



Review article

ICU management of severe acute pancreatitis

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Abstract

In intensive care medicine, severe acute pancreatitis (SAP) remains a very challenging disease with multiple complications and high mortality. The main pathophysiological mechanisms determining outcome are an uncontrolled systemic hyperinflammatory response early on and infection of pancreatic necrosis later on in the disease process. Despite a better understanding in recent years of the mechanisms and the mediators involved in the hyperinflammatory response, there is, as yet, no generally recognized specific treatment for this disease. Since early identification and aggressive treatment of associated organ dysfunction can have a major impact on outcome, early assessment of prognosis and severity is important. The evidence available indicates that patients with severe acute pancreatitis do not benefit from therapy with available antisecretory drugs or protease inhibitors. Supportive therapy, such as vigorous hydration, analgesia, correction of electrolyte and glycemia disorders, and pharmacological or mechanical support targeted at specific organs, is still the mainstay of therapy. In spite of meager evidence, prophylactic antibiotics with good penetration in pancreatic tissue are recommended in severe acute pancreatitis. Enteral nutrition via a nasojejunal tube has become the preferred route of feeding. Most patients with sterile necrosis do not benefit from surgical intervention. In patients with proven infection of pancreatic tissue, surgery is necessary. Percutaneous, radiological drainage techniques may eventually become an alternative form of drainage in selected patients.

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1. Introduction

The clinical spectrum of acute pancreatitis ranges from a transient, self-limited inflammation with minimal organ dysfunction and uneventful recovery to necrotizing pancreatitis with multiple organ failure and death. Based on a consensus conference, severe acute pancreatitis (SAP) is defined as acute pancreatitis associated with other end organ failure and/or local complications such as necrosis, abscess, or pseudocyst [1]. Necrosis of pancreatic tissue develops in 14–40% of all cases of acute pancreatitis, with the higher incidences reported in patients admitted to tertiary care centers [2–4]. While the overall mortality of acute pancreatitis without necrosis is close to zero, the mortality of acute necrotizing pancreatitis (ANP) depends very much on possible infection of the necrotic tissue. Depending on patient selection and institutional differences, infection of necrotic pancreatic tissue may occur in 30–70% of patients [5–7]. This ominous complication accounts for a major percentage of the observed mortality and at least doubles the mortality from less than 10% in patients with sterile necrosis without additional organ failure to more than 25% and even up to 70% in those with infected necrosis and multiple organ failure [5,7–10].

Over the last decade the benefit of early surgical intervention has been challenged and early, aggressive intensive medical care has become commonplace [11–13]. In this review I will give an informed opinion on the general management of patients with SAP admitted to an intensive care unit (ICU) and I will also discuss some controversial issues emphasizing evidence from recent clinical trials and recommendations from consensus conferences.

2. Pathophysiology

In the European Union, the United States, and in Asia, gallstones and alcohol together account for approximately 80% of all cases of SAP. Other less common causes of the disease include endoscopic retrograde cholangiopancreatography (ERCP), hyperlipidemia, hypercalcemia, drugs, pancreas divisum, abdominal trauma, and hereditary disease. In about 10% of cases, no specific cause can be identified [2].

Regardless of the cause, acute pancreatitis appears to be initiated with the premature intrapancreatic activation of digestive enzymes in conjunction with microcirculatory changes. A local inflammatory reaction ensues. In severe pancreatitis, the local inflammation is amplified through induction of a generalized, cytokine-mediated, hyperinflammatory systemic response. Inflammatory and anti-inflammatory cytokine production begins shortly after the onset of pain and typically lasts for several days [14,15]. An imbalance in this process seems to be ultimately responsible for the organ failures observed early on in the course of the

disease [16]. Infection of necrotic tissue accounts for a major percentage of the mortality later in the disease. There is evidence pointing to bacterial translocation from the intestines as the source of pancreatic infection [17]. The exact mechanism of transmural migration and the route of migration of the micro-organisms to the pancreas are still unclear.

3. General management

For diagnostic purposes and at the time of admission to the ICU, not all patients with acute pancreatitis are in need of immediate, dynamic, contrast-enhanced, tomographic scanning (CECT). However, this imaging procedure is the modality of choice for the detection of necrosis and for radiological staging. Even though pancreatic necrosis appears to develop within 24–48 h after the onset of symptoms, CECT performed within the first 12 h may show only equivocal findings [18]. CECT obtained 48–72 h after the onset of symptoms is more accurate in the depiction of necrotizing pancreatitis and has a sensitivity of close to 100%. Follow-up scans within 7–10 days are recommended in patients with one or more peripancreatic fluid collections, in those with retroperitoneal air, and in case of clinical deterioration when pancreatic infection is suspected to be the cause [19]. If necrosis is present, simultaneous fine needle aspiration should be performed.

Once the diagnosis is established and the patient stable, the management strategy involves several steps. First, there should be ongoing adequate fluid resuscitation, pain control, early detection and treatment of additional organ failures, and assessment of severity. Then, choices will have to be made regarding the use of prophylactic antibiotics, the route of nutrition, the timing of ERCP (in the case of biliary pancreatitis), and the possible benefit of antisecretory or anti-inflammatory treatment modalities. Finally, in some patients, the indications and timing of surgical therapy will need to be considered.

4. Resuscitation, pain control, and treatment of organ dysfunction

At the time of admission to the ICU, patients with SAP are usually volume-depleted due to poor oral intake, third space loss, and increased vascular permeability due to the generalized inflammatory response. Rehydration may require large amounts of fluid (up to 10 l in the first 24 h). In the absence of important cardiac dysfunction, crystalloids are the preferred solution. Patients with SAP should be given an arterial catheter, at least two peripheral lines (and, in cases of simultaneous renal dysfunction or hemodynamic instability, a central venous line), continuous oxygen saturation and electrocardiogram monitoring, and a

urinary catheter. Some patients with multiple organ failure may benefit from more invasive hemodynamic monitoring with a pulmonary artery catheter. After initial rapid resuscitation, fluid replacement should aim at 35 ml/kg body weight per day. If these patients develop shock it is usually of a distributive type, and noradrenaline is a good first choice in this clinical context.

For obvious reasons, adequate pain control is important in many patients. Paracetamol and nonsteroidal anti-inflammatory drugs are often insufficient. The latter need to be used with caution, especially if the patients are hypovolemic and oliguric due to possible exacerbating renal dysfunction. Opiates are often needed and there are no compelling human data suggesting that one opiate is superior to another [19]. In a recent randomized trial with 107 patients, continuous intravenous infusion of procaine hydrochloride was shown to be significantly less effective than an opiate such as pentazocine [20].

Organ dysfunction in the course of SAP is frequent, and early detection and treatment are of paramount importance. Progression to multiple organ failure may occur within a few hours of the onset of symptoms, placing the patient at a very high risk of death from cardiovascular or pulmonary failure. Simple, readily available biochemical and clinical parameters are enough to calculate the sequential organ failure assessment (SOFA) score, which is a practical means to detect and objectively grade organ dysfunction early on [21]. Respiratory failure may be expected in 56–63% of cases, shock in 23–51%, renal failure in 13–42%, and coagulopathy in 19–42% of cases [10,22–25]. The rules for the management of organ dysfunction are the same as for other critically ill patients. However, control of glycemia and intensive monitoring of serum electrolytes are of particular importance in these patients.

5. Assessment of severity

Objective assessment of the severity of acute pancreatitis, though often neglected, is important for a number of reasons, including better identification of patients at risk of developing severe disease, better utilization of costly ICU resources, and timely and specific treatment that may have a positive impact on the outcome. A number of parameters to predict severity in acute pancreatitis have been investigated in the past, i.e., clinical assessment, scoring systems, biochemical parameters, and imaging procedures. Clinical assessment of severity of illness in acute pancreatitis at the time of admission will misclassify approximately 60% of patients [26,27]. Forty-eight hours after admission, however, correct prediction based on clinical grounds will increase to approximately 83%. In recent years, a number of markers of immunological activation or pancreatic injury, such as interleukin-6, urinary trypsinogen activation peptide, procalcitonin, phospholipase A₂, and polymorphonu-

clear elastase, have been shown to be good candidates for the early stratification of patients with acute pancreatitis [28,29]. However, at the present time, none of these tests are available for use in routine practice because they are expensive and time-consuming. The C-reactive protein (CRP) is a good discriminator between severe and mild disease 48 h after the onset of symptoms. A cut-off level of 150 mg/l is accepted in the literature as a good predictor of severe disease [30]. Both the Ranson's score and the Glasgow (Imrie) score have a good predictive value, but after 48 h they are not much better than intuitive prediction based on physical findings [31–33]. The Acute Physiology and Chronic Health Evaluation score (APACHE II score) comprises biochemical and clinical variables as well as several co-morbidities that have been proven to influence outcome. Since the predictive accuracy for death or complications with the APACHE II score at 24 h is as effective as the former scoring systems at 48 h, this score has been recommended as the best choice if a multiple factor scoring system is to be used [30]. An APACHE II score of 9 or more indicates a severe disease, but will exclude many with a lower score who will develop a complication. An APACHE II score of 6 or more will include nearly all complications (sensitivity 95%), but only half of the patients will develop a complication (positive predictive value 50%) [34]. On the basis of a combination of peripancreatic inflammation, phlegmon, and degree of pancreatic necrosis, a CT severity index can be completed that correlates well with morbidity and mortality [18,35]. Obesity, as shown by a body mass index (BMI) above 30, is a reliable predictor of severe outcome independently of age [36,37]. Left-sided or bilateral pleural effusions on chest X-ray performed within 24 h of admission have also proven to be indicative of subsequent complications or fatal outcome [38]. Based on the aforementioned and on the 1999 Santorini consensus document on the management of acute pancreatitis [30], this author favors the following practical approach to predicting severity requiring admission to an ICU: a BMI above 30, left-sided or bilateral effusion on chest radiography performed within 24 h of admission, an APACHE II score of at least 8 at 24 h after admission, and a CRP above 150 mg/l or a Ranson score above 3 at 48 h after admission. The development of organ failure or pancreatic necrosis (i.e., SAP by definition) also warrants immediate transfer to an ICU.

6. The role of prophylactic antibiotics

In acute pancreatitis, infected necrosis accounts for approximately 80% of all deaths. The incidence of infection depends on the duration of the pancreatitis. In a prospective, clinical study of 114 patients with ANP, the infection rate in the first week was 24%, in the second week 36%, and it reached a peak of 71% in the third week [5]. Forty-three to eighty-six percent of the organisms found in pancreatic

infection are gram-negative rods, 28–36% are staphylococci and streptococci, 4–11% anaerobes, and 7–37% *Candida* species [10,22,39]. Thus, prevention of infection by means of anti-infectives could, theoretically, be a beneficial therapy. However, the role and optimal duration of prophylactic antibiotic therapy are still controversial issues. Clearly, an antibiotic agent has to reach a therapeutic tissue level in the pancreas and must cover the flora commonly encountered in pancreatic infection. For this purpose, carbapenems, followed by quinolones, are by far the most efficacious antibiotics [17,40].

Between 1993 and 2003, seven prospective, controlled studies with prophylactic intravenous anti-infectives, with or without selective digestive decontamination (SDD), were published [41–47]. In most of these studies, the incidence of pancreatic infection was reduced, usually significantly, and in two studies mortality was significantly lower. The largest of these trials randomized 71 patients, the smallest 23. Nonetheless, all guidelines and consensus conferences recommend prophylactic intravenous antibiotics in SAP [19,30,34]. The number of complications may be expected to decrease but not the mortality. There is no place for prophylactic antibiotics in acute mild pancreatitis. SDD improved outcome in one good randomized study, and its use seems to be a rational and logical approach in preventing late infection of pancreatic necrosis. Because of the workload associated with its use in a group of patients who already place huge demands on ICU resources, unconditional endorsement of SDD has been delayed until further evidence is available. The duration of prophylactic antibiotic treatment is unclear, but there seems to be no significant advantage of 3- versus 2-week treatment duration [22].

7. Nutritional support

For years, TPN has been considered the standard for nutritional support in SAP. The main argument favoring this practice was that intravenous nutritional support was a way of ‘resting the pancreas’ by eliminating the hormonal stimulation and consequent exocrine secretion associated with classical nasogastric enteral nutrition. Several studies, however, conclusively failed to demonstrate an effect on survival [48,49]. Nowadays, enteral nutrition (EN) is favored [50]. The rationale for the use of EN is based on the premise that enteral feeding maintains the barrier function of the intestinal tract, promotes gut motility, possibly reduces translocation of bacteria or endotoxins, and avoids the infectious complications associated with TPN. Between 1997 and 2003, six randomized trials were published that compared TPN and EN in patients with acute pancreatitis [51–56]. The largest study randomized 96 patients, the smallest 26. Although further studies are necessary, the published data suggest that EN is safe and may be advantageous over

TPN in ANP. One definite benefit of EN in the setting of ANP is reduced costs; probable benefits include reduced septic complications. The following recommendations have been made [19,30]:

1. Most patients with mild pancreatitis do not benefit from nutritional support.
2. In patients with severe pancreatitis, EN via a nasojejunal tube inserted beyond the ligament of Treitz should be started early in the course of the disease.
3. TPN is advised only in circumstances of intolerance to EN, or of increasing pain with significant increases in amylase and lipase during EN, or when a nasojejunal tube cannot be placed.
4. Patients who require an operation should have a jejunal tube placed at the time of surgery.

8. Indications and timing of ERCP

Common bile duct stones are the cause of SAP in about 40% of cases. ERCP is only indicated when a biliary cause is strongly suspected or, preferably, proven. The ideal timing of ERCP and endoscopic sphincterotomy (ES) has been evaluated in four prospective, randomized studies including from as few as 120 to as many as 238 patients [57–60]. These four trials differ importantly with regard to inclusion criteria, study design, and definitions. Definite conclusions about the timing of ERCP are, therefore, not possible. However, the following recommendations have been issued by the 1998 United Kingdom guidelines for the management of acute pancreatitis and have been endorsed by the Santorini consensus document [30,34]:

1. In the presence of severe pancreatitis with sonographically detected gallstones and jaundice (or bilirubin level equal or greater to twice the upper limit to normal) or aspartate or alanine transaminase at least twice the upper limit of normal or in the case of cholangitis, urgent ERCP with sphincterotomy is recommended.
2. In the absence of these biochemical and clinical signs, conservative treatment is justified in suspected gallstone-pancreatitis. However, if the patient’s condition fails to improve within 48 h in spite of intensive resuscitation, therapeutic ERCP is also indicated.
3. Whenever performed, ERCP should be carried out by an experienced endoscopist and the patient should receive antibiotic coverage.

9. Antisecretory or anti-inflammatory treatment modalities

Somatostatin and its long-acting analogue, octreotide, are potent inhibitors of pancreatic exocrine secretion and

have been reported to decrease mortality in experimental acute pancreatitis. Since significant effects on mortality rate have only been shown in meta-analysis, therapy with somatostatin in acute clinical pancreatitis has not found its way into standard practice [63–66]. A large randomized, double-blind, multicenter trial with octreotide in moderate to severe acute pancreatitis showed no benefit [67]. Platelet-activating factor (PAF), a pro-inflammatory lipid mediator, plays a significant role in the systemic immune response syndrome that follows SAP. The only PAF antagonist that has been studied in humans is lexipafant, and initial double-blind trials with this compound have shown a promising trend towards a reduction in mortality and a reduced incidence of systemic complications [68]. These encouraging findings were later discredited by the results of a large multicenter, phase III, double-blind, randomized study involving 290 patients with predicted SAP (APACHE II >6) [69]. Lexipafant, administered within the first 72 h after the onset of symptoms, was no better than placebo in preventing new organ failure or mortality.

Given the available evidence, there is general consensus that none of the available antisecretory drugs or protease inhibitors is beneficial in the treatment of any degree of acute pancreatitis [19,30,34,].

10. Surgical treatment

Surgical intervention is necessary for many patients hospitalized with SAP in an ICU. The controversy surrounding the appropriate indication and timing has recently been addressed in a consensus document of the International Society of Pancreatology [13]. The following guidelines have been endorsed.

(1) Infected necrosis is generally accepted as an absolute indication for aggressive surgical debridement. Surgery should be performed as soon as possible after confirmation of pancreatic infection, usually by CT-guided fine needle aspiration of pancreatic necrosis and subsequent gram stain and culture.

(2) The available data do not support a general operative policy towards patients with sterile necrosis, although subgroups may benefit from surgical intervention. These subgroups may include patients continuing to deteriorate from multiple organ failure despite full intensive care, patients continuing to exhibit a septic picture 10 days or more after onset, and patients with recurrent abdominal pain or hyperamylasemia following attempts at oral feeding 3–4 weeks after onset.

In the opinion of this author, a clinical course resulting in an abdominal compartment syndrome with intra-abdominal pressures exceeding 20–25 mm Hg and progressive organ failure should prompt consideration of decompressive laparotomy. Surgical therapies should favor an organ-reserving approach with no technique being clearly superior to another.

Positive results have been reported with less invasive drainage methods, such as percutaneous catheter drainage or percutaneous necrosectomy, but the value of these newer methods has yet to be confirmed in controlled studies.

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