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Advances in Management of Acute Pancreatitis

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Abstract

This chapter will review advances in the management of acute pancreatitis. Medical treatment has been primarily supportive for this diagnosis in the past, and despite extensive research efforts, there are no pharmacologic therapies that improve prognosis. The current mainstay of management, notwithstanding the ongoing debate regarding the volume, fluid type, and rate of administration, is aggressive intravenous fluid resuscitation. While in the past antibiotics were used consistently for prophylaxis in severe acute pancreatitis to prevent infection, they are no longer used unless infection is documented. Enteral nutrition, especially in patients with severe acute pancreatitis, is considered a cornerstone in management of this disease.

Keywords

Acute pancreatitis; medical management; fluid resuscitation; antibiotics; walled-off pancreatic necrosis; BiSAP; prognostication

Introduction

Acute pancreatitis is a frequently devastating pancreatic inflammation that has been associated with significant morbidity, mortality, and hospitalization costs [1]. The incidence of acute pancreatitis has been increasing and features an overall mortality rate of 5% that may be as high as 30% in the most severe cases [2-4]. It was the most common inpatient gastrointestinal diagnosis in 2009, totaling over 270,000 United States hospitalizations and incurring costs of over 2.6 billion dollars [5]. The updated Atlanta classification divides acute pancreatitis into mild and severe types [6,7]. Mild, characterized by pancreatic inflammation without necrosis or organ failure, is known as interstitial edematous pancreatitis, which is usually self-limiting and resolves in about one week. Severe

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pancreatitis, occurring in about 20% of cases, predisposes to local complications such as pancreatic necrosis, abscess formation, and pseudocysts. Severe pancreatitis is subdivided further into moderate and severe depending on the presence and duration (> 48 hours) of organ failure. In this chapter, we will detail treatment of acute pancreatitis, including highlighting new insights into prognostication and focusing on intravenous fluid resuscitation and the current evidence behind the use of antibiotics and pharmacologic therapies.

Predicting Severity

- Simple, universally obtainable markers such as the change in BUN level are equally predictive of severity when compared with more complicated systems

Predicting the severity of acute pancreatitis can be challenging. Since 1974, when the Ranson's criteria were first proposed, multiple scoring systems (APACHE-II, BiSAP, Marshall Score, etc.) have been developed as a means of improving the ability to predict severity in acute pancreatitis. However, despite the use of these often complex systems, laboratory abnormalities in hematocrit, creatinine, and blood urea nitrogen (BUN) can be used as effective prognostic indicators with equivalent accuracy. For example, an increased risk of pancreatic necrosis has been linked with an elevated hematocrit at admission or within the first 24 hours, as well as an elevated creatinine level within the first 48 hours [8-10]. With regards to BUN, A 2011 meta-analysis of 1043 acute pancreatitis cases demonstrated that a BUN ≥ 20 mg/dl (OR 4.6, 4.3 respectively) at admission, or an increase in levels within the first 24 hours, was associated with an increased risk of mortality and death [11]. Thus, it is recommended that a simple marker, such as BUN, be used as means of assessing severity and potential progression to organ failure.

Fluid Resuscitation

- Goal to decrease hematocrit and BUN within the first 24 hours of hospitalization.
- Early aggressive fluid resuscitation with 250-500mL per hour of isotonic crystalloid in the first 12-24 hours or a goal urine output of at least 0.5 ml/kg/hr.
- Lactated Ringer's solution should be used as the resuscitation fluid of choice.

Now commonly recognized as the primary form of initial management, the importance of adequate fluid resuscitation cannot be understated. In severe cases, acute pancreatitis can lead to pancreatic necrosis and ongoing pancreatic enzyme release [12]. One of the triggers of necrosis is thought to be inadequate glandular perfusion. The pancreatic microcirculation encompasses the celiac and superior mesenteric arteries that branch off to supply the pancreatic acinus. Acute pancreatitis invokes a state of hypovolemia, causing a combination of microangiopathic effects and pancreatic edema that decreases blood flow. This disruption in perfusion may be an important factor responsible for the transition from mild, interstitial edematous disease to severe, necrotizing pancreatitis [13-17]. Current proposed mechanisms of this pathophysiology include hypercoagulability with microthrombi, endothelial damage from free radicals, increased capillary permeability, and hypovolemia [18]. The resultant ischemia produces a flush of cytokines and inflammatory mediators, which can progress into

the development of the systemic inflammatory response syndrome (SIRS) and pancreatic necrosis and eventually lead to persistent (>48 hour) organ failure.

As the above data suggests, inadequate fluid resuscitation leading to poor pancreatic microcirculatory perfusion has been associated with acute necrotizing pancreatitis [19]. Specifically, we now know that early fluid resuscitation has more of a therapeutic effect than delayed fluid resuscitation. In one study evaluating specifically the time course of IV hydration, early was defined as receiving greater than one-third of the total 72 hours fluid volume within the first 24 hours of hospitalization; whereas, late was defined as receiving less than one-third of the total volume [20]. While the investigation did not focus on the total infused fluid volume, it concluded that the group receiving early fluid resuscitation experienced less mortality than those receiving later resuscitation. Other studies have since supported this claim, including a retrospective analysis of 436 acute pancreatitis patients, which found an association between early fluid resuscitation and decreased SIRS, organ failure at 72 hours, length of hospital stay, and a lower rate of ICU admission [21].

Though early fluid resuscitation is generally agreed upon as an intervention of paramount importance, there are currently no standard guidelines on the optimal fluid type, volume, rate, or duration of treatment [22]. Though human studies regarding the rate of hydration consistently show decreased morbidity and mortality with aggressive hydration in the first 24 hours, the total volume of hydration at the 48-hour mark seems to have a limited effect on patient outcomes. The current American College of Gastroenterology (ACG) guidelines have recommended 250-500mL per hour of isotonic crystalloid solution in the first 12-24 hours with frequent re-evaluation every 6 hours, with an ultimate goal of decreasing the BUN levels [23]. Some experts recommend that in addition to the 1-2 L fluid bolus given in the emergency department, the starting infusion should be at a rate of 250-300 ml/h or enough to produce a urine output of at least 0.5 ml/kg/hr [24]. The goal within the first 24 hours is a total infusion volume of 2.5-4 L, with adjustments to be made based on the patient's age, weight, physical exam, and comorbid conditions [25].

The type of resuscitation fluid has not been satisfactorily studied. However, in the most widely cited prospective study of fluid resuscitation in acute pancreatitis, Wu and colleagues found that the use of Lactated Ringer's solution, as opposed to normal saline, resulted in less SIRS and a decreased c-reactive protein at 48 hours [26]. There have been no other prospective fluid studies evaluating different types of resuscitative fluid, and thus it is generally recommended, in the absence of better evidence, that Lactated Ringer's be used as the resuscitative fluid of choice.

It is also very important to recognize the consequences of over-resuscitation – most notably the development of intra-abdominal compartment syndrome. In a study of patients with predicted severe pancreatitis whose hematocrit was aggressively lowered upon admission, those with aggressive lowering of their hematocrit had greater morbidity and mortality [27].

Pharmacologic Strategies

Antibiotics

- Not recommended for prophylaxis of infected pancreatic necrosis, though indicated if another source of infection is clinically suspected.

Infected pancreatic necrosis continues to be the most common cause of death in patients with acute pancreatitis who survive the early phase, accounting for up to 70% of all mortality. Though initially present in about 5% of patients with acute pancreatitis, pancreatic necrosis puts patients at a very high risk of pancreatic bed infection, occurring in 50-70% of cases [2,6]. Antibiotic prophylaxis and therapy have been a long-contested solution to this problem, with the potential for reduction in the morbidity and mortality associated with severe acute pancreatitis.

Use of antibiotics in previous years as prophylaxis for infected necrosis was recommended and common in practice, supported by early research demonstrating broad-spectrum antibiotics to decrease the rate of infected pancreatic necrosis [28]. A meta-analysis in 2001, which included three randomized controlled trials, compared antibiotic prophylaxis to no prophylaxis in the setting of acute necrotizing pancreatitis [29]. They found a reduction of 21.2% in sepsis and 12.3% in mortality in patients receiving prophylactic antibiotics; however, there was no difference in the incidence of pancreatic infection.

Studies since then have continued to have conflicting results, with a meta-analysis published in 2008, which included the same three previously mentioned randomized controlled trials, demonstrating no difference in the rates of pancreatic infection or mortality between the group receiving antibiotics versus placebo [30]. An evaluation of the same trials by a Cochrane review confirmed no difference in mortality but found a significant difference with the use of Imipenem alone in terms of preventing infection [31]. Most recently in 2011, an evaluation of 14 randomized controlled trials totaling 841 patients compared those receiving antibiotics versus placebo. No significant differences were reported in mortality, incidence of infected pancreatic necrosis, non-pancreatic infection, and surgical intervention [32]. There may even be an association with antibiotic use and pancreatic fungal infections [33].

There has been some consideration of using probiotics for prevention of infection in acute pancreatitis; however a meta-analysis in 2009 demonstrated no reduction in the risk of pancreatic infection or associated mortality [34]. There may be some benefit in selective gut decontamination, which is the process of using oral antibiotics to eradicate enteric gram-negative rods and thus reduce bacterial translocation from the GI tract into the pancreas, but further studies need to be performed [35].

Ultimately, prophylactic antibiotics are not recommended for use in acute pancreatitis and should not be administered in the first 24 hours of the episode unless there is clinical suspicion for concurrent extrapancreatic infection. Patients may present initially with sepsis, SIRS, and/or multi-organ failure. Treatment with antibiotics is appropriate if evaluation of the patient, via blood cultures and fine needle aspirations of pancreatic necrosis, reveals

infection. However, if there is no obvious source of infection, antibiotics should be discontinued [23].

Emerging Pharmacologic Therapies

- No evidence to suggest that any of the current targeted therapies provide benefit.

There has been extensive research evaluating pharmacologic agents such as somatostatin, octreotide, atropine, glucagon, and cimetidine that specifically reduce pancreatic secretions. Most of the research has had disappointing outcomes. For example, cimetidine, assessed via a meta-analysis of 5 randomized controlled trials in 2002, has also proven to be no more effective than placebo in decreasing complications or pain [36,37].

Since acute pancreatitis features autodigestion from proteases, protease inhibitors would theoretically provide benefit. However, studies on gabexate mesilate and aprotinin have not demonstrated an improvement in patient outcomes [38,39]. Numerous other attempts at targeted pharmacologic therapy, such as lexipafant (platelet activating factor antagonist), antioxidants, corticosteroids, nitroglycerin, IL-10 or TNF- α antibodies, have shown no benefit in the treatment of acute pancreatitis and should not be used at this time [40].

Nonpharmacologic Strategies

Nutrition

- Enteral feeding if tolerated is strongly preferred over parenteral feeding
- Mild acute pancreatitis: start enteral feeds within the first week of hospitalization
- Severe acute pancreatitis: start enteral feeds within the first 72 hours of hospitalization

In the past, patients with acute pancreatitis were kept nothing by mouth – with the intent of providing pancreatic and bowel rest - until pain resolution. The practice did not have any demonstrable benefit as bowel rest is associated with intestinal mucosal atrophy and increased infectious complications due to bacterial translocation [41]. Therefore, in order to maintain gut barrier function, enteral feeding is preferred over parenteral feeding in the management of acute pancreatitis [42,43].

In mild acute pancreatitis, early initiation of oral intake with a low-fat soft solid diet is often tolerated and has been demonstrated to be as equally efficacious as tube feedings [44]. Enteral feeding is recommended within one week of hospitalization, typically after cessation of nausea, vomiting, discontinuation of parenteral analgesics, reduction in abdominal pain, and return of bowel sounds [45].

In patients with severe acute pancreatitis, it is recommended to initiate enteral nutrition via nasoenteric tubes within the first 72 hours of hospitalization. A 2012 meta-analysis of 381 patients with severe acute pancreatitis confirms the benefit of enteral vs. parenteral feeds. With two groups randomized to receive each variation of nutrition, those with enteral feeds benefitted in mortality, infection, organ failure, and had a lower surgical rate [46]. Nasojejunal feeding has long been preferred, although there is evidence that nasogastric

have similar clinical efficacy [47]. Although evidence shows a preference towards enteral feeding, should the patient be unable to tolerate it, or not meet nutritional goals, parenteral nutrition should be initiated while maintaining a slow rate of enteral feeds [23].

Management of Underlying Etiology

- Evaluate for gallstones with abdominal ultrasound in all acute pancreatitis patients
- Cholecystectomy is recommended for those with acute pancreatitis and gallstones found on imaging.
- ERCP should not be used in acute pancreatitis unless there is ascending cholangitis or clinical decompensation in the setting of elevated liver tests

Identifying and treating the underlying etiology remains the most effective means of preventing a recurrence of acute pancreatitis. The most common cause is gallstones (40-70%) followed by alcohol use (25-35%) [48-50]. For this reason, an abdominal ultrasound is recommended for all those presenting with acute pancreatitis to evaluate for gallstones; should they be present, an elective cholecystectomy is suggested prior to discharge [23].

In patients with acute biliary pancreatitis, endoscopic retrograde cholangiopancreatography (ERCP) should only be used in the context of ascending cholangitis, or worsening liver tests with concomitant clinical deterioration [23,51]. In general therefore, ERCP should be avoided in the management of acute pancreatitis. The role of ERCP in gallstone pancreatitis is discussed in detail elsewhere in this volume.

Recurrence

The recurrence rate of acute pancreatitis is roughly 25% but can be up to 50% in patients whose predisposing factors have not been identified or addressed [52]. As stated above, identifying and treating the underlying etiology is the most important step in preventing recurrence. In the case of a recurrent episode, additional imaging modalities are recommended to evaluate the anatomy of the region and possibly biliary or pancreatic ductal sludge as well as obstructive calcifications. A computed tomography scan, magnetic resonance cholangiopancreatography exam or endoscopic ultrasound may be employed to visualize the area effectively [23].

Summary

While there continues to be high mortality and morbidity associated with acute pancreatitis, treatment remains largely supportive with early aggressive intravenous fluid resuscitation in the first 24 hours used to maintain the pancreatic microcirculation and prevent progression to severe acute pancreatitis, SIRS, multi-organ failure, and pancreatic necrosis. Optimal type, volume, and rate of infusion for the IV fluids require further randomized controlled trials. No pharmacologic therapies have been shown to be of benefit in reducing the risk of these devastating complications. Furthermore, antibiotics are not recommended for prophylaxis of infected pancreatic necrosis and have shown no benefit in multiple large-

scale studies. Identifying and treating the underlying etiology is the best way to prevent recurrence.

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Key points

- Early aggressive fluid resuscitation with lactated Ringer's with a goal total infusion of 2.5-4 L in the first 24 hours.
- Antibiotics are not recommended for prophylaxis of infected pancreatic necrosis, though indicated if another source of infection is clinically suspected.
- Enteral feeding if tolerated is strongly preferred over parenteral feeding, especially in severe acute pancreatitis.
- ERCP in acute gallstone pancreatitis should not be performed unless there is evidence of ascending cholangitis or there is clinical deterioration in the context of rising liver tests.
- Cholecystectomy is recommended prior to discharge for those with acute pancreatitis and gallstones found on imaging.