CME

American College of Gastroenterology Guideline: Management of Acute Pancreatitis

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This guideline presents recommendations for the management of patients with acute pancreatitis (AP). During the past decade, there have been new understandings and developments in the diagnosis, etiology, and early and late management of the disease. As the diagnosis of AP is most often established by clinical symptoms and laboratory testing, contrast-enhanced computed tomography (CECT) and/or magnetic resonance imaging (MRI) of the pancreas should be reserved for patients in whom the diagnosis is unclear or who fail to improve clinically. Hemodynamic status should be assessed immediately upon presentation and resuscitative measures begun as needed. Patients with organ failure and/or the systemic inflammatory response syndrome (SIRS) should be admitted to an intensive care unit or intermediary care setting whenever possible. Aggressive hydration should be provided to all patients, unless cardiovascular and/or renal comorbidites preclude it. Early aggressive intravenous hydration is most beneficial within the first 12–24 h, and may have little benefit beyond. Patients with AP and concurrent acute cholangitis should undergo endoscopic retrograde cholangiopancreatography (ERCP) within 24 h of admission. Pancreatic duct stents and/or postprocedure rectal nonsteroidal anti-inflammatory drug (NSAID) suppositories should be utilized to lower the risk of severe post-ERCP pancreatitis in high-risk patients. Routine use of prophylactic antibiotics in patients with severe AP and/or sterile necrosis is not recommended. In patients with infected necrosis, antibiotics known to penetrate pancreatic necrosis may be useful in delaying intervention, thus decreasing morbidity and mortality. In mild AP, oral feedings can be started immediately if there is no nausea and vomiting. In severe AP, enteral nutrition is recommended to prevent infectious complications, whereas parenteral nutrition should be avoided. Asymptomatic pancreatic and/or extrapancreatic necrosis and/or pseudocysts do not warrant intervention regardless of size, location, and/or extension. In stable patients with infected necrosis, surgical, radiologic, and/or endoscopic drainage should be delayed, preferably for 4 weeks, to allow the development of a wall around the necrosis.

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Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract, leading to tremendous emotional, physical, and financial human burden (1,2). In the United States, in 2009, AP was the most common gastroenterology discharge diagnosis with a cost of 2.6 billion dollars (2). Recent studies show the incidence of AP varies between 4.9 and 73.4 cases per 100,000 worldwide (3,4). An increase in the annual incidence for AP has been observed in most recent studies. Epidemiologic review data from the 1988 to 2003 National Hospital Discharge Survey showed that hospital admissions for AP increased from 40 per 100,000 in 1998 to 70 per 100,000 in 2002. Although the case fatality rate for AP has decreased over time, the overall population mortality rate for AP has remained unchanged (1).

There have been important changes in the definitions and classification of AP since the Atlanta classification from 1992 (5). During the past decade, several limitations have been recognized that led to a working group and web-based consensus revision (6). Two distinct phases of AP have now been identified: (i) early (within 1 week), characterized by the systemic inflammatory response syndrome (SIRS) and/or organ failure; and (ii) late (>1 week), characterized by local complications. It is critical to recognize the paramount importance of organ failure in determining disease severity. Local complications are defined as peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocysts, and walled-off necrosis (sterile or infected). Isolated extrapancreatic necrosis is also included under the term necrotizing pancreatitis; although

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Table 1. GRADE system of quality of evidence and strength of recommendation

High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of the effect is very uncertain.

outcomes like persistent organ failure, infected necrosis, and mortality of this entity are more often seen when compared to interstitial pancreatitis, these complications are more commonly seen in patients with pancreatic parenchymal necrosis (7). There is now a third intermediate grade of severity, moderately severe AP, that is characterized by local complications in the absence of persistent organ failure. Patients with moderately severe AP may have transient organ failure, lasting <48 h. Moderately severe AP may also exacerbate underlying comorbid disease but is associated with a low mortality. Severe AP is now defined entirely on the presence of persistent organ failure (defined by a modified Marshall Score) (8).

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. Early management focuses on advancements in our understanding of aggressive intravenous hydration, which when applied early appears to decrease morbidity and mortality (9,10). The evolving issues of antibiotics, nutrition, and endoscopic, radiologic, surgical, and other minimally invasive interventions will be addressed.

A search of MEDLINE via the OVID interface using the MeSH term "acute pancreatitis" limited to clinical trials, reviews, guidelines, and meta-analysis for the years 1966–2012 was undertaken without language restriction, as well as a review of clinical trials and reviews known to the authors were performed for the preparation of this document. The GRADE system was used to grade the strength of recommendations and the quality of evidence (11). An explanation of the quality of evidence and strength of the recommendations is shown in **Table 1**. Each section of the document presents the key recommendations related to the section topic, followed by a summary of the supporting evidence. A summary of recommendations is provided in **Table 2**.

DIAGNOSIS

Recommendations

1. The diagnosis of AP is most often established by the presence of 2 of the 3 following criteria: (i) abdominal pain consistent with the disease, (ii) serum amylase and/or lipase greater than three times the upper limit of normal, and/or (iii) characteristic findings from abdominal imaging (strong recommendation, moderate quality of evidence).
2. Contrast-enhanced computed tomography (CECT) and/or magnetic resonance imaging (MRI) of the pancreas should be reserved for patients in whom the diagnosis is unclear or who fail to improve clinically within the first 48–72 h after hospital admission or to evaluate complications (strong recommendation, low quality of evidence).

DIAGNOSIS: CLINICAL PRESENTATION

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 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 may be helpful to determine the diagnosis of AP in patients with atypical presentations.

DIAGNOSIS: LABORATORY PARAMETERS

Because of limitations in sensitivity, specificity, and positive and negative predictive value, serum amylase alone cannot be used reliably for the diagnosis of AP and serum lipase is preferred. Serum amylase in AP patients generally rises within a few hours after the onset of symptoms and returns to normal values within 3–5 days; however, it may remain within the normal range on admission in as many as one-fifth of patients (12,13). 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. Serum amylase concentrations might be high in the absence of AP in macroamylasaemia (a syndrome characterized by the formation of large molecular complexes between amylase and abnormal immunoglobulins), in patients with decreased glomerular filtration rate, in diseases of the salivary glands, and in extrapancreatic abdominal diseases associated with inflammation, including acute appendicitis, cholecystitis, intestinal obstruction or ischemia, peptic ulcer, and gynecological diseases.

Serum lipase appears to be more specific and remains elevated longer than amylase after disease presentation. Despite recommendations of previous investigators (14) and guidelines for the management of AP (15) that emphasize the advantage of serum lipase, similar problems with the predictive value remain in certain patient populations, including the existence of macrolipasemia. Lipase is also found to be elevated in a variety of nonpancreatic diseases, such as renal disease, appendicitis, cholecystitis, and so on. In addition, an upper limit of normal greater than 3–5 times may be needed in diabetics who appear to have higher median lipase compared with nondiabetic patients for unclear reasons (16,17). A Japanese consensus conference to determine appropriate "cutoff" values for amylase and

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Table 2. Summary of recommendations

Diagnosis	
1.	The diagnosis of AP is most often established by the presence of two of the three following criteria: (i) abdominal pain consistent with the disease, (ii) serum amylase and/or lipase greater than three times the upper limit of normal, and/or (iii) characteristic findings from abdominal imaging (strong recommendation, moderate quality of evidence).
2.	Contrast-enhanced computed tomographic (CECT) and/or magnetic resonance imaging (MRI) of the pancreas should be reserved for patients in whom the diagnosis is unclear or who fail to improve clinically within the first 48–72 h after hospital admission (strong recommendation, low quality of evidence).
Etiology	
3.	Transabdominal ultrasound should be performed in all patients with acute pancreatitis (strong recommendation, low quality of evidence).
4.	In the absence of gallstones and/or history of significant history of alcohol use, a serum triglyceride should be obtained and considered the etiology if >1,000 mg/dl (conditional recommendation, moderate quality of evidence).
5.	In a patient older than 40 years, a pancreatic tumor should be considered as a possible cause of acute pancreatitis (conditional recommendation, low quality of evidence).
6.	Endoscopic investigation in patients with acute idiopathic pancreatitis should be limited, as the risks and benefits of investigation in these patients are unclear (conditional recommendation, low quality of evidence).
7.	Patients with idiopathic pancreatitis should be referred to centers of expertise (conditional recommendation, low quality of evidence).
8.	Genetic testing may be considered in young patients (<30 years old) if no cause is evident and a family history of pancreatic disease is present (conditional recommendation, low quality of evidence).
Initial assessment and risk stratification	
9.	Hemodynamic status should be assessed immediately upon presentation and resuscitative measures begun as needed (strong recommendation, moderate quality of evidence).
10.	Risk assessment should be performed to stratify patients into higher- and lower-risk categories to assist triage, such as admission to an intensive care setting (conditional recommendation, moderate quality of evidence).
11.	Patients with organ failure should be admitted to an intensive care unit or intermediary care setting whenever possible (strong recommendation, low quality of evidence).
Initial management	
12.	Aggressive hydration, defined as 250-500 ml per hour of isotonic crystalloid solution should be provided to all patients, unless cardiovascular and/or renal comorbidites exist. Early aggressive intravenous hydration is most beneficial the first 12–24 h, and may have little benefit beyond (strong recommendation, moderate quality of evidence).
13.	In a patient with severe volume depletion, manifest as hypotension and tachycardia, more rapid repletion (bolus) may be needed (conditional recommendation, moderate quality of evidence).
14.	Lactated Ringer's solution may be the preferred isotonic crystalloid replacement fluid (conditional recommendation, moderate quality of evidence).
15.	Fluid requirements should be reassessed at frequent intervals within 6 h of admission and for the next 24–48 h. The goal of aggressive hydration should be to decrease the blood urea nitrogen (strong recommendation, moderate quality of evidence).
ERCP in acute pancreatitis	
16.	Patients with acute pancreatitis and concurrent acute cholangitis should undergo ERCP within 24 h of admission (strong recommendation, moderate quality of evidence).
17.	ERCP is not needed in most patients with gallstone pancreatitis who lack laboratory or clinical evidence of ongoing biliary obstruction (strong recommendation, low quality of evidence).
18.	In the absence of cholangitis and/or jaundice, MRCP or endoscopic ultrasound (EUS) rather than diagnostic ERCP should be used to screen for choledocholithiasis if highly suspected (conditional recommendation, low quality of evidence).
19.	Pancreatic duct stents and/or postprocedure rectal nonsteroidal anti-inflammatory drug (NSAID) suppositories should be utilized to prevent severe post-ERCP pancreatitis in high-risk patients (conditional recommendation, moderate quality of evidence).
The role of antibiotics in acute pancreatitis	
20.	Antibiotics should be given for an extrapancreatic infection, such as cholangitis, catheter-acquired infections, bacteremia, urinary tract infections, pneumonia (strong recommendation, high quality of evidence).
21.	Routine use of prophylactic antibiotics in patients with severe acute pancreatitis is not recommended (strong recommendation, moderate quality of evidence).
22.	The use of antibiotics in patients with sterile necrosis to prevent the development of infected necrosis is not recommended (strong recommendation, moderate quality of evidence).
23.	Infected necrosis should be considered in patients with pancreatic or extrapancreatic necrosis who deteriorate or fail to improve after 7–10 days of hospitalization. In these patients, either (i) initial CT-guided fine needle aspiration (FNA) for Gram stain and culture to guide use of appropriate antibiotics or (ii) empiric use of antibiotics without CT FNA should be given (strong recommendation, low quality of evidence).

Table 2 continued on the following page

Table 2. Continued

24.	In patients with infected necrosis, antibiotics known to penetrate pancreatic necrosis, such as carbapenems, quinolones, and metronidazole, may be useful in delaying or sometimes totally avoiding intervention, thus decreasing morbidity and mortality (conditional recommendation, low quality of evidence).
25.	Routine administration of antifungal agents along with prophylactic or therapeutic antibiotics is not recommended (conditional recommendation, low quality of evidence).
Nutrition in acute pancreatitis	
26.	In mild AP, oral feedings can be started immediately if there is no nausea and vomiting, and abdominal pain has resolved (conditional recommendation, moderate quality of evidence).
27.	In mild AP, initiation of feeding with a low-fat solid diet appears as safe as a clear liquid diet (conditional recommendations, moderate quality of evidence).
28.	In severe AP, enteral nutrition is recommended to prevent infectious complications. Parenteral nutrition should be avoided unless the enteral route is not available, not tolerated, or not meeting caloric requirements (strong recommendation, high quality of evidence).
29.	Nasogastric delivery and nasojejunal delivery of enteral feeding appear comparable in efficacy and safety (strong recommendation, moderate quality of evidence).
The role of surgery in acute pancreatitis	
30.	In patients with mild AP, found to have gallstones in the gallbladder, a cholecystectomy should be performed before discharge to prevent a recurrence of AP (strong recommendation, moderate quality of evidence).
31.	In a patient with necrotizing biliary AP, in order to prevent infection, cholecystectomy is to be deferred until active inflammation subsides and fluid collections resolve or stabilize (strong recommendation, moderate quality of evidence).
32.	The presence of asymptomatic pseudocysts and pancreatic and/or extrapancreatic necrosis do not warrant intervention, regardless of size, location, and/or extension (strong recommendation, moderate quality of evidence).
33.	In stable patients with infected necrosis, surgical, radiologic, and/or endoscopic drainage should be delayed preferably for more than 4 weeks to allow liquefication of the contents and the development of a fibrous wall around the necrosis (walled-off necrosis) (strong recommendation, low quality of evidence).
34.	In symptomatic patients with infected necrosis, minimally invasive methods of necrosectomy are preferred to open necrosectomy (strong recommendation, low quality of evidence).

AP, acute pancreatitis; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

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lipase could not reach consensus on appropriate upper limits of normal (18). Assays of many other pancreatic enzymes have been assessed during the past 15 years, but none seems to offer better diagnostic value than those of serum amylase and lipase (19). 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 a doubt regarding the diagnosis of AP exists, abdominal imaging, such as CECT, is recommended.

DIAGNOSIS: ABDOMINAL IMAGING

Abdominal imaging is useful to confirm the diagnosis of AP. CECT provides over 90% sensitivity and specificity for the diagnosis of AP (20). Routine use of CECT in patients with AP is unwarranted, as the diagnosis is apparent in many patients and most have a mild, uncomplicated course. However, in a patient failing to improve after 48–72 (e.g., persistent pain, fever, nausea, unable to begin oral feeding), CECT or MRI imaging is recommended to assess local complications such as pancreatic necrosis (21–23). Computed tomography (CT) and MRI are comparable in the early assessment of AP (24). MRI, by employing magnetic resonance cholangiopancreatography (MRCP), has the advantage of detecting choledocholithiasis down to 3 mm diameter and pancreatic duct disruption while providing high-quality imaging for diagnostic and/or severity purposes. MRI is helpful in patients with a contrast allergy and renal insufficiency where T2-weighted images without gadolinium contrast can diagnose pancreatic necrosis (24).

ETIOLOGY

Recommendations

1. Transabdominal ultrasound should be performed in all patients with AP (strong recommendation, low quality of evidence).
2. In the absence of gallstones and/or history of significant history of alcohol use, a serum triglyceride should be obtained and considered the etiology if >1,000 mg/dl. (conditional recommendation, moderate quality of evidence).
3. In a patient >40 years old, a pancreatic tumor should be considered as a possible cause of AP (conditional recommendation, low quality of evidence).
4. Endoscopic investigation of an elusive etiology in patients with AP should be limited, as the risks and benefits of investigation in these patients are unclear (conditional recommendation, low quality of evidence).

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5. Patients with idiopathic AP (IAP) should be referred to centers of expertise (conditional recommendation, low quality of evidence).
6. Genetic testing may be considered in young patients (< 30 years old) if no cause is evident and a family history of pancreatic disease is present (conditional recommendation, low quality of evidence).

ETIOLOGY: GALLSTONES AND ALCOHOL

The etiology of AP can be readily established in most patients. The most common cause of AP is gallstones (40–70%) and alcohol (25–35%) (25–27). Because of the high prevalence and importance of preventing recurrent disease, abdominal ultrasound to evaluate for cholelithiasis should be performed on all patients with AP (28–30). Identification of gallstones as the etiology should prompt referral for cholecystectomy to prevent recurrent attacks and potential biliary sepsis (29,30). Gallstone pancreatitis is usually an acute event and resolves when the stone is removed or passes spontaneously.

Alcohol-induced pancreatitis often manifests as a spectrum, ranging from discrete episodes of AP to chronic irreversible silent changes. The diagnosis should not be entertained unless a person has a history of over 5 years of heavy alcohol consumption (31). "Heavy" alcohol consumption is generally considered to be > 50 g per day, but is often much higher (32). Clinically evident AP occurs in < 5% of heavy drinkers (33); thus, there are likely other factors that sensitize individuals to the effects of alcohol, such as genetic factors and tobacco use (27,33,34).

OTHER CAUSES 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 hyperparathyroidism are rare causes, often falsely identified as causing AP (35–37). Although some drugs such as 6-mercaptopurine, azathioprine, and DDI (2′,3′-dideoxyinosine) can clearly cause AP, there are limited data supporting most medications as causative agents (35). Primary and secondary hypertriglyceridemia can cause AP; however, these account for only 1–4% of cases (36). Serum triglycerides should rise above 1,000 mg/dl to be considered the cause of AP (38,39). A lactescent (milky) serum has been observed in as many as 20% of patients with AP, and therefore a fasting triglyceride level should be re-evaluated 1 month after discharge when hypertriglyceridemia is suspected (40). Although most do not, any benign or malignant mass that obstructs the main pancreatic can result in AP. It has been estimated that 5–14% of patients with benign or malignant pancreatobiliary tumors present with apparent IAP (41–43). Historically, adenocarcinoma of the pancreas was considered a disease of old age. However, increasingly patients in their 40s—and occasionally younger—are presenting with pancreatic cancer. This entity should be suspected in any patient > 40 years of age with idiopathic pancreatitis, especially those with a prolonged or recurrent course (27,44,45). Thus, a contrast-enhanced CT scan or MRI is needed in these patients. A more extensive evaluation including endoscopic ultrasound (EUS) and/or MRCP may be needed initially or after a recurrent episode of IAP (46).

IDIOPATHIC AP

IAP is defined as pancreatitis with no etiology established after initial laboratory (including lipid and calcium level) and imaging tests (transabdominal ultrasound and CT in the appropriate patient) (47). In some patients an etiology may eventually be found, yet in others no definite cause is ever established. Patients with IAP should be evaluated at centers of excellence focusing on pancreatic disease, providing advanced endoscopy services and a combined multidisciplinary approach.

Anatomic and physiologic anomalies of the pancreas occur in 10–15% of the population, including pancreas divisum and sphincter of Oddi dysfunction (48). It remains controversial if these disorders alone cause AP (49). There may be a combination of factors, including anatomic and genetic, that predispose to the development of AP in susceptible individuals (48). Endoscopic therapy, focusing on treating pancreas divisum and/or sphincter of Oddi dysfunction, carries a significant risk of precipitating AP and should be performed only in specialized units (50,51). The influence of genetic defects, such as cationic trypsinogen mutations, SPINK, or CFTR mutations, in causing AP is being increasingly recognized. These defects, furthermore, may also increase the risk of AP in patients with anatomic anomalies, such as pancreas divisum (48). However, the role of genetic testing in AP has yet to be determined, but may be useful in patients with more than one family member with pancreatic disease (34). Individuals with IAP and a family history of pancreatic diseases should be referred for formal genetic counseling.

INITIAL ASSESSMENT AND RISK STRATIFICATION

Recommendations

1. Hemodynamic status should be assessed immediately upon presentation and resuscitative measures begun as needed (strong recommendation, moderate quality of evidence).
2. Risk assessment should be performed to stratify patients into higher- and lower-risk categories to assist triage, such as admission to an intensive care setting (conditional recommendation, low to moderate quality of evidence).
3. Patients with organ failure should be admitted to an intensive care unit or intermediary care setting whenever possible (strong recommendation, low quality of evidence).

SUMMARY OF EVIDENCE

Definition of severe AP

Most episodes of AP are mild and self-limiting, needing only brief hospitalization. Mild AP is defined by the absence of organ failure and/or pancreatic necrosis (5,6). By 48 h after admission, these

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patients typically would have substantially improved and begun refeeding. In patients with severe disease, two phases of AP are recognized: early (within the first week) and late. Local complications include peripancreatic fluid collections and pancreatic and peripancreatic necrosis (sterile or infected). Most patients with severe disease present to the emergency room with no organ failure or pancreatic necrosis; unfortunately, this has led to many errors in clinical management of this disease (52). These errors include failure to provide adequate hydration, failure to diagnose and treat cholangitis, and failure to treat early organ failure. For this reason, it is critical for the clinician to recognize the importance of not falsely labeling a patient with mild disease within the first 48 h of admission for AP.

Severe AP occurs in 15–20% of patients (53). Severe AP is defined by the presence of persistent (fails to resolve within 48 h) organ failure and/or death (6). Historically, in the absence of organ failure, local complications from pancreatitis, such as pancreatic necrosis, were also considered severe disease (5,6,53). However, these local complications (including pancreatic necrosis with or without transient organ failure) define moderately severe AP (see **Table 3**). Moderately severe acute pancreatitis is characterized by the presence of transient organ failure or local or systematic complications in the absence of persistent organ failure (6). An example of a patient with moderately severe acute pancreatitis is one who has peripancreatic fluid collections and prolonged abdominal pain, leukocytosis and, fever, causing the patient to remain hospitalized for 7-10 days. In the absence of persistent organ failure, mortality in patients with this entity is less than severe acute pancreatitis. If persistent organ failure develops in a patient with necrotizing pancreatitis, it is then considered severe disease.

Organ failure had previously been defined as shock (systolic blood pressure <90 mm Hg), pulmonary insufficiency (PaO_2 <60 mm Hg), renal failure (creatinine >2 mg/dl after rehydration), and/or gastrointestinal bleeding (>500 ml of blood loss/24 h) (53). The Revised Atlanta Criteria now define organ failure as a score of 2 or more for one of these organ systems using the modified Marshall scoring system (6,8). The authors feel that rather than calculate a Marshal score (which may be complex for the busy clinician), relying on the older Atlanta definitions would be as useful. Further study is needed to validate the need for using the Marshal score.

Pancreatic necrosis is defined as diffuse or focal areas of nonviable pancreatic parenchyma >3 cm in size or >30% of the pancreas (53). Pancreatic necrosis can be sterile or infected (discussed below). In the absence of pancreatic necrosis, in mild disease the edematous pancreas is defined as interstitial pancreatitis. Although there is some correlation between infection, pancreatic necrosis, hospital length of stay, and organ failure, both patients with sterile necrosis and infected necrosis may develop organ failure (55,56). The presence of infection within the necrosis probably does not increase the likelihood of present or future organ failure. Patients with sterile necrosis can suffer from organ failure and appear as ill clinically as those patients with infected necrosis. Persistent organ failure is now defined by a Modified Marshal Score (6,8).

Table 3. Definitions of severity in acute pancreatitis: comparison of Atlanta and recent revision

Atlanta criteria (1993)	Atlanta Revision (2013)
Mild acute pancreatitis	**Mild acute pancreatitis**
Absence of organ failure	Absence of organ failure
Absence of local complications	Absence of local complications
Severe acute pancreatitis	Moderately severe acute pancreatitis
1. Local complications **AND/OR**	1. Local complications **AND/OR**
2. Organ failure	2. Transient organ failure (<48 h)
GI bleeding (>500 cc/24 hr)	**Severe acute pancreatitis**
Shock – SBP ≤90 mm Hg	Persistent organ failure >48 h[a]
PaO 2 ≤60 %	
Creatinine ≥2 mg/dl	

GI, gastrointestinal; SBP, systolic blood pressure.
[a]Persistent organ failure is now defined by a Modified Marshal Score (6,8)

Isolated extrapancreatic necrosis is also included under the term necrotizing pancreatitis. This entity, initially thought to be a nonspecific anatomic finding with no clinical significance, has become better characterized and is associated with adverse outcomes, such as organ failure and persistent organ failure, but these outcomes are less frequent. Extrapancreatic necrosis is more often appreciated during surgery than being identified on imaging studies. Although most radiologists can easily identify pancreatic parenchymal necrosis, in the absence of surgical intervention, extrapancreatic necrosis is appreciated less often (7).

Predicting severe AP

Clinicians have been largely unable to predict which patients with AP will develop severe disease. Uniformly, severity scoring systems are cumbersome, typically require 48 h to become accurate, and when the score demonstrates severe disease, the patient's condition is obvious regardless of the score (52,57,58). The new scoring systems, such as the BISAP (59), have not shown to be more accurate than the other scoring systems (60,61). In general, AP-specific scoring systems have a limited value, as they provide little additional information to the clinician in the evaluation of patients and may delay appropriate management (52).

Although laboratory testing such as the hematocrit and blood urea nitrogen (BUN) can assist clinicians (52,62,63), no laboratory test is practically available or consistently accurate to predict severity in patients with AP (64–66). Even the acute-phase reactant C-reactive protein (CRP), the most widely studied inflammatory marker in AP, is not practical as it takes 72 h to become accurate (54). CT and/or MRI imaging also cannot reliably determine severity early in the course of AP, as necrosis usually is not present on admission and may develop after 24–48 h (24,67). Thus, in the absence of any available test to determine severity, close examination to assess early fluid losses, hypovolemic shock, and symptoms suggestive of organ dysfunction is crucial.

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

Patient characteristics
Age >55 years (53,57)
Obesity (BMI >30 kg/m^2) (68)
Altered mental status (69)
Comorbid disease (53)
The systemic inflammatory response syndrome (SIRS) (6,53,54,70,71) Presence of >2 of the following criteria:
– pulse >90 beats/min
– respirations >20/min 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 mg/dl (63)
Rising BUN (63)
HCT >44% (62)
Rising HCT (62)
Elevated creatinine (72)
Radiology findings
Pleural effusions (73)
Pulmonary infiltrates (53)
Multiple or extensive extrapancreatic collections (67)

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 acute pancreatitis.

Rather than depending on a scoring system to predict severity of AP, clinicians need to be aware of intrinsic patient-related risk factors, including laboratory and imaging risk factors, for the development of severe disease (**Table 4**). These include: a patient's age, comorbid health problems, body mass index (74), the presence of SIRS (70,71), signs of hypovolemia such as an elevated BUN (63) and an elevated hematocrit (62), presence of pleural effusions and/or infiltrates (73), altered mental status (69), and other factors (54,72) (**Table 3**).

During the early phase of the disease (within the first week), death occurs as a result of the development, persistence, and progressive nature of organ dysfunction (75,76). The development of organ failure appears to be related to the development and persistence of SIRS. The reversal of and early organ failure has been shown to be important in preventing morbidity and mortality in patients with AP (77,78). Although the presence of SIRS during the initial 24 h has a high sensitivity for predicting organ failure and mortality, the presence of SIRS lacks specificity for severe disease (41%). The lack of specificity is due to the fact that the presence of SIRS is not as important as its persistence. For this reason, patients with persistent SIRS, particularly those who are tachypnic and/or tachycardic, should be admitted to an intensive care unit or similar unit for aggressive intravenous hydration and close monitoring.

INITIAL MANAGEMENT

Recommendations

1. Aggressive hydration, defined as 250–500 ml per hour of isotonic crystalloid solution should be provided to all patients, unless cardiovascular, renal, or other related comorbid factors exist. Early aggressive intravenous hydration is most beneficial during the first 12–24 h, and may have little benefit beyond this time period (strong recommendation, moderate quality of evidence).
2. In a patient with severe volume depletion, manifest as hypotension and tachycardia, more rapid repletion (bolus) may be needed (conditional recommendation, moderate quality of evidence).
3. Lactated Ringer's solution may be the preferred isotonic crystalloid replacement fluid (conditional recommendation, moderate quality of evidence).
4. Fluid requirements should be reassessed at frequent intervals within 6 h of admission and for the next 24–48 h. The goal of aggressive hydration should be to decrease the BUN (strong recommendation, moderate quality of evidence).

EARLY AGGRESSIVE INTRAVENOUS HYDRATION

Despite dozens of randomized trials, no medication has been shown to be effective in treating AP (32,53). However, an effective intervention has been well described: early aggressive intravenous hydration. Recommendations regarding aggressive hydration are based on expert opinion (10,52,53), laboratory experiments (79,80), indirect clinical evidence (62,63,81,82), epidemiologic studies (59), and both retrospective and prospective clinical trials (9,83).

The rationale for early aggressive hydration in AP arises from observation of the frequent hypovolemia that occurs from multiple factors affecting patients with AP, including vomiting, reduced oral intake, third spacing of fluids, increased respiratory losses, and diaphoresis. In addition, researchers hypothesize that a combination of microangiopathic effects and edema of the inflamed pancreas decreases blood flow, leading to increased cellular death, necrosis, and ongoing release of pancreatic enzymes activating numerous cascades. Inflammation also increases vascular permeability, leading to increased third space fluid losses and worsening of pancreatic hypoperfusion that leads to increased pancreatic parenchymal necrosis and cell death (84). Early aggressive intravenous fluid resuscitation provides micro- and macrocirculatory support to prevent serious complications such as pancreatic necrosis (10).

Although there are limited prospective data that aggressive intravenous hydration can be monitored and/or guided by

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laboratory markers, the use of hematocrit (62), BUN (63,83), and creatinine (72) as surrogate markers for successful hydration has been widely recommended (10,15,52,53). Although no firm recommendations regarding absolute numbers can be made at this time, the goal to decrease hematocrit (demonstrating hemodilution) and BUN (increasing renal perfusion) and maintain a normal creatinine during the first day of hospitalization cannot be overemphasized.

Although some human trials have shown a clear benefit to aggressive hydration (9,85,86), other studies have suggested that aggressive hydration may be associated with an increased morbidity and mortality (87,88). These variable study findings may be partly explained by critical differences in study design. Although these studies raise concerns about the continuous use of aggressive hydration over 48 h, the role of early hydration (within the first 6–12 h) was not addressed in these negative studies. In addition, these negative studies included sicker patients who would have required large volumes of hydration by the 48 h time point (87,88). Consistently, the human studies in AP that focused on the initial rate of hydration early in the course of treatment (within the first 24 h) demonstrated a decrease in both morbidity and mortality (9,85,86). Although the total volume of hydration at 48 h after admission appears to have little or no impact on patient outcome, early aggressive intravenous hydration, during the first 12–24 h, with close monitoring is of paramount importance.

In a well-designed prospective randomized trial, hydration with a lactated Ringer's solution appears to be more beneficial, resulting in fewer patients developing SIRS as compared with patients receiving normal (0.9%) saline (83). The benefit of using lactated Ringer's solution in large-volume resuscitation has been shown in other disease states to lead to better electrolyte balance and improved outcomes (89,90). In AP, there are additional theoretical benefits to using the more pH-balanced lactated Ringer's solution for fluid resuscitation compared with normal saline. Low pH activates the trypsinogen, makes the acinar cells more susceptible to injury and increases the severity of established AP in experimental studies. Although both are isotonic crystalloid solutions, normal saline given in large volumes may lead to the development of a non-anion gap, hyperchloremic metabolic acidosis (83).

It is important to recognize that aggressive early hydration will require caution for certain groups of patients, such as the elderly, or those with a history of cardiac and/or renal disease in order to avoid complications such as volume overload, pulmonary edema, and abdominal compartment syndrome (91). Measurement of the central venous pressure via a centrally placed catheter is most commonly used to determine volume status in this setting. However, data indicate that the intrathoracic blood volume index may have a better correlation with cardiac index than central venous pressure. Measurement of intrathoracic blood volume index may therefore allow more accurate assessment of volume status for patients managed in the intensive care unit. Patients not responding to intravenous hydration early (within 6–12 h) may not benefit from continued aggressive hydration.

ERCP IN AP

The role of ERCP in AP is related to the management of choledocholithiasis. Although ERCP can be used to identify pancreatic ductal disruption in patients with severe AP, possibly leading to interventions for the so-called dislocated duct syndrome, a consensus has never emerged that ERCP should be performed routinely for this purpose (52).

Recommendations

1. Patients with AP and concurrent acute cholangitis should undergo ERCP within 24 h of admission (strong recommendation, moderate quality of evidence).
2. ERCP is not needed early in most patients with gallstone pancreatitis who lack laboratory or clinical evidence of ongoing biliary obstruction (strong recommendation, moderate quality of evidence).
3. In the absence of cholangitis and/or jaundice, MRCP or EUS rather than diagnostic ERCP should be used to screen for choledocholithiasis if highly suspected (conditional recommendation, moderate quality of evidence).
4. Pancreatic duct stents and/or postprocedure rectal nonsteroidal anti-inflammatory drug (NSAID) suppositories should be utilized to lower the risk of severe post-ERCP pancreatitis in high-risk patients (conditional recommendation, moderate quality of evidence).

THE ROLE OF ERCP IN AP

Fortunately, most gallstones that cause AP readily pass to the duodenum and are lost in the stool (92). However in a minority of patients, persistent choledocholithiasis can lead to ongoing pancreatic duct and/or biliary tree obstruction, leading to severe AP and/or cholangitis. Removal of obstructing gallstones from the biliary tree in patients with AP should reduce the risk of developing these complications.

There have been several clinical trials performed to answer the question: does early ERCP (within 24–72 h of onset) in acute biliary pancreatitis reduces the risk of progression of AP to severe disease (organ failure and/or necrosis)? Neoptolemos *et al.* (93) studied 121 patients with probable acute biliary pancreatitis, stratified for severity according to the modified Glasgow criteria. The trial was performed in a single center in the United Kingdom. Patients with predicted severe AP had fewer complications if they underwent ERCP within 72 h of admission (24% vs. 61%, $P<0.05$). When patients with concurrent acute cholangitis (who would obviously benefit from early ERCP) were excluded, the difference remained significant (15% vs. 61%, $P=0.003$). Mortality was not significantly different in the two groups. Fan *et al.* (94) reported a study of 195 patients with suspected biliary pancreatitis stratified for severity according to Ranson's criteria. Patients in the study group underwent ERCP within 24 h of admission and those in the control group were offered conservative management. The control group was offered ERCP if acute cholangitis developed. Those who underwent early ERCP had fewer complications (13% vs. 54%, $P=0.002$).

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Based on these studies, it was unclear whether patients with severe AP in the absence of acute cholangitis benefit from early ERCP. Therefore, Folsch *et al.* (95) organized a multicenter study of ERCP in acute biliary pancreatitis that excluded patients most likely to benefit, namely those with a serum bilirubin >5 mg/dl. Thus, patients with acute cholangitis and/or obvious biliary tree obstruction underwent early ERCP and were not included in the study. This study focused on determining the benefit of early ERCP in preventing severe AP in the absence of biliary obstruction. Although this study has been widely criticized for design flaws and the unusually high mortality of patients with mild disease (8% compared with an expected 1%), no benefit in morbidity and/or mortality was seen in patients who underwent early ERCP. From this study, it appears that the benefit of early ERCP is seen in patients with AP complicated by acute cholangitis and biliary tree obstruction, but not severe AP in the absence of acute cholangitis.

More recent studies have confirmed that early ERCP within 24 h of admission decreases morbidity and mortality in patients with AP complicated by biliary sepsis (96,97). A dilated biliary tree in the absence of an elevated bilirubin and other signs of sepsis should not be confused with cholangitis, but may indicate the presence of a common bile duct stone. In patients with biliary pancreatitis who have mild disease, and in patients who improve, ERCP before cholecystectomy has been shown to be of limited value and may be harmful. Noninvasive imaging studies are the preferred diagnostic modalities in these patients (EUS and/or MRCP). However, it is not clear if any testing needs to be performed in patients who improve.

PREVENTING POST-ERCP PANCREATITIS

AP remains the most common complication of ERCP. Historically, this complication was seen in 5–10% of cases and in 20–40% of certain high-risk procedures (50,98). Over the past 15 years, the risk of post-ERCP pancreatitis has decreased to 2–4% and the risk of severe AP to <1/500 (50,98). In general, the decrease in post-ERCP AP and severe AP is related to increased recognition of high-risk patients and high-risk procedures in which ERCP should be avoided and the application of appropriate interventions to prevent AP and severe AP (50).

Patients with normal or near-normal bile duct and liver tests have a lower likelihood of a common bile duct stone and/or other pathology (stricture, tumor). In these patients, diagnostic ERCP has largely been replaced by EUS or MRCP as the risk of post-ERCP pancreatitis is greater in a patient with normal caliber bile duct and normal bilirubin (odds ratio 3.4 for post-ERCP pancreatitis) as compared with a patient who is jaundiced with a dilated common bile duct (odds ratio 0.2 for post-ERCP pancreatitis) (99). Furthermore, MRCP and EUS are as accurate as diagnostic ERCP and pose no risk of pancreatitis (98).

For patients undergoing a therapeutic ERCP, three well-studied interventions to decrease the risk of post-ERCP pancreatitis, especially severe disease, include: (i) guidewire cannulation, (ii) pancreatic duct stents, and (iii) rectal NSAIDs. Guidewire cannulation (cannulation of the bile duct and pancreatic duct by a guidewire inserted through a catheter) decreases the risk of pancreatitis (100) by avoiding hydrostatic injury to the pancreas that may occur with the use of radiocontrast agents. In a study of 400 consecutive patients randomized to contrast or guidewire cannulation, there were no cases of AP in the guidewire group as compared with 8 cases in the contrast group ($P<0.001$). A more recent study in 300 patients prospectively randomized to guidewire cannulation compared with conventional contrast injection also found a decrease in post-ERCP pancreatitis in the guidewire group (101). However, the reduction in post-ERCP pancreatitis may not be entirely related to guidewire cannulation (102) and may have been related to less need for precut sphincterotomy in patients undergoing guidewire cannulation. Regardless, guidewire cannulation compared with conventional contrast cannulation appears to decrease the risk of severe post-ERCP AP (103,104).

Placement of a pancreatic duct stent decreases the risk of severe post-ERCP pancreatitis in high-risk patients, such as those undergoing ampullectomy, endoscopic sphincter of Oddi manometry, or pancreatic interventions during ERCP. A 2007 meta-analysis published by Andriulli *et al.* (105), which evaluated 4 randomized, prospective trials including 268 patients, showed that pancreatic duct stent placement affords a two-fold drop in the incidence of post-ERCP pancreatitis (24.1% vs. 12%; $P=0.009$; odds ratio: 0.44, 95% confidence interval: 0.24–0.81). Although further study is needed, smaller 3 French (Fr) unflanged pancreatic stents appear to lower the risk of post-ERCP pancreatitis ($P=0.0043$), pass more spontaneously ($P=0.0001$), and cause less pancreatic ductal changes (24% vs. 80%) as compared with larger 4 Fr, 5 Fr, or 6 Fr stents (106). However, 3 Fr pancreatic stent placement is more technically demanding because of the need to use a very floppy (0.018-inch diameter) guidewire. Although prophylactic pancreatic duct stenting is a cost-effective strategy for the prevention of post-ERCP pancreatitis for high-risk patients (107), a higher incidence of severe pancreatitis has been reported in patients with failed pancreatic duct stenting (108). Pancreatic duct stenting is not always technically feasible, with reported failure rates ranging from 4 to 10% (108). In addition, long-term complications from pancreatic duct stenting, such as chronic pancreatitis, may occur and further study is needed (49).

Although a large number of pharmacologic interventions for prophylaxis against post-ERCP pancreatitis have been studied (50), the results of the studies have been largely disappointing. The most promising group of drugs to attenuate the inflammatory response of AP are NSAIDs (109,110). Two clinical trials have shown that a 100 mg rectal suppository of diclofenac reduces the incidence of post-ERCP pancreatitis (111,112). In addition, a recent multicenter, double-blind, randomized placebo controlled trial of 602 patients undergoing a high-risk ERCP demonstrated a significant reduction of post-ERCP pancreatitis in patients given postprocedure rectal indomethacin (113). It is important to note that this study included only patients at a

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high risk of developing post-ERCP pancreatitis and severe AP, which is the population that would benefit the most. When considering the costs, risks, and potential benefits reviewed in the published literature, rectal diclofenac and/or indomethacin should be considered before ERCP, especially in high-risk patients. Although further study is needed to define the optimal dose, at present it is reasonable to consider placement of two indomethacin 50 mg suppositories (total 100 mg) after ERCP in patients at a high risk of developing post-ERCP AP. However, until further study is performed, the placement of rectal NSAIDs does not replace the need for a pancreatic duct stent in the appropriate high-risk patient.

THE ROLE OF ANTIBIOTICS IN AP

Recommendations

1. Antibiotics should be given for an extrapancreatic infection, such as cholangitis, catheter-acquired infections, bacteremia, urinary tract infections, pneumonia (strong recommendation, moderate quality of evidence).
2. Routine use of prophylactic antibiotics in patients with severe AP is not recommended (strong recommendation, moderate quality of evidence).
3. The use of antibiotics in patients with sterile necrosis to prevent the development of infected necrosis is not recommended (strong recommendation, moderate quality of evidence).
4. Infected necrosis should be considered in patients with pancreatic or extrapancreatic necrosis who deteriorate or fail to improve after 7–10 days of hospitalization. In these patients, either (i) initial CT-guided fine-needle aspiration (FNA) for Gram stain and culture to guide use of appropriate antibiotics or (ii) empiric use of antibiotics after obtaining necessary cultures for infectious agents, without CT FNA, should be given (strong recommendation, moderate evidence).
5. In patients with infected necrosis, antibiotics known to penetrate pancreatic necrosis, such as carbapenems, quinolones, and metronidazole, may be useful in delaying or sometimes totally avoiding intervention, thus decreasing morbidity and mortality (conditional recommendation, moderate quality of evidence).
6. Routine administration of antifungal agents along with prophylactic or therapeutic antibiotics is not recommended (conditional recommendation, low quality of evidence).

Infectious complications

Infectious complications, both pancreatic (infected necrosis) and extrapancreatic (pneumonia, cholangitis, bacteremia, urinary tract infections, and so on), are a major cause of morbidity and mortality in patients with AP. Many infections are hospital-acquired and may have a major impact on mortality (114). Fever, tachycardia, tachypnea, and leukocytosis associated with SIRS that may occur early in the course of AP may be indistinguishable from sepsis syndrome. When an infection is suspected, antibiotics should be given while the source of the infection is being investigated (53). However, once blood and other cultures are found to be negative and no source of infection is identified, antibiotics should be discontinued.

PREVENTING THE INFECTION OF STERILE NECROSIS

The paradigm shift and controversy over 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%) (53). For this reason, preventing infection of pancreatic necrosis is important. Although it was previously believed that infectious complications occur late in the course of the disease (115,116), a recent review found that 27% of all cases of infected necrosis occur within the first 14 days (117); in another study, nearly half of all infections appear to occur within 7 days of admission (118).

Although early unblinded trials suggested that administration of antibiotics may prevent infectious complications in patients with sterile necrosis (119,120), subsequent, better-designed trials have consistently failed to confirm an advantage (121–125). Because of the consistency of pancreatic necrosis, few antibiotics penetrate when given intravenously. The antibiotics shown to penetrate and used in clinical trials include carbapenems, quinolones, metronidazole, and high-dose cephalosporins (52,116,123). Since 1993, there have been 11 prospective, randomized trials with proper study design, participants, and outcome measures that evaluated the use of prophylactic antibiotics in severe AP (126). From this meta-analysis, the number needed to treat was 1,429 for one patient to benefit. It remains uncertain if a subgroup of patients with severe AP (such as extensive necrosis with organ failure) may benefit from antibiotics, but large studies required to determine whether any benefit exists will be difficult to perform. Based on the current literature, use of prophylactic antibiotics to prevent infection in patients with sterile necrosis (even predicted as having severe disease) is not recommended.

Prevention of fungal infections in these patients is also not recommended. Although it was suggested that fungal infection may be a more common cause of mortality in AP, further study has not confirmed this finding (127). There is one successful randomized controlled, clinical trial that used selective decontamination of the bowel, targeting both bacteria and fungi, in order to prevent infected necrosis (128). Because of the decreased morbidity and mortality in this trial in patients with severe AP who had undergone selective decontamination, further study in this area is needed. Finally, probiotics should not be given in severe AP. Although earlier trials suggested a benefit, a very well-conducted, randomized controlled clinical trial demonstrated increased mortality (129). This lack of benefit has also been shown in a recent meta-analysis (130).

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Infected necrosis

Rather than preventing infection, the role of antibiotics in patients with necrotizing AP is now to treat established infected necrosis. 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 (131–134). Garg *et al.* (134) reported 47/80 patients with infected necrosis over a 10-year period who were successfully treated conservatively with antibiotics alone (134). The mortality in the conservative group was 23% as compared with 54% in the surgical group. The same group published a meta-analysis of 8 studies involving 409 patients with infected necrosis of whom 324 were successfully treated with antibiotics alone (135). Overall, 64% of the patients with infected necrosis in this meta-analysis could be managed by conservative antibiotic treatment with 12% mortality, and only 26% underwent surgery. Thus, a select group of relatively stable patients with infected pancreatic necrosis could be managed by antibiotics alone without requiring percutaneous drainage. However, it should be cautioned that these patients require close supervision and percutaneous or endoscopic or necrosectomy should be considered if the patient fails to improve or deteriorates clinically.

THE ROLE OF CT FNA

The technique of computed tomography guided fine needle aspiration (CT FNA) has proven to be safe, effective, and accurate in distinguishing infected and sterile necrosis (53,136). As patients with infected necrosis and sterile necrosis may appear similar with leukocytosis, fever, and organ failure (137), it is impossible to separate these entities without needle aspiration. Historically, the use of antibiotics is best established in clinically proven pancreatic or extrapancreatic infection, and therefore CT FNA should be considered when an 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 (**Figure 1**). In many patients, the CT FNA would not influence the management (138). Increased use of conservative management and minimally invasive drainage have decreased the use of FNA for the diagnosis of infected necrosis (54). Many patients with sterile or infected necrosis either improve quickly or become unstable, and decisions on intervention via a minimally invasive route will not be influenced by the results of the aspiration. A consensus conference concluded that FNA should only be used in select situations where there is no clinical response to antibiotics, such as when a fungal infection is suspected (54).

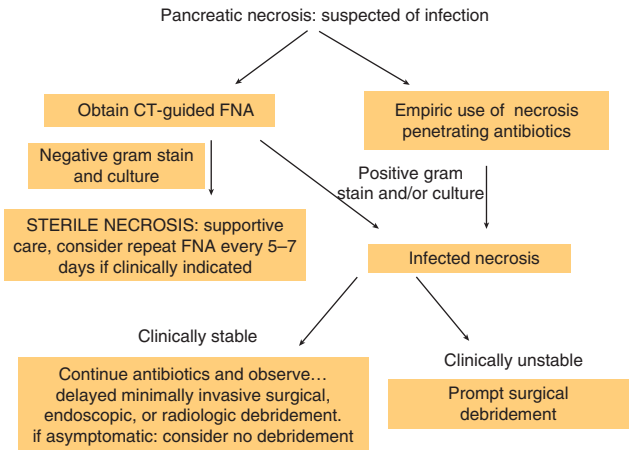


Figure 1. Management of pancreatic necrosis when infection is suspected. Infected necrosis should be considered in patients with pancreatic or extrapancreatic necrosis who deteriorate or fail to improve after 7–10 days of hospitalization. In these patients, either (i) initial computed tomography-guided fine needle aspiration (CT FNA) for Gram stain and culture to guide use of appropriate antibiotics or (ii) empiric use of antibiotics without CT FNA should be given. In patients with infected necrosis, antibiotics known to penetrate pancreatic necrosis may be useful in delaying intervention, thus decreasing morbidity and mortality. In stable patients with infected necrosis, surgical, radiologic, and/or endoscopic drainage should be delayed by preferably 4 weeks to allow the development of a wall around the necrosis (walled-off pancreatic necrosis).

NUTRITION IN AP

Recommendations

1. In mild AP, oral feedings can be started immediately if there is no nausea and vomiting, and the abdominal pain has resolved (conditional recommendation, moderate quality of evidence).
2. In mild AP, initiation of feeding with a low-fat solid diet appears as safe as a clear liquid diet (conditional recommendations, moderate quality of evidence).
3. In severe AP, enteral nutrition is recommended to prevent infectious complications. Parenteral nutrition should be avoided, unless the enteral route is not available, not tolerated, or not meeting caloric requirements (strong recommendation, high quality of evidence).
4. Nasogastric delivery and nasojejunal delivery of enteral feeding appear comparable in efficacy and safety (strong recommendation, moderate quality of evidence).

SUMMARY OF EVIDENCE

Nutrition in mild AP

Historically, despite the absence of clinical data, patients with AP were kept NPO (nothing by mouth) to rest the pancreas (32). Most guidelines in the past recommended NPO until resolution of pain and some suggested awaiting normalization of pancreatic enzymes or even imaging evidence of resolution of inflammation before resuming oral feedings (53). The need to place the pancreas at rest until complete resolution of AP no longer

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seems imperative. The long-held assumption that the inflamed pancreas requires prolonged rest by fasting does not appear to be supported by laboratory and clinical observation (139). Clinical and experimental studies showed that bowel rest is associated with intestinal mucosal atrophy and increased infectious complications because of bacterial translocation from the gut. Multiple studies have shown that patients provided oral feeding early in the course of AP have a shorter hospital stay, decreased infectious complications, decreased morbidity, and decreased mortality (117,140–143).

In mild AP, oral intake is usually restored quickly and no nutritional intervention is needed. Although the timing of refeeding remains controversial, recent studies have shown that immediate oral feeding in patients with mild AP appears safe (139). In addition, a low-fat solid diet has been shown to be safe compared with clear liquids, providing more calories (144). Similarly, in other randomized trials, oral feeding with a soft diet has been found to be safe compared with clear liquids and it shortens the hospital stay (145,146). Early refeeding also appears to result in a shorter hospital stay. Based on these studies, oral feedings introduced in 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 when the patient appears to be improving.

Total parenteral nutrition should be avoided in patients with mild and severe AP. There have been multiple randomized trials showing that total parenteral nutrition is associated with infectious and other line-related complications (53). As enteral feeding maintains the gut mucosal barrier, prevents disruption, and prevents the translocation of bacteria that seed pancreatic necrosis, enteral nutrition may prevent infected necrosis (142,143). A recent meta-analysis describing 8 randomized controlled clinical trials involving 381 patients found a decrease in infectious complications, organ failure, and mortality in patients with severe AP who were provided enteral nutrition as compared with total parenteral nutrition (143). Although further study is needed, continuous infusion is preferred over cyclic or bolus administration.

Although the use of a nasojejunal route has been traditionally preferred to avoid the gastric phase of stimulation, nasogastric enteral nutrition appears as 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 (117). There have been some reports of nasogastric feeding slightly increasing the risk of aspiration. For this reason, patients with AP undergoing enteral nutrition should be placed in a more upright position and be placed on aspiration precautions. Although further study is needed, 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 should be preferred (147). A large multicenter trial sponsored by the National Institutes of Health (NIH) is currently being performed to investigate whether nasogastric or nasojejunal feedings are preferred in these patients because of significant experimental and some human evidence of superiority of distal jejunal feeding in AP.

THE ROLE OF SURGERY IN AP

Recommendations

1. In patients with mild AP, found to have gallstones in the gallbladder, a cholecystectomy should be performed before discharge to prevent a recurrence of AP (moderate recommendation, moderate quality of evidence).
2. In a patient with necrotizing biliary AP, in order to prevent infection, cholecystectomy is to be deferred until active inflammation subsides and fluid collections resolve or stabilize (strong recommendation, moderate evidence).
3. Asymptomatic pseudocysts and pancreatic and/or extrapancreatic necrosis do not warrant intervention regardless of size, location, and/or extension (moderate recommendation, high quality of evidence).
4. In stable patients with infected necrosis, surgical, radiologic, and/or endoscopic drainage should be delayed preferably for more than 4 weeks to allow liquefication of the contents and the development of a fibrous wall around the necrosis (walled-off necrosis) (strong recommendation, low quality of evidence).
5. In symptomatic patients with infected necrosis, minimally invasive methods of necrosectomy are preferred to open necrosectomy (strong recommendation, low quality of evidence).

SUMMARY OF EVIDENCE

Cholecystectomy

In patients with mild gallstone pancreatitis, cholecystectomy should be performed during the index hospitalization. The current literature, which includes 8 cohort studies and one randomized trial describing 998 patients who had and who had not undergone cholecystectomy for biliary pancreatitis, 95 (18%) were readmitted for recurrent biliary events within 90 days of discharge (0% vs. 18%, $P<0.0001$), including recurrent biliary pancreatitis ($n=43$, 8%) (148). Some of the cases were found to be severe. Based on this experience, there is a need for early cholecystectomy during the same hospitalization, if the attack is mild. Patients who have severe AP, especially with pancreatic necrosis, will require complex decision making between the surgeon and gastroenterologist. In these patients, cholecystectomy is typically delayed until (i) a later time in the typically prolonged hospitalization, (ii) as part of the management of the pancreatic necrosis if present, or (iii) after discharge (148,149). Earlier guidelines recommended a cholecystectomy after 2 attacks of IAP, with a presumption that many such cases might be because of microlithiasis. However, a population-based study found that cholecystectomy performed for recurrent attacks of AP with no stones/sludge on ultrasound and no significant elevation of liver tests during the attack of AP was associated with a >50% recurrence of AP (150).

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In the majority of patients with gallstone pancreatitis, the common bile duct stone passes to the duodenum. Routine ERCP is not appropriate unless there is a high suspicion of a persistent common bile duct stone, manifested by an elevation in the bilirubin (151). Patients with mild AP, with normal bilirubin, can undergo laproscopic 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 or EUS can be used preoperatively, but routine use of MRCP is unnecessary. In patients with mild AP who cannot undergo surgery, such as the frail elderly and/or those with severe comorbid disease, biliary sphincterotomy alone may be an effective way to reduce further attacks of AP, although attacks of cholecystitis may still occur (53).

DEBRIDEMENT OF NECROSIS

Historically, open necrosectomy/debridement was the treatment of choice for infected necrosis and symptomatic sterile necrosis. Decades ago, patients with sterile necrosis underwent early debridement that resulted in increased mortality. For this reason, early open debridement for sterile necrosis was abandoned (32). However, debridement for sterile necrosis is recommended if associated with gastric outlet obstruction and/or bile duct obstruction. In patients with infected necrosis, it was falsely believed that mortality of infected necrosis was nearly 100% if debridement was not performed urgently (53,152). In a retrospective review of 53 patients with infected necrosis treated operatively (median time to surgery of 28 days) mortality fell to 22% when necrosectomy necrosis was delayed (118). After reviewing 11 studies that included 1,136 patients, the authors found that postponing necrosectomy in stable patients treated with antibiotics alone until 30 days after initial hospital admission is associated with a decreased mortality (131).

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 (6,54). In one report (133) of 28 patients given antibiotics for the management of infected pancreatic necrosis, 16 avoided surgery. There were two deaths in the patients who underwent surgery and two 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 rate in both the surgical and nonsurgical groups was similar. The concept that urgent surgery is required in patients found to have infected necrosis is no longer valid. Asymptomatic pancreatic and/or extrapancreatic necrosis does not mandate intervention regardless of size, location, and extension. It will likely resolve over time, even in some cases of infected necrosis (54).

Although unstable patients with infected necrosis should undergo urgent debridement, current consensus is that the initial management of infected necrosis for patients who are clinically stable should be a course of antibiotics before intervention to allow the inflammatory reaction to become better organized (54). If the patient remains ill and the infected necrosis has not resolved, minimally invasive necrosectomy by endoscopic, radiologic, video-assisted retroperitoneal, laparoscopic approach, or combination thereof, or open surgery is recommended once the necrosis is walled-off (54,153–156).

MINIMALLY INVASIVE MANAGEMENT OF PANCREATIC NECROSIS

Minimally invasive approaches to pancreatic necrosectomy including laproscopic surgery either from an anterior or retroperitoneal approach, percutaneous, radiologic catheter drainage or debridement, video-assisted or small incision-based left retroperitoneal debridement, and endoscopy are increasingly becoming the standard of care. Percutaneous drainage without necrosectomy may be the most frequently used minimally invasive method for managing fluid collections complicating necrotizing AP (54,68,148,152–157). The overall success appears to be ~50% in avoiding open surgery. In addition, endoscopic drainage of necrotic collections and/or direct endoscopic necrosectomy has been reported in several large series to be equally successful (53,54,155). Sometimes these modalities can be combined at the same time or sequentially, for example, combined percutaneous and endoscopic methods. Recently, a well-designed study from the Netherlands using a step-up approach (percutaneous catheter drainage followed by video-assisted retroperitoneal debridement) (68,156) demonstrated the superiority of the step-up approach as reflected by lower morbidity (less multiple organ failure and surgical complications) and lower costs compared with open surgical necrosectomy.

Although these guidelines cannot discuss in detail the various methods of debridement, or the comparative effectiveness of each, because of limitations in available data and the focus of this review, several generalizations are important. Regardless of the method employed, minimally invasive approaches require the pancreatic necrosis to become organized (54,68,154–157). 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 that makes removal more amenable to open and laproscopic surgery, percutaneous radiologic catheter drainage, and/or endoscopic drainage.

Currently, a multidisciplinary consensus favors minimally invasive methods over open surgery for the management of pancreatic necrosis (54). A recent randomized controlled trial clearly demonstrated the superiority of endoscopic debridement over surgery (154). Although advances in surgical, radiologic, and endoscopic techniques exist and are in development, it must be stressed that many patients with sterile pancreatic necrosis, and select patients with infected necrosis, clinically improve to a point where no intervention is necessary (54,134). The management of patients with pancreatic necrosis should be individualized, requiring consideration of all the available data (clinical, radiologic, laboratory) and using available expertise. Early referral to a center of excellence is of paramount importance, as delaying intervention with

maximal supportive care and using a minimally invasive approach have both been shown to reduce morbidity and mortality.

CONFLICT OF INTEREST

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