Severe Acute Pancreatitis: Medical Management

IntroductIon

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While the incidence of acute pancreatitis appears to be rising, the mortality rate appears to be decreasing. The decreased mortality is likely related to advancements in the early and late management of the disease. Aggressive early hydration, early identification and treatment of biliary sepsis and the early recognition of complicated disease requiring admission to a monitored setting have contributed to the decrease in morbidity and mortality observed over the past decade. Yet, despite the decrease in morbidity and mortality observed, many persons continue to suffer and die from complications of acute pancreatitis largely due to errors in early management of patients with acute pancreatitis. The purpose of this review is to update clinicians on the important decisions and interventions needed in the management of patients with acute pancreatitis.

INTRODUCTION

T
reatment of acute pancreatitis is the third most common disease of the gastrointestinal tract for which patients are admitted to hospitals (1, 2). Clinicians often have difficulty managing patients with acute pancreatitis as the disease is complicated by an obscure pathogenesis, few effective remedies, and an often unpredictable outcome. Many patients initially identified as having mild disease progress to severe disease indolently over the initial 48 hours. Early recognition of severe disease and applying appropriate therapy requires vigilance as decisions regarding management will need to be made shortly after admission, often within the first 24-72 hours. During the first week, severity of acute pancreatitis is related to the presence of organ failure. While most patients recover and are discharged in less than a week, some patients will have a complicated course. Although only 15%-20% of patients enter this second phase, which is characterized by anatomic complications of the disease, it is crucial for clinicians to be aware of the definitions of these complications and their natural history and management.
Establishing the Diagnosis

The diagnosis of acute pancreatitis is established by two of the following three features: (A) appropriate clinical symptoms, such as epigastric pain, nausea, and vomiting, (B) an elevation of the amylase and/or lipase greater than 3 times the upper limit of normal, and/or (C) imaging confirmation of the diagnosis, computed tomography (CT) or magnetic resonance imaging (MRI) (3). If neither the serum amylase or lipase are conclusive nor the clinical setting is unclear, a non-contrast CT is a reliable simple test to establish the diagnosis. The absence of intravenous contrast during the CT exam only limits the ability to distinguish the absence or presence of necrosis, thus limiting the ability to determine severity (4). CT should be performed when the diagnosis is unclear, in the setting of atypical symptoms and/or amylase/lipase less than three times the upper limit of normal.

The Problem of Identifying Patients with Severe Disease and Predicting a Development of Severe Disease

The management of patients with acute pancreatitis is complicated by the inability to distinguish patients with mild disease from patients with severe disease during the early stages (3,4,5). Most patients who have a complicated course and eventually die from acute pancreatitis initially present with what appears to be mild disease, characterized by the absence of organ failure and/or pancreatic necrosis. CT on admission can show enhancement of the pancreas consistent with interstitial pancreatitis (Figure 1) and then after 48 hours, demonstrate complete necrosis of the gland with no perfusion of the pancreas (Figure 2). It is imperative that clinicians do not label a patient with mild disease within the first 48 hours of admission. This is a common problem leading to substantial morbidity and mortality as patients are often left unmonitored after falsely labeled as having mild disease.

Historically, prospective scoring systems using clinical criteria have been developed to determine severity in patients with acute pancreatitis. These systems include: Ranson criteria (6), Imrie/Glasgow criteria (7), and APACHE score (8). Unfortunately, these systems are cumbersome, requiring multiple measurements. More importantly, the systems are not accurate until 48 hours after presentation. Severity is better defined by the Atlanta Symposium (9). The Atlanta Symposium utilizes the outcome of disease as the determining factor for severity, pancreatic necrosis and/or organ failure, such as cardiovascular, pulmonary, renal insufficiency and/or gastrointestinal bleeding. The Atlanta symposium does not attempt to predict severity but rather defines severity as the presence of the factors known to be associated with mortality.

The Atlanta symposium has its limitations. Over the last decade, it has become clear that organ failure is a more important determinant of severity than pancreatic necrosis (3). In the setting of multisystem organ failure,
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the mortality rate of patients with acute pancreatitis is almost 50%. Conversely, regardless of the presence of necrosis, in the absence of organ failure, mortality is 0% (10, 11, 12). Many patients with pancreatic necrosis do well and do not develop significant organ failure (13, 14). There is no clear relationship between the presence of organ failure and pancreatic necrosis. Additionally, the extent of pancreatic necrosis and infection of the necrosis do not appear to correlate with risk of developing organ failure. Some investigators have proposed that patients with pancreatic necrosis in the absence of organ failure who merely have a prolonged hospital course be labeled as “moderately severe acute pancreatitis” (15). There also is a difference between patients who develop transient organ failure and those with persistent organ failure. Currently, the Atlanta symposium is being revised to reflect these changes in our understanding.

It is very important to differentiate the concept of “predicting” severe disease from “establishing” the presence of severe disease. Severe disease is not difficult to establish, it is best defined as the presence of organ failure, pancreatic necrosis and/or death. The more difficult question is whether clinicians can accurately “predict” if a patient with mild disease at admission will progress to severe disease. The answer is: No! To date, there have been no studies establishing the superiority of one scoring system, imaging or laboratory parameter in having the ability to predict the future development of severe disease (organ failure, pancreatic necrosis and/or death) in patients with acute pancreatitis early in the course of the disease. In general, clinicians should focus on a combination of patient characteristics that increase the likelihood of developing severe disease. These characteristics include physical findings, laboratory parameters, scoring systems and imaging (3).

A variety of studies have shown that patients at risk of developing severe disease are of older age (> 55 years), obese (BMI > 30), often present with their first attack of acute pancreatitis, and have many comorbid conditions (4,5). Many are found to have pleural effusion and/or infiltrates on initial chest radiography. The presence of the systemic inflammatory response syndrome (SIRS) also has been shown to denote a risk for severe disease (16). SIRS is be defined by presence of 2 or more of the following criteria: (A) pulse >90 beats/min, (B) rectal temperature <36°C or >38°C, (C) white blood count <4000 or >12,000 per mm³, and/or (D) respirations >20/min or PCO₂ <32 mm Hg.

Many single laboratory tests have been studied as markers of severity with little success (16). The height of elevation of the serum amylase and lipase do not correlate with severity. It has been shown that hematocrit (HCT) (17), blood urea nitrogen (BUN) (18) and creatinine (19) may serve as early predictors of severity in patients with acute pancreatitis. Unlike other markers of severity studied, such as C-reactive protein, the HCT, BUN, and creatinine are not surrogate markers of inflammation but reflect complications in pancreatic perfusion (discussed below). A hematocrit greater than 44 on admission or fails to decrease over the first 24 hours is associated with pancreatic necrosis (17). Similarly, an elevated or a rise in the BUN within the first 24 hours after admission is associated with increased mortality in patients with acute pancreatitis (18). Similar to BUN and HCT, an elevated creatinine, as a marker of decreased intravascular volume, decreased renal perfusion has been shown to be associated with severe disease (pancreatic necrosis) (19).

Imaging on occasion may be effective in identifying patients with severe disease early in the course of acute pancreatitis. Contrast enhanced CT and MRI have been shown to be sensitive for the identification of pancreatic necrosis (20). The use of early imaging in the determination of severity is limited by several important factors: (A) only a quarter of patients with acute pancreatitis develop necrosis; (B) pancreatic necrosis may not develop until after 24-48 hours; and (C) the presence of pancreatic necrosis and the amount of pancreatic necrosis does not correlate with the development of organ failure (3, 14, 15).

Patients with one or more of these characteristics may require treatment in a highly supervised area, such as a step-down unit or an intensive care unit (ICU) (3, 5, 21). At present, regardless of risk factors, predictors, score on the variety of systems, all patients should be monitored closely for the development of organ failure. If organ failure develops, such as renal, cardiovascular or pulmonary insufficiency, aggressive treatment in an ICU has been shown to be associated with a survival benefit if the organ failure is reversed (22). Increased morbidity and mortality is associated with persistent organ failure, lasting beyond the first 48 hours. Transient organ failure is of less importance in predicting morbidity and mortality.

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Preventing Severe Disease: Vigorous Intravenous Hydration

The most important advancement in the management of patients with acute pancreatitis has been the recognition of the importance of early aggressive hydration. Over a decade ago, it was shown that an elevated hematocrit is associated with increased morbidity, pancreatic necrosis (17). It is now understood that the relationship of hematocrit to severity is related to hemoconcentration (3,5). As the inflammatory process progresses early in the course of the disease, there is an extravasation of protein-rich intravascular fluid into the peritoneal cavity resulting in hemoconcentration. The intravascular hypovolemia that accompanies acute pancreatitis subsequently leads to a decrease in pancreatic blood flow. Pancreatic ischemia leads to the activation of inflammatory mediators. The decreased blood flow also causes stasis and thrombi leading to subsequent necrosis which then exacerbates the inflammatory process (23). The decreased perfusion pressure into the pancreas leads to microcirculatory changes leading to widespread pancreatic necrosis in some patients (24). A vicious cycle develops where pancreatic inflammation leads to more extravasation of protein rich intravascular fluid into the peritoneum causing more necrosis. Currently, the only way to halt this cycle is to provide vigorous intravenous hydration leading to intravascular volume repletion, hemodilution, increased pancreatic perfusion and decreased pancreatic necrosis (24). Unfortunately, despite multiple guidelines explaining the importance of early aggressive intravenous hydration, patients with acute pancreatitis are too often given suboptimal intravenous hydration (3,4,25,26).

How much fluid is needed early in the treatment of acute pancreatitis? Many experts have proposed amounts much higher than that typically given (Table 1). One must recognize that acute pancreatitis is a hypercatabolic disease leading to increased respiratory losses in addition to the intravascular losses. If one considers that liters of fluid typically enter the peritoneum from the intravascular space, the amount of intravenous fluid needed is appreciated better. One of the markers of severity previously defined by Ranson and colleagues is related to intravascular losses. Ranson and colleagues found that a sequestration of over 6 liters of fluids during the first 48 hours was an independent predictor of severity (6). If this amount is added to the minimal intravenous fluid requirements of a 70 kg person during the first 48 hours (FDA: www.fda.gov/cder/cancer/caloricframe.htm), intravenous hydration should be at least 250-500 cc per hour depending on BMI. The rate of hydration appears to be most important during the first 6-12 hours (5,24). Unfortunately, this may be when the patient with acute pancreatitis is most at risk.

<table>
<thead>
<tr>
<th>Author</th>
<th>Initial resuscitation recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandol (66)</td>
<td>Severe volume depletion: 500–1000 cc/h Nonpancreatic fluid loss: 300–500 cc/h</td>
</tr>
<tr>
<td></td>
<td>No volume depletion: 250–350 cc/h</td>
</tr>
<tr>
<td>Whitcomb (67)</td>
<td>Fluid bolus to achieve hemodynamic stability followed by 250–500 mL/h of crystalloid</td>
</tr>
<tr>
<td>Banks and Freeman (3)</td>
<td>Aggressive IV fluid replacement</td>
</tr>
<tr>
<td>Forsmark and Baillie (4)</td>
<td>Aggressive IV fluid replacement</td>
</tr>
<tr>
<td>Vege (68)</td>
<td>Aggressive fluid resuscitation</td>
</tr>
<tr>
<td>Tenner (5)</td>
<td>At least 250–300 cc/h for 48 hours</td>
</tr>
</tbody>
</table>
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The Role of Urgent ERCP in Gallstone Pancreatitis

The pathogenesis of gallstone pancreatitis defines on the presence of a common bile duct (CBD) stone. The vast majority of these stones pass easily and quickly from the CBD to the duodenum to be excreted in the stool (28). In some patients, gallstones can persist in the CBD and may lead to severe acute pancreatitis complicated by biliary sepsis. Defining the presence of a persistent CBD stone as the cause of severe, complicated acute pancreatitis can be problematic. Although considered the gold standard for cholelithiasis, abdominal ultrasonography in the setting of acute pancreatitis is not sensitive for the detection of choledocholithiasis, CBD stones. Gallstones may be present in the CBD and missed due to air in the duodenum. Even in the absence of biliary ductal dilatation on abdominal ultrasound, CBD stones can exist in a patient with gallstone pancreatitis complicated by biliary sepsis (29).

Laboratory testing may assist in the early identification of CBD stones. Although elevated transaminases have a poor sensitivity for determining gallstone pancreatitis, a high specificity can be reached with laboratory testing. A greater than 3-fold elevation of AST or ALT in the presence of acute pancreatitis has a positive predictive value of 95% in diagnosing gallstones as the etiology of pancreatitis (30). On multivariate analysis, serum total bilirubin on hospital day 2 was the best predictor of a persistent CBD stone. A serum total bilirubin level >1.35 mg/dl has a sensitivity of over 90%. Unfortunately the specificity for CBD stones is only 63% (31). Other investigators

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Time of ERCP*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoptolemos (33)</td>
<td>121</td>
<td>72 hours</td>
<td>Decreased Morbidity in Patients with Severe Disease</td>
</tr>
<tr>
<td>Fan (34)</td>
<td>195</td>
<td>24 hours</td>
<td>Decrease Mortality in Patients with Biliary Sepsis</td>
</tr>
<tr>
<td>Folsch (35)</td>
<td>121</td>
<td>72 hours</td>
<td>No Effect on Outcome</td>
</tr>
</tbody>
</table>

Excluded Bilirubin > 5 mg/dl

*ERCP was performed within a time frame prior to the hours cited.
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have found that a rising bilirubin or rising transaminases within 24-48 hours of admission in patients with acute pancreatitis predicted a persistent CBD stone (29).

Regardless of findings on laboratory testing and ultrasonography, ERCP remains the gold standard in identifying whether gallstones are retained in the CBD. ERCP is safe in a patient with biliary sepsis, especially if the CBD is dilated. However, in the patient with a normal CBD diameter and relatively normal liver function tests, the risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis is higher. In these patients, if needed, endoscopic ultrasound (EUS) (32) and MRI (20) provide excellent visualization of the CBD and can be used to determine the presence of CBD stones with less risk.

Three published studies addressing the issue of urgent ERCP in the management of patients with acute pancreatitis build upon each other and provide clarity (Table 2). The first randomized study by Neoptolemos and colleagues (33) found that early ERCP (within 72 hours) decreased morbidity in patients with severe acute pancreatitis (defined by Ranson’s Criteria). No benefit was found for early ERCP in patients with mild acute pancreatitis. Shortly after this study, Fan and colleagues (34) showed that early ERCP in patients with acute pancreatitis (within 24 hours) decreased the incidence of biliary sepsis in patients with severe acute pancreatitis significantly (12% vs 0%). There was a survival benefit in patients with acute pancreatitis who underwent early ERCP if biliary sepsis was present. However, there were no differences between the two groups regarding local or systemic complications of acute pancreatitis. Interestingly, the incidence of complications was lower in Fan’s series compared to that of Neoptolemos. This suggests that the earlier the intervention, within 24 hours, may be more beneficial than waiting 72 hours.

The role of ERCP in patients with severe acute pancreatitis was further clarified in a final study by Folsch and colleagues (35). In this study, patients with obvious biliary obstruction, bilirubin greater than 5 mg/dl, were excluded. It was assumed that they had biliary sepsis and these patients, due to the two prior studies, should go directly to ERCP. Unlike the earlier studies, by excluding jaundiced patients, this study focused on the role of early ERCP in patients with severe acute pancreatitis in the absence of cholangitis. This study showed that early ERCP was no more effective than medical treatment in patients with severe acute pancreatitis. Thus, early ERCP, within 24-72 hours, is effective in patients with severe acute pancreatitis when there is evidence of biliary obstruction, cholangitis, and an elevated bilirubin. There is no evidence that urgent ERCP alters the course of patients with severe acute pancreatitis in the absence of biliary obstruction (Table 1).

Pseudocysts

During the early course of acute pancreatitis, liters of fluid typically leave the intravascular compartment forming fluid collections in the abdomen. Most of this fluid is eventually reabsorbed. In almost a third of patients, the fluid will persist and eventually develop a fibrous wall (3). Early in the course of acute pancreatitis, within the first 2-3 weeks, calling a fluid collection a pseudocyst is inappropriate. In a patient, with no past medical history of chronic pancreatitis, who presents with acute pancreatitis and is found on admission to have a cystic lesion that appears to be a pseudocyst, the lesion may very likely be a cystic neoplasm rather than a pseudocyst.

Anatomically, another important differentiation affecting the clinical care of patients with acute pancreatitis is that of a pseudocyst versus walled off pancreatic necrosis. A walled off fluid collection appears similar to walled off pancreatic necrosis on CT. Although cystic fluid in the pancreas has an attenuation lower than that of normal pancreatic tissue, pancreatic necrosis appears similar. Pancreatic necrosis, especially walled-off pancreatic necrosis (WOPN) cannot be differentiated from a pseudocyst by CT. This is important as the treatment of a symptomatic or infected pseudocyst (abscess) and pancreatic necrosis are quite different. The differentiation between pancreatic necrosis and pseudocysts can only be made by the location of the cyst in relation to the pancreas. Whereas pseudocysts are located outside the parenchyma of the pancreas or adjacent, pancreatic necrosis will always involve the pancreas. MRI and EUS can determine the presence of tissue in WOPN but these imaging modalities are typically not used.

In the past, the dogma was that pseudocysts greater than 6 cm or those that are enlarging on serial imaging or become symptomatic warrant drainage. Studies showed that asymptomatic pseudocysts that develop after an attack of acute pancreatitis, regardless of size, can be managed conservatively, with no intervention (continued on page 40)
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(3,4, 25, 26). Pseudocysts can become infected, and when this occurs, they are best described as an abscess (abscesses require drainage). Pseudocysts can become painful, cause early satiety and weight loss when their size affects the stomach and bowel. When confronted with a patient who has a symptomatic pseudocyst, regardless of infection, drainage is recommended. Drainage can be performed via endoscopic radiologic or surgical techniques depending on the location of the cyst and the expertise available. No randomized prospective trials have compared these methods. The myriad of size, locations, anatomy, and local expertise make prospective randomized trials difficult.

Pancreatic Necrosis

Most patients with acute pancreatitis have interstitial

Table 3. Summary of Randomized Trials Evaluating Antibiotics in the Prevention of Infection in Patients with Necrotizing Pancreatitis.

No significant benefit to using prophylactic antibiotics to prevent infection of pancreatic necrosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>Risk Ratio (Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infection</td>
<td>Total</td>
<td>Infection</td>
</tr>
<tr>
<td>Pederzoli (43)</td>
<td>5</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>Sainio (44)</td>
<td>9</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>Schwarz (45)</td>
<td>8</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Nordback (46)</td>
<td>8</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Isenmann (47)</td>
<td>7</td>
<td>41</td>
<td>5</td>
</tr>
<tr>
<td>Dellinger (48)</td>
<td>9</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Rokke (70)</td>
<td>2</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Garcia-Barrasa (71)</td>
<td>8</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Xue (72)</td>
<td>8</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>263</td>
<td>68</td>
</tr>
</tbody>
</table>
pancreatitis, characterized by normal pancreatic perfusion but edema of the pancreas, peripancreatic stranding and fluid collections. Gross destruction of the pancreatic gland, pancreatic necrosis, is seen in 20% of patients with acute pancreatitis (3,4). In the absence of autopsy or laparotomy, pancreatic necrosis is defined as greater than 30% of non-enhancement on contrast enhanced CT. Pancreatic necrosis is an early complication of acute pancreatitis, usually recognized within 4 days of the onset of symptoms. Although pancreatic necrosis can be identified on a CT obtained at admission, necrosis may develop over the next 48-72 hours (or later).

Pancreatic necrosis typically is considered sterile early in the course, but can become infected later, clinically apparent after 7-14 days. Both infected

Table 4. Trials Comparing Enteral to Parenteral Feeding In Patients with Acute Pancreatitis Evaluating the Risk of Death.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>Risk Ratio (Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death</td>
<td>Total</td>
<td>Death</td>
</tr>
<tr>
<td>Abou-Assi (54)</td>
<td>8</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Kalfarentzos (55)</td>
<td>1</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Olah (56)</td>
<td>2</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>McClave (57)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Petrov (73)</td>
<td>2</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Casas (74)</td>
<td>0</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Gupta (75)</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Louie (76)</td>
<td>0</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>
| Total            | 13    | 165   | 29    | 183   | 0.50 (0.28-0.91)     | p = 0.20
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pancreatic necrosis and sterile pancreatic necrosis can lead to organ failure, cardiopulmonary insufficiency, renal failure and gastrointestinal bleeding (3-5,13,14). Sterile necrosis is treated supportively. Due to the increased risk of complications, infection and organ failure, patients with pancreatic necrosis should be cared for in a monitored setting. The goal should be to prevent infection by minimizing intravenous lines, avoiding parenteral nutrition and providing enteral nutrition. Typically, patients should be kept NPO with enteral nutrition for 3-4 weeks before an attempt is made to orally feed them. At this time, if there is an inability for the patient to tolerate oral feeding, debridement may be necessary (3,4,5,36).

Preventing Infected Necrosis: The Role of Antibiotics

Once sterile pancreatic necrosis exists, prevention of infection is of paramount importance. The presence of infected necrosis necessitates surgical debridement. Surgical intervention, while necessary in patients with infected necrosis, increases the morbidity and mortality rate in patients with acute pancreatitis (36). The surgical management of infected necrosis is an issue that is typically addressed after the first or second week of managing a patient with acute pancreatitis. During the first week, the vast majority of patients with necrosis have sterile necrosis (37). Surgical intervention during this time is avoided.

The origin of the bacteria leading to pancreatic infection is unclear. However, current consensus is that infection of the necrosis occurs by either direct transmural spread or transmigration of bacteria from the colon (38). Other sources include intravenous lines, including those used for parenteral nutrition. In an attempt to decrease pancreatic infection, initial trials in the 1970s with ampicillin showed a lack of efficacy when given prophylactically (39-41). Almost 2 decades later, Beger and colleagues (42) showed that only a few antibiotics penetrate pancreatic necrosis, including imipenem, quinolones, and metronidazole. Subsequently, a prospective, randomized trial comparing imipenem to placebo in the prevention of infected necrosis showed a significant decrease in septic complications (43). This study was followed by several other trials demonstrating decreased morbidity and mortality in patients with necrotizing pancreatitis treated with antibiotics within 72 hours of admission (44,45). Multiple reviews, including a Cochrane review in 2004 (46) concluded that pancreatic penetrating antibiotics were useful in patients with necrotizing pancreatitis. Based on these initial unblinded studies, most clinicians began the widespread use of antibiotics in patients with necrotizing pancreatitis with the belief that infectious necrosis would be avoided.

Two new, large, multicenter, randomized, double blinded trials have changed our opinion regarding the use of antibiotics in sterile necrosis (Table 3). Isenmann and colleagues (47) provided evidence that the routine use of ciprofloxacin and metronidazole will not prevent infectious complications in patients with severe pancreatitis. Although this trial was blinded, there are several limitations to the study. Almost a third of the patients did not have surgical or imaging (CT or MRI) confirmation of the presence of necrosis. Pancreatic necrosis was defined by an elevated of C-reactive protein. Also, the incidence of infection in the control group (9%) was unexpectedly low. Of interest, almost half of the placebo patients eventually were placed on antibiotics on an “open label”. As the enrollment of patients in this study included patients “predicted as having severe disease”, this study demonstrates that the routine use of antibiotics in the absence of pancreatic necrosis is unwarranted.

Dellinger and colleagues (48) performed a multi-center, double-blind, placebo-controlled randomized study set in 32 centers in North America and Europe. One hundred patients were equally randomized to receive either meropenem (1 gram intravenously every 8 hours) or placebo within 5 days of the onset of symptoms. The medication was continued for 7-21 days. This eloquent study demonstrated no statistically significant difference between the treatment groups for pancreatic or peripancreatic infection, mortality, or requirement for surgical intervention. Based on these last two studies, in the absence of biliary sepsis or obvious pancreatic, peripancreatic infection, routine use of antibiotics to prevent infection of pancreatic necrosis is not warranted (3,4) (Table 3).

Enteral vs Parenteral Nutrition in Severe Acute Pancreatitis

The physical stress of acute pancreatitis leads to a catabolic state promoting nutritional deterioration in the setting of a systemic inflammatory response. Adequate supply of nutrients may play an important role early in
the management of patients. The use of total parenteral nutrition (TPN) early in patients with acute pancreatitis has not been shown to be beneficial (49). TPN requires a break in the mucosal barrier for delivery leading to an increased incidence of infection. Several early studies found that enteral nutrition will reduce septic morbidity in conditions such as trauma (50) and thermal injury (51). Early enteral nutrition through a nasojejunal tube maintains the integrity and function of the intestinal barrier while providing adequate nutrition (52).

In patients with severe acute pancreatitis, enteral feeding is safe and as effective as parenteral nutrition (Table 4). Enteral nutrition attenuates the acute inflammatory response and improves disease severity in acute pancreatitis (48). Several randomized, prospective studies comparing nasojejunal vs parenteral nutrition have shown a decrease in morbidity and mortality in patients given enteral nutrition early in the course of disease (49-56). By providing nutrients and altering the bacterial flora, there is a significant decrease in the development of infected pancreatic necrosis (57). There is a consensus among the trials demonstrating decreased infectious complications, length of stay, significant cost savings and decreased mortality (54-57, 73-77, Table 4). In patients with acute pancreatitis, the use of enteral nutrition has been delayed by the old belief that pancreatic rest is required to prevent complications. This reasoning appears untrue. Although the nasojejunal route has been used in several trials, a nasogastric route may also be safe (58). In a comparison of patients with severe acute pancreatitis randomized to nasojejunal vs nasogastric feeding, there was no apparent differences in safety, pain score, narcotic requirements, morbidity and mortality. Although further study is needed regarding the timing of initiating enteral nutrition in patients with severe acute pancreatitis, it is clear that enteral nutrition is preferred to parenteral nutrition.

Infected Necrosis

Approximately a third of patients with necrotizing pancreatitis develop infected necrosis (3). The infection usually becomes clinically apparent after 10-14 days of illness. Most patients with infected necrosis have systemic toxicity, such as fever and leukocytosis. Almost half of the patients with infected necrosis have persistent organ failure (14,15). In a person suspected of having infection of pancreatic necrosis, a CT guided fine needle aspiration of the pancreatic or peripancreatic bed should occur (Figure 3). The gram stain alone of this aspirate (Figure 4), if handled correctly, often (approaching 95% sensitivity) will establish the presence or absence of infection (59). In the absence of infection, sterile necrosis is treated conservatively. Infected necrosis is treated by targeting microbes with the pancreatic penetrating antibiotics, such as carbapenems, quinolones in combination with metronidazole, or high-dose cephalosporins. If a patient cannot undergo CT guided aspiration and infection is strongly suspected, antibiotics should be initiated regardless (not for the purpose of preventing infection, but for the purpose of treating infection strongly suspected). Drainage, whether surgically, endoscopically, or radiologically should be timed based on the patient’s condition (60).
In the past, the diagnosis of infected necrosis led to prompt surgical intervention. This had been the standard of care until recently. In a retrospective review of 53 patients where the median time to surgery was 28 days, when necrosectomy for infected necrosis was delayed, mortality decreased 22% (61). After reviewing 11 studies which included 1136 patients, the authors also found a significant correlation between the timing of surgery and mortality. It appears that postponing necrosectomy in stable patients with antibiotics until 30 days after initial hospital admission is associated with a decreased mortality.

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 (65,66,77,78). In one report of 28 patients given antibiotics for the management of infected pancreatic necrosis, 16 patients avoided surgery (65). 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 group were similar.

Current consensus is that the initial management of infected necrosis for patients who are clinically stable should be a 2- to 4-week course of antibiotics prior to surgery to allow the inflammatory reaction to become better organized (3). At this time, with a well defined wall, liquefied material within, the decision and method of drainage can be considered. For patients with symptomatic WOPN, a combined multimodality approach bringing together both minimally invasive surgery with endoscopic drainage appear to be more effective, safer and results in a shorter hospitalization (78). Although further study is needed, the concept that urgent surgery is required in patients found to have infected necrosis is no longer valid (Figure 5).

**Summary of Management**

The initial management of a patient with acute pancreatitis relies on close monitoring and vigorous hydration. Although monitoring for clinical scoring criteria, such as Ranson and/or APACHE may be helpful, assessing risk factors for severe disease and following patients for the development of organ dysfunction is of utmost importance. Patients who are older than 55 years, obese, presenting or developing an elevated HCT and/or BUN, and/or have pleural effusions/infiltrates on chest radiograph are at a higher risk of complications. Following the HCT and/or BUN as a surrogate marker of intravascular volume will assist in the prognosis and guide the rate of intravenous hydration.

In patients who are deteriorating over the first 24 hours, developing signs of organ dysfunction, and not improving, a CBD stone should be suspected. If the bilirubin is elevated, over 3-5 mg/dl, in a patient with severe acute pancreatitis, manifested as organ dysfunction, cardiopulmonary or renal failure, early ERCP with sphincterotomy and stone extraction should be performed early in the course.

CT and MRI should be reserved for patients who appear persistently ill despite supportive care. In these patients, pancreatic necrosis may be present. Pancreatic necrosis should be considered sterile during the early days following admission. Sterile necrotizing pancreatitis may appear as sepsis in the early phase of acute pancreatitis and may require maximal supportive care. In patients with severe disease, especially pancreatic necrosis, enteral nutrition should be utilized. As most patients with acute pancreatitis have mild
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disease and resume oral feeding within several days, the routine placement of nasojejunal tubes in all patients with acute pancreatitis is inappropriate. Early enteral feeding should be utilized in patients with pancreatic necrosis when identified or suspected.

Recent evidence suggests that prophylactic antibiotics do not prevent sterile necrosis from becoming infected, and thus, it is not an appropriate treatment of severe disease, in the absence of obvious infection. Antibiotics should be reserved for patients found to have an infection and/or biliary sepsis. Fine needle aspiration of suspected infected pancreatic necrosis to guide antibiotic and/or surgical intervention typically becomes of importance after the first week to 10 days. Infected necrosis warrants the use of antibiotics and typically will often lead to surgical debridement. The timing of debridement is controversial and under intense study. Currently, each case should be considered individually. Most patients with sterile necrosis and some patients with infected necrosis will not require surgical debridement. And in many patients, less invasive methods of drainage can be applied if the expertise is available.

References

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77. Sarr M, Seewald S. Do all patients with documented infected necrosis require necrosectomy/drainage. *Clinical Gastroenterology and Hepatology* 2010; December 1000-1001.


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**Academic Gastroenterologist**

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