Clinics in Surgery

Review Article
Published: 26 Apr, 2017

Necrotizing Pancreatitis: Advances in Management

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Abstract

Acute pancreatitis is a common disease process that results in significant morbidity and mortality. While the disease course may be mild and self-limited, 15%-25% of patients develop necrotizing pancreatitis, which may become secondarily infected. The use of standardized scoring systems and clinical classification schemes has allowed multicenter trials to evaluate the management of necrotizing pancreatitis and have greatly improved outcomes. Supportive care with fluid resuscitation, nutrition, and appropriate use of antibiotics are the mainstays of early management. Once fluid collections have progressed to walled-off necrosis, catheter-based drainage is generally sufficient, with few patients requiring surgical intervention. Complications of necrotizing pancreatitis include mesenteric venous thrombosis, abdominal compartment syndrome, bowel perforation, and hemorrhage. Further understanding the appropriate timing of interventions may potentially lead to fewer complications, decreased length of hospitalization, and improved outcomes.

Introduction

Acute pancreatitis is a common disease process with greater than 275,000 hospital admissions annually in the United States [1]. Moreover, the incidence of acute pancreatitis is on the rise, with a 12% increase in emergency department visits and a 15% increase in hospital admissions annually over the past decade [2]. With the incidence increasing, annual health care costs to treat acute pancreatitis now exceed $2.6 billion annually [1]. Despite aggressive critical care, acute pancreatitis remains deadly with over 8000 deaths per year in the United States and an overall mortality of approximately 2% [2].

A wide range of etiologies can cause acute pancreatitis. The most common cause of acute pancreatitis worldwide is gallstone disease, accounting for approximately 40% of cases. Alcohol-induced pancreatitis, the second most common cause, accounts for 30% of cases. Hypertriglyceridemia, drugs, genetic and autoimmune causes, endoscopic retrograde cholangiopancreatography (ERCP), trauma, congenital malformations, infections, and surgical complications each account for a small percentage of the remainder of cases. Diabetes, smoking, and obesity are common risk factors that may be associated with idiopathic cases.

The majority of patients with acute pancreatitis have a self-limited disease course requiring a short hospital admission for supportive care. However, 15-25% of patients with pancreatitis develop pancreatic necrosis, which significantly increases both morbidity and mortality [3]. While sterile pancreatic necrosis carries a 10% mortality risk, the mortality associated with infected necrosis may be as high as 30%.

Clinical Diagnosis and Scoring

The International Association of Pancreatology (IAP) and American Pancreatic Association (APA) suggest that a clinical diagnosis of acute pancreatitis requires 2 of 3 criteria: clinical signs and symptoms (abdominal pain), laboratory abnormalities (serum amylase or lipase greater than 3 times upper limit of normal), and/or characteristic imaging findings (computed tomography (CT) or magnetic resonance imaging (MRI)) [4]. The Atlanta classification, originally described in 1992 and updated in 2012, remains the standard classification for acute pancreatitis and relies on both clinical symptoms and radiographic imaging [5]. Acute pancreatitis is clinically classified as mild, moderately severe, or severe. Mild pancreatitis has no organ failure or local or systemic complications, and usually resolves in approximately a week. Moderately severe pancreatitis is characterized by transient organ failure (less than 48 hours), local complications (such as necrosis or fluid collections) or exacerbation of co-morbid disease. Severe acute pancreatitis is characterized by

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Received Date: *13 Jan 2017*
Accepted Date: *19 Apr 2017*
Published Date: *26 Apr 2017*

Citation:
Moore SA, Dumas RP, Sims CA. Necrotizing Pancreatitis: Advances in Management. Clin Surg. 2017; 2: 1437.

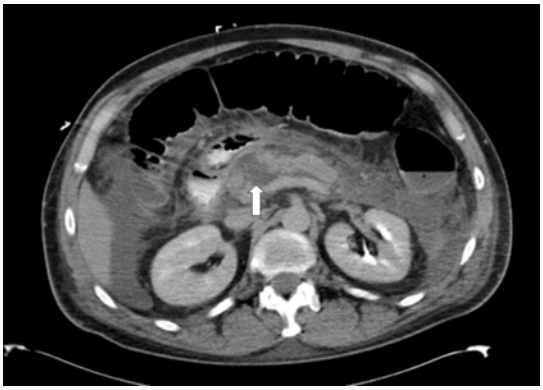

Figure 1: Acute necrotizing pancreatitis with non-enhancement of pancreatic neck (arrow), and extensive peripancreatic inflammation without defined fluid collections.

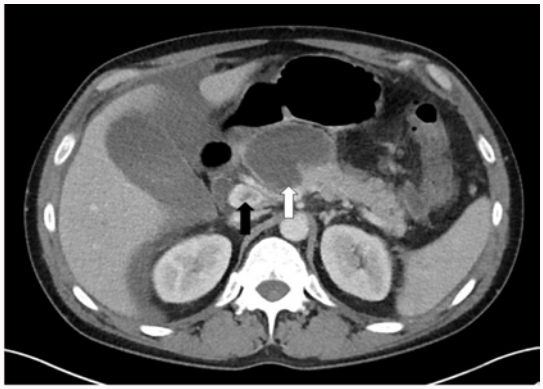

Figure 2: Acute necrotizing pancreatitis with acute necrotic collection adjacent to pancreatic neck (white arrow) and non-occlusive portal vein thrombus (black arrow).

Table 1: Atlanta Imaging Classification.

Type	Acuity	Wall/Capsule	Necrosis
Acute peripancreatic fluid collection	<4 weeks	No	No
Pseudocyst	>4 weeks	Yes	No
Acute Necrotic Collection	<4 weeks	No	Yes
Walled-Off Necrosis	>4 weeks	Yes	Yes

Table 2: Ranson's Criteria.

At Admission:	**At 48 hours:**
Age in years > 55 years	Serum calcium <8.0 mg/dL (<2.0 mmol/L)
WBC count > 16000 cells/ mm^3	Hematocrit fall > 10%
Blood glucose>200 mg/ dL(>11 mmol/L)	Hypoxemia PaO_2< 60 mmHg
Serum AST> 250 IU/L	BUN increased by 5 or more mg/dL(1.8 or more mmol/L) after IV fluid hydration
Serum LDH> 350 IU/L	Base deficit (negative base excess) > 4 mEq/L
	Sequestration of fluids > 6 L

persistent single or multiple organ failure. The Atlanta classification further standardizes diagnosis using strict imaging criteria. Acute pancreatitis is subdivided into two types: interstitial edematous pancreatitis and necrotizing pancreatitis. Interstitial edematous pancreatitis is characterized by enlargement of the pancreatic gland due to inflammatory edema, with homogenous enhancement of the gland on contrast-enhanced CT. The majority of interstitial edematous pancreatitis resolves within a week. In contrast, necrotizing pancreatitis demonstrates non-enhancement of pancreatic and/or peri pancreatic tissues (Figure 1). Necrotizing pancreatitis develops in 5-10% of patients and may evolve over the course of the first week of clinical symptoms. As such, necrotizing pancreatitis may be missed on early cross-sectional imaging. Pancreatic necrosis will further evolve over time;it may remain solid or liquefy, become infected or remain sterile, or it may persist or resolve. Importantly, there is no correlation between the degree of necrosis and the likelihood for development of infection [5].

In addition, the Atlanta classification includes standardization of local complications, including acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis (Table 1). Acute peripancreatic fluid collections develop early in the course of pancreatitis, usually in the setting of interstitial edematous pancreatitis. Collections are homogenous and confined to fascial planes adjacent to the pancreas without development of a wall or capsule, and no necrosis is present. Pancreatic pseudocysts develop later in the course of interstitial edematous pancreatitis and have a well-formed wall or capsule. Pseudocysts form adjacent to the pancreatic parenchyma and their maturation requires 4 or more weeks. Acute necrotic collections develop exclusively in necrotizing pancreatitis and present early in the course. These collections are heterogeneous, with both solid and liquid components, and lack a well-defined wall (Figure 2). Walled-off necrosis can develop later in the course of necrotizing pancreatitis and is characterized by a well-developed inflammatory wall with heterogeneous contents (Figure 3). Both acute necrotic collections and walled-off necrosis may be within the pancreatic parenchyma or in the peripancreatic space. Additionally, these collections may be infected or sterile.

A number of clinical classification schemes have been proposed to help predict the morbidity and mortality of acute pancreatitis including Ranson's criteria and the Bedside Index of Severity in Acute Pancreatitis (BISAP). Developed in the 1970's, Ranson's criteria attempts to risk-stratify patients with acute pancreatitis using clinical data from admission and then 48 hours later [6]. To calculate a score, one point is assigned for each criteria met (Table 2). A score of 0-2 predicts a mortality of 1% or less, a score of 3-4 predicts a mortality of 15%, a score of 5-6 predicts a mortality of 40%, and a score of 7 or greater predicts a 100% mortality [6]. Unfortunately, Ranson's criteria cannot be calculated before 48 hours, thus limiting its usefulness in real-time. Others have attempted to simplify risk-stratification using fewer variables [7]. In particular, an admission hematocrit >44% and/or a rise inserum BUN within24 hours are strongly predictive of increased morbidity and mortality. If either criterion is fulfilled, rates of persistent organ failure and pancreatic necrosis reached 53.6% and 60.3%, respectively [8]. In contrast, the BISAP is a mortality-based prognostic scoring system that evaluates only 5 clinical variables within the first 24 hours of admission [9] (Table 3). That being said, although BISAP is certainly more simplistic, it does not appear to outperform any other scoring schema in predicting the severity of acute pancreatitis [10].

Management

Management of acute pancreatitis is remains supportive with attention to pain control, hemodynamic status, endpoints of resuscitation, and nutrition. Patients with organ failure or evidence of systemic inflammatory response should be admitted to an intensive care unit.

Table 3: Bedside Index of Severity in Acute Pancreatitis (BISAP).

Within 24 hours of Admission 1 point for each of the following:	Score	Mortality
BUN > 25	≤1	<1%
Age >60 years	2	2%
Systemic Inflammatory Response Syndrome (defined by the presence of ≥ 2 of following criteria) Pulse > 90 beats/min Respirations >20/min or $PaCO_2$<32 mmHg Temperature >38°C or <36°C WBC >12,000 or <4000 cells/mm^3 or >10% bands	3 4 5	<10% <20% >20%
Altered Mental Status		
Pleural Effusion on Chest X-ray		

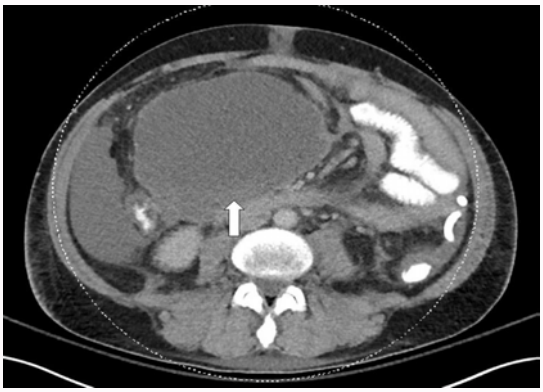

Figure 3: Necrotizing pancreatitis with a large area of walled-off necrosis (arrow).

Fluid Management

Fluid resuscitation should be provided to all patients within the first 12-24 hours. Although few studies have demonstrated a significant difference in outcome based on the type of intravenous fluid selected, one small randomized controlled trial showed a decrease in the incidence of SIRS when Lactated Ringer's was used compared to normal saline [11]. Similarly, the volume expander, hydroxyethyl starch, has been shown to increase risk of renal failure and mortality in patients with sepsis, and thus is not currently recommended for resuscitation [12].

While under-resuscitation can clearly be detrimental, overly-aggressive fluid resuscitation can also be harmful. In a study comparing5-10 ml/kg/hrto 10-15 ml/kg/hr of resuscitation, the group receiving less fluid had lower rates of mechanical ventilation, abdominal compartment syndrome, sepsis, and mortality [13]. The benefit of judicious fluid administration was recently demonstrated in a randomized trial investigating hemodilution as resuscitation target. One hundred and fifteen patients were randomized to a resuscitation target hematocrit of either >35% or <35% at 48 hours. Patients undergoing slower hemodilution, and thus decreased fluid resuscitation, had lower rates of sepsis (58% vs 79%) and mortality (66% vs 85%) [14].

Although endpoints of resuscitation in acute pancreatitis have not been well studied, it seems prudent to follow standardized critical care resuscitation guidelines within the first 24 hours. Specific goals include targeting a central venous pressure of 8-12 mmHg, a mean arterial pressure of ≥65 mmHg, a urine output of ≥0.5 ml/kg/hr, a central venous oxygen saturation of 70%, and a normalization of lactate levels [15].

Antibiotic Therapy

Despite their common use, there is noben efit in using prophylactic antibiotics for sterile necrotizing pancreatitis [16,17]. In two randomized, blinded, placebo-controlled trials, the use of antibioticsfailed to demonstrate a benefit to prophylactic antibiotics [18,19]. More recently, two large meta-analyses also failed to demonstrate a benefit with routine antibiotics, although the use of imipenem may be promising [20,21]. In fact, use of prophylactic antibiotics has been associated with increased infection with multi-drug resistant organisms and Candida albicans [22]. Pending further study, both the Infectious Disease Society of America and the American College of Gastroenterology recommend against prophylactic antibiotics for necrotizing pancreatitis without evidence of infection [23]. Antibiotics are absolutely recommended for infected pancreatitis and should be targeted toward the specific organism.

Nutritional Support

Historically, enteral nutrition was thought to be contraindicated in acute pancreatitis, and patients were supported completely with total parenteral nutrition (TPN) and bowel rest. However, it is now well-established that enteral nutrition is both safe and beneficial. Significant evidence exists regarding the benefit early initiation of feeds, with most studies suggesting reduced mortality, decreased incidence of intra-abdominal hypertension, fewer infectious complications, and less multi-organ failure when feeds are initiated within the first 48 hours [24,25]. In mild acute pancreatitis, it is not necessary restrict to a clear liquid diet and low fat oral nutrition should be introduced promptly [26]. In more severe pancreatitis, enteral feeds are preferable. In a recent Cochrane review comparing TPN to enteral nutrition in patients with acute pancreatitis, enteral nutrition absolutely provided superior support [27]. Enteral nutrition was associated with reduced mortality (relative risk 0.50), reduced multi-organ failure (relative risk 0.55), reduced systemic infection (relative risk 0.39), decreased operative interventions (relative risk 0.44), and decreased local complications (relative risk 0.74). Although it is difficult to determine how enteral feeds are clinically protective, proposed mechanisms include the prevention of gut luminal atrophy and stasis the enhancement of intestinal barrier function with decreased inflammatory activation, and the prevention of gut bacterial and endotoxin translocation. Given these benefits, the American College of Gastroenterology recommends avoiding parenteral nutrition entirely unless an enteral route is not available, not tolerated, or does not result in adequate calories [23].

While it is important to initiate enteral feeds early in severe pancreatitis, the route by which nutrition is delivered does not appear to be important. In fact, nasogastric, nasoduodenal, or nasojejeunal feeds appear to be clinically equivalent with no difference in rates of tracheal aspiration, worsening of abdominal pain, diarrhea, or achieving caloric goals. Additionally, the route of enteral nutrition did not impact mortality [28].

Diagnosis of Infected Necrosis

Although infected necrosis most commonly develops 2-4 weeks after the onset of pancreatitis, it may occur at any time and the transition from sterile to infected necrosis can be difficult to determine [29]. Risk factors include: elevated intra-abdominal pressure, ileus, hypotension, parenteral nutrition, and increased severity of illness as measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score [30-32]. Elevated D-dimer levels also appear

predictive and likely are a proxy for disease severity.

The development of infected necrosis is confirmed by the pathognomonic CT imaging findings of extra luminal gas within pancreatic or peripancreatic tissues. However, this radiographic finding may not always be present even with infection. Thus, the diagnosis of infected necrosis must be suspected based on clinical signs and symptoms, including fever, tachycardia, and leukocytosis. In fact, in one retrospective analysis, only 12- 40% of patients with infected necrosis had evidence of extra luminal gas on cross-sectional imaging[29,33]. CT-guided aspiration has been suggested as a method of confirming infection when imaging is inconclusive. CT guided aspiration, however, has a reported 25% risk of false-negative results [34]. Given the risk of under diagnosing infection, as well as the small risk of introducing bacteria, there has not been universal adoption of this technique. As such, the diagnosis of infected pancreatic necrosis remains largely based on clinical suspicion.

When infected necrosis is suspected, antibiotics should be initiated promptly. The majority of infections are monomicrobial with gut-derived bacteria. The most common organisms include *Escherichia coli*, *Staphylococcus aureus*, and *Enterococcus faecalis*, but other pathogens are becoming more prevalent and increasingly more drug resistant [22,35]. Additionally, patients treated with prophylactic broad spectrum antibiotics have been found to have increased incidence of infection from *Candida albican* [17]. If empiric therapy is initiated, antimicrobials known to penetrate pancreatitis necrosis (carbapenems, or quinolones,and metronidazole) should be chosen initially. Antibiotic coverage may be expanded to include antifungals or gram positives if the clinical picture fails to improve.

Drainage

Understanding the timing and indications for imaging-guided drainage of necrotizing pancreatitis is critical. Acute peripancreatic fluid collections rarely require any intervention, and largely resolve on their own with supportive care. Similarly, pancreatic pseudocysts (especially those less than 6 centimeters in size) tend to resolve with supportive care. Pseudocysts that do not resolve are largely treated successfully with endoscopic techniques and rarely require surgery [36]. Non-infected pancreatic necrosis is also generally managed with supportive care, allowing collections to evolve from acute necrotic collections to organized walled-off necrosis. In the absence of infection, the only indication for acute intervention is compressive symptoms. Conversely, suspected or proven infected necrosis generally requires percutaneous drainage, at a minimum.

Over the last few decades, interventions for pancreatitis have changed greatly [37]. With increasing access to imaging-guided or endoscopic drainage techniques, the role of open surgical drainage/ debridement has become increasingly limited andnecrosectomy has largely been replaced by a well-described "Step-up" approach encompassing imaging-guided catheter drainage, followed by minimally invasive videoscopic or endoscopic necrosectomy in a sequential fashion depending on clinical response to escalating therapy. In 2010, the Dutch Pancreatitis Study group directly compared the minimally invasive Step-Up approach to surgical necrosectomy in 88 patients with acute necrotizing pancreatitis (PANTER trial).The Step-up approach was associated with fewer complications including multi-organ failure, incisional hernia and new-onset diabetes [38]. Similarly, are sent Cochrane review found that minimally invasive approaches resulted in fewer adverse events,

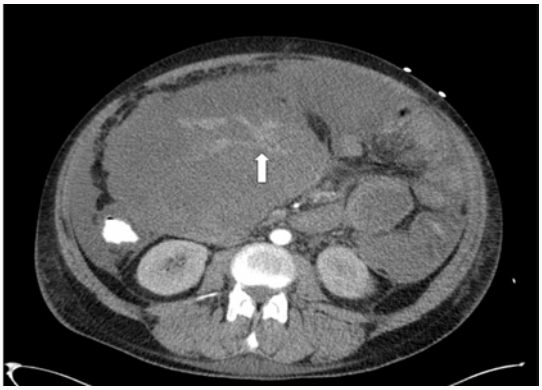

Figure 4: Hemorrhage (arrow) from ruptured pseudoaneurysm into peripancreatic fluid collection.

organ failure, and lower costs [37]. In fact, recent studies have shown that over 60% of patients treated with percutaneous catheter drainage had resolution of sepsis, with nearly half of these patients avoiding surgery entirely [39]. Most guidelines suggest that any intervention should be delayed until the necrosis can be walled off, which usually takes at least 4 weeks [38,40].However, this recommendation is largely based on the era of open necrosectomy. With the majority of patients in the modern era being treated with a minimally invasive approach, it is unclear if delaying intervention is still prudent. In addition, certain conditions such as persistent SIRS, sepsis, or abdominal compartment syndrome may force earlier catheter drainage or surgical intervention. Moreover, increasing data suggest that early intervention may be more beneficial than first appreciated. In fact, early catheter drainage in the setting of suspected necrosis may mitigated the need for further surgical necrosectomy [41]. The optimum timing of any percutaneous intervention, however, remains unknown. Currently, The Dutch Pancreatitis Study Group is conducting the POINTER trial, a randomized controlled trial, which will determine if early or delayed catheter drainage leads to improved outcomes [42].

Complications

Pseudoaneurysm and hemorrhage

Hemorrhage in the setting of necrotizing pancreatitis is a relatively common complication. Hemorrhage is typically due to the effect of inflammatory changes on nearby vasculature, resulting in abnormalities in vascular wall and development of pseudoaneurysms. Necrotic collections may also erode into vessels, causing hemorrhage (Figure 4). In addition, mesenteric venous thrombosis may result in sinastral portal hypertension, causing gastric varices and upper gastrointestinal hemorrhage. Patients classically present with a sentinel hemorrhage, followed by a larger, often fatal hemorrhage. In one case series of over 1300 patients with acute pancreatitis, 1% developed hemorrhagic complications, with a 34% mortality [43] Other case series have reported similar mortality rates [44] Angiographic embolization is usually both diagnostic and therapeutic, with a sensitivity rate of >95%, and rates of successful hemostasis approaching 90%.[45,46].

Mesenteric venous thrombosis

Mesenteric venous thrombosis is a common complication of acute pancreatitis, with a reported incidence of 14%. In patients with necrotizing pancreatitis, however, the risk of thrombosis increases

significantly with a reported incidence of 50% [47]. Interestingly, in this case series, no patients developed complications from mesenteric venous thrombosis, despite infrequent use of anticoagulation. In another series, spontaneous recanalization was noted in up to one third of patients [48]. The feared complication of upper gastrointestinal bleed from gastric varices as a result of sinastral portal hypertension is also quite rare, with an incidence of 4%-12% [49,50].

Intestinal complications

Local inflammation in necrotizing pancreatitis can affect not only the regional vasculature, but also the intestines. The incidence of intestinal complications ranges from 10 to 44%, with the transverse colon being the most commonly affected [51,52]. Complications include fistulization, stricture, or necrosis with perforation. These complications may be a result of local inflammation, vascular compromise, or drain placement. Surgical management remains the mainstay of management, although some fistulas may be amenable to non-operative treatment.

Abdominal compartment syndrome

Abdominal compartment syndrome (ACS) is diagnosed by a combination of sustained intra-abdominal hypertension (IAH), defined as a bladder pressure >12 mmHg, along with evidence of end-organ failure. While the incidence of IAH in patients with severe acute pancreatitis is 60-80%, thankfully the incidence of ACS is only 27% [53]. Although randomized, controlled trials regarding the management of ACS in pancreatitis are lacking, surgical decompression should be viewed as a last resort. Other therapies include decompression with nasogastric and rectal tubes, minimizing fluid resuscitation if possible, and abdominal wall relaxation with sedation and neuromuscular blockade. Percutaneous drainage of intra-abdominal fluid is recommended if a large volume of ascites is noted on imaging. As would be expected, mortality in patients requiring decompressive laparotomy is high and exceeds 50% [53].

Conclusion

Acute pancreatitis is an increasingly common cause of morbidity and mortality worldwide. Significant advances in management have been made over the past two decades, with better understanding of the role of enteral nutrition and utilization of minimally invasive techniques for management of infected pancreatic necrosis. Although evidence-based management guidelines have been published, areas of uncertainty still exist regarding optimal use of antibiotic therapy, the diagnosis of infected necrosis, and timing for intervention in the setting of infected necrosis. The formation of large international consortium groups and multicenter trials will continue to advance the care of patients with acute pancreatitis and significantly improve our understanding of this physiologically complex disease.

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