Severe Acute Pancreatitis: A Review*

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Abstract

Background: Severe acute pancreatitis continues to be a difficult problem in clinical management. This paper provides a contemporary definition of the condition and explores the controversial issues that surround its diagnosis and management.

Methods: Review of pertinent English language literature.

Results: The use of various imaging techniques is discussed, with particular emphasis on the assessment of pancreatic necrosis and the evaluation of choledocholithiasis as a cause of the pancreatitis. Prophylactic antibiotics generally are discouraged and early and aggressive nutritional support is advocated. Delayed surgical intervention is recommended to avoid the severe consequences associated with prematurely early attempts at resection of the infarcted pancreas and adjacent retroperitoneal fat.

Conclusions: Better quality evidence, especially regarding the utility or lack thereof of antibiotic prophylaxis, is beginning to inform optimal management of patients with severe acute pancreatitis.

Acute Pancreatitis is a challenge in clinical management. Whereas the majority of patients are discharged from the hospital within days, acute pancreatitis remains an unpredictable disease with a high mortality rate (10%–15%) among a defined proportion of those affected. Recent work has brought additional insights into the pathophysiology of the condition and new directions for treatment, with much of the new information challenging established dogma. This is of particular interest for intensivists or surgeons taking care of these critically ill patients.

This review highlights several of the controversies, with a particular focus on patients with severe acute pancreatitis (SAP). Consistent with international consensus guidelines, SAP is defined as pancreatitis in the context of acute organ dysfunction [1]. We hope to advance the implementation of new evidence into practice through a focus on risk assessment, infection prophylaxis, nutrition, issues of concern regarding biliary pancreatitis in particular, timing of surgery, and the surgical approach [2].

Identification of the Patient at Risk

To guide decision making about appropriate monitoring and resuscitation, it is crucial to identify the patients at risk for either local or systemic complications. Whereas many metrics have been used to estimate risk, they may be classified broadly into general or pancreatitis-specific (e.g., Glasgow or Ranson criteria). Review of the literature suggests that general measures of disease severity that quantify either the degree of acute physiologic derangement or organ dysfunction are more accurate at identifying patients who might benefit from monitoring in a critical care environment [3,4]. Apart from the general criteria for intensive care unit (ICU) admission, there is evidence to suggest, for example, that patients with a Acute Physiology and Chronic Health Evaluation (APACHE) II score > 8 points or a high hematocrit (> 44%) should be admitted to a critical care unit (Table 1). These relatively simple criteria might help operationalize protocols for decision making. Biological markers (C-reactive protein, interleukin-6, trypsinogen activation peptide) have not been validated sufficiently for identifying patients at risk; however, of those studied, procalcitonin appears to offer the greatest promise, with concentrations of > 3.8 ng/mL predictive with high accuracy (sensitivity 79%, specificity 93%) of later organ dysfunction [5].

The extent of pancreatic necrosis has been used to identify patients at risk for the development of SAP. Whereas the extent of necrosis is accurate for the prediction of local complications, there also is a strong association between the presence of extensive necrosis (> 50%) and greater degrees of organ dysfunction [6]. The extent of pancreatic necrosis is estimated by dynamic computed tomography (CT) using intravenous contrast medium. To lessen the risk of contrast nephropathy, it is crucial to assure that patients are resusci-

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*Presented at the 27th annual meeting of the Surgical Infection Society, Toronto, Ontario, Canada, April 21, 2007.
tated appropriately with crystalloid prior to administration of contrast medium. Unfortunately, imaging might not provide a true picture of the extent of pancreatic necrosis at the time of presentation, and might be most informative 48–72 h later. Using the Balthazar classification scheme for estimating prognosis, the accuracy appears to be greatest at one week [7]. The Extra-Pancreatic Inflammation on CT (EPIC) score might provide prognostic information within the first 24 h, and focuses on the surrounding inflammation (e.g., pleural effusion, ascites, retroperitoneal and mesenteric inflammation) rather than necrosis and might predict systemic complications better [8]. It is important to weigh the benefits of early imaging with the risk of contrast-induced acute kidney injury. Ideally, imaging should be deferred until the yield is the highest. Earlier imaging is indicated, however, if the diagnosis is in doubt or there is a high suspicion of complications that might mandate surgical intervention.

Patients should be assessed for subtle degrees of organ dysfunction and physiologic assessment with the goal of identifying the need for admission to an ICU. Additionally, patients with limited reserve (e.g., elderly patients), obese patients, and those with hypovolemia should be admitted to a unit with the capacity for frequent monitoring, given their potential for rapid decompensation.

Role of Prophylactic Antibiotics

Infection frequently complicates the course of SAP and might manifest as infected pancreatic necrosis, pancreatic abscess, or an infected peripancreatic fluid collection. Infected pancreatic necrosis is the most challenging to manage. This complication occurs in 3–7% of all cases of pancreatitis, and is highly correlated with the extent of necrosis. In patients with necrosis involving more than one-half of the pancreas, the incidence of subsequent infection is as high as 40–70%. Infection typically occurs in the second or third week after presentation [9]. The underlying pathophysiology believed to be responsible is increased intestinal permeability, with translocation of bacteria and bacterial proliferation within necrotic tissue [10]. The predominant bacteria are enteric gram-negative bacilli such as Escherichia coli and Klebsiella spp., along with Enterococcus spp., but recently, the microbiologic pattern has shifted toward more resistant gram-negative bacilli, gram-positive cocci, and yeast, a reflection of exposure to broad-spectrum antimicrobial agents [11]. Given the morbidity associated with infection, many commentators have advocated prophylactic antimicrobial therapy in patients with necrosis to the point that this measure has been incorporated into routine practice. However, there is controversy over the risks and potential benefit.

The debate has been fueled by several randomized controlled trials, with differing methodologic quality, regimens, and outcome measures (Table 2) [12]. Recent meta-analyses have demonstrated a lack of benefit [13,14]. The most recent randomized controlled trial, which is of high methodologic quality, strengthens the observation that there is no benefit of prophylaxis [14]. Dellinger et al. assessed the utility of early antibiotic treatment with meropenem vs. placebo for severe acute necrotizing pancreatitis. The endpoints were pancreatic/peripancreatic infection within 42 days of presentation, the requirement for surgical intervention, and death. No statistical difference could be found for any endpoint, adding further to the argument for withholding of antimicrobial therapy until the presence of infection is proved.

As in other clinical settings, antimicrobial agents are best utilized when directed against a particular pathogen at a particular site. However, the diagnosis of infection in the context of critical illness with SAP is problematic. Many patients have fever and leukocytosis as a result of the retroperitoneal inflammation, which in most cases is sterile. Additionally, instrumentation (e.g., central venous catheters, endotracheal tubes) increases substantially the risk of infection outside the pancreatic bed. As a result, it is crucial to identify using fine needle aspiration (FNA) whether pancreatic necrosis might be causal in the manifestations of sepsis. Whereas many patients with pancreatic necrosis have risk factors for fungal sepsis, there are no data supporting routine administration of antifungal prophylaxis [15].

Antimicrobial prophylaxis using non-absorbable, oral antibiotics (selective digestive decontamination; SDD) has been examined given the underlying pathophysiology of bacterial translocation. Luten et al. showed a reduction in the risk of infected pancreatic necrosis and a lower mortality rate in patients receiving SDD in a randomized controlled trial [16]. In a report by Sawa et al. [17], the combination of SDD and enteral nutrition was associated with lower rates of organ dysfunction (70% vs. 59%) and death (40% vs. 28%).

In summary, antimicrobial agents should be restricted to patients with proved infection. The sole exception is a decompensating patient in whom infection is strongly suspected but not yet proved. Whereas there is some evidence

### Table 1. Predictors of Adverse Outcomes in Severe Acute Pancreatitis

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<tr>
<th>Prediction of organ dysfunction</th>
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<tr>
<td>Acute Physiology and Chronic Health Evaluation II score ≥ 8</td>
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<tr>
<td>Multiple organ dysfunction score &gt; 3 at 72 h</td>
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<tr>
<td>Sequential organ failure assessment score &gt; 4 at 48 h</td>
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<tr>
<td>Ranson score ≥ 3 at 48 h</td>
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<td>Modified Glasgow score ≥ 3</td>
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<th>Prediction of local complications</th>
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<tr>
<td>Balthazar C, D, E CT grade at one week a</td>
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<tr>
<td>Hematocrit &gt; 44%</td>
<td></td>
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<tr>
<td>Body mass index &gt; 30</td>
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*AC = Inflammation of pancreas or peripancreatic fat; D = single fluid collection; E = two or more fluid collections and/or retroperitoneal air.*
of the utility of SDD, the strength of the evidence is insufficient to incorporate this modality into routine practice.

**Nutritional Support**

Conventional dogma dictated that “total rest” of the pancreas was necessary during the support of patients with SAP. The rationale was that enteral nutrition (EN) would stimulate the secretion of pancreatic enzymes that might aggravate the retroperitoneal inflammation further. However, several lines of evidence suggest that EN is without harm and might even be beneficial, especially if delivered directly into the jejunum via feeding tube [18]. A prospective, non-randomized six-year sequential study (three years of use of parenteral nutrition, then three years of enteral nutrition) demonstrated lower rates of organ failure, infected necrosis, and mortality for those fed enterally [19]. These data are further supported by a randomized, controlled trial comparing enteral with enteral nutrition in SAP, with clear evidence of a mortality benefit among those receiving EN [20]. A meta-analysis preceding this report provided further confirmation of the superiority of EN over parenteral nutrition (PN), with attenuated inflammatory response, fewer infectious complications, fewer surgical interventions, shorter hospital stay, and better survival [21].

Whereas there is a suggestion of benefit with jejunal compared with intragastric feeding, the evidence evaluating the utility and safety of intragastric feeding is less clear. It is clear that jejunal feeding results in less exocrine stimulation than does gastric feeding. One report suggests an increase in complications among those receiving gastric compared with jejunal feeding; however, these complications were relatively minor (e.g., atelectasis) [22]. A small randomized, controlled trial suggested good tolerance and equivalent outcomes in those receiving nasogastric and nasojejunal feeding [23].

Taken together, these data suggest that early EN is safe and indeed preferable to PN. The evidence is strongest for nutrition delivered into the jejunum. If jejunal access is not possible, intragastric feeding should be considered. If enteral feeding is not tolerated after five days, PN should be used to meet caloric and protein requirements [24].

**Biliary Pancreatitis and Utility of Endoscopic Retrograde Cholangiopancreatography**

Gallstones play a suspected causal role in 40–60% of all cases of pancreatitis. Although the precise mechanism whereby stones cause pancreatitis is not understood despite more than a century of study, it generally is believed that stones obstruct the pancreatic duct of those patients with a common biliopancreatic duct channel within the ampulla of Vater. Ductal obstruction usually is transient, with the stone passing spontaneously within 48 h in the majority of cases [25]. High pancreatic ductal pressure and extravasation of pancreatic juice with subsequent activation of proteolytic enzymes begins the process of autodigestion of the pancreas and surrounding tissues. Digestive enzyme release is amplified with lysis of acinar cells, leading to a vicious cycle of inflammation and necrosis.

Given the pathogenesis of biliary pancreatitis, the use of endoscopic retrograde cholangiopancreatography (ERCP) has been considered for decompression of the pancreatic ductal system through the removal of retained stones. However, it is crucial to identify those patients in whom an impacted gallstone is likely to be responsible for the inflammation. Unfortunately, abdominal ultrasonography has limited sensitivity for detecting gallstones in the context of acute pancreatitis: 80% for detecting cholelithiasis and only 50% for identification of choledocholithiasis. Magnetic resonance cholangiopancreatography (MRCP), a non-invasive radiologic investigation, appears to be as accurate as ERCP for the identification of choledocholithiasis and bile duct obstruction, while avoiding the potential complications of ERCP. However, the role of MRCP in those with SAP, and the cumbersome logistics of performing MRI on a critically ill, unstable patient preclude its routine use in this context [26].

Endoscopic retrograde cholangiopancreatography with ductal clearance is clearly indicated in acute pancreatitis when there is evidence of biliary obstruction (e.g., hyper-
bled. When intervention can be delayed, the process of se-

some advantages to temporizing until the area of infected 

sociated with a high mortality rate [38]. However, there are 

There is little doubt that antimicrobial therapy alone is as-

formed before any antibiotic treatment is instituted. Once the 

case of suspected infected necrosis, FNA should be per-

portant that the intervention be limited to aspiration, as at-

mation are all counterintuitive, but appear to offer benefit in 

the observation that a higher reoperation rate may result,

mortality rates. Several changes in surgical and 

ment, but a deteriorating patient will require intervention ir-

pective of clinical complexity, even in the presence of 

sterile necrosis. The extension of the necrosis (> 50%) and 

development or worsening of multiple organ dysfunction 

syndrome are strong arguments favoring operative inter-

mission is unclear or those who develop a 

catastrophic complication of pancreatitis (e.g., hemorrhage, 

bowel infarction, or perforation) will benefit from surgical 

management. Similarly, those patients who develop ab-

dominal compartment syndrome may derive substantial im-

provement after abdominal decompression.

More controversial is the utility of surgical intervention in 

those with SAP without any of the above indications. Sufficient 
evidence exists to argue against a role for operative de-

bridence in patients with sterile pancreatic necrosis, as 

most patients will incur all the risks of operation (open ab-

domen, fistula, hemorrhage, infection) without any potential 

for benefit [33]. Thus, the focus should be directed first to 

identifying patients with infected pancreatic necrosis. Whereas attempts to differentiate patients with and without 
infected pancreatic necrosis using biological markers such as 
C-reactive protein or procalcitonin have been described, CT-
guided fine needle aspiration (FNA) of the area of necrosis 
remains the gold standard. Aspiration, guided by ultrasound or CT scan, is a safe and reliable investigative tool to look 
for evidence of infected necrosis or a collection of pus 
[33–35]. Gram stain and culture of the aspirate is accurate for 
the diagnosis of infection, with both a positive predictive 
value and negative predictive value around 90% and most 
inaccuracies occurring during the first week [34]. It is im-
portant that the intervention be limited to aspiration, as at-
tempts to drain what might be a sterile collection may lead 
to bacterial contamination and subsequent infection [36]. In 
case of suspected infected necrosis, FNA should be per-
formed before any antibiotic treatment is instituted. Once the 
diagnosis has been made, the results of cultures can direct 
antimicrobial therapy.

Once infected necrosis has been proved, the next area of 
controversy is the means and timing of intervention [37]. 
There is little doubt that antimicrobial therapy alone is as-
associated with a high mortality rate [38]. However, there are 
some advantages to temporizing until the area of infected 
necrosis is sufficiently demarcated that debridement is facil-
itated. When intervention can be delayed, the process of se-
questration and demarcation is accompanied by liquefaction 
such that the “necrosis” becomes a pancreatic abscess that 
might be amenable to percutaneous rather than operative 
drainage, or perhaps to laparoscopy rather than celiotomy.

Historical series suggest that early surgical intervention 
often results in unnecessary procedures, with an increase in 
the number of deaths [39]. One randomized controlled trial 
comparing early (48–72 h) to late (> 12 days) intervention 
showed a trend toward a better survival rate with delayed intervention; interestingly, 20% of the patients randomized 
to late surgery improved without operation [40]. A recent 
abstract reported a clear association between death and the 
timing of surgery after the onset of symptoms, especially if 
surgery was postponed beyond 30 days [41]. The clinical sta-
 tus of the patient will dictate whether temporizing is prudent, 
but a deteriorating patient will require intervention ir-

pective of clinical complexity, even in the presence of 
sterile necrosis. The extension of the necrosis (> 50%) and 
development or worsening of multiple organ dysfunction 
syndrome are strong arguments favoring operative inter-

vention in the presence of clinical deterioration [42].

The conventional surgical approach typically involves a 
midline laparotomy and often necessitates open-abdomen 
management with some form of temporary closure, particu-
larly if performed early in the course of disease. However, 
many surgeons are advocating less extensive procedures in 
the form of a minimally invasive retroperitoneal pancreatic necro-
sectomy [43] or video-assisted retroperitoneal debridement 
(VARD) through flank incisions [44]. Whereas it is difficult to 
establish if one technique offers benefit over another, these al-
ternate approaches argue against a “one size fits all” strategy, 
and emphasize the importance of careful patient selection. One 
limitation of these minimally invasive debridement techniques 
is the observation that a higher reoperation rate may result, 
with potentially greater morbidity than is seen with open sur-
gery [45]. The ability to delay interventions to allow better de-

marcation and liquefaction of pancreatic necrosis offers greater 
opportunity for success of minimally invasive techniques, and 
might become the standard of care in the future. Investigators 
are now comparing the step-up approach with standard open 
nectrosectomy. This approach involves an attempt at percuta-
aneous drainage, followed by VARD, among those who fail per-
cutaneous drainage [46], prior to celiotomy.

Conclusions

Severe acute pancreatitis carries with it substantial mor-
bidity and mortality rates. Several changes in surgical and 
ICU management have reduced the mortality rate in recent 
years, many of which have challenged surgical dogma. Less 
antimicrobial use, early enteral feeding, and delayed opera-
tion are all counterintuitive, but appear to offer benefit in 
this critically ill patient population.

Author Disclosure Statement

No competing financial interests exist.

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