

# MANAGEMENT OF THE CRITICALLY ILL PATIENT WITH SEVERE ACUTE PANCREATITIS

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## WHAT IS ACUTE PANCREATITIS?

Acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems.

In about 15-20% of patients with acute pancreatitis, severe damage to the pancreas may lead to a life threatening illness that is often associated with prolonged hospitalization, multiple surgical procedure and death in some patients.

Severe acute pancreatitis (SAP) is a serious and life threatening disease and require intensive and aggressive management of multiple organ failure and severe infective complication that develop in these patient. Many of the complications seen in severe acute pancreatitis are associated with the presence of the dead pancreatic tissue in the abdomen. This dead pancreas tissue is called pancreatic necrosis and the dead fatty around the pancreas is called peripancreatic necrosis. Severe acute pancreatitis usually develops when parts of the pancreas become necrotic (dead) from the acute inflammation.

## WHAT IS PANCREATIC NECROSIS?

Severe pancreatitis causes death of parts of the pancreas. The injured dying pancreas releases digestive enzymes in the gland, which causes extensive death of fatty tissue in the abdomen. As a consequence, patients with severe pancreatitis have dead pancreatic tissue and also widespread death of fatty tissue around the pancreas.

## SAP – MORTALITY RATE?

The patients who require admission to an intensive care unit have mortality rates in the range of 30 – 50% and a mean hospital length of stay > 1 month. Mortality varies with etiology, the development of complication or necrosis and the number and severity of co-morbid medical conditions.

The cost of care for these patients is substantial, with estimates of total direct and indirect costs ranging from \$ 3.6 billion to \$ 6 billion annually.

### **Recommendation 1**

The etiology of acute pancreatitis should be determined in at least 80% of cases and no more than 20% should be classified as idiopathic. (Grad B)

Patients with SAP may benefit from an environment with more intensive monitoring given their potential for progressive organ dysfunction and/or life-threatening local complication but, avoiding unnecessary ICU admission may limit the risk of nosocomial infection and iatrogenic complications.

Patients with SAP who fulfill conventional criteria for ICU admission should be admitted as well as those patients at high risk of rapid deterioration (elderly, significant obesity, requiring ongoing volume resuscitation and patient with evidence of substantial pancreatic necrosis).

### **Recommendation 2**

Admission in ICU is recommended for patients with SAP who fulfill conventional criteria for ICU admission as well as those patients at high risk of rapid deterioration (elderly, significant obesity, requiring ongoing volume resuscitation and patient with evidence of substantial pancreatic necrosis >30%).

(Grad D, level 5 evidence)

### Recommendation 3

Critically ill patients with pancreatitis will be cared for by an intensivist leader, multidisciplinary team with ready access to physicians skilled in endoscopy, ERCP, surgery, and interventional radiology. (Grad B, level 3a evidence)

### Recommendation 4

Close clinical observation of patients with pancreatitis is strongly recommended. These patients require early and aggressive fluid resuscitation. They are at the risk for the early development of organ dysfunction as a result of inadequate resuscitation and systemic and local complication of pancreatitis.

Clinical monitoring should focus on intravascular volume assessment (physical examination, urine output, acid – base status) and pulmonary function.

(Grad D, level 5 evidence)

### Recommendation 5

Jury recommends against the routine use of markers such CRP or procalcitonin to guide clinical decision making, predict the clinical course of pancreatitis or triage patients. (Grad D , level 5 evidence)

### Recommendation 6

In presence of diagnostic uncertain at the time of initial presentation, a CT scan of the abdomen (with intravenous contrast in the absence of contraindication) may be performed after adequate fluid resuscitation to confirm the diagnostic of pancreatitis and to rule out alternate diagnosis. An admission CT scan may also serve as baseline for future scan. (Grad D, level 5 evidence)

### Recommendation 7

CT to identify local complications will be delayed for 48 -72 hrs when possible, as necrosis might not be visualized earlier. (Grad D, level 5 evidence)

Should patients with severe acute pancreatitis receive prophylactic antibiotics?

Infection of necrotic pancreas develops in 30-50% of patients with necrosis documented by CT or surgery.

Infection might occur within first week, but its incidence tend to peak in the third week of disease.

Rates of organ failure and mortality appear to be highest among patients with infected pancreatic necrosis.

The lack of any consistent benefit across studies, their variable inclusion criteria, variable methodological quality, different antimicrobial regimen and the significant potential for harm preclude recommendation for routine intravenous prophylactic antimicrobial therapy in patients with SAP.

Prophylactic antimicrobial have been associated with a change in the spectrum of pancreatic isolates from enteric Gram - negative to fungi and Gram – positive organisms.

### Selective decontamination of digestive tract

No further evidence has been published to support the one large randomized controlled trial which has been conducted in patient with severe acute pancreatitis, to examine the effect of selective gut decontamination in combination with intravenous antibiotic on outcome in acute pancreatitis. In that study there was no statistically significant reduction in mortality rate. It is no clear whether the reported benefit arose from the use of intravenous antibiotics or from gut decontamination.

### Recommendation 8

No routine use of prophylactic systemic antibacterial or antifungal agents in patients with necrotizing pancreatitis in light of inconclusive and divided expert opinion. Subsets of patients who benefit from prophylactic antibiotic may be identified by further investigation. (Grad B, level 2b evidence)

Summary of randomized trials examining routine prophylactic antibiotics for SAP:

Reference	Agent	Duration (days)	Pancreatic infection		Deaths	
			Treated	Control	Treated	Control
Federoli <sup>39</sup>	Imipenem	14	5/41	10/33	3/41	4/33
Sainio <sup>40</sup>	Cefuroxime	14	9/30	12/30	1/30	7/30
Delcenserie <sup>36</sup>	Ceftazidime, amikacin, metronidazole	10	0/11	3/12	1/11	3/12
Schwartz <sup>41</sup>	Ofloxacin, metronidazole	>10	8/13	7/13	0/13	3/13
Nordback <sup>38</sup>	Imipenem/cilastatin	Not stated	2/25	14/33	2/25	5/33
Izenmann <sup>37</sup>	Ciprofloxacin, metronidazole	14 (3–23)	7/38	5/56	3/38	4/56
Total			31/178	51/177	10/178	26/177

What is the optimal mode and timing of nutritional support for patients with SAP?

Patients with SAP are hypercatabolic; timely institution of feeding is important if malnutrition is to be avoided or treated. A large body of evidence, suggests that there are several potential benefit from enteral nutrition compared with parenteral nutrition including a reduction in microbial translocation, improved in gut blood flow and preservation of gut mucosal surface immunity.

Eight trial have directly compared enteral nutrition and parenteral nutrition.

Two studies demonstrated an attenuated inflammatory response as measured by resolute of SIRS, reduction level of circulating CRP, TNF $\alpha$ , or IL-6. In remaining studies which compare parenteral nutrition with jejunal feed, outcome related to infections, organ failure and mortality were either similar or lower.

### **Recommendation 9**

Enteral nutrition should be used in preference to parenteral nutrition in patients with SAP.

Enteral nutrition should be initiated after initial resuscitation.

The jejunal route should be used if possible. (Grad A, level 1a evidence)

### **Recommendation 10**

Parenteral nutrition will be used only when attempts for enteral nutrition have failed after 5 to 7 day trial. (Grad D, level 5 evidence)

### **Recommendation 11**

When used, parenteral nutrition should be enriched with glutamine. (Grad D, level 5 evidence)

### **Recommendation 12**

Both enterally and parenterally fed, will be managed with protocol ensuring strict glycemic control. (Grad A, level 1b evidence)

### **Recommendation 13**

No routine use of immune-enhancing enteral feed formula or probiotics. (Grad D, level 5 evidence)

What are the indication for surgery in SAP and what is the optimal timing for intervention? What are the roles for less invasive approach including percutaneous drainage and laparoscopy?

There are several incontrovertible indications for operative intervention in patients with SAP:

- intestinal infarct or perforation
- exsanguinating hemorrhage
- abdominal compartment syndrome

Routine operative of the peripancreatic fluid col-

lection and pancreatic necrosis is not necessary and may infect otherwise sterile tissues.

The presence of tissue necrosis further exacerbate or impairs the resolution of local and systemic inflammatory response. Nonviable tissue might be seeded by enteric organisms, resulted infected necrosis. Necrosis in context of severe clinical disease mandates repeated assessment of need for intervention. Later in the disease, the necrotic pancreas demarcates from viable tissue leading to an easier and safer debridement. Over time the area of necrosis undergoes liquefaction resulting an abscess that might be more amenable to percutaneous drainage.

The optimal type of intervention depends on clinical course of the patient and the precise timing of intervention.

Discrimination between sterile and infected pancreatic necrosis:

- SAP –archetypical examples of sterile inflammatory process leading to organ dysfunction
- the clinical picture is often one of SIRS and can be indistinguishable from severe sepsis.

In the critical ill patients with evidence of SIRS or sepsis, it is essential to discriminate between sterile and infected pancreatic necrosis. CT is helpful because the finding of retroperitoneal air is generally indicative of the presence of gas-forming organisms and thus, infected necrosis. In absence of retroperitoneal gas, ultrasound or CT-guided fine needle aspiration (FNA) of the necrotic tissue with Gram-negative stain and culture can discriminate between sterile and infected necrosis.

Management of infected pancreatic necrosis:

- several large cases series suggest that the diagnosis of infected pancreatic necrosis warrants consideration of a single or a series of intervention designed to achieve the goal of a pancreatic debridement and/or drainage.

- there are no reports suggesting that antimicrobial therapy alone is adequate.

From more studies results that patients with SAP and without evidence of pancreatic infection can be managed without operation with low rates of mortality and morbidity even in face of organ dysfunction. The significant risk of iatrogenic bowel injuries, hemorrhage on open abdomen and infecting sterile pancreatic necrosis should be considered before proceeding with operative debridement of sterile necrosis.

### **Recommendation 14**

Ultrasonographic or CT guided FNA with Gram stain and culture of pancreatic or peripancreatic tissue help to discriminate between sterile and infected

necrosis in patients with radiological evidence of pancreatic necrosis and clinical feature consistent with infection. (Grad C, level 4 evidence)

#### **Recommendation 15**

No debridement and/or drainage in patients with sterile necrosis. (Grad C, level 4 evidence)

#### **Recommendation 16**

Debridement and/or drainage in patients with infected necrosis and/or abscess confirmed by radiological evidence of gas or results of FNA. The gold standard for achieving this goal is open operative debridement. Minimally invasive techniques including laparoscopic and/ or percutaneous interventions might be effective in selected patients. (Grad C, level 4 evidence)

#### **Recommendation 17**

When possible, operative necrosectomy and/or drainage be delayed at least 2- 3 weeks to allow for demarcation of the necrotic pancreas. However, the clinical picture (severity and evolution) should be primary determinant of the timing of intervention. (Grad C, level 4 evidence)

Under what circumstances should patients with gallstones pancreatitis undergo interventions for clearance of the bile duct?

Gallstones represent one of the most common etiologies of acute pancreatitis, accounting for 40-60%. All patients with pancreatitis should be evaluated for the presence of gallstones since this etiology has specific therapeutic implications. The mechanism by which gallstones initiate the process of pancreatitis is by temporary or persistent obstruction of the sphincter of Oddi.

Given this purported mechanism, it has postulated that prompt removal of stone would attenuate the inflammatory response.

Identification for the patients with biliary pancreatitis:

Ultrasonography should be performed to assess for gallbladder stones as a potential cause of pancreatitis and the abdominal CT scan should be reviewed with this in mind.

The sensitivity of ultrasound for identification of cholelithiasis in presence of acute pancreatitis is approximately 85%, whereas the sensitivity for choledocholithiasis is < 50%

Endoscopic ultrasound offers significantly more sensitivity and specificity.

A three-fold or greater increase in alanine aminotransferase had a positive predictive value in identifying pancreatitis with biliary etiology.

#### **Timing of biliary clearance:**

For patients with severe acute gallstones pancreatitis, urgent biliary drainage and clearance of the bile duct must be considered. There is a general consensus that patients with severe acute gallstones pancreatitis with obstructive jaundice should undergo urgent ETCP and if gallstones are identified, endoscopic sphincterotomy should be performed.

#### **Recommendation 18**

Gallstone pancreatitis should be suspected in all patients with SAP and therefore all patients should have evaluation with sonography and biochemical tests. (Grad C, level 4 evidence)

#### **Recommendation 19**

In the setting of obstructive jaundice (or other evidence of acute obstruction of the of the biliary and/ or pancreatic tract) and acute pancreatitis due to suspected or confirmed gallstones, urgent ERCP should be performed within 72 hours of onset of symptoms. (Grad D, level 5 evidence)

#### **Recommendation 20**

In the absence of obstructive jaundice, but with SAP due to suspected or confirmed gallstones, ERCP be strongly considered within 72 hours of onset of symptoms. (Grad B, level 1c evidence)

Is there a role for therapy targeting the inflammatory response in the patients with SAP?

The physiologic response and many of the complications of SAP occur as result of an uncontrolled inflammatory response. Recent therapeutic strategies have been directed toward interrupting the SIRS to mitigate the development of organ dysfunction. The role of many inflammatory mediators (TNF $\alpha$ , IL-1 $\alpha$ , IL-6, IL-8, PAF etc.) but there is a limited human data. Recombinant human activated protein C (rh-APC) has been shown to reduce mortality from severe sepsis. TNF $\alpha$  is considered to be a key mediator in shock and is found in high circulating concentrations in acute pancreatitis. There are no data available on its effectiveness in SAP. PAF blockade – lexipafant - PAF antagonist have been shown to attenuate the inflammatory response and to lower the incidence of organ dysfunction in two small trials. Modulation of the coagulation cascade–rh-APC has proven effectiveness in reducing mortality in patients with severe sepsis.

#### **Recommendation 21**

General supportive measure used in the critically ill should be employed in patients with SAP as these interventions might play an important role in attenuat-

ing the inflammatory response. (Grad A, level 1 b evidence)

Lung – protective ventilation strategies for patient with acute lung injury (Grad A, level 1 evidence)

#### **Recommendation 22**

Once the presence of infection is documented or highly suspected and patients with SAP meet the definition of severe sepsis that management according to current sepsis guidelines be initiated. These therapy include the use of rh-ACP (grade A level 1b)

and low dose corticosteroid (Grade B level 1b evidence). The careful consideration should be used before administration of rh – ACP based on the theoretical but unproven concern of retroperitoneal hemorrhage. (Grad D, level 5 evidence)

#### **Recommendation 23**

No use for other immuno-modulating therapies targeting inflammatory mediators in SAP as anti-TNF $\alpha$  therapy and lexipafant. (Grad A, level 1 evidence for lexipafant; Grad D level 5 evidence for all other therapy)