CME

Managing severe acute and necrotizing pancreatitis

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ABSTRACT

Acute pancreatitis is associated with significant morbidity and mortality, and is one of the most common gastrointestinal disorders requiring hospitalization. This article describes current concepts in the diagnosis and management of severe acute and necrotizing pancreatitis. Management of this disease requires IV fluids, pain control, and advanced medical and interventional care. Early identification and intervention may help to prevent patient morbidity and mortality.

Keywords: pancreatitis, severe, necrotizing, acute, interventional gastroenterology, gastrointestinal

Learning objectives

- Identify the diagnostic criteria for acute pancreatitis.
- Understand the classification of various pancreatic and peri-pancreatic fluid collections.
- Describe medical and interventional modalities used for the management of severe acute and necrotizing pancreatitis.
- Recognize optimal timing for interventions and potential complications.

In most patients, acute pancreatitis is mild, self-limited, and follows an uncomplicated course.[1] However, 15% to 20% of all patients have severe acute pancreatitis, and 5% to 10% of them will develop necrosis of the pancreatic glands, peripancreatic tissue, or both.[2] In severe cases, if the necrotic collection becomes infected, patient mortality can reach 30%.[3]

The incidence of acute pancreatitis requiring hospitalization in the United States continues to rise, with a 13.2% increase between 2009 and 2012 compared with 2002 to 2005.[4] Gallstone-related disorders may be the cause of this increase in the United States, because of increases in obesity and the aging population, although it also may be related to an increased frequency of testing (**Figure 1**).[4] This comes at a huge cost to the healthcare system, with more than $2.4 billion spent per year in the United States alone.[5]

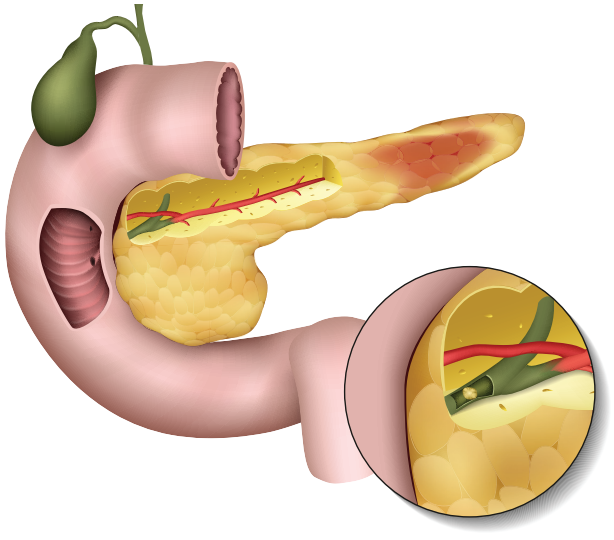

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FIGURE 1. Gallstones are a common cause of acute pancreatitis.

Management of acute pancreatitis has changed considerably in the past 10 years, including a multidisciplinary methodology, and tailored interventions with a minimally invasive endoscopic approach rather than open surgical intervention for complications.[6] To reduce patient morbidity and mortality, clinicians must be familiar with the presentation, diagnosis, and management of this disease.

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Key points

- For a diagnosis of acute pancreatitis, a patient must have two or more of the following: lipase greater than three times upper limit of normal, CT findings of acute pancreatitis, and abdominal pain in the epigastric region that radiates to the back.
- Early identification and treatment with aggressive IV fluid therapy in the initial 12 to 24 hours of symptom onset improves patient morbidity and mortality.
- Advanced endoscopic interventions are first-line therapy for large walled-off collections and necrosis.

PRESENTATION AND DIAGNOSIS

A diagnosis of acute pancreatitis requires two of the following criteria:

- typical abdominal pain, described as located in the epigastric region and radiating to the back
- an elevated lipase level more than three times the upper limit of normal
- radiographic evidence of acute pancreatitis on cross-sectional imaging.[7]

Establishing the underlying cause After the diagnosis of acute pancreatitis has been established, the clinician should identify the cause. A thorough history, laboratory testing, and imaging (ultrasound, CT, or MRI) are critical. The most common sources of pancreatitis are gallstone pancreatitis (40%) and chronic alcohol use or abuse (35%).[8] Less common causes include endoscopic retrograde cholangio-pancreatography (ERCP) (4%), medication use (2%), and abdominal trauma (1.5%).[8] If no source is identified, endoscopic ultrasound is recommended to evaluate for possible pancreatic mass or structural abnormality after the patient is stable and the acute inflammation has resolved.

Often, the cause is easily identified during a thorough patient history. Ask patients how often they consume alcohol and how much. Ask if the patient has a gallbladder or has had a recent ERCP, family history of hyperlipidemia or gallstone disease, medication history of any new or change in medications, and any recent trauma. Laboratory data can give insight as well, including checking an alcohol level if the history is unclear. Liver enzymes can demonstrate an alcohol pattern with AST twice as high as the ALT or a cholestatic pattern from possible gallstone cause with an elevated total bilirubin and alkaline phosphatase. First-line imaging includes a limited right upper quadrant ultrasound to evaluate for the presence of gallstones and possible choledocholithiasis. Reserve CT and MRI imaging for patients whose diagnosis is not clear or who are not improving 48 to 72 hours after hospital admission; imaging also can be used to evaluate complications.[9] All patients with acute pancreatitis, regardless of cause, should be started on aggressive IV fluids unless contraindicated by cardiovascular, renal, or other comorbidities. The next steps in management depend on the cause of the acute pancreatitis.

TABLE 1. Revised Atlanta classification[26,31]

	Mild	Moderately severe	Severe
Organ failure	No	<48 hours	>48 hours
		Transient organ failure	Persistent organ failure
Local or systemic complications	No	Without persistent organ failure	Single or multiple organ failure

For patients with gallstone pancreatitis, endoscopic ultrasound and ERCP with sphincterotomy and stone extraction can alleviate any biliary obstruction present.[10]

Patients with alcohol-induced pancreatitis should stop drinking alcohol and adhere to a sustainable alcohol cessation plan. The social work department is a critical component of the care team to provide these patients with local resources to help with alcohol cessation.

For patients with hypertriglyceridemia-induced acute pancreatitis, additional therapies such as insulin infusion and plasmapheresis are needed to reduce triglyceride levels.[11] Long-term management with diet modification and lipid management with fibrates such as fenofibrate may help prevent future episodes of pancreatitis.[11]

Medication-induced acute pancreatitis is rare but should always be considered, especially in patients taking drugs such as valproic acid, lisinopril, furosemide, pravastatin, or simvastatin.[12] After the culprit medication is identified, the patient should stop taking it or switch to an alternate acceptable therapy.

Neoplasms causing acute pancreatitis often cause compression of the pancreatic ducts, and patients may require endoscopic stent placement or surgical intervention to alleviate the biliary compression contributing to the pancreatitis.[13]

Classifying and predicting severity The clinical course of patients with acute pancreatitis can vary greatly, from mild disease to severe acute pancreatitis with necrosis. Several classification systems have been developed to assist with determining the severity of cases. The two systems most commonly used in clinical practice are the Revised Atlanta Classification (RAC) and the Determinant-Based Classification (DBC) (**Tables 1** and **2**). These classifications assess the risk of patient morbidity and mortality based on the severity of pancreatitis. The RAC categorizes acute pancreatitis as mild, moderately severe, or severe, based on the presence of organ failure and local or systemic complications. Mild acute pancreatitis, the most common form, usually resolves on its own within 1 week.[2]

Diagnosis of peripancreatic collections Classifying local complications of pancreatitis is important for directing

treatment and management. The RAC system defines four types of collections associated with acute pancreatitis (**Table 3**). The inflammatory cascade leads to the leaking of pancreatic enzymes into the peritoneal cavity causing interstitial edematous pancreatitis (IEP) and necrotizing pancreatitis.[14] Classification of these pancreatic fluid collections is based on three factors: content (fluid versus necrosis), degree of encapsulation (walled-off versus undefined wall), and chronicity (acute if less than 4 weeks, or chronic if more than 4 weeks from the episode of pancreatitis).[14]

IEP is more common, accounting for about 85% of fluid collections in patients with acute pancreatitis.[15] Complications associated with IEP include acute peripancreatic fluid collections or chronic pancreatic pseudocyst. Acute peripancreatic fluid collections do not have a defined wall surrounding them and typically are seen early on in the disease process. Chronic pancreatic pseudocysts develop from the peripancreatic fluid collections after the body encapsulates the fluid.[16]

Necrotizing pancreatitis, although less common, accounts for 15% of fluid collections and has a higher rate of morbidity and mortality.[15] The complications associated with necrotizing pancreatitis include acute necrotic collections (pancreatic or peripancreatic necrosis without a defined wall) or chronic walled-off necrosis (pancreatic or peripancreatic necrosis with a defined wall, with a mix of solids/fluid).[14] Pancreatic necrosis can be seen as nonenhancement of pancreatic parenchyma on contrast-enhanced CT, best assessed more than 72 hours after presentation.[3,7,16] Infected necrosis may be presumed in the presence of gas noted in the fluid collection on CT or based on deterioration of the patient's clinical course without other identified source. This typically is seen 3 to 4 weeks after initial presentation.[16] Fine-needle aspiration for culture is not recommended because of the high rate of false negatives.[3] Patients with diagnosed infected pancreatic necrosis may need antibiotics and active intervention.[6]

MANAGEMENT

Initial treatment for patients with severe acute pancreatitis focuses on fluid resuscitation and pain management. Early aggressive IV fluid resuscitation is critical because the effective resuscitation window of acute pancreatitis is narrow, ideally initiated within 12 to 24 hours of symptom onset, and cannot be missed. Patients often appear well on admission but can decompensate quickly. Fluid resuscitation can halt the inflammatory cascade, improve local tissue perfusion, and improve oxygen delivery. The American Gastroenterological Association (AGA) recommends goal-directed therapy for fluid management: adjusting IV fluid administration to meet perfusion targets as measured by heart rate, mean arterial pressure, central venous pressure, urine output, blood urea nitrogen (BUN) concentration, and hematocrit level.[6] American College of Gastroenterology guidelines recommend 250 to 500 mL/h of isotonic crystalloid solution in the initial 12 to 24 hours. In patients with severe volume depletion evidenced by hypotension or tachycardia, boluses may need to be repeated.[9] Assess patients' fluid requirements often within the first 6 hours of admission and for the next 24 to 48 hours.[9]

TABLE 2. DBC for acute pancreatitis

DBC	Mild	Moderate	Moderately severe	Severe
(Peri) pancreatic necrosis	No	Sterile	Infected	Infected
	and	*and/or*	*or*	*and*
Organ failure	No	Transient	Persistent	Persistent

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Pain control is another critical part of management. Patients often require high doses of IV opioids in the acute phase of pancreatitis in order to adequately control their pain. Keep patients NPO while they are on IV opioids, and when pain decreases and the patient no longer requires opioids, slowly advance the diet to clear liquids then to a low-fat diet as tolerated. If the patient cannot be weaned from opioids, consider initiating enteral nutrition.[8,17]

Preventing infection Early identification and treatment of alternate sources of infection, such as pneumonia or bacteremia, is critical to improving patient outcomes and preventing sepsis. Patients with pancreatic or peripancreatic necrosis can develop secondary infections via bacterial translocation of microorganisms from the intestinal lumen, resulting in sepsis, prolonged ICU care, and death.[18] However, prophylactic antibiotics are not routinely recommended in patients with acute pancreatitis and have been associated with multidrug-resistant bacteria and fungal superinfection.[6]

Nutrition Traditionally, patients with severe acute pancreatitis were kept NPO; however, the literature has not supported this and has actually shown that in contrast, adequate nutrition is a key element in management.[19] Optimizing nutrition promotes healing and early recovery. The AGA guidelines recommend initiating oral or enteral nutrition within the first 24 hours of admission.[20] Optimal nutrition assists in restoring the anabolic state, maintains gut barrier function, and provides important immunomodulatory and antioxidant effects.[20] Nasogastric or nasojejunal feeding tubes can be used in patients requiring enteral nutrition.[6] The European Society for Clinical Nutrition and Metabolism guideline on clinical nutrition categorizes nutrition recommendations based on mild, moderate, or severe pancreatitis, and recommends starting nutrition within 24 to 72 hours of admission and using the gut even if only a small amount is tolerated.[17] Clinicians should only

TABLE 3. Collections associated with acute pancreatitis[2,26]

	IEP	Necrotizing pancreatitis
<4 weeks	Acute (peri)pancreatic fluid collection—homogenous fluid without a definite wall adjacent to the pancreas	Acute necrotic collection—intra- and/or extrapancreatic necrotic collection without a defined wall
≥4 weeks	Pancreatic pseudocyst—an encapsulated, well defined, typically extrapancreatic fluid collection with minimal solids	Walled-off necrosis—intra- and/or extrapancreatic necrotic collection with a well-defined wall

consider peripheral nutrition if the patient cannot meet target nutrition via oral or enteral routes.[17] A percutaneous endoscopic transgastric-jejunostomy (PEG-J) tube is beneficial if nutrition support is needed for longer than 6 weeks, such as in patients with large necrotic collections, gastric outlet obstruction, or ileus.[17]

Interventions in necrotizing pancreatitis Endoscopic-guided drainage has changed the landscape of the treatment of severe necrotizing pancreatitis. Because they lead to significantly improved outcomes and fewer complications, these minimally invasive procedures have replaced the traditional management of surgical debridement and peritoneal lavage.[21] These less-invasive procedures, performed by advanced endoscopists who complete an additional year of fellowship in advanced endoscopy, minimize complications including new-onset organ failure, external fistulas, exocrine and endocrine pancreatic insufficiency, and incisional hernias.[3,6,22]

Cystenterostomy is the endoscopic procedure to treat walled-off necrosis. It is followed by a *necrosectomy*, which may need to be repeated multiple times over several days, weeks, or months depending on the size of the necrotic cavity.[23] In a cystenterostomy, endoscopic ultrasound is used to identify an area of walled-off necrosis. The therapeutic endoscope creates a channel between the necrotic collection and the stomach or duodenum. This lets the body expel the necrotic tissue and fluid through the gastrointestional (GI) tract. After the opening between the cyst and the stomach is created, a stent can be placed to ensure transluminal drainage.

Necrosectomy is a second procedure that involves inserting a therapeutic endoscope into the cavity through the cystenterostomy opening in order to remove necrotic tissue and relocate it into the stomach. This procedure often needs to be repeated until all the dead tissue has been removed, thus allowing the healthy tissue to heal and regenerate. CT scans are used to evaluate progress and resolution. Compared with the surgical step-up approach, the endoscopic step-up approach has significantly lower rates of pancreatic fistula formation and averaged 16 fewer days in the hospital.[24]

Proton pump inhibitors (PPIs) and other antacids are not recommended after a cystenterostomy because it is thought that the acidity of the stomach assists in the elimination of the necrotic tissue. Discontinuing PPIs has been shown to reduce the number of endoscopic procedures required.[25] Antibiotics are only indicated in patients with infected necrosis and are not recommended for patients with necrotizing pancreatitis without infection.

Current guidelines recommend waiting at least 3 to 4 weeks from the onset of pancreatitis for interventions to allow the collection to become encapsulated and enable liquefaction.[3,9,26] However, patients who develop abdominal compartment syndrome (ACS) may need emergency and lifesaving procedures. Emergency surgical intervention also may be needed for patients with severe hemorrhage not amenable to angiographic or other coiling/embolization, ischemic bowel infarction, or perforation of a hollow viscus.[26]

COMPLICATIONS OF SEVERE DISEASE

The major complications of severe acute pancreatitis include necrosis, splanchnic vein thrombosis, pseudoaneurysmal bleeding, abdominal compartment syndrome, pancreatic fistulae formation, and disconnected pancreatic duct.

Splanchnic vein thrombosis This is a common vascular complication in patients with severe acute pancreatitis because of the proinflammatory environment associated with the disease.[26] The splenic vein usually is affected as a result of its close proximity to and contact with the pancreatic gland. Splanchnic vein thrombosis can be associated with development of left-sided portal hypertension resulting in esophageal varices and ascites.[27] The role of anticoagulation for splanchnic vein thrombosis alone is controversial because it increases the risk for life-threatening bleeding.[26]

Pseudoaneurysmal bleeding Pseudoaneurysm development is associated with the fluid collection eroding into surrounding arteries, most commonly the splenic artery. Identifying vascular complications early with cross-sectional imaging is crucial because pseudoaneurysmal bleeding is associated with significant morbidity and mortality, historically reported as high as 34% to 52%.[26,27] First-line therapy includes angiography with embolization and possible stenting of distal vessels.

IAH and ACS Intra-abdominal hypertension (IAH) is defined as sustained intra-abdominal pressure greater than 12 mg Hg; ACS is sustained intra-abdominal pressure greater than 20 mm Hg.[27] IAH and ACS are thought to be related to inflammatory changes resulting in intra-abdominal edema, pancreatic fluid collections, and ascites, as well as to medical interventions including aggressive fluid over-resuscitation.[24] IAH and ACS are associated with new or significantly worsening organ failure and contribute to

substantial morbidity and mortality in patients with severe necrotizing pancreatitis.[28] The first-line treatment for ACS is percutaneous catheter drainage. If it is unsuccessful, surgical intervention is indicated.[27]

Pancreatic fistula A damaged pancreatic duct can lead to the formation of a fistula. An internal pancreatic fistula connects the pancreatic duct and the peritoneal cavity, mediastinum, or other organs or spaces. An external pancreatic fistula communicates to the abdominal wall; this is called a pancreatico-cutaneous fistula. Pancreatic fistulas can lead to pancreatic ascites, pleural effusion, and enzymatic mediastinitis. Between 75% and 100% of fistulas resolve over time with conservative treatment or transpapillary stenting.[29,30]

Invasive interventions should be reserved for patients who do not respond to medical management, as well as for those patients with pancreatic ascites, pancreaticopleural fistula, or high output from an external fistula.[27]

Disconnected pancreatic duct A disconnected pancreatic duct is a disruption in the pancreatic ductal system caused by central necrosis leading to the discontinuity between pancreatic secretions and the GI system. This can result in persistent or recurrent fluid collections, pancreatic ascites, and pancreatic-pleural and pancreatic fistulas. The most common method to reduce the risk of recurrent fluid collections is to leave cystenterostomy stents indefinitely; this maintains the patency of the internal fistula and diverts pancreatic enzymes into the GI lumen.[26]

CONCLUSION

Understanding initial management is critical for all healthcare providers who care for patients with acute pancreatitis. These patients often present initially to community clinics, urgent care centers, and EDs, which may not have the interventional gastroenterology specialists needed to appropriately manage the time-sensitive care of these patients. Knowing when to transfer patients to a tertiary care center staffed with interventional gastroenterologists is critical for optimal treatment and for reducing morbidity and mortality. Prompt intervention and treatment at such a tertiary care center can greatly improve patient outcomes.

Clinicians across all specialties can assist with correctly identifying acute pancreatitis, initiating proper management, and identifying the underlying cause. Frontline healthcare providers can quickly identify acute pancreatitis and begin proper acute phase management, thereby ensuring advanced specialty care is appropriately used. Clinicians can provide patient education, support, and guidance. They can provide follow-up care including monitoring for improvement, preventing readmissions, guaranteeing that radiographic imaging is obtained at the correct time, and coordinating stent removal and exchanges. PAs are a critical part of the medical team to ensure the successful treatment of patients with acute pancreatitis. **JAAPA**

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