MEDICAL MANAGEMENT OF ACUTE PANCREATITIS
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In the last decade, there has been a significant amount of active and enthusiastic research which has changed the way we treat acute pancreatitis (AP) within the first 24 hours of presentation. Herein, we highlight the importance of rapid initiation of treatment to help prevent the considerable morbidity and mortality which can occur when interventions are delayed. We review recent data which validates simple and accurate tools for prognostication of AP to replace the older more tedious methods which relied on numerous factors and required up to 48 hours to complete. Additionally, we aim to provide evidence-based guidelines and endpoints for fluid resuscitation. Finally, we hope to bring clarification to a previously controversial topic in acute pancreatitis treatment: the use of prophylactic antibiotics.

Introduction
Acute pancreatitis (AP) is responsible for approximately 210,000 hospital admissions per year in the United States and 5% of all patients with AP die. Despite extensive morbidity and mortality, no targeted pharmacologic treatment exists to effectively alter the disease course. However, in the last decade, several interventions have been identified as critical in the first 24 hours to minimize morbidity and maximize survival. Comparable to the narrow diagnostic and therapeutic window in both acute cardiac and cerebral ischemia, prompt recognition and management of acute pancreatitis during these “golden hours” is essential to improving patient outcomes. This review highlights the importance of accurate disease prognostication and triage, fluid resuscitation, and prophylactic antibiotic use.

Prognostication
Although the majority of cases of AP are categorized as mild, it is necessary to promptly identify those patients who are at risk of severe morbidity or death. Assessment of severity has been an area of intense investigation with multiple scoring systems proposed. Until recently, no scoring system has been able to balance accuracy with simplicity. However, the Bedside Index for Severity of Acute Pancreatitis (BISAP) score was developed as a simple tool to assess risk of in-hospital mortality in acute pancreatitis and, to date, is the most facile tool available for predicting severity. The BISAP score is used to predict mortality and to guide early management of AP, due to the recognition that earlier and more aggressive interventions are likely to prevent adverse outcomes, particularly in severe cases. The score is calculated using five variables available in the first 24 hours: BUN >25 mg/dl, impaired mental status (Glasgow Coma Score <15), presence of the systemic inflammatory response syndrome (SIRS), age >60 years, and pleural effusion detected on imaging. It was initially validated to predict mortality using retrospective data from 18,256 cases of AP from 177 centers in 2004-2005, and was further validated prospectively using data from 397 consecutive cases in 2005-2007. Each positive variable adds one point to the total score and scores of 3, 4, and 5 correspond with a hospital mortality of 5.3, 12.7, and 22.5%, respectively. Additionally the BISAP score can predict persistent organ failure (organ failure present >48 hours) which is a strong independent risk factor for mortality.

The Harmless Acute Pancreatitis Score (HAPS) is another simple scoring system which includes three factors that can be measured within 30 minutes of admission: absence of rebound tenderness and/or guarding, normal hematocrit, and normal serum creatinine. The authors concluded that the HAPS predicted a non-severe disease course with 96-97% specificity and 98% positive predictive value. However, it is unclear from the published data what the hospital interventions were in these cases. For example, if patients were treated optimally for AP with aggressive fluid resuscitation, pain control, and early enteral nutrition, then a severe course may have been averted in those who may have had a normal HAPS on admission but would have progressed to severe AP without those interventions.

The BISAP and HAPS scores have several advantages over earlier methods of attempting to predict severity of disease. Ranson’s criteria scoring cannot be completed prior to 48 hours into the hospitalization. The APACHE II score was validated on critically ill patients and calculation requires arterial blood gas, which is not routinely obtained in the emergency department, and knowledge of the patient’s past medical history, which may not be attainable in the acute setting. The CT severity index relies on contrast-enhanced CT which is generally not necessary upon presentation in most cases of AP, and in fact may not be possible in the setting of renal dysfunction or hypovolemia.

Even simpler than the BISAP score, markers of hemococoncentration seem to predict mortality in AP performs as well as more complex markers. The prognostic ability of measurements of BUN and hematocrit stem from the ability to mirror intravascular volume depletion, a critical risk factor for death in AP. In a recent validation study using three large databases
including 1,043 patients with acute AP in three centers, a BUN level of 20 mg/dL or higher was associated with an odds ratio (OR) of 4.6 (95% confidence interval [CI], 2.5-8.3) for mortality. Any rise in BUN level at 24 hours was associated with an OR of 4.3 (95% CI, 2.3-7.9) for death. Elevated hematocrit upon admission or failure of the hematocrit to decrease in the first 24 hours of treatment, are additionally helpful in predicting a more severe disease course.

Ultimately the treating physician must cautiously consider all available information, taking into account patient age, laboratory and physical examination data, and comorbid conditions including obesity. These recent simplified scoring systems, when compared with those used historically, are simple, accurate and timely. They should enable practitioners to more rapidly triage appropriate patients to a tertiary care center or to the intensive care unit, and allow for more informed discussions with patients and their families about prognosis at the time of hospital presentation.

**Fluid Resuscitation**

AP initially causes the release of cytokines and other pro-inflammatory mediators leading to vasodilatation, intravascular volume depletion and end-organ hypoperfusion. Long under-valued as a life-saving intervention early in the disease course, aggressive fluid resuscitation is a cornerstone in the treatment of AP during the first 24 hours. Under-resuscitation is associated with increased morbidity (including the development of SIRS, necrotizing pancreatitis, organ failure) and mortality. Recent studies have demonstrated the critical importance of maintaining perfusion of the microcirculation of the pancreas and intestine to prevent intestinal ischemia and subsequent bacterial translocation and secondary pancreatic infection.

In adult patients, we almost universally begin infusion with rates of between 250-300 ml/hr, or enough to produce at least 0.5 ml/kg/hr of urine output. This follows a 1,000-2,000 ml fluid bolus given in while the patient is still in the emergency room. This initial rate should be adjusted based on patient age, weight, physical exam findings, and comorbid conditions such as pulmonary edema or renal failure. Hemoconcentration and elevation of BUN both reflect the amount of intravascular depletion and can be used, in addition to measurement of urine output and monitoring for the development of pulmonary edema, to guide the rate of fluid resuscitation. Since intravascular volume repletion is vital to re-establishing or maintaining the microcirculation of the pancreas, these measures should be taken into account upon admission to assist with gauging severity and again at intervals such as every 12h after admission.

In patients with underlying cardiac or renal disease or in those of advanced age, caution should be used in administering aggressive IVF. These patients should be monitored closely for fluid overload using the physical examination (particularly development of hypoxia, elevation of jugular venous pulsations, development of S3 on cardiac auscultation or rales on pulmonary auscultation). In these cases, measurement of central venous pressure may be helpful. While the type of IV fluids has always been a source of debate, recent randomized controlled data suggest that lactated ringer’s solution may be superior to normal saline in preventing SIRS.

Two studies have concluded that aggressive IV fluid resuscitation may be harmful; however, we believe that this conclusion is limited by the research design of these investigations. Both studies included only patients with severe acute pancreatitis upon admission. The first, a retrospective evaluation of 99 patients, found that patients receiving 4 liters or more in the first 24 hours developed more respiratory complications and were more likely to require ICU-level care than those who received less than 4 liters. It is not clear from the data precisely what the pulmonary complications were or the reasons for ICU-level care, although it is stated that pulmonary edema was not noted in any patient. More information about these details is required before drawing the conclusion that the more aggressive fluid regimen led to poorer outcomes for the patients.

The second study, a randomized trial of 115 patients in China, concluded that in patients with severe AP, rapid hemodilution is associated with increased sepsis and mortality. However, the study was performed to target a hematocrit <35% in the rapid hemodilution group and ≥35% in the slow hemodilution group over the first 72 hours. In contrast to this approach, we recommend that fluid administration be adjusted not to a particular hematocrit level, but rather to target adequate urine output; stabilization of blood pressure and heart rate; normalization of central venous pressure; and modest decrease in hematocrit. Additionally in this study, fluids were administered over 72 hours with most of the fluid provided during the second 24-hour period. As has been shown in our prior research, the best outcomes are obtained when greater than 1/3 of the 72-hour fluid total is given in the first 24 hours.

The importance of aggressive IV fluid resuscitation cannot be overstated during the first 24 hours of admission for acute pancreatitis. This intervention, although often overlooked, is a simple therapy that can dramatically improve patient outcomes.
Prophylactic Antibiotics

The use of prophylactic antibiotics given at the time of detection of pancreatic necrosis in severe AP has been an area of considerable debate. A meta-analysis published in 2001 of several randomized controlled trials (RCTs) comparing antibiotic prophylaxis with no prophylaxis in cases of necrotizing pancreatitis showed no reduction in local pancreatic infections but significantly reduced rates of sepsis and mortality in those treated with antibiotics (21.1% and 12.3% reductions, respectively). However, their meta-analysis included only three RCTs and a total of only 160 patients. In 2008, an updated meta-analysis of RCTs exploring whether prophylactic antibiotics reduced infected pancreatic necrosis and mortality in necrotizing AP. The meta-analysis included seven trials (including the three trials in the 2001 meta-analysis) and 467 patients, and found that antibiotics did not reduce the incidence of infected pancreatic necrosis (p = 0.32) or mortality (p = 0.17). A 2010 Cochrane Review of the same 7 trials analyzed in 2008, again found no significant difference in mortality, despite a significantly lower rate of pancreatic infection in those treated with imipenem.

The most recent meta-analysis, published in 2011, reviewed 14 trials with a total of 841 patients and included all of the trials included in the prior three meta-analyses and no difference in rates of mortality or infection were detected. As a result of these findings, as well as the fact that prolonged prophylactic antibiotics are associated with the development of intra-abdominal fungal infections, prophylactic antibiotics are not recommended for use as a prophylactic therapy in AP and should not be given in the first 24 hours to prevent infection.

Conclusion

In summary, the first 24 hours of care of the patient with AP is crucial to reducing the morbidity and mortality associated with this disease process. During these “golden hours,” initial assessment using a severity scoring system such as the BISAP or HAPS score, as well as markers of hemoconcentration such as BUN and hematocrit, can guide triage and early management. Adequate early fluid resuscitation is essential to decrease inflammation and maintain organ perfusion. We recommend using lactated Ringer’s solution and ongoing assessment of urine output and markers of hemoconcentration. Prophylactic antibiotics should not be routinely used, even in cases of pancreatic necrosis, unless infection is suspected to be present based on lab, culture, or imaging data. As patients enter the second 48 hours of their hospitalization, issues such as the initiation of enteral feeding will need to be addressed to help prevent persistent organ failure, prolonged hospitalization, readmission or death.

REFERENCES


