

# Severe Acute Pancreatitis

Vege Santhi Swaroop, MD

Suresh T. Chari, MD

Jonathan E. Clain, MD

IN THE UNITED STATES, OF THE APPROXIMATELY 210 000 patients admitted to hospitals each year with acute pancreatitis,<sup>1</sup> about 20% have severe acute pancreatitis (SAP), and primary care physicians and internists are often the first clinicians to care for these patients. In contrast to mild acute pancreatitis, which has a mortality rate of less than 1%,<sup>2</sup> the death rate for SAP is much higher: 10% with sterile and 25% with infected pancreatic necrosis.<sup>3</sup> Hospitalization for patients with SAP may extend beyond 2 weeks and frequently involves an intensive care unit (ICU) stay.

This review article addresses recent trends in the diagnosis and management of SAP. We searched MEDLINE from 1990 to the present using the Medical Subject Headings terms *pancreatitis*, *acute necrotizing pancreatitis*, and *alcoholic pancreatitis*, and the key word *pancreatitis*. Important clinical guidelines, randomized controlled trials (RCTs), meta-analyses, large case series from centers of excellence, and consensus conference reports form the basis of this article.

## Classification and Definitions

The widely used Atlanta classification<sup>4</sup> categorizes acute pancreatitis as mild or severe. Pancreatitis without parenchymal necrosis is referred to as interstitial or edematous pancreatitis and is usually mild (FIGURE). Patients with pancreatitis are classified as having SAP if

See also Patient Page.

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they meet any of the following 4 criteria. (1) Organ failure with 1 or more of the following: shock (systolic blood pressure <90 mm Hg), pulmonary insufficiency ( $\text{PaO}_2 \leq 60$  mm Hg), renal failure (serum creatinine level >2 mg/dL [ $>176.8 \mu\text{mol/L}$ ] after rehydration), and gastrointestinal tract bleeding (>500 mL in 24 hours); (2) local complications such as necrosis, pseudocyst, or abscess; (3) at least 3 of Ranson's criteria (BOX)<sup>5</sup>; or (4) at least 8 of the Acute Physiology and Chronic Health Evaluation II (APACHE II) criteria.<sup>7</sup>

Three local complications of SAP are pancreatic necrosis, pseudocyst, and abscess. Pancreatic necrosis is the presence of a diffuse or focal area of non-viable pancreatic parenchyma, often associated with peripancreatic necrosis. Severe acute pancreatitis with pancreatic or peripancreatic necrosis is also referred to as necrotizing pancreatitis. Initially a sterile necrosis (mortality, 10%), necrotizing pancreatitis becomes infected with bacteria of gut origin in 40% to 70% of cases<sup>2</sup> and is then called infected necrosis (mortality, 25%). Pancreatic pseudocyst is a collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue that develops as a result of a persistent leak of pancreatic juice from the pancreatic duct. Pancreatic abscess is a circumscribed intra-abdominal collection of pus that sometimes contains gas. It follows infection of a limited area of pancreatic or peripancreatic necrosis and usually takes 4 to 6 weeks to evolve.

## Epidemiology and Etiology

From several large studies describing patients with SAP, the 2 most common causes of SAP are chronic heavy alcohol use (approximately 40% of patients) and gallstones (approximately 35% of patients). Severe acute pancreatitis occurs in men more often than in

women. Alcoholic pancreatitis is more common among men; gallstone pancreatitis is more common among women. Less common causes of SAP are trauma to the pancreas, hypercalcemia, hypertriglyceridemia, and complications from endoscopic retrograde cholangiopancreatography (ERCP) or surgery. In about 20% of patients, no cause can be identified.

## Diagnosis

Patients with SAP typically complain of fairly sudden onset of severe upper abdominal pain, radiating to the back, often associated with nausea and vomiting. Differential diagnosis includes acute cholecystitis, perforated peptic ulcer, mesenteric ischemia, and bowel obstruction or perforation.

Marked elevations in serum amylase and/or lipase (>3 times the upper limit of normal) support the diagnosis of pancreatitis in a patient with severe abdominal pain. However, modest elevations of pancreatic enzymes may be observed in other intra-abdominal emergencies. The degree of enzyme elevation does not correlate with the severity of pancreatitis and normalization of enzyme levels is not necessarily a sign of resolution. In the presence of pancreatitis, an increase in liver enzyme values, especially of alanine aminotransferase to more than 3 times normal, suggests a biliary cause.<sup>8</sup> A history of fasting triglyceride levels higher than 1000 mg/dL (11.3 mmol/L) or the persistence of elevated triglyceride levels after resolution of the attack suggests that hyper-

**Author Affiliations:** Division of General Internal Medicine (Dr Vege) and Division of Gastroenterology (Drs Chari and Clain), Department of Internal Medicine, Mayo Clinic, Rochester, Minn.

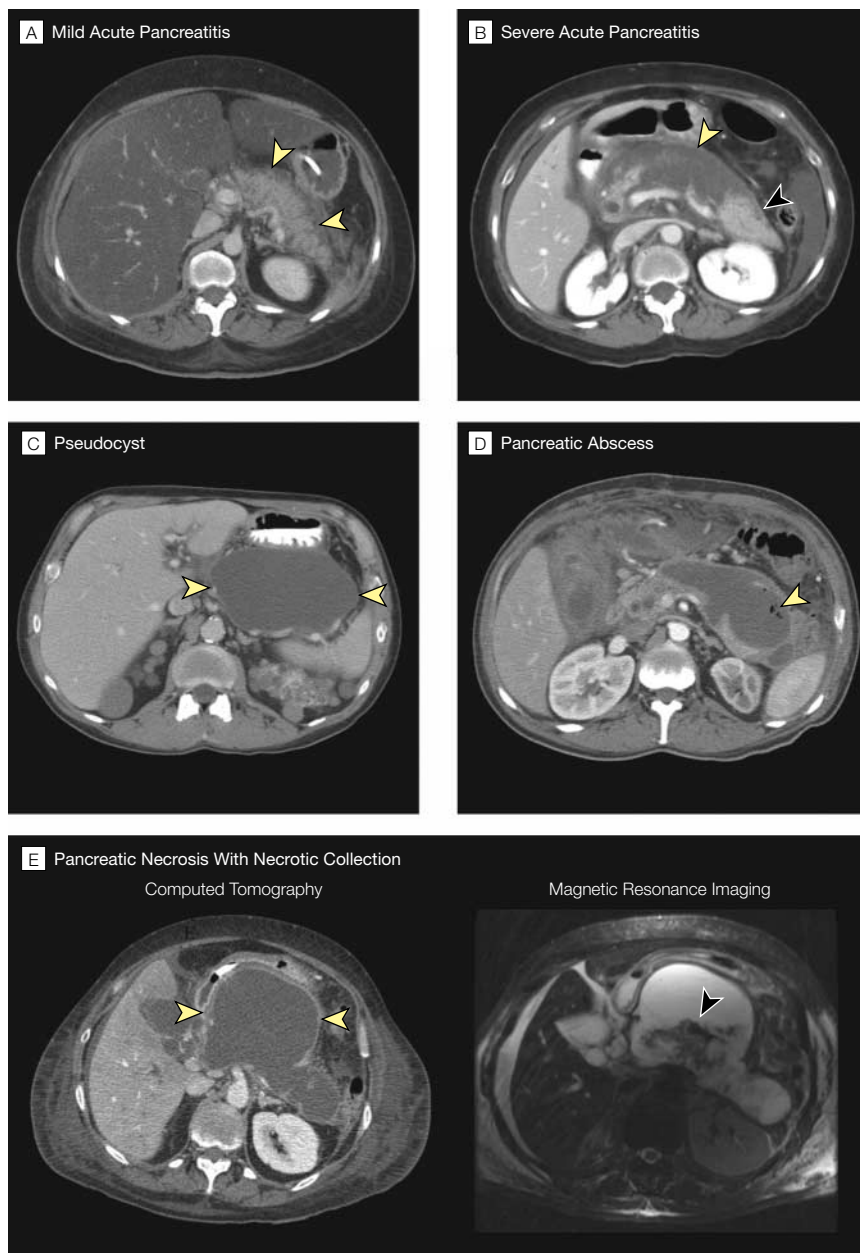
**Corresponding Author:** Vege Santhi Swaroop, MD, Division of General Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (vege.santhi@mayo.edu).

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triglyceridemia may be the cause of pancreatitis. Fasting serum calcium levels may be spuriously normal or low in

patients with SAP and should be rechecked after the pancreatitis has resolved.

**Figure.** Computed Tomography and Magnetic Resonance Imaging Appearance of Pancreatitis



Panels A through E (left), computed tomography (CT) images; panel E (right), magnetic resonance imaging (MRI). A, Mild acute pancreatitis showing normal enhancement of the body of pancreas (arrowheads) after intravenous contrast. B, Severe acute pancreatitis showing pancreatic necrosis with areas of the pancreas not enhancing (yellow arrowhead) after contrast administration compared with areas that are normally perfused (black arrowhead). C, Pseudocyst of the pancreas (arrowheads) with clear-appearing fluid within the collection near the pancreas. D, Pancreatic abscess with presence of gas (arrowhead) inside the cavity. E, Pancreatic necrosis (necrotic collection), which appears on CT scan as a clear fluid collection (yellow arrowheads). The same collection on MRI shows areas of necrotic debris (black arrowhead) not observed on CT scan, a distinction that has prognostic and therapeutic implications.

**Abdominal Imaging.** Abdominal ultrasonography can be used to detect gallstones, although bowel gas may limit its accuracy in the acute setting. Contrast-enhanced computed tomography (CT) is useful for differentiating SAP from other conditions presenting with abdominal pain and elevated pancreatic enzymes. It also helps to delineate local complications associated with SAP. Pancreatic or peripancreatic necrosis is diagnosed when some or all of the pancreas or surrounding area fails to enhance with contrast (Figure, E). To determine whether a necrotic area is infected, it can be sampled by fine-needle aspiration under CT guidance and analyzed with Gram stain and culture for evidence of gut-derived bacteria and/or fungal organisms. Magnetic resonance imaging is better than CT for distinguishing between an uncomplicated pseudocyst and one that contains necrotic debris (Figure, E).<sup>9</sup> Magnetic resonance cholangiopancreatography and endoscopic ultrasonography can detect small bile duct stones as a cause of SAP.

**Assessment of Severity.** Early diagnosis of SAP is important so that aggressive treatment can be instituted. Scoring systems commonly used in clinical practice are Ranson's criteria,<sup>5</sup> Glasgow criteria,<sup>10</sup> APACHE II,<sup>7</sup> and CT severity index.<sup>11</sup> The presence of 3 or more of Ranson's criteria (Box) predicts adverse outcome but the analysis cannot be completed before 48 hours. APACHE II,<sup>7</sup> which can be used at 24 hours and then daily thereafter, predicts complications and mortality at a score of 8 or higher.<sup>12</sup> A score of 7 or higher on the CT severity index (TABLE) usually implies SAP with high mortality and morbidity.<sup>11</sup>

A body mass index (calculated as weight in kilograms divided by the square of height in meters) of more than 30 and older age (>70 years) often predict increased mortality.<sup>13</sup> Absence of hemoconcentration (hematocrit >43% for men and >39.6% for women) with pancreatitis has a high negative predictive value for SAP.<sup>14</sup> An elevated C-reactive protein level (>150 mg/L) at 48 hours predicts a severe attack<sup>3</sup> and later predicts progression. Serum trypsinogen ac-

tivation peptide, polymorphonuclear elastase, carboxypeptidase activation-peptide, IL-6 and IL-8, and procalcitonin are being studied as potential predictive markers.

### Treatment

**General.** The initial treatment of SAP is supportive. Aggressive fluid resuscitation, oxygen supplementation, and pain relief with intravenous morphine or fentanyl are critical. Nearly half the patients with SAP have organ failure and require management by a multidisciplinary team,<sup>13</sup> consisting of gastroenterologists, interventional radiologists, endoscopists for ERCP, intensivists, pathologists, and pancreatic surgeons.

**Nutrition.** In the past, patients with SAP were administered parenteral nutrition in an effort to avoid stimulation of the pancreas. More recently, it has been shown in animal models that enteral nutrition prevents intestinal atrophy and improves the barrier function of the gut mucosa.<sup>15</sup> Three RCTs have demonstrated that enteral feeding is not only safe and feasible but is also associated with fewer infectious complications, and is less expensive than parenteral nutrition.<sup>16-18</sup> Whenever possible, enteral feeding should be used, with parenteral nutrition reserved for patients who do not tolerate enteral feeding or in whom an adequate infusion rate cannot be reached within 2 to 4 days.

**Prevention of Pancreatic Infection.** Pancreatic or peripancreatic infection develops in 40% to 70% of patients with pancreatic necrosis and is the leading cause of morbidity and mortality in patients with SAP.<sup>2</sup> Infection usually occurs at least 10 days after the onset of SAP. Efforts to prevent or reduce the incidence of infection in patients with SAP include selective gut decontamination and prophylactic systemic antibiotics.

Selective gut decontamination is aimed at minimizing the risk of pancreatic infection by eliminating pathogenic intestinal flora. Although it is an attractive concept, its effectiveness has not been proven.

Recently published guidelines support the use of prophylactic antibiotics in patients with SAP.<sup>2,3,13</sup> A meta-

### Box. Ranson's Criteria\*

#### At Admission

Age >55 years  
White blood cell count >16000/ $\mu$ L  
Serum glucose level >200 mg/dL (>11.1 mmol/L)  
Serum lactate dehydrogenase >350 IU/L  
Aspartate aminotransferase >250 IU/L

#### During Initial 48 Hours

Hematocrit decrease >10%  
Blood urea nitrogen increase >5 mg/dL (>1.8 mmol/L)  
Calcium <8 mg/dL (<2 mmol/L)  
PaO<sub>2</sub> <60 mm Hg  
Base deficit >4 mEq/L  
Fluid sequestration >6 L

\*Reproduced with permission from Balthazar.<sup>6</sup> For a diagnosis of severe acute pancreatitis in a patient with pancreatitis, 3 or more of the above criteria must be present.

**Table.** CT Severity Index\*

CT Grade†	Points	Necrosis		CT Severity Index‡
		Percentage	Additional Points	
A	0	0	0	0
B	1	0	0	1
C	2	<30	2	4
D	3	30-50	4	7
E	4	>50	6	10

Abbreviation: CT, computed tomography.

\*Reproduced with permission from Balthazar.<sup>6</sup>

†A indicates normal pancreas; B, enlarged pancreas; C, pancreatic and/or peripancreatic inflammation; D, a single peripancreatic collection; E, at least 2 peripancreatic collections and/or retroperitoneal air.

‡Grade points are added to points assigned for percentage of necrosis.

analysis of 8 RCTs found that reduction in mortality was limited to patients with SAP who were administered broad-spectrum antibiotics that could penetrate pancreatic tissue.<sup>19</sup> However, a recent RCT, using ciprofloxacin and metronidazole, found no difference in the incidence of pancreatic infection vs placebo in patients with SAP.<sup>20</sup> Fungal superinfection has been reported in patients receiving prophylactic antibiotics.<sup>21</sup> Limiting the use of antibiotics to 5 to 7 days may avoid this complication.<sup>21</sup> If fever or leukocytosis persists or develops beyond 7 to 10 days without an obvious source of infection, fine-needle aspiration of the necrotic area should be performed to rule out infection.

**Endoscopic Sphincterotomy in Severe Biliary Pancreatitis.** A meta-analysis of 4 RCTs of endoscopic sphincterotomy in patients with severe biliary pancreatitis showed that sphincter-

otomy reduced complications and mortality of SAP in patients with biliary obstruction or cholangitis.<sup>22</sup> The role of early ERCP in patients without biliary obstruction or cholangitis is unclear. One study reported higher mortality after ERCP in such patients.<sup>23</sup> An accepted practice is to perform endoscopic sphincterotomy in patients with evidence of biliary obstruction (cholangitis, jaundice) or elevated liver test results except in those with rapidly normalizing test results.

**Surgery.** Debridement by surgery or a less invasive technique is indicated in patients with infected necrosis.<sup>2</sup> Outcomes are better if surgery is delayed until the necrosis has organized, usually about 4 weeks after disease onset. This organization makes separation of tissue planes easier, thus avoiding the need for organ resection.<sup>2</sup> The only prospective RCT comparing early (<72 hours) with late (>12 days after the on-

set of symptoms) debridement was aborted prematurely because of concerns about high mortality in the early-surgery group.<sup>24</sup> Surgery is not indicated for patients with sterile necrosis unless there is clinical deterioration despite intensive medical care.<sup>2</sup>

The preferred surgical procedure for SAP is necrosectomy (debridement) with the placement of wide-bore drains for continuous postoperative irrigation. Abdominal zipper or open packing of the wound allows repeated abdominal access for subsequent debridement. For patients who are poor surgical candidates or who have well-contained infection, minimal-access necrosectomy by either percutaneous<sup>25</sup> or endoscopic<sup>26</sup> routes has shown encouraging results. Access to the necrotic area can be achieved percutaneously with CT guidance, endoscopically through the stomach or duodenum, or surgically with a limited lumbar incision. For patients with biliary pancreatitis, cholecystectomy should be performed during the initial hospitalization or after the resolution of intra-abdominal inflammation to prevent recurrence.<sup>2</sup> In patients too ill to undergo cholecystectomy, endoscopic sphincterotomy is an alternative.<sup>2</sup> Interventions used in the past aimed at resting the pancreas (nasogastric suction and acid suppression), diminishing secretion of enzymes (glucagon and somatostatin administration), and countering the damaging effects of enzymes (use of aprotinin, gabexate, or leixipafant) do not improve outcomes. Peritoneal lavage, likewise, has no beneficial effect.<sup>27</sup>

### Morbidity and Mortality

Approximately half the deaths of patients with SAP occur within 2 weeks of onset.<sup>28</sup> Early morbidity and mortality in patients with SAP are attributable to organ failure secondary to systemic inflammatory response syndrome. The remaining deaths occur because of later complications of infected necrosis. Exocrine and endocrine insufficiency can occur among survivors of SAP, especially if there has been loss of a significant portion of pancreatic parenchyma from scar-

ring or resection.<sup>29</sup> Pancreatic duct strictures, pancreatic duct leak with recurrent pseudocyst, or complete disconnection of the duct in the head of the gland from that in the body and tail may also occur. Recurrent pseudocyst formation caused by a disconnected duct may require surgical removal of the disconnected pancreatic tail, leading to further loss of pancreatic function.

### Conclusion

Important recent advances have improved our understanding of the natural history of SAP. Disease activity can be more accurately assessed using various clinical, biochemical, and immunologic markers, along with the several scoring systems for early assessment of severity. Interventions, such as endoscopic sphincterotomy, prophylactic antibiotics, enteral nutrition, and minimally invasive surgery, and the timing of such interventions are also better understood. Despite these advances, SAP continues to have considerable mortality and morbidity. The exact role of proteases and cytokines in the pathogenesis of SAP is being critically evaluated. Several new organ failure scoring systems and biochemical and immunologic markers for earlier diagnosis are being studied prospectively. Antiprotease and anticytokine agents are being evaluated in animal models. Patients with SAP are currently best treated in centers with multidisciplinary expertise. Continuing advances in understanding the natural history of the disease, pathogenesis, and severity assessment will be translated into improved management of SAP, with hopefully better outcomes.

### REFERENCES

1. Russo MW, Wei JT, Thiny MT, et al. Digestive and liver disease statistics. *Gastroenterology*. 2004;126:1448-1453.
2. Uhl W, Warshaw A, Imrie C, et al. IAP guidelines for the surgical management of acute pancreatitis. *Pancreatol*. 2002;2:565-573.
3. Dervenis C, Johnson CD, Bassi C, et al. Diagnosis, objective assessment of severity, and management of acute pancreatitis. *Int J Pancreatol*. 1999;25:195-210.
4. Bradley EL III. A clinically based classification system for acute pancreatitis: summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11-13, 1992. *Arch Surg*. 1993;128:586-590.
5. Ranson JH, Rifkind KM, Roses DF, et al. Prognos-

6. Balthazar EJ. Acute pancreatitis: assessment of severity with clinical and CT evaluation. *Radiology*. 2002;223:603-613.
7. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818-829.
8. Tenner S, Dubner H, Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. *Am J Gastroenterol*. 1994;89:1863-1866.
9. Morgan DE, Baron TH, Smith JK, et al. Pancreatic fluid collections prior to intervention. *Radiology*. 1997;203:773-778.
10. Blamey SL, Imrie CW, O'Neill J, et al. Prognostic factors in acute pancreatitis. *Gut*. 1984;25:1340-1346.
11. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. *Radiology*. 1990;174:331-336.
12. Lankisch PG, Warnecke B, Bruns D, et al. The APACHE II score is unreliable to diagnose necrotizing pancreatitis on admission to hospital. *Pancreas*. 2002;24:217-222.
13. Toouli J, Brooke-Smith M, Bassi C, et al. Guidelines for the management of acute pancreatitis. *J Gastroenterol Hepatol*. 2002;17(suppl):S15-S39.
14. Lankisch PG, Mahlke R, Blum T, et al. Hemocentration: an early marker of severe and/or necrotizing pancreatitis? *Am J Gastroenterol*. 2001;96:2081-2085.
15. Dejong CH, Greve JW, Soeters PB. Nutrition in patients with acute pancreatitis. *Curr Opin Crit Care*. 2001;7:251-256.
16. Kalfarentzos F, Kehaqui J, Mead N, et al. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis. *Br J Surg*. 1997;84:1665-1669.
17. McClave SA, Greene LM, Snider HL, et al. Comparison of the safety of early enteral vs parenteral nutrition in mild acute pancreatitis. *JPEN J Parenter Enteral Nutr*. 1997;21:14-20.
18. Windsor AC, Kanwar S, Li AG, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut*. 1998;42:431-435.
19. Golub R, Siddiqi F, Pohl D. Role of antibiotics in acute pancreatitis. *J Gastrointest Surg*. 1998;2:496-503.
20. Isenmann R, Runzi M, Kron M, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis. *Gastroenterology*. 2004;126:997-1004.
21. Yousaf M, McCallion K, Diamond T. Management of severe acute pancreatitis. *Br J Surg*. 2003;90:407-420.
22. Sharma VK, Howden CW. Meta-analysis of randomized controlled trials of endoscopic retrograde cholangiography and endoscopic sphincterotomy for the treatment of acute biliary pancreatitis. *Am J Gastroenterol*. 1999;94:3211-3214.
23. Folsch LR, Nitsche R, Ludtke R, et al. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. *N Engl J Med*. 1997;336:237-242.
24. Mier J, Leon EL, Castillo A, et al. Early versus late necrosectomy in severe necrotizing pancreatitis. *Am J Surg*. 1997;173:71-75.
25. Carter CR, McKay CJ, Imrie CW. Percutaneous necrosectomy and sinus tract endoscopy in the management of infected pancreatic necrosis: an initial experience. *Ann Surg*. 2000;232:175-180.
26. Baron TH, Thaggard WG, Morgan DE, Stanley RJ. Endoscopic therapy for organized pancreatic necrosis. *Gastroenterology*. 1996;111:755-764.
27. British Society of Gastroenterology. United Kingdom guidelines for the management of acute pancreatitis. *Gut*. 1998;42(suppl 2):S1-S13.
28. Mutinga M, Rosenbluth A, Tenner SM, et al. Does mortality occur early or late in acute pancreatitis? *Int J Pancreatol*. 2000;28:91-95.
29. Sabater L, Pareja E, Aparisi L, et al. Pancreatic function after severe acute biliary pancreatitis: the role of necrosectomy. *Pancreas*. 2004;28:65-68.