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EXPERT REVIEWS

Management of acute pancreatitis

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Acute pancreatitis (AP) is a common medical condition with extensive morbidity and mortality. Approximately 210,000 Americans are hospitalized each year; and 5% of patients with AP will die. It is also an expensive condition, costing 2.6 billion dollars (United States) in 2009 alone. Moreover, the incidence is increasing – the National Hospital Discharge Survey showed hospitalizations increased from 78 per 100,000 in 2007 to 90 per 100,000 just three years later in 2010. There is no proven pharmacologic entity to treat the inflammatory response associated with acute pancreatitis; supportive care with IV fluids, bowel rest and pain control are the mainstays of therapy. Recently, new developments to help increase survival and minimize morbidity with several key interventions have been investigated. This summary highlights new studies and meta-analyses to provide current opinion on treatment of this morbid condition.

Keywords: acute pancreatitis • direct endoscopic necrosectomy • ERCP • fluid resuscitation • management • VARD

Diagnosis

While not the primary focus of this manuscript, making the appropriate diagnosis is essential to the management of this disease. First published in 1992 and updated in 2013, the Atlanta Classification mandates that acute pancreatitis (AP) be diagnosed if any one of the following two features is present: typical clinical symptoms of elevation in pancreatic specific enzymes and/or representative findings on cross-sectional imaging [1].

Clinical presentation

Because of sympathetic innervation from the celiac plexus, pain due to pancreatitis is largely experienced in the epigastric region. It is typically sharp and burning in character, severe, constant and often radiates to the back or shoulder blades. It is rarely colicky, intermittent or dull, and rarely presents in the lower abdomen; other diagnoses should be considered in these instances. Patients often present with fever, tachycardia and tachypnea; the latter almost exclusively due to the development of pleural effusions secondary to capillary leak syndrome.

Laboratory evaluation

Pancreatic specific serological enzymes, lipase and amylase, remain the best diagnostic tests for pancreatitis. Lipase is made and stored in the pancreatic acinar cells and 99% is secreted from the pancreatic ductal system. It is 100 times more prevalent in the pancreas than in the liver, duodenum and small bowel. It has been shown to have greater sensitivity and specificity over amylase with exact numbers depending on the cutoffs used in different studies [2]. Amylase has been shown to return to normal levels faster than lipase, as early as 3–5 days, and may even be in the normal range on admission in approximately 20% of patients [3]. It has especially poor sensitivity in pancreatitis caused by hypertriglyceridemia and alcohol [2]. Amylase may also be elevated at times without pancreatitis in patients with macroamylasemia (a condition in which amylase forms complexes with abnormal antibodies), disorders of the salivary glands, impaired glomerular filtration rate, salivary gland injury or ischemic/inflammatory bowel injury.

Lipase, however, is not a perfectly sensitive marker of pancreatitis. It can be falsely elevated in peptic ulcer disease, kidney disease, appendicitis, diabetic ketoacidosis or cholecystitis [2]. Despite the high sensitivity and specificity of lipase, clinical correlation is paramount because of these instances of spurious elevation. In the absence of a history of gallbladder disease or alcohol use, hypertriglyceridemia should be considered and triglyceride levels measured. Previously, measuring pancreatic and salivary isoamylases have also been proposed as more specific tests than total amylase; however,

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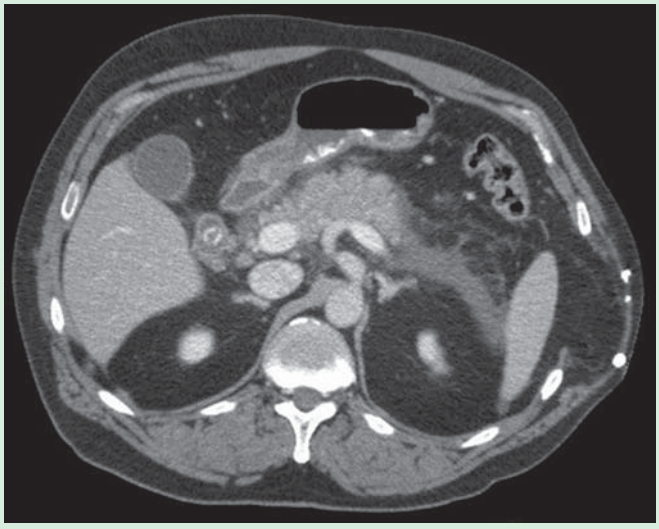

Figure 1. Admission CT scan demonstrating normal perfusion of the pancreas neck and proximal body with peripancreatic edema at the tail.

pancreatic isoamylase was also found to be elevated in serious conditions such as biliary disease, perforated duodenal obstruction, ruptured abdominal aortic aneurysm or bowel ischemia. Immunoreactive trypsinogen and elastase have also been proposed as serological markers but were found to be unhelpful due to ease of use and poor specificity, respectively [2].

Imaging

While contrast enhanced computed tomography is about 80% sensitive and 85% specific for AP [4], it is not necessary to make the diagnosis. A well-taken history and physical examination with confirmatory laboratory values is sufficient, as these can spare unwarranted radiation and reduce the cost of treatment. However, if laboratory data are inconsistent or there is little improvement in the first 48–72 h after admission, computed tomography (CT) or MRI is indicated. They are particularly helpful for determining complications from AP such as fluid collection, necrosis and/or hemorrhage [4,5]. While CT and MRI have similar utility in diagnosing AP, MRI has added advantages of quantifying the degree of pancreatic necrosis in collections, reducing radiation exposure in young patients and assessing for choledocholithiasis. However, abdominal ultrasound is recommended in the cases of biliary pancreatitis as a first-line test for choledocholithiasis because of its low cost and lack of ionizing radiation. However, ultrasound sensitivity is highly dependent on the skill of the ultrasonographer and small stones can be missed. See Figures 1–3 for representative CT images of pancreatic necrosis in evolution.

Clinical classification & course

AP is generally classified according to the revised Atlantic Criteria, an approach to standardize the severity of pancreatitis, described by a panel of experts in pancreatic disease [1]. Mild pancreatitis, the majority of cases, is defined as pancreatic inflammation without necrosis or organ failure. By 48 h after presentation, these patients are generally able to tolerate oral feeds and typically have much improved symptoms.

Severe AP, occurring in around 20% of patients, is further divided into moderately severe pancreatitis and severe pancreatitis. The key differentiating factor between moderately severe and severe is the presence of persistent organ failure in severe cases. Organ failure has been shown to be a greater predictor of severity and mortality than the degree of pancreatic necrosis. It is often not possible to definitively differentiate between moderately severe and severe on initial presentation, but rather the true discrimination comes after 48 h of admission – patients with severe pancreatitis will have persistent organ failure. Organ failure has been defined by the revised Atlantic Criteria as two or more on the Marshall scale, which utilizes PaO_2/FIO_2, serum creatinine and systolic blood pressure as a measure of overall organ damage (see Table 1).

The complications of AP can be divided into early (within the first week) and late as well as local and systemic. Early complications include pancreatic fluid collection, necrosis (infected or sterile) and end-organ damage from hypoperfusion, disseminated intravascular coagulation and adult respiratory distress syndrome. These early manifestations can be either transient, with the patient making a full recovery, or cause long-term morbidity and/or death. Late complications are generally more localized and can occur as walled-off necrosis (due to both pancreatic and extra-pancreatic necrosis), pseudocysts, splenic vein thrombosis and/or pancreatic fistulae. Early recognition and accurate prognostication of AP is vital in limiting morbidity and mortality [6].

Prognostication

Most cases of AP are mild and do not require prolonged periods of hospitalization; however, because 5% of hospitalized patients will die from this disease, prognostic criteria are needed to determine high-risk cases [7]. Multiple systems have been developed, but have had difficulty achieving accuracy by a user-friendly tool. The Bedside Index for Severity of Acute Pancreatitis (BISAP) is a straightforward method to determine the risk of mortality in AP during hospitalization [8]. It is calculated using five measures readily available in the first 24 h: blood urea nitrogen (BUN) over 25 mg/dl, altered mental status (Glasgow Coma Scale <15), the presence of systemic inflammatory response syndrome (SIRS), age greater than 60 years and the presence of pleural effusion on imaging.

The BISAP was shown to predict mortality retrospectively with 18,256 cases in 177 centers in 2004–2005 [8], and validated prospectively in 397 cases in 2005–2006 [9]. Each positive value adds one point and scores of 3–5 predict mortality of 5.3, 12.7 and 22.5%, respectively, and also persistent organ failure later than 48 h [9] (see Table 2).

The Harmless acute pancreatitis score is an additional scoring system to identify cases of mild pancreatitis that is simple to use [10]. Patients with the absence of several worrisome features were found to have a nonsevere disease course with 97% specificity and 98% positive predictive value [10,11]. It utilizes

three factors that can be determined within 30 min of admission: rebound tenderness, hematocrit level (abnormal, >43% for men or >39.6% for women) and serum creatinine level (abnormal, ≥2 mg/dl). However, caution must be advised that patients with normal harmless acute pancreatitis score may still be in the early phase of pancreatitis and will progress. It is unclear from the validating study whether patients with this presentation were treated appropriately in an early phase which prevented serious complications [6].

The BISAP has been found to have a similar predictive utility when compared to the APACHE II and the Ranson's criteria for predicting pancreatic necrosis, severity and mortality [12]. However, these tests have benefits over the older prediction tools of ease of use and timeliness [6]. The Ranson's criteria cannot be calculated until 48 h after admission, and by then the golden window of treatment would have been already closed. The importance of treatment in the first 24 h will be discussed below.

The APACHE II, while well validated for many critical conditions, cannot be calculated as quickly and easily as the BISAP score. It requires an arterial blood gas measurement, which is rarely done in the emergency department, and knowledge of past medical history which can be unobtainable in a mentally impaired patient.

The CT severity index is another test utilized for the prognostication of AP [5]; however, CT imaging as mentioned before is frequently not necessary for the diagnosis [13]. Moreover, a CT scan can cause renal damage in the setting of SIRS-induced hypovolemia. Ultimately, all these prediction tools have similar efficacy, but BISAP is the easiest and quickest validated test.

Beyond simply punching values into a predefined algorithm, it is important to understand the ramifications of laboratory data utilized for prediction. Since the defining criteria between severe and moderately severe pancreatitis is persistent organ failure, these tests generally aim to predict its presence [1]. Inflammatory cascades cause fluid extravasation, which in turn leads to distributive hypovolemia and hypoperfusion. Prediction of morbidity uses data from anywhere along this pathway, that is, elevations in BUN and hematocrit indicate hypovolemia; leukocytosis and fluid sequestration are indicators of the inflammatory cascade; creatinine, elevated liver tests and hypoxia are indicators of organ damage; and low calcium is reflective of fat necrosis saponification (end-organ damage) and also an indicator of hypovolemia. Essentially, the prediction of AP severity depends on identifying indications of end-organ damage in a timely manner and can be done through a combination of variables including age, known comorbidities, physical examination, bedside algorithm and knowledge of pathophysiology.

Identification of a cause

During the initial admission for AP, it is imperative that a cause for the disease be aggressively pursued. This is because the recurrence rate of AP is up to 50% if the underlying mechanism of disease is not found [7]. Patients should be queried extensively about alcohol use, family history of pancreatitis (to suggest a hereditary cause of the disease) and any previous abdominal trauma – even if they have not previously been aware of a pancreatic injury. At minimum, patients should have a right upper quadrant ultrasound and serum calcium and triglyceride levels determined during the initial admission. Should any abnormality be found that could potentially be the cause – biliary disease, hypertriglyceridemia, etc. – these should be treated prior to discharge.

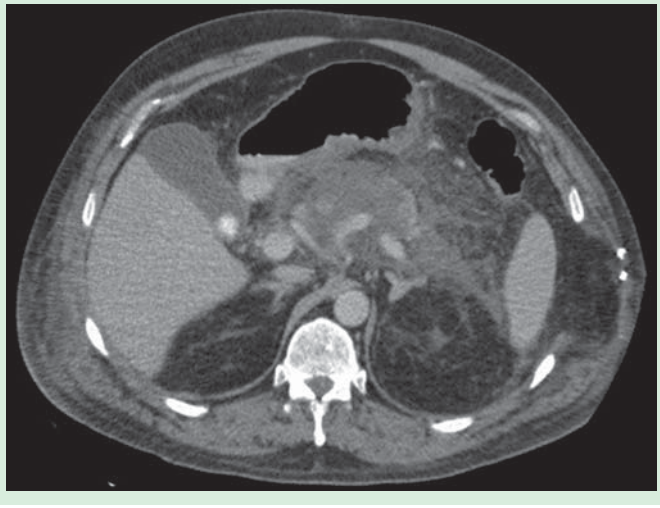

Figure 2. CT scan performed 6 days after admission demonstrating complete necrosis of the pancreas neck and body.

Fluid resuscitation

Just as the prediction of morbidity in early pancreatitis is focused on determining organ damage from hypoperfusion, one key to early management is aggressive hydration and resuscitation [6]. Inadequate fluid resuscitation has been associated

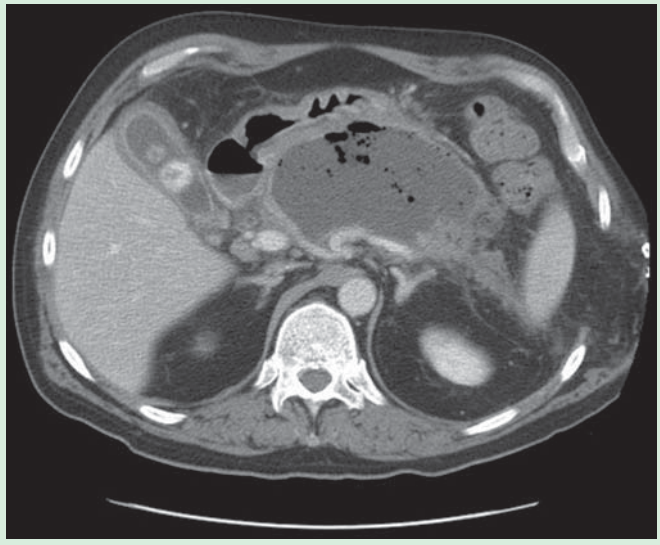

Figure 3. CT scan performed 6 weeks after admission demonstrating walled-off pancreatic necrosis with air bubbles indicating infection.

Table 1. Classification of acute pancreatitis according to the Atlantic Criteria of 2013.

Severity	Criteria
Mild pancreatitis	No organ failure No local or systemic complications Resolves in the first week
Moderately severe pancreatitis	Transient organ failure and/or Local complications and/or Worsening of comorbid conditions
Severe pancreatitis	Persistent end-organ failure >48 hours

with increased morbidity from SIRS, pancreatic necrosis and organ failure as well as higher mortality [14,15]. Hydration is needed to prevent ischemia of the pancreas to avoid bacterial translocation [7].

We recommend hydration with a bolus of 1–2 l of crystalloid while still in the emergency department and maintenance rates between 250 and 300 ml/h or enough to produce 0.5 ml/kg/h urine output [16]. Of course, caution must be exercised with any patient with renal failure, heart failure or pulmonary edema. Monitoring for signs of fluid overload, particularly hypoxia, is necessary. Central venous pressure measurements may be helpful in these patients where delicate fluid balance is needed. These values should be tailored to the patient's clinical response.

Hematocrit and BUN, checked every 8 h in the first 24 h of admission, can be followed as measures of hemodilution in addition to urine output [17]. In the first 24 h after presentation to the hospital, we have found that BUN is the best simple universally available target for resuscitation volume. If the BUN continues to rise despite fluid resuscitation, more fluid should be given. Conversely, if the BUN is falling during the first 24 h, less volume can be given. While there is significant debate regarding the choice of crystalloid, recent data in a randomized control trial suggest that lactated Ringer's solution may have advantages over normal saline in preventing SIRS [18].

While two recent studies suggest that aggressive fluid hydration may be harmful, they are both limited in design, and it is difficult to draw conclusions from them. One article, a retrospective study, found that patients receiving 4 l or more fluid in the first 24 h were more likely to require intensive care unit transfer and also had more pulmonary complications [19]; however, the specific reasons for intensive care unit admission and pulmonary complications were not detailed. Another study from China found increased rates of mortality and sepsis in patients where hematocrit was targeted to be under 35% in the first 24 h compared with 35% or greater over 72 h [20].

Instead of targeting a target for hemodilution, fluids should be tailored to the heart rate, blood pressure and urine output as a measure of fluid hydration. The purpose of fluid resuscitation is to provide intravascular volume, not dilute the blood.

Table 2. Bedside index for severity of acute pancreatitis.

Criteria	
Blood urea nitrogen	>25 mg/dl
Altered mental status	GCS <15
Presence of systemic inflammatory response syndrome	Two or more of HR >90 RR >20 or $PaCO_2$<32 mm Hg Temperature >38°C or <36°C WBC >12,000 mm^3, WBC <4 mm^3 or 10% bands
Age	>60 years
Pleural effusion	Present on imaging

Prophylactic antibiotics

Antibiotic usage as prophylaxis for necrotizing pancreatitis has been the subject of substantial debate, and has recently been shown to be ineffective through several meta-analyses. In 2001, a meta-analysis comparing antibiotic prophylaxis to no prophylaxis in patients with necrotizing pancreatitis showed no difference with local pancreatic infections, but reduced rates of sepsis and mortality by 21.1 and 12.3%, respectively [21]. However, this meta-analysis only included three trials and an updated meta-analysis was done in 2008 [22]. This paper included seven studies and 476 patients, and did not find any improvements in either mortality or local pancreatic infections.

A Cochrane review published in 2010 with the same seven studies did not find any improvement, although imipenem was shown to decrease pancreatic infections [23]. Most recently, a meta-analysis in 2011 reviewed 14 trials, including the previous trials, with 841 patients, and also found no difference in mortality or infection [24]. As data accrues, antibiotics are appearing less and less helpful and are not recommended for pancreatitis unless there is concomitant cholangitis, pneumonia, line infection, bacteremia or other documented infections.

Additionally, the use of antibiotics has been demonstrated to increase the risk of developing fungal infections. Fungal infections (most commonly caused by *Candida albicans*) have a reported incidence of 5–68% in severe AP [25]. However, a randomized control study administering antibiotics in 103 patients targeting gram-negative bacteria and amphotericin was shown to decrease mortality as well as gram-negative pancreatic infections [26]. However, these data have not been replicated by numerous meta-analyses published after this 1995 article. Probiotics should not be given either in AP and have been proven ineffective in a 2009 meta-analysis [27] and even increased mortality in a randomized control trial [28].

Enteral feeding

Enteral feeding whenever possible is critical for the successful management of AP. In patients with mild AP, oral feeding generally begins within a week of admission and can be initiated with a low-fat diet [29]. In patients with severe pancreatitis, multiple studies have demonstrated improvement in morbidity and mortality with enteral feeding [30]. Therefore, it is

recommended that patients with severe or predicted severe pancreatitis begin enteral feeding via tube feeding within 72 h of hospitalization. While historically nasojejunal tube feeding has been preferred, recent evidence suggests that nasogastric feeding may be just as effective. In addition, the type of tube feeding is no longer considered critical – that is, elemental formulas have not demonstrated efficacy over nonelemental formulas [13].

Parenteral feeding should be initiated only if patients are not able to meet nutritional support goals with tube feeds after 1 week of hospitalization. However, it is critical that enteral feeding be continued, even if not providing full nutritional support, as this intervention can help mitigate against bacterial translocation into the gut.

Surgical management

Biliary pancreatitis

Endoscopic retrograde cholangiopancreatography (ERCP) is thought to be important in the early management of acute biliary pancreatitis. However, a randomized controlled study performed in 2007 including 102 patients found no difference in the rate of organ failure, local complications, overall morbidity or mortality [31]. A prospective study comparing ERCP with conservative management found fewer complications in the ERCP group with cholestasis after ERCP although there was no difference in mortality after ERCP [32]. A Cochrane review published in 2004 reviewing data from three studies with 511 patients found significantly lower complications in patients with severe pancreatitis, but no difference in patients with mild disease who underwent ERCP. There were no mortality improvements found in patients with either severe or mild pancreatitis. This study included patients with cholangitis, and an effort was made to control this as a possible confounder [33]. Another meta-analysis of five studies found no difference in local complications with ERCP [34].

Based on inconsistencies in data and lack of strong consensus, we do not advocate ERCP be routinely performed in all patients with biliary pancreatitis on the first day. There are, however, instances where ERCP is indicated within 24 h of presentation: AP in the setting of cholangitis or deterioration of clinical course with increasing liver enzymes. Because ERCP is a risk factor for AP independently of biliary disease, patients should be chosen carefully. Stable patients with choledocholithiasis without worrisome signs should receive ERCP after resolution of AP.

Early surgical consultation for patients with biliary pancreatitis is essential, and laparoscopic cholecystectomy (CCY) should be performed before patient discharge to prevent future bouts of biliary pancreatitis. In fact, 20–50% of patients are estimated to have recurrence of AP within 6–8 weeks if they do not undergo CCY [35]. In patients who are poor surgical candidates, endoscopic sphincterotomy has been shown to be an acceptable alternative to CCY [36]. While surgery has traditionally been done after laboratory tests normalize, a randomized controlled trial of 50 patients with mild pancreatitis (Ranson's score ≤3) demonstrated that CCY within the first 48 h of hospital stay resulted in shorter hospital stays (3.5 vs 5.8 days) without technical difficulty or postoperative complications [37].

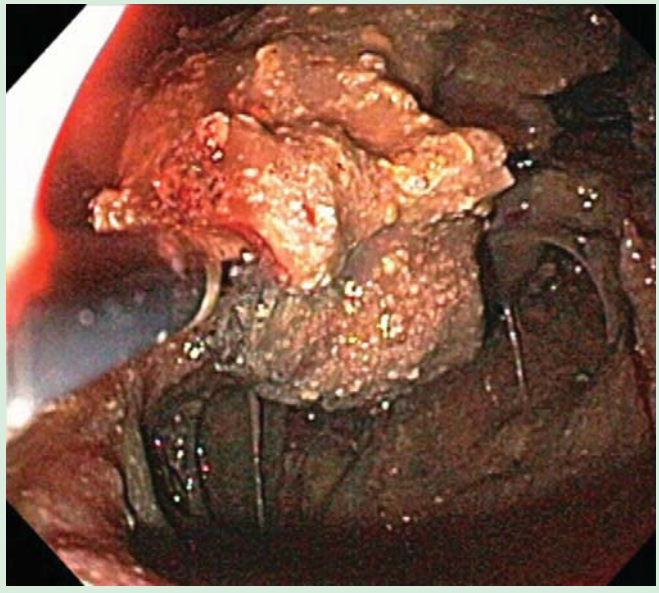

Figure 4. Active debridement of necrotic debris using rat-toothed forceps.

Previously, it was common practice to perform CCY in the cases of idiopathic acute pancreatitis with the hypothesis that microlithiasis may play a role; however, a population-based study found a >50% recurrence of AP if no stones or sludge were found on the right upper quadrant) ultrasound [38]. We therefore do not recommend CCY for idiopathic acute pancreatitis.

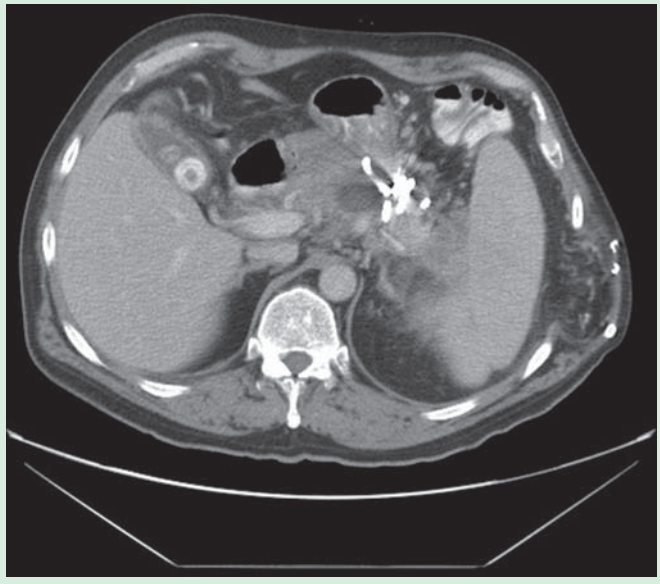

Figure 5. Near resolution of the walled-off necrosis following endoscopic creation of cystgastrotomy and stent placement.

Pancreatic necrosis

Debridement of pancreatic necrosis has been the mainstay of treatment for many years [39]. However, debridement of sterile necrosis without associated complications such as mass-like compression of the stomach or duodenum causing gastric outlet obstruction has been shown to actually increase mortality, and it is no longer the standard of care.

Infected pancreatic necrosis is a serious complication of AP and carries a high morbidity and mortality. Prophylactic antibiotics have been shown to be ineffective as discussed above and this condition must be treated with debridement and/or antibiotics. Open debridement has been the traditional therapy and mortality has been incorrectly assumed to be 100% unless surgery was done urgently [13]. However, meta-analyses of 11 studies and 1136 patients demonstrated decreased mortality after treating medically for 30 days with antibiotics prior to surgery over urgent intervention [40]. Clearly, a more tempered approach to surgery is preferred.

Moreover, surgery is only necessary in a subset of patients with infected pancreatic necrosis. In fact, a recent study demonstrated that 47 of 80 patients with infected pancreatic necrosis were treated with antibiotics and avoided surgery, and mortality was lower in the group treated medically (54 vs 23%) [41]. The authors of the same study later published a meta-analysis of 8 studies, which supported medical treatment of infectious pancreatic necrosis. They found that 64% of patients with infected necrosis could be treated medically with 12% mortality and only 26% underwent surgery [42].

Asymptomatic pancreatic necrosis is no cause for surgery regardless of extent and will likely resolve on its own. Close monitoring and observation is critical in these patients and necrosectomy or drainage should be performed only if any worrisome clinical signs or symptoms occur.

Minimally invasive approaches to necrosectomy are replacing open surgery in most cases. Various techniques have been developed including percutaneous drainage, laparoscopic surgery, video-assisted or small incision-based left retroperitoneal debridement and direct endoscopic necrosectomy. Percutaneous drainage is the most commonly used approach and can prevent necrosectomy in approximately 50% of cases. Endoscopy has also been shown to be equally effective in multiple studies [13], and it has been combined with percutaneous drainage with both procedures being done at the same time (see Figures 4 & 5).

While the comparison of various surgical approaches to pancreatic debridement is beyond the scope of this article, several issues should be considered when referring for surgical opinion. The timing of any drainage procedure is important regardless of whether laparoscopic surgery, percutaneous radiologic drainage or endoscopy is utilized. After approximately 4 weeks a fibrinous wall develops around the necrosis and facilitates its removal as a contained mass. Additionally, a less invasive test is always preferable when possible. A multidisciplinary consensus in 2012 advocated a step-up approach starting with percutaneous drainage followed by minimally invasive video-assisted retroperitoneal debridement and endoscopic debridement [43]. Additionally, a recently published randomized control trial demonstrates the efficacy of endoscopic debridement over surgical debridement for infected necrosis [44].

Expert commentary & five-year view

While AP causes extensive worldwide morbidity and mortality, with few exceptions treatment remains largely supportive. As the defining characteristic of severe pancreatitis is end-organ damage from SIRS-induced hypovolemia, early fluid resuscitation in the first 24 h has been shown to be a critical intervention to reduce morbidity and mortality. In the next five years, new data to determine the best rates of resuscitation, the optimal fluid type and resuscitation complications will be further defined. Additionally, there is a trend toward using a more conservative approach for infected pancreatic necrosis. Minimally invasive approaches are becoming increasingly available. Studies to identify which patients will respond to minimally invasive approaches, as well as comparative effectiveness trials between techniques, should become available. The most important development in the next five years will undoubtedly be the discovery of a novel pharmacological therapy which specifically targets the inflammatory response in AP. Multiple clinical studies are currently underway to determine if such a treatment can be effectively developed.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- Generous IV fluid administration in the first 24 h is the most crucial intervention to prevent morbidity and mortality.
- Aggressive work-up to determine the cause of pancreatitis is indicated to prevent further attacks.
- Prophylactic antibiotics have not been shown to prevent morbidity or mortality, even in severe necrotizing pancreatitis.
- Prediction of severity using the bedside index for severity of acute pancreatitis is the preferred technique because of its comparative effectiveness and superior ease of use.
- Antibiotics should be given with any documentation of infection and then tailored to cultures based on computed tomography-drainage.
- In biliary pancreatitis, cholecystectomy should be performed prior to discharge.
- Minimally invasive surgical approaches, such as direct endoscopic necrosectomy, are preferred to treat walled-off necrosis.

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