symptomatic walled off pancreatic necrosis, a combined multimodality approach bringing together both minimally invasive surgery with endoscopic drainage seems to be more effective, safer and results in a shorter hospitalization (168,203,204). Although further study is needed, the concept that urgent surgery is required in patients found to have infected necrosis is no longer valid (Figure 2).

Minimally invasive management of pancreatic necrosis. Minimally invasive approaches to pancreatic necrosectomy including laparoscopic surgery, radiologic catheter drainage, and endoscopy are increasingly becoming the more common approaches. Although these guidelines cannot discuss in detail the methods of debridement nor the comparative effectiveness of each, due to limitations in data and focus of this review, several generalizations are important.

In general, regardless of the method, minimally invasive approaches require the pancreatic necrosis to become better organized (171,204,206,207). Whereas early in the course of the disease (within the first 7–10 days), pancreatic necrosis is a diffuse solid and/or semisolid inflammatory mass, after 4 weeks, a fibrous wall develops around the necrosis, which makes removal more amenable to surgery, laparoscopic surgery, radiologic catheter drainage, and/or endoscopic drainage.

Sometimes, these modalities can be combined. A well-designed study from the Netherlands using a step-up approach (percutaneous catheter drainage followed by video-assisted retroperitoneal debridement) demonstrated the superiority of the step-up approach by way of lower morbidity (less multiple organ failure and surgical complications) and lower costs (207). The investigators confirmed a higher mortality with open surgery both as an emergency (78%) and planned (30%) compared with a minimally invasive approach.

Percutaneous drainage without necrosectomy may be the most frequent minimally invasive method (208). The overall success seems to be approximately 50% in avoiding surgery. Endoscopic drainage of necrotic collections and later direct endoscopic necrosectomy have been reported in several large series. Two recent large multicenter studies (German and American) described the results of direct endoscopic necrosectomy. In this endoscopic approach, where endoscope is introduced into the necrotic cavity typically through the gastric wall and necrotic tissue is removed under direct vision, results have been comparable (209,210). In a recent well-designed randomized controlled clinical trial, endoscopic necrosectomy seems to be superior to surgical necrosectomy (211).

Regardless of the method, it must be remembered that many patients with sterile necrosis, and select patients with infected necrosis, seem to improve and remain asymptomatic, and no intervention may be necessary (212). The management of patients with necrosis is therefore very individualized, requiring consideration of both the clinical appearance of patients and the expertise available at the institution. Referral to centers of expertise is of paramount importance because delaying intervention with maximal supportive care and using a minimally invasive approach have both shown to be of benefit in reducing morbidity and mortality in patients with acute necrotizing pancreatitis.

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CONFLICTS OF INTEREST

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