Acute Pancreatitis: Diagnosis and Management

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Introduction

The management of patients with acute pancreatitis is complicated by an obscure pathogenesis, numerous causes, few effective remedies, and an often unpredictable outcome (1). Despite the importance of recognizing severe disease early in the course, many patients initially identified as having mild disease progress to severe disease indolently over the initial 48 hours. This poses a challenge to the busy clinician who may not be monitoring the patient closely. Over the last decade, clinical studies have led to several new concepts which directly affect the management of patients with acute pancreatitis. 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.

The diagnosis of acute pancreatitis is established by two of the following three features: (1) appropriate clinical symptoms (epigastric pain, nausea, vomiting), (2) an elevation of the amylase and/or lipase greater than 3 times the upper limit of normal, and/or (3) CT imaging confirmation of the diagnosis. The specificity of serum amylase and or lipase less than three times normal is too low to be considered. Any inflammatory condition in the abdomen can result in an amylase or lipase rise of 1-2 fold.

A lipase level is not necessarily required when the amylase is greater than 3 times normal in the appropriate clinical setting. However, certain conditions, such as alcoholic pancreatitis and hypertriglyceridemia may limit the “rise” of serum amylase. In these patients, a serum lipase offers a higher sensitivity to the diagnosis. If neither the serum amylase or lipase are conclusive or 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.

The Identification of Severe Disease

The management of patients with acute pancreatitis is complicated by the inability to distinguish mild from severe disease during the early stages (8). The height of elevation of the serum amylase and lipase do not correlate with severity. Prospective systems using clinical criteria have been developed to determine severity in patients with acute pancreatitis. These systems include: Ranson criteria (9), Imrie/Glasgow criteria (10), and APACHE score (11). Unfortunately, these systems are cumbersome, requiring multiple measurements. Additionally, the systems are not accurate until 48 hours after presentation. Severity is now defined by the Atlanta Symposium, which utilizes the outcome of disease as the determining factor, pancreatic necrosis and/or organ failure, such as cardiovascular, pulmonary, renal insufficiency and/or gastrointestinal bleeding (8). This scoring system does not attempt to prognosticate patients early but determines the severity based on whether the patient, at any time, develops a related complication.

Early intensive care to prevent complications would require the early identification of patients with severe disease or at risk of developing severe disease. Older age (> 55), obesity (BMI > 30), organ failure at admission, and pleural effusion and/or infiltrates are risk factors for severity that should be noted at admission. Patients with these characteristics may require treatment in a highly supervised area, such as a step-down unit or an intensive care unit (11A).

The need for a simple test that identifies patients early in the course cannot be overemphasized. Many single laboratory tests have been studied as markers of severity with little success (12). It has been shown that hematocrit (HCT) and urinary trypsinogen activation peptide (TAP) may serve as early predictors of severity in patients with acute pancreatitis (13,14). Unlike other markers of severity studied, such as C-reactive protein, the hematocrit and TAP are not surrogate markers of inflammation.

Normally trypsinogen is cleaved to trypsin in the intestinal lumen by the enzyme enterokinase. Premature, intra-pancreatic activation during acute pancreatitis results in the release of trypsinogen activation peptide (TAP). The degree of pancreatic necrosis and systemic inflammatory response – sepsis is

directly related to TAP concentration (15,16). Elevated urinary TAP correlates with severe disease. The test can be applied within 12 hours of admission. There is a 100% negative predictive value if the urinary TAP concentration is less than 30 nmol/L. Although the sensitivity and positive predictive value are lower, patients with severe disease would not be inappropriately identified as having mild disease (14). A more aggressive clinical approach can then be applied to these patients. Biotrin (Dublin) will be introducing a urinary dipstick that would quickly identify patients with elevated TAP (personal communication).

Imaging can be effective in identifying patients with severe disease early in the course of acute pancreatitis. Contrast Enhanced Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) have been shown to be sensitive for the identification of pancreatic necrosis (17). The use of early imaging in the determination of severity is limited by several important factors: (1) only a quarter of patients with acute pancreatitis develop necrosis; (2) pancreatic necrosis may not develop until after 24-48 hours; and (3) the presence of pancreatic necrosis and the amount of pancreatic necrosis does not correlate with the development of organ failure (18).

To date, there have been no studies comparing the accuracy of scoring systems, imaging and laboratory parameters. Clinicians must rely on a combination of laboratory parameters, scoring systems and imaging, if necrosis is suspected. Patients must be monitored closely for the development of organ failure. This monitoring does not require an Intensive Care Unit (ICU), unless there are signs or organ failure. However, depending on the institution, an ICU or “stepdown” unit may be necessary to provide the monitoring these patients need during the first 48 hours.

Preventing Severe Disease: Vigorous Intravenous Hydration

The role of hematocrit in determining severity is related to hemoconcentration (13). 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 decreased

perfusion pressure into the pancreas leads to microcirculatory changes that lead to pancreatic necrosis (19). An admission HCT of $\geq$ 47 percent and/or a failure of the admission HCT to decrease at 24 hours have been shown to be predictors of necrotizing pancreatitis (13).

The relationship of HCT to severity implies that the opposite is also true. Early vigorous intravenous hydration for the purpose of intravascular resuscitation is of foremost importance. The goal is to decrease the hematocrit, hemodilution. Laboratory and clinical studies with intravenous dextran to promote hemodilation have suggested efficacy in preventing severe disease (20).

Too often patients with acute pancreatitis are given suboptimal intravenous hydration. Acute pancreatitis typically results in significant intravascular losses. 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 (9). If this amount is added to the minimal intravenous fluid requirements of a 70 kg person during the first 48 hours (6 Liters), intravenous hydration should be at least 250-300 cc per hour for 48 hours. The rate of hydration is likely to be more important during the first 24 hours where a rising HCT has been shown to correlate closely with severe disease.

The Role of Urgent ERCP in Gallstone Pancreatitis

The pathogenesis of gallstone pancreatitis depends on the presence of a common bile duct stone. The vast majority of these stones pass easily and quickly. In some patients, gallstones can persist in the common bile duct (CBD) and may lead to severe disease complicated by biliary sepsis. Defining the presence of a persistent common bile duct 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 evaluation of choledocholithiasis, CBD stones.

Gallstones may be present in the common bile duct even in the absence of biliary ductal dilatation on abdominal ultrasound (21).

Laboratory testing may assist in the early identification of common bile duct 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 (22). 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% (23). Other investigators have found that a rising bilirubin or transaminases within 24-48 hours of admission for acute pancreatitis predicted a persistent CBD stone (21).

Regardless of findings on laboratory testing and ultrasonography, ERCP remains the gold standard in identifying whether gallstones are retained in the common bile duct. Endoscopic ultrasound (24) and Magnetic Resonance Imaging (17) provide excellent visualization of the common bile duct and can be used to determine the presence of common bile duct stones with less risk.

The role of ERCP in acute pancreatitis continues to evolve. Since the days of Opie, Osler and Halstead, clinicians have pondered the following question: will removing a stone impacted at the ampulla affect the course of acute pancreatitis? It must be remembered that the vast majority of stones that cause acute pancreatitis rapidly pass out of the common bile duct (25). Three published studies addressing the issue of urgent ERCP in the management of patients with acute pancreatitis build upon each other and provide clarity. The first randomized study by Neoptolemos and colleagues (2) found that early ERCP (within 72 hours) decreased morbidity in patients with severe acute pancreatitis (defined by Ranson’s Criteria). No benefit of ERCP in patients with acute pancreatitis was seen in patients with mild disease. Similarly, Fan and colleagues (3) 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 percent vs 0 percent (8). 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 (26). In this study, patients with obvious biliary obstruction, bilirubin greater than 5 mg/dl, were excluded. Unlike the earlier studies by Neoptolemos and Fan, by excluding jaundiced patients, this study showed that early ERCP was no more effective than medical treatment in patients with acute pancreatitis (3). Thus, early ERCP, within 24-72 hours, is effective in patients with severe acute pancreatitis who have 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).

Preventing the Development of Pancreatic Necrosis: Vigorous Intravenous Hydration

Gross destruction of the pancreatic gland, pancreatic necrosis is seen in 20 percent of patients with acute pancreatitis. In the absence of autopsy or laparotomy, pancreatic necrosis is defined as greater than 30 percent of non-enhancement on contrast enhanced Computed Tomography. 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 can be either infected or sterile. Both infected pancreatic necrosis and sterile pancreatic necrosis can lead to organ failure, cardiopulmonary insufficiency, renal failure and gastrointestinal bleeding (18). Sterile necrosis is treated supportively. Once pancreatic necrosis becomes infected, the management is altered. Whereas patients with sterile necrosis are

usually managed medically, patients with infected necrosis should be treated with operative necrosectomy and debridement (27). When infection is suspected in necrotizing pancreatitis, fine needle aspiration of the pancreatic or peripancreatic bed should be performed. The procedure is safe and effective. The gram stain of the fluid has a >90% sensitivity. A positive aspirate should lead to urgent surgical intervention (28).

Impairment of the microcirculation of the pancreas appears to lead to pancreatic necrosis (29,30). A vicious cycle develops where pancreatic inflammation leads to extravasation of protein rich intravascular fluid into the peritoneum. 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 leads to stasis and thrombi leading to subsequent necrosis which then exacerbates the inflammatory process. The association of hemoconcentration with pancreatic necrosis illustrates this process (13).

Vigorous intravenous hydration leads to hemodilution and relief of hemoconcentration. The finding by Baillargeon and colleagues that a decreased hematocrit is associated with mild disease and that a falling hematocrit during the first 24 hours of care leads to a decrease in morbidity suggests that vigorous intravenous hydration can prevent the development of necrosis.

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 (31). 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 (29). Surgical intervention during this time is avoided.

The origin of the bacteria leading to pancreatic infection is unclear. Several facts suggest that in acute pancreatitis, there is either direct transmural spread or transmigration of bacteria from the colon (32). In an attempt to decrease pancreatic infection, initial trials in the 1970s with ampicillin showed a lack of efficacy (33, 34,35). Almost 2 decades later, Beger and colleagues (36) 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 (4). 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 (5,6). Multiple reviews, including a Cochrane review in 2004 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. Isenmann and colleagues (37) 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 percent) 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 (47) 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 two groups, Meropenem (1 gram intravenously every 8 hours) or placebo within 5 days on 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 are not warranted.

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 (38). 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 (39) and thermal injury (40). Early enteral nutrition through a nasojejunal tube maintains the integrity and function of the intestinal barrier while providing adequate nutrition (41).

In patients with severe acute pancreatitis, enteral feeding is safe and as effective as parenteral nutrition. Enteral nutrition attenuates the acute inflammatory response and improves disease severity in acute pancreatitis (42). Several randomized prospective studies comparing nasojejunal vs parenteral nutrition have shown a decrease in morbidity (41-45) and mortality (7) in patients given enteral nutrition early in the course of disease. By providing nutrients and altering the bacterial flora, there is a significant decrease in the development of infected pancreatic necrosis (7). There is a consensus among the trials demonstrating decreased infectious complications, length of stay and significant cost savings (43). 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 (46). In a comparison of patients with severe acute pancreatitis randomized to naso-jejunal feeding vs naso-gastric feeding, there was no apparent differences in safety, pain score, narcotic requirements, morbidity and mortality. As the medical intervention trials have previously shown, this study continues to place doubt on the theory that the pancreas should be kept at rest during an attack of acute pancreatitis. Further study is needed regarding the timing of initiating enteral nutrition.

Infected Necrosis

Approximately a third of patients with necrotizing pancreatitis develop infected necrosis. The infection usually occurs 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. The distinction between sterile and infected necrosis is important typically in the second or third weeks when surgical intervention is feasible. The technique of percutaneous CT guided fine needle aspiration (FNA) has been shown to be safe and effective. A gram stain of the peripancreatic bed that is carefully observed can lead to a diagnosis in most cases, cultures should be considered confirmatory.

The standard of care for infected pancreatic necrosis is surgical debridement. Currently, there is controversy in the surgical literature regarding the time of surgery. Although urgent surgical intervention was the consensus years prior, some authors have now suggested that a prolonged period of antibiotics be given prior to surgery to allow the inflammatory reaction to subside. In addition, several novel techniques, minimally invasive endoscopic and radiologic techniques have been described to debride infected necrosis. There are also several published reports of patients with infected necrosis undergoing successful treatment with intravenous antibiotics without any surgical, endoscopic or radiologic intervention. Given the controversy, each case of

infected necrosis must be considered individually. The timing of surgical intervention should be determined by the pancreatic surgeon.

Summary of Management

The initial management of a patient with acute pancreatitis relies on close monitoring and vigorous hydration (48). Monitoring for clinical scoring criteria (Ranson Score), organ dysfunction is of utmost importance. However, it must be remembered that the accuracy of these scoring systems is not reached until 48 hours after admission. Patients who are older than age 55, who are obese, have elevated HCT and/or blood urea nitrogen, and/or have pleural effusions/infiltrates on chest radiograph are at a higher risk of complications. Following the HCT as a surrogate marker of hemoconcentration will assist in the prognosis and guiding intravenous hydration. The goal is hemodilution, with the HCT falling during the first 24 hours. Preventing and/or reversing organ dysfunction in the first 24-48 hours will decrease morbidity and mortality.

In patients who are deteriorating over the first 24 hours, developing signs of organ dysfunction, and not improving, a common bile duct stone should be suspected. If the bilirubin is elevated, over 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 within 24-72 hours after admission. MRCP and EUS can be used when there is a lower suspicion for CBD stones.

CT and MRI should be reserved for patients who appear persistently ill despite supportive care. In these patients, pancreatic necrosis may be present. In patients with severe disease, especially pancreatic necrosis, enteral nutrition should be utilized. As most patients with acute pancreatitis have mild disease and resume oral feeding within several days, it is difficult to recommend the routine placement of naso-jejunal tubes in all patients with acute pancreatitis. Further study is warranted to determine if the enteral feeding is beneficial in patients with mild disease.

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. Fine needle aspiration of suspected infected pancreatic necrosis to guide surgical intervention typically becomes of importance after the first week to 10 days. The 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. Infected necrosis warrants the use of antibiotics and typically will lead to surgical debridement. The timing of debridement is controversial and under intense study. Currently, each case should be considered individually.

Prevention of the septic and non-septic complications in patients with severe acute pancreatitis depends largely on the monitoring, vigorous hydration, and early recognition of pancreatic necrosis and choledocholithiasis. Understanding these issues in the management of patients with acute pancreatitis can decrease severity, morbidity and mortality.

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Table 1. Randomized Trials Comparing Urgent ERCP to Medical Therapy

Study	*# of Patients*	*Time of ERCP**	*Outcome*
Neoptolemos (2)	121	72 hours	Decreased Morbidity in Severe Disease
Fan (3)	195	24 hours	Decrease in Biliary Sepsis
Folsch (25)	121	72 hours	No Effect on Outcome Excluded Bilirubin > 5 mg/dl

***ERCP was performed within a time frame prior to the hours cited.**

Table 2. Randomized Placebo Controlled Studies of Antibiotics Shown to Have Efficacy in Patients with Necrotizing Acute Pancreatitis

Study	*Antibiotic*	*Dose*	*Outcome*
Pederzoli (4)	Imipenem	500 mg IV q 8 hr	Decreased infected necrosis
Siano (5)	Cefuroxime	1.5 g IV q 8 hr	Decreased mortality
Schwartz (6)	Ofloxacin Metronidazole	200 mg IV bid 250 mg IV tid	Decreased infected necrosis
Isenmann* (37)	Ciprofloxacin Metronidazole	400 mg IV bid 500 mg IV bid	No Benefit
Dellinger* (47)	Meropenem	1 gram IV q 8 hr	No Benefit

* Blinded Study

Table 3. Randomized Trials Comparing Enteral Nutrition to Parenteral Nutrition in Patients with Acute Pancreatitis

Study	*# Patients*	*Delivery*	*Outcome*
McCLave (44)	32	Elemental-Nasojejunal	Lower Costs
Windsor (41)	34	Polymeric-Nasojejunal	Decreased morbidity
Olah (7)	89	Elemental-Nasojejunal	Decreased MSOF. Infected Necrosis, Mortality.
Abou-Assi (42)	53	Elemental-Nasojejunal	Decreased Sepsis Costs, LOS
Kalfarentzos (43)	38	Elemental-Nasojejunal	Decreased Sepsis
Eatock (46)	50	Nasojejunal vs Nasogastric	Equally effective

LOS = length of stay
MSOF = multisystem organ failure
Outcome defined by statistically significant advantages of enteral nutrition over parenteral nutrition.