Modern Management of Acute Pancreatitis

Neeraj Anand, MD, Jung H. Park, MD, Bechien U. Wu, MD, MPH*

KEYWORDS

- Acute pancreatitis • BISAP • Mortality • Management
- Complications • Fluid Resuscitation • Necrosis

BURDEN OF ACUTE PANCREATITIS IN THE MODERN ERA

Recent national survey data indicate a rising incidence of acute pancreatitis in the United States, attributed primarily to a rise in biliary pancreatitis. At present, there are more than 300,000 admissions for acute pancreatitis on an annual basis[1] at a direct cost exceeding $2 billion.[2] Although acute pancreatitis is typically a self-limited illness, up to 15% of patients experience a severe life-threatening form of disease.[3] Length of stay and direct costs vary considerably by severity of disease. In this age of cost containment, modern management of acute pancreatitis has evolved to emphasize effective interventions for prevention and management of complications, as well as appropriate resource utilization. This article addresses recent developments in the management of acute pancreatitis starting from initial hospital presentation extending through discharge and includes discussion of approaches secondary prevention.

INITIAL ASSESSMENT OF SEVERITY

Since the Ranson criteria were originally published in 1974,[4] numerous clinical prognostic scoring systems have been developed, the most prominent of which is the APACHE II score.[5] Although it is a widely validated instrument and clearly useful for research purposes, the APACHE II score has failed to gain widespread application in clinical practice as a result of its complexity. A simplified scoring system known as the Bedside Index of Severity in Acute Pancreatitis (BISAP) was developed based on data from 177 U.S hospitals and more than 17,000 cases of acute pancreatitis[6] (**Table 1**). This five-factor scoring system contains elements that are routinely available at the time of hospital admission and its use during the initial 24 hours of hospitalization has now been validated in several prospective cohort studies.[7,8] Two specific elements of the BISAP score warrant further discussion. First, blood urea nitrogen (BUN) has

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Department of Gastroeneterology, Kaiser Permanente Los Angeles Medical Center, 1526 North Edgemont Avenue, Los Angeles, CA 90027, USA
* Corresponding author.
E-mail address: Bechien.u.wu@kp.org

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Table 1
BISAP score and its associated mortality

Parameters	Value	If Present, Points Allocated
Serum BUN	>25	1
Mental status	Impaired	1
SIRS	Present	1
Age of the patient	>60 years	1
Pleural effusion	Present	1
	Total Score	**Mortality (%)**
	0	0.20
	1	0.60
	2	2
	3	5–8
	4	13–19
	5	22–27

received renewed interest as an early prognostic marker in acute pancreatitis. Either an elevated BUN at admission or early rise in BUN was found to be a strong risk factor for mortality in several retrospective and prospective cohort studies of acute pancreatitis.[9,10] Another component of the BISAP, the systemic inflammatory response syndrome (SIRS), has also been evaluated as a potential risk factor for severe acute pancreatitis (**Table 2**). Several prospective cohort studies of acute pancreatitis have shown that persistent SIRS,[11] lasting 48 hours or more, is associated with increased risk of necrosis, multiorgan failure, and death (**Fig. 1**).[12,13]

EARLY FLUID RESUSCITATION

Vigorous fluid resuscitation is a cornerstone of therapy during the early management of acute pancreatitis. However, recommendations on fluid resuscitation have been based primarily on expert opinion and data from animal models.[14] One retrospective study suggested that timing of fluid resuscitation may be more important than the total volume of fluid administered; in this study, patients receiving a greater proportion of their total fluid resuscitation during the initial 24 hours had reduced complications.[15] However, there are potential hazards associated with vigorous fluid resuscitation, such as pulmonary sequestration, as suggested by a prospective cohort study from Spain.[16] The data are difficult to interpret because fluid resuscitation parameters were driven by clinician judgment, and as such patients with more severe disease would most likely be those

Table 2
SIRS criteria, defined by the presence of two or more

Parameters	Value
Temperature	<36°C or >38°C
Heart rate	>90 per minute
Respiratory rate	>20 per minute or $Paco_2$ <32 mm Hg
White blood cell count	<4000 cells/mm^3 or >12,000 cells/mm^3 or 10% bands

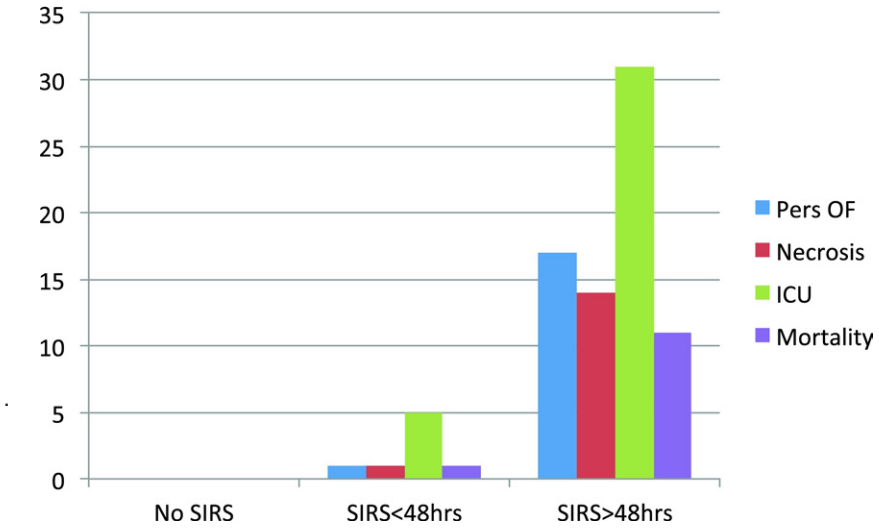

Fig. 1. Association of SIRS with Severe Acute Pancreatitis. Pers OF = persistant organ failure; Necrosis = pancreatic Necrosis; ICU = ICU admission; Mortality = Death.

receiving the more aggressive fluid resuscitation. An additional randomized controlled trial (RCT) from China showed that patients who were randomized to rapid hemodilution (targeting hematocrit <35%) received on average more than 10 L of fluid on the first hospital day and experienced greater frequency of sepsis and higher mortality.[17] Although these findings are difficult to generalize to Western populations because of variations in the underlying treatment of acute pancreatitis, these findings underscore the potential risks associated with very aggressive fluid resuscitation without hemodynamic monitoring. As a result of these potential concerns, a recent RCT evaluated the impact of a targeted approach to early fluid resuscitation in acute pancreatitis.[18] Although the study was underpowered to assess the effect of a goal-directed resuscitation algorithm because of a significant crossover effect, the study investigators found a reduction in SIRS based on the type of fluid used for initial resuscitation. Specifically, use of the more pH-balanced lactated Ringer's solution led to greater reduction in SIRS compared to the use of normal saline. In addition, there was no evidence of pulmonary sequestration among the 40 patients included in the trial.

APPROPRIATE USE OF RADIOGRAPHIC IMAGING IN THE EARLY PHASE OF ACUTE PANCREATITIS

Several studies have called attention to the increased use of cross-sectional imaging in the setting of acute pancreatitis, which has not been associated with either greater severity of disease or change in outcomes.[19,20] Based on several studies that have indicated a lack of sensitivity of early cross-sectional abdominal imaging to detect necrosis,[21] as well as the unlikely presence of infected necrosis within the first week of hospitalization,[22] current practice guidelines do not recommend computed tomography (CT) in the early phase of acute pancreatitis.[3,23] In contrast, transabdominal ultrasound is warranted to evaluate for the presence of possible gallstones as an etiology of pancreatitis. CT may be indicated if a

patient experiences persistent SIRS or clinical deterioration after the first 72 hours of illness, or to exclude alternative intra-abdominal processes if the diagnosis of acute pancreatitis is uncertain.

NUTRITIONAL SUPPORT

The most recent Cochrane meta-analysis of enteral versus parenteral nutrition in acute pancreatitis, published in 2010, included eight RCTs.[24] Overall, there was a reduction in mortality, systemic infection, and multiorgan dysfunction in pooled analyses for the patients receiving enteral nutrition; therefore, enteral nutrition is strongly preferred over parenteral nutrition for patients with severe acute pancreatitis. Several trials, including one non-inferiority study, have failed to detect a difference between nasogastric compared to nasojejunal route of enteral nutrition,[25–27] indicating that early enteral nutrition through nasogastric feeding may be sufficient. A multicenter study from the University of Pittsburgh (Study of Enteral Nutrition in Acute Pancreatitis) is underway to address the optimal form of enteral nutrition in acute pancreatitis. In addition, a multicenter prospective RCT is underway in the Netherlands to address the impact that timing of enteral nutrition has on outcome in patients with severe acute pancreatitis. Although initially demonstrating promising results in small nonrandomized clinical trials, the addition of probiotics to enteral nutrition has been shown to be potentially detrimental in a large-scale RCT among patients with severe acute pancreatitis[28]; therefore, use of probitics is not recommended.

MANAGEMENT OF LOCAL COMPLICATIONS

Local complications from acute pancreatitis include pancreatic necrosis, acute fluid collections, and ductal disruption. Although previous small trials have suggested a benefit of prophylactic antibiotics in the setting of necrotizing pancreatitis, two more recent adequately powered double-blind RCTs[29,30] and the most recent Cochrane meta-analysis of seven RCTs, published in 2010,[31] did not demonstrate any impact on the incidence of infected necrosis or mortality with use of prophylactic antibiotics. At present, if infected necrosis is suspected, then the necrosis should be sampled by fine-needle aspiration. Once infected necrosis is confirmed, in addition to antibiotic treatment, a “step-up” approach can be pursued whereby percutaneous drainage is used as a temporizing maneuver, followed by minimally invasive retroperitoneal débridement if the patient fails to improve over the course of the next 72 hours. Such an approach has been shown to produce better overall outcome compared to traditional open débridement.[32] Overall, there has been a trend toward more conservative, less invasive approaches to management of necrosis, as well as infected necrosis, supported by observational studies that have demonstrated improved survival with delayed surgical intervention.[33]

Gallstone Pancreatitis and the Role of Endoscopic Retrograde Cholangiopancreatography

There are several clearly defined roles for endoscopic retrograde cholangiopancreatography (ERCP) in acute pancreatitis. Urgent ERCP—within 24 hours—is indicated in patients who have severe acute biliary pancreatitis with organ failure or cholangitis or both. Elective ERCP with sphincterotomy can be considered in patients with persistent or incipient biliary obstruction, those deemed to be poor candidates for cholecystectomy, and those in whom there is strong suspicion of bile duct stones after cholecystectomy. ERCP also is indicated for pancreatic ductal disruptions that

occur as part of the inflammatory process and result in persistent peripancreatic fluid collections, pleural effusion, or ascites.

MANAGEMENT OF SYSTEMIC COMPLICATIONS

Systemic complications in acute pancreatitis include extrapancreatic infection, as well as distant organ failure.

Extrapancreatic Infection

Two large multicenter studies have called attention to the impact of extrapancreatic infection in acute pancreatitis. In a study from the Netherlands, more than 25% of patients with acute pancreatitis developed either bacteremia or pneumonia during their hospitalization.[22] The majority of these infections occurred within the first 2 weeks. By contrast, infected necrosis occurred on average 4 weeks after presentation. In a separate cohort study involving U.S. hospitals, hospital-acquired extrapancreatic infection was associated with a greater than twofold increased risk of mortality, even after adjusting for disease severity.[34] The clinical implication of these findings is that an extensive evaluation for potential sources of extrapancreatic infection should be undertaken and, if detected, these infections should be treated aggressively.

Respiratory failure is the most common form of organ dysfunction in acute pancreatitis.[35] Circulatory shock and renal insufficiency are also observed in severe cases. Although various measures of organ failure exist, the majority of recommendations define respiratory compromise as a room air oxygen saturation less than 90%, a systolic blood pressure less than 90 mm Hg, or a serum creatinine greater than 2.0 g/dL after initial fluid resuscitation.[36] Up to 20% of patients may have evidence of persistent organ failure 48 hours into their hospitalization. Patients with multiorgan dysfunction are at the greatest risk for mortality and should be managed in a critical care setting with a multidisciplinary care team. Recent data have suggested that centers with higher volume of acute pancreatitis cases achieve reduced mortality and costs.[37]

SECONDARY PREVENTION

The disease recurrence rate varies according to etiology of acute pancreatitis. Overall recurrence rates for acute pancreatitis range from 16.5% to 25%, with the majority of episodes occurring within the first several years of the initial attack. Continued alcohol consumption, smoking, and recurrent biliary complications are the major risk factors for disease recurrence. Prevention of disease recurrence is a major focus in acute pancreatitis. Appropriate prevention strategies vary according to etiology. Alcohol abstinence is the key to prevention of recurrence in the case of alcohol-associated pancreatitis. A RCT demonstrated that repeated alcohol cessation intervention at 6-month intervals was associated with reduced recurrence of acute pancreatitis compared to a one-time intervention session.[38]

Based on several retrospective and prospective observational cohort studies that demonstrate up to a 30% recurrence rate of gallstone pancreatitis, the recommendation for prevention of recurrent episodes of gallstone-associated pancreatitis is cholecystectomy. Although there is some variation in the recommended timing of cholecystectomy, most guidelines recommend operation before discharge whenever possible. In patients unable to undergo surgery, endoscopic sphincterotomy has been shown to reduce the risk of recurrent biliary pancreatitis, albeit to a lesser extent than cholecystectomy.[39]

ADDITIONAL ETIOLOGIES

Although less common, additional forms of acute pancreatitis such as medication-associated, hypertriglyceridemic-induced, and hypercalcemia-induced pancreatitis each require individualized strategies for prevention of recurrence. Discontinuation of any potentially offending medication is indicated in the case of suspected medication-associated pancreatitis.[40] Reduction of triglyceride levels through use of statin and fibrate medications is indicated in the case of acute pancreatitis secondary to hyperlipidemia.[41] Finally, treatment of the underlying cause of hypercalcemia is paramount for the prevention of acute pancreatitis due to hypercalcemia.

SUMMARY

There is a rising incidence of acute pancreatitis in the United States. Numerous clinical prognostic scoring systems have been developed, including the BISAP score. Vigorous fluid resuscitation remains a cornerstone of early management of acute pancreatitis. Cross-sectional imaging in the early phase of evaluation has not been associated with improvement of outcomes. There is no role for prophylactic antibiotics in early management. However, there is growing emphasis on the identification and treatment of extrapancreatic infections. Enteral nutrition in severe acute pancreatitis has reduced mortality, systemic infection, and multiorgan dysfunction compared to parenteral nutrition. Conservative management consisting of percutaneous drainage and delayed surgical intervention is now favored for local complications, such as infected necrosis. These developments have contributed to improved outcomes for patients with acute pancreatitis.

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