Acute Pancreatitis: Contemporary Diagnosis and Management

Ryan C. Van Woerkom, MD, and Douglas G. Adler, MD

ABSTRACT

• **Objective:** To review the diagnosis and management of patients with acute pancreatitis.
• **Methods:** Literature review.
• **Results:** Commonly encountered pancreatitis etiologies include alcoholic, biliary, idiopathic, hereditary, hypertriglyceridemia, hypercalcemia, and drug-induced. Imaging is not typically indicated unless the diagnosis is ambiguous or clinical judgement suggests a severe course, with the type of imaging dependent upon suspicion of underlying etiology. Management mainstays include bowel rest, pain/nausea relief, correcting underlying cause, and fluid resuscitation. Nutrition management and surgery may be required in selected severe cases.
• **Conclusion:** Acute pancreatitis is a final common pathway by which various heterogeneous etiologies enter for this not uncommonly encountered pathology. Current trends in acute pancreatitis clinical research focuses on further refining questions regarding the biomarkers/scoring systems for prognostication, type and amount of fluid required for resuscitation, and further delineating the circumstance under which each imaging modality should be utilized.

Acute pancreatitis describes an acute inflammatory process of the pancreas that rapidly depletes intravascular water and promotes, if unchecked, regional inflammation. The spectrum of severity ranges from mild interstitial pancreatitis to more severe forms such as pancreatic necrosis, which is frequently associated with concomitant multiorgan failure. In 2005 and 2007, an estimated 230,000 patients were treated for acute pancreatitis in hospitals in the United States [1,2]. Recent studies have demonstrated an increase in the incidence of acute pancreatitis, and some have projected the incidence to be substantially higher than previously reported rates, although case-fatilities have remained stable since 1970 [3]. The increased frequency of acute pancreatitis may be due to the rising incidence of obesity, a risk factor for the development of gallstones and, by extension, gallstone pancreatitis [4], although an increase in surveillance bias cannot be excluded.

Acute pancreatitis confers a heavy financial burden. A recent study estimated that the average cost per hospitalization is $9870 [5]. Acute pancreatitis is responsible for $2.2 billion in U.S. health care expenditures annually. The average length of hospital stay for a patient with acute pancreatitis is approximately 5 to 6 days; children have shorter hospital stays and adults 45 to 64 years of age have on average 1 day longer hospital stays [3,6,7]. Acute pancreatitis may be accompanied by life-threatening complications as well as significant morbidity and mortality. This article reviews the diagnosis and management of patients with acute pancreatitis.

ETIOLOGY

**Gallstones or Biliary Pancreatitis**

Biliary pancreatitis, synonymous with gallstone pancreatitis, is a form of acute pancreatitis caused by the passage of gallstones through the cystic duct and into the distal common bile duct where they can obstruct the flow of bile and digestive enzymes from the biliary and pancreatic ducts into the duodenum. Pancreatic ductal obstruction is felt to be the inciting event in gallstone pancreatitis [8]. One study that evaluated data on consecutive patients admitted with acute pancreatitis to a community hospital reported an incidence rate of 45 cases per 100,000 person-years for gallstone acute pancreatitis [8]. Incidence is highest in patients with small gallstones or microlithiasis, as these stones are more likely to escape the gallbladder and transit the cystic duct to reach the common bile duct [9]. Large stones are more likely to be retained in the gallbladder.

From the Division of Gastroenterology, University of Utah School of Medicine, Salt Lake City, UT.
A recent study noted that the incidence of all causes of acute pancreatitis rose between 1994 and 2001 from 33.2 cases to 43.8 cases per 100,000 adults, without a reduction of mortality rate. The increase in acute pancreatitis was felt to be mainly due to the rise in the incidence of biliary pancreatitis [10].

Caucasians, Hispanics, and American Indians are more likely than African Americans to develop biliary acute pancreatitis [7,9,11]. One study demonstrated that gallstone pancreatitis typically presented at a younger age in Hispanics; this population had a more benign clinical course with infrequent intensive care unit (ICU) admissions [12]. Obesity is a risk factor for the development of gallstone pancreatitis and may increase the risk for the development of severe pancreatitis, including pancreatic necrosis [13]. Obesity also increases the risk of developing local complications such as pancreatic fluid collections [13]. However, obesity is not associated with increased mortality in acute pancreatitis. Pregnancy is also a risk factor for the development of gallstone pancreatitis, with an incidence ranging from 1 case per 1000 to 3333 pregnancies [14–16]. Elevated alanine aminotransferase, advancing age, weight gain, female sex, and rapid weight loss are all risk factors associated with the development of biliary acute pancreatitis [11,17]. Unsaturated fats, coffee, and moderate alcohol consumption appear to reduce the risk of developing gallstones and, thus, biliary acute pancreatitis [18–20]. Elevated alanine aminotransferase (ALT) in a patient with suspected acute pancreatitis may lead to the diagnosis of a biliary etiology; varying thresholds have been utilized and sensitivity in distinguishing between alcohol-related and non–alcohol-related acute pancreatitis ranges from 72% to 84%. Microlithiasis can be a potential cause of acute pancreatitis as well.

**Alcoholic Pancreatitis**

Alcohol is a common precipitant of acute pancreatitis, although the incidence of acute pancreatitis in heavy alcohol consumers is not more than 2% to 3% per year [21]. This suggests that there are as yet undetermined environmental or genetic factors that influence the development of acute pancreatitis in this population. Yadav and Whitcomb found that alcoholic acute pancreatitis usually occurred after more than 5 years of heavy drinking; the role of tobacco use in relation to alcoholic acute pancreatitis is still being investigated though it is thought to propagate an accelerated course in established acute pancreatitis [22]. Currently, 17.6 million Americans have a form of an alcohol use disorder, and some data suggest that the incidence of alcoholic acute pancreatitis is on the rise [6,23]. Of note, the alcoholic acute pancreatitis incidence rate may be similar in heavy drinkers of both sexes (91.5 cases per 100,000 persons in men versus 81.9 in women). Alcoholic acute pancreatitis incidence rates peak between the ages of 35 and 44 years [10]. Furthermore, alcoholic acute pancreatitis has the highest associated risk of overall mortality, a 90% increased odds compared to biliary pancreatitis [10], possibly due to poor baseline nutrition. Tobacco use has been recently implicated with development of nonbiliary acute pancreatitis [24]. Its strength as an independent risk factor in acute pancreatitis appears synergistic with concomitant alcohol use [25].

**Idiopathic Acute Pancreatitis**

Between 10% and 30% of cases of acute pancreatitis may be idiopathic in nature [26]. African Americans have the highest age- and sex-standardized incidence rate of idiopathic pancreatitis [10]. A substantial proportion of acute pancreatitis of unclear cause may be explained by such etiologies as undetected microlithiasis, unrecognized drug-induced pancreatitis [27], or the controversial sphincter of Oddi dysfunction, among other possibilities [28].

**Inherited Forms**

Hereditary pancreatitis, first reported in 1952, is a rare disease characterized by mutations in the pancreatic secretory cationic trypsinogen inhibitor (PTSI or PRSS1) gene, R122H or N29I, or in the serine protease inhibitor Kazal type 1 (SPINK1), resulting most often in an autosomal dominant phenotype [29,30]. It should be considered in patients with recurrent pancreatitis who also have a family history of pancreatitis. This recurrent form of acute, relapsing pancreatitis often manifests first in childhood (although it may not manifest until age 30), with a cumulative incidence of pancreatic cancer of 40% by the age of 70 years [31]. Hereditary pancreatitis almost always develops into chronic pancreatitis and is associated with an increased incidence of pancreatic cancer. Other rare genetic sequences are risk factors for severity of acute pancreatitis such as the MCP-1-2518 G allele; the individual PRSS1 mutation does not appear to contribute to severity risk [32,33].
Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) allele have been associated with the development of pancreatitis. Mutations in CFTR can be present in as many as 10% of patients with acute pancreatitis, although it is often difficult to exclusively attribute the development of pancreatitis to CFTR mutations [34]. Abnormally functioning CFTR genes may cause inspissation of pancreatic secretions, leading to pancreatic ductal obstruction and pancreatitis [35]. CFTR gene mutations are often associated with recurrent acute pancreatitis and/or chronic pancreatitis. A single episode of acute pancreatitis should not prompt genetic testing for CFTR mutations [36]. Recurrent idiopathic pancreatitis that results from CFTR mutations may be more aptly classified as, and often develops into, chronic pancreatitis in this population.

**Drug-Induced Pancreatitis**

Drug-induced pancreatitis may account for as much as 7% of all cases of acute pancreatitis [37] and may represent the 3rd most common cause of acute pancreatitis. Medications implicated (albeit with varying levels of evidence) in the development of drug-induced pancreatitis are listed in the Table [38]. Women, children, the elderly, patients with underlying Crohn’s disease, or hematologic malignancies, and those who have received multiple cancer chemotherapy agents appear to comprise populations with an increased risk of drug-associated acute pancreatitis [39]. Many drugs have been implicated as causes of acute pancreatitis, and a careful evaluation of the patient's medications is warranted in all patients with acute pancreatitis of unclear etiology. Drug-induced acute pancreatitis may occur any time during the course of the implicated pharmaceutical agent. Classification systems have been developed that may assist the clinician in determining the level of evidence that implicates a given drug because of the potential for both over and under diagnosing [40,41]. As rules of thumb, the development of acute pancreatitis must occur during treatment with the drug, all other causes of acute pancreatitis must be excluded, and the acute pancreatitis should be seen to resolve with discontinuation of the offending drug. Additionally, acute pancreatitis recurs when the drug is readministered, although medico-ethical concerns often prevents clinical testing of this with a rechallenge of the drug—it may be reintroduced when the drug is crucial for the patient’s health, the character of the disease is concerning, and/or when the etiology is not clearly defined [42].

**Iatrogenic Pancreatitis**

Iatrogenic pancreatitis most commonly occurs following endoscopic retrograde cholangiopancreatography (ERCP) [43]. One review that evaluated complication rates reported in prospective studies of ERCP computed a 3.47% incidence rate of iatrogenic acute pancreatitis, although the rate is dependent on the type of procedure performed and individual patient risk factors [44]. Studies evaluating a variety of medications to reduce the risk of post-ERCP pancreatitis have been largely unrevealing, and no currently available agent has been shown to clearly reduce the incidence of post-ERCP pancreatitis (PEP). Recent data have demonstrated that prophylactic stent placement in the pancreatic duct of high-risk patients reduces the risk of developing PEP and reduces the severity of PEP in patients who develop it [45,46]. This is further supported by a contemporary meta-analysis that found that regardless of the severity of

---

**Table. Medications Implicated in the Development of Drug-Induced Pancreatitis**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial</td>
<td>Tetracycline, sulfonamide, pentamidine, didanosine, metronidazole</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Furosemide, thiazides</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td>Azathioprine, 6-mercaptopurine</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory</td>
<td>Sulindac, salicylate, indomethacin</td>
</tr>
<tr>
<td>Antiproliferative</td>
<td>Tamoxifen, L-asparaginase</td>
</tr>
<tr>
<td>Other</td>
<td>Estrogen, bethaneol, oral contraceptives, ACE inhibitors, SSRI antidepressants, angiotensin II receptor blockers, statins</td>
</tr>
</tbody>
</table>
PEP, prophylactic stents were beneficial [47]. Furthermore, careful patient selection and minimally traumatic endoscopic techniques appear to offer additional protection against the development of PEP [46,48]. Pancreatitis may also occur following abdominal surgery, cardiac surgery (ischemia related with bypass surgery), liver biopsy, and abdominal procedures performed by interventional radiologists and can be caused by retained intra-abdominal foreign bodies as well as iatrogenic hypercalcemia due to total parental nutrition, among other causes [49–53].

**Infectious Causes**

Infectious causes of acute pancreatitis are rare and have mostly been described in case reports. The most common parasitic infections linked to the development of acute pancreatitis are *Toxoplasma, Cryptosporidium,* and *Ascaris* [54]. Viruses known to cause acute pancreatitis include mumps, Coxsackie, hepatitis B, cytomegalovirus, and the varicella zoster virus [57]. Only a few bacteria are well established as causes of acute pancreatitis: *Mycoplasma, Legionella, Leptospira,* and *Salmonella* [57,58]. *Aspergillus* is the only fungus that has been strongly associated with causing acute pancreatitis [57].

**Hypertriglyceridemia and Hypercalcemia**

Hypertriglyceridemia is a well recognized cause of acute pancreatitis and should be treated appropriately. Hypercalcemia is also a recognized etiology of acute pancreatitis [57]. Hypercalcemia can be associated with a malignancy (often in the setting of bony metastases or multiple myeloma), total parenteral nutrition (as mentioned above), sarcoidosis, vitamin D toxicity and infusions of perioperative high-dose calcium during cardiopulmonary bypass [58]. If muscular/myopathic, urologic, or nervous systems symptoms coexist with acute pancreatitis, patients should be evaluated for hyperparathyroidism [59].

**Other Causes**

Less commonly encountered causes of acute pancreatitis include autoimmune pancreatitis, most often seen in Asian populations, trauma-induced pancreatitis (often following motor vehicle accidents), and scorpion stings [60]. Autoimmune pancreatitis should be suspected in those patients with an elevated immunoglobulin G subclass 4 level [61]. Pediatric acute pancreatitis can also be seen and can be associated with multisystem disease and systemic infection [62]. Rarely, tumors such as ampullary cancer or intraductal papillary mucinous neoplasm of the pancreas can cause acute pancreatitis. Congenital malformations, including pancreas divisum, annular pancreas, and anomalous pancreaticobiliary union, among others, have also been implicated.

**Risk of Recurrence**

If underlying causes are not identified and treated, the risk of recurrent acute pancreatitis can be high. Gallstone pancreatitis carries a significantly lower risk of recurrence of approximately 10% [63] because recognition of gallstones as a cause is usually followed by a procedure to clear the bile duct and subsequent cholecystectomy. Therefore, a watch-and-wait approach cannot be advocated in these patients given the high risk of recurrence. A recent well-constructed meta-analysis showed a decrease in mortality following cholecystectomy in patients undergoing biliary sphincterotomy and duct clearance, further bolstering this argument [64]. Most studies report a negative correlation between mortality and recurrent acute pancreatitis [65].

**Pathophysiology**

In pancreatic acinar cells, a primary injury promotes compartmentalization of lysozomal enzymes (eg, cathepsin B and exocrine pancreatic enzymes) [66], which activates catalytic proteins with subsequent enzymatic “spilling” leading to the typical inflammatory cascade seen in acute pancreatitis [67]. Trypsin activates other proteases like elastase and chymotrypsin, components of the complement and coagulation cascades and kinins [68]. The enzymes diffuse into the interstitial and endothelial spaces and begin autodigestion of the gland. acute pancreatitis can be thought of as a breakdown of regulatory pathways which can be predominantly attributed to overproduction or inappropriate activation of pancreatic zymogens or defective inactivation by the serine protease inhibitors [69]. Tissue breakdown products potentiate vascular injury, with local recruitment of cytokine and arachidonic acid metabolite–secreting leukocytes with TNFα acting as a central mediator [71]. These agents produce edema and reactive oxygen species which are thought to be mediators of systemic organic dysfunction; interestingly, patients with diminished glutathione S-transferase activity due to polymorphisms have a higher incidence of
developing severe acute pancreatitis[70]. The increase in vascular permeability promotes thrombosis and hemorrhage and can lead to pancreatic ischemia and necrosis [70]. Increased vascular permeability can lead to bacterial translocation into the pancreatic bed and result in infected pancreatic necrosis, a life-threatening complication of acute pancreatitis. In severe cases, systemic inflammatory response syndrome (SIRS), renal failure, shock, myocardial stress, fever, or acute respiratory distress syndrome may develop.

Most of the final inflammatory pathways are identical regardless of etiology although alcoholic acute pancreatitis may slightly vary. Alcohol potently stimulates the release of secretin and cholecystokinin, which are the major contributors to pancreatic secretion [71]. Also, the rising ethanol concentration in acinar cells causes an increase in cytosolic calcium, which is required for vesicular zymogen activation. This relationship between cytosolic calcium and zymogen activation may also help to explain the association between hypercalcemia and acute pancreatitis [71].

**DIAGNOSIS**

The classic presentation of acute pancreatitis includes mild to severe epigastric abdominal pain (often radiating to the back) as well as nausea and vomiting. The pain is typically constant in nature and is not aggravated by coughing, movement, or respiration. The pain tends to be more severe in a supine position and may lessen if the patient leans forward in a sitting position. Patients may appear pale and distressed, jaundiced, or tachycardic, and may be febrile and have a distended abdomen [72]. Turner’s sign (flank bruising) or Cullen’s sign (bruising surrounding the umbilicus) may be present in severe cases. Some patients may have a more florid presentation that includes hypotension or shock due to intravascular volume depletion and third spacing of fluids.

Commonly accepted criteria for a clinical diagnosis of acute pancreatitis necessitates the presence of 2 of the 3 following features: serum amylase and lipase elevated at least 3 times above the upper limit of normal; characteristic epigastric abdominal pain as described above; and typical radiologic features as found on computed tomography (CT), magnetic resonance imaging (MRI) or transabdominal ultrasound. Dehydration can be present in acute pancreatitis and may manifest with elevated blood urea nitrogen (BUN) and hematocrit and decreased urine output. The latter findings may be seen in more severe presentations, including hypotension despite volume replacement and a corresponding rise in hematocrit secondary to hemoconcentration, metabolic acidosis, acute respiratory distress syndrome/respiratory failure, renal failure, and fluctuation in serum calcium levels [73,74].

Classification systems are currently being revised which include a four-tier system, with a moderate severe acute pancreatitis category defined as pancreatitis with complications but without multiorgan system dysfunction [75].

**Biochemical Diagnostic Parameters**

Elevation of serum amylase and lipase to at least greater than 3 times the upper limit of normal in conjunction with the appropriate clinical history are mainstays in the diagnosis of acute pancreatitis. Prospective studies comparing the selective evaluation of lipase versus amylase demonstrate a slight diagnostic advantage to lipase because amylase may have a lower sensitivity (ie, it may be normal in patients with acute pancreatitis) [76–78]. In general, amylase and lipase levels do not correlate with either the severity of the attack or with overall prognosis. In addition, serum amylase and lipase levels neither assist in generating an overall prognosis nor in predicting complications of acute pancreatitis [79–81]. Most practicing physicians do not follow serum amylase and lipase levels beyond the first few days once the diagnosis has been established. A fall in enzymes, however, accompanied by clinical improvement often adequately demonstrates a resolving acute pancreatitis in most patients. Persistent elevation of serum amylase and lipase may suggest pancreatic ductal disruption and/or necrosis. Finally, amylase and lipase assays do not need to be ordered simultaneously as this may incur higher health care costs [82].

Serum alkaline phosphatase and bilirubin levels are not useful in isolation in the diagnosis of acute biliary pancreatitis, although a threefold elevation of ALT has a positive predictive value of 96%, and aspartate transaminase is nearly as useful as ALT according to one meta-analysis [83]. If liver function enzymes and amylase and lipase levels are elevated, an etiology of biliary pancreatitis is more likely, although pancreatic edema causing extrinsic compression of the distal common bile duct can produce similar laboratory findings. Currently, serum hematocrit and C-reactive protein (CRP; 48 hours after onset) have assumed greater predictive roles in determi-
nation of vascular and gastrointestinal complications (see below) [84,85].

Imaging

When clinicians suspect that acute pancreatitis may be atypical in presentation, imaging may be particularly helpful. Abdominal radiographs are of some value in patients with pancreatitis. The presence of calcifications may suggest chronic pancreatitis as an underlying diagnosis. Signs that may be seen on radiograph in acute pancreatitis include a “sentinel loop,” or a dilated segment of small intestine or colon displaying ileus, and “colon cut-off sign,” a functional spasm in the descending colon resulting in a termination of air in the distal colon near the splenic flexure. Plain radiographs may not be as sensitive as other imaging modalities and not quantitate the amount of pancreatic necrosis or completely describe complications like pancreatic pseudocyst.

A hyperechoic, diffusely enlarged pancreas is often seen on transabdominal ultrasound in acute pancreatitis. Ultrasonography does not assist in diagnosing the extent of pancreatic necrosis or inflammation.

CT scans with intravenous contrast should be strongly considered in patients with suspected pancreatic necrosis because CTs may assist in triaging the patient within the hospital. The entire pancreas, including necrotic changes, can be well visualized and complications of pancreatitis such as fluid collections and/or pseudocysts can be rapidly identified (Figure 1). CT findings such as peripancreatic stranding and enlargement of part or all of the pancreas may suggest acute pancreatitis. Contrast-enhanced CT demonstrated an excellent correlation between imaging results and the development of early and late necrosis [87]. The degree of necrosis is also an excellent prognostic factor. Small areas of necrosis can still be missed via contrast CT imaging [88].

Abdominal MRI is typically utilized when CTs are contraindicated or to search for common bile duct stones via magnetic resonance cholangiopancreatography (MRCP). Studies performed with MRI use gadolinium for contrast, which carries a lower risk of side effects or renal injury than contrast used with CT scans. MRI is also highly effective at identifying fluid collections and pancreatic necrosis [90]. MRI has a greater sensitivity for detecting mild acute pancreatitis as compared with CT scan [91]. MRI may be preferred over CT scan if biliary pancreatitis is suspected as MRCP can be performed at the same time and stones within the common bile duct can be readily identified [91]. Cost and accessibility limit the availability and use of MRI in rural areas.

Endoscopic ultrasound has a defined role in acute pancreatitis—it is used to evaluate the common bile duct for the presence of stones in cases when the diagnosis is equivocal and can be subsequently followed with therapeutic ERCP (or if neoplasms are suspected). In biliary pancreatitis, the best timing of when to use endoscopic ultrasound versus ERCP is controversial. Current evidence is showing a trend of early endoscopic ultrasound imaging over ERCP due to better cost-benefit ratios (especially in severe biliary pancreatitis) [89,90] and improved diagnoses (positive predictive value) [91,92] and outcomes (according to a recent meta-analysis) [93]. ERCP should be used before (or in place of) endoscopic ultrasound when acute pancreatitis is accompanied by signs of cholangitis. If impacted stones are suspected, they are, in addition to cholangitis, another potential indication.
for ERCP. Endoscopic ultrasound has some additional diagnostic advantages over CT and transabdominal ultrasound: it may show the presence of microlithiasis, occult malignancies of the pancreas [94], and pancreas divisum. If stones are seen via endoscopic ultrasound, ERCP can typically be performed at the same time. A meta-analysis designed to compare the accuracy of MRCP and endoscopic ultrasound in detecting choledocholithiasis showed the 2 modalities are equivalent in this regard (Figure 2) [95]. Additionally, there is some prognostic potential for the early prediction of severe acute pancreatitis when peripancreatic edema is seen on endoscopic ultrasound [96]. If a neoplasm is suspected, endoscopic ultrasound (possibly with concomitant ERCP) is the preferred diagnostic imaging; it should generally be performed when the acute pancreatitis episode has resolved.

PROGNOSTIC FACTORS/PREDICTORS

Etiology alone cannot be used as a key predictor of clinical course. Several biomarkers have been investigated as possible indicators of prognosis and/or severity. Many of the candidate biomarkers have not undergone complete analyses and standardized validation [97]. Due to these methodologic flaws, no single biomarker has been accepted into wide clinical practice [98]. Several scoring systems to assess the severity and prognosis of patients with acute pancreatitis (eg, Ranson criteria, Imrie scoring system, and Acute Physiology and Chronic Health Evaluation II [APACHE-II]) have been developed [99–101]. In 1976, Ranson reported the use of a series of 11 objective findings that correlate with severity in patients with acute pancreatitis (eg, age, serum levels of various markers, and serum calcium levels). APACHE II is most recommended by society guidelines [102–104] although rarely utilized in clinical practice outside of research studies. These scoring systems may help early in the clinical course of a patient with acute pancreatitis, although their usefulness diminishes as the disease progresses [104]. Generally, renal failure, respiratory failure, multiorgan system failure, fluid collections, necrosis, increased ICU length of stay, and shock are all poor prognostic factors [105]. In a study that assessed the use of scoring systems, CT, and serum markers to predict acute pancreatitis outcomes, imaging the pancreas alone was poorly predictive of outcome [106].

Although these systems are excellent predictors of the severity of acute pancreatitis, they can be cumbersome to use. CRP may predict need for further supportive care within 24 to 48 hours of admission: it has better negative predictive value than Ranson’s criteria with preserved good positive predictive value [107], but not in all studies [108]. Brown and colleagues have demonstrated that hemoconcentration is an early marker for organ failure and pancreatic necrosis when evaluated 24 hours after hospital admission, again suggesting the importance of adequate hydration in acute pancreatitis [85]. Hemoconcentration markers have a sensitivity of 94% for detecting necrotizing pancreatitis and a negative predictive value of 96% [85]. Adequate hydration should be expected to reverse hemoconcentration and may reduce the risk of developing severe pancreatitis by increasing perfusion of the gland. When used as a prognostic factor, hematocrit determination is at least as accurate as APACHE-II scores but is available in less than half the time of the scoring systems and is much easier to use. Follow-up studies, unfortunately, have failed to validate the accuracy of this hemoconcentration in prognosis of acute pancreatitis [109–111]. BUN at admission, as well as an increase during the first 24 hours of hospitalization, indicated higher mortality and may direct fluid resuscitation in the management of acute pancreatitis [112].

A newer scoring system that incorporates BUN > 25 mg/dL, impaired mental status, SIRS, age > 60 years or the presence of a pleural effusion (BISAP) can predict mortality prior to organ failure within the first 24 hours but is not more simplistic or accurate than existing scor-
Acute Pancreatitis

MANAGEMENT
Fluid Resuscitation
Most patients with mild acute pancreatitis recover with supportive measures. Patients should have NPO status for at least 24 to 48 hours in mild acute pancreatitis and longer in severe acute pancreatitis. In the absence of cardiopulmonary complications, vigorous hydration with intravenous fluids should be administered until adequate urine output is achieved and maintained [77]. Published studies have suggested rates from 250 to 1000 mL/hr with careful monitoring and ongoing reassessment of the patient in order to establish adequate fluid resuscitation and to avoid fluid overload, although care must be individualized; obese patients may need greater fluid resuscitation [115,116]. The exact volume, rate, and type of aggressive hydration have not been universally defined and ultimately care must be individualized, as discussed above. Hematocrit and BUN can be used to aid in tailoring fluid resuscitation. Early fluid resuscitation promotes lower rates of SIRS, organ failure, shorter hospitalizations, ICU admissions than those patients with interstitial AP who adequately rehydrated [117]. Wu et al recently suggested the superiority of lactated ringers solution when compared against normal saline in a small randomized control study, but treatment should be individualized [118].

Nutrition
Nutrition, as defined by total parenteral nutrition (TPN) and enteral nutrition (EN), plays a central role in the therapy of acute pancreatitis. If pancreatic necrosis is seen, enteral feeding using a nasoenteric tube with the distal tip placed beyond the ligament of Treitz (enteral) is often performed to reduce the risk of bacterial translocation from the gut to the necrotic pancreatic bed, improve intestinal wall integrity, and promote gut motility [119,120]. Although nasogastric tube feeding in severe acute pancreatitis appears safe according to a recent meta-analysis, an adequately powered randomized controlled study comparing it to nasojejunal feeding has been recommended and would prove useful in further investigation [121]. One recent randomized controlled trial comparing nasogastric versus nasojejunal feeding did not demonstrate inferiority of nasogastric feeding [122]. Despite clinical guidelines, practice greatly depends upon regional, institutional, and provider factors, and tailoring to individual patients [123]. TPN was once recommended in patients with severe pancreatitis, but it has been associated with increased length of stay, costs, and complication and mortality rates as well as increased systemic and local infections as compared with enteral nutrition [123,124]. If the patient has not tolerated PO intake by day 7, one may consider beginning nasojejunal feeding.

Aggressive pain management and intravenous fluid replacement are recommended [125]. Vital signs and urine output should be monitored every few hours for the first 24 to 48 hours by a multidisciplinary team.

Antibiotics and Other Interventions
A strong preventative measure for reducing infections in pancreatic necrosis is to avoid IV nutrition and use enteral nutrition [126]. The risk of developing infected pancreatic necrosis rises as the proportion of the involved/necrotic pancreas increases [119]. The presence of physiologic organ failure may be a more important prognostic factor than the presence of sterile or infected necrosis [127]. Infected pancreatic necrosis is generally seen after day 7 to 10 and can be seen with new fever spikes, leukocytosis, worsening pain, and SIRS development. CT-guided needle aspiration and Gram stain of the aspirate are often sufficient to make the diagnosis, though if the pancreas is sterile there is an increased risk of introducing infection. Infected pancreatic necrosis was traditionally treated by surgical debridement. Minimally invasive techniques such as percutaneous endoscopic drainage and minimally invasive retroperitoneal necrosectomy have been applied in a stepwise methodology in patients with infected pancreatic necrosis and have shown efficacy while reducing complication rates, although these procedures are not widely performed [128]. The timing of surgical intervention is variable—if patients are septic and the infected pancreatic fossa is felt to be responsible, surgical therapy may be required urgently. Current trends include delaying surgery to at least 4 weeks after the onset of symptoms, if possible, which may allow necrotic pancreatic tissue to be well demarcated at the time of surgery [129]. Multiple surgeries may be required to fully debride necrotic pancreatic tissue [130]. Infected
pancreatic necrosis, pancreatic abscesses, and infected pseudocysts are the most common indicators for surgery in the acute phase of the illness, with more minimally invasive techniques favored if possible, although open abdominal procedures may be required [131]. Patients with known or suspected infected necrosis often undergo needle aspiration to confirm infection, which can be performed via CT- or ultrasound-guided biopsies [132,133]. In rare cases, patients with infected necrosis can be treated conservatively with aggressive antibiotics and avoid or significantly delay surgical intervention [134].

The use of prophylactic antibiotics in patients with pancreatic necrosis (in an attempt to avoid infection) remains controversial. Some studies have demonstrated benefit in this regard, while others have not shown an advantage [135–139]. Imipenem, meropenem, and fluoroquinolones are commonly used in this setting as these agents have a high degree of pancreatic penetrance. Although antibiotic prophylaxis cannot be universally recommended in the setting of acute pancreatitis, indications for administering antibiotics set by Lanksich and Lerch may assist the clinician in prophylactic antimicrobial use: SIRS or sepsis, multisystem organ failure, proven extrapancreatic or pancreatic infections, or an increase in CRP with evidence of pancreatic or extrapancreatic infection [140].

**Other Considerations**

Pain management, typically with narcotics, should be implemented as well. Some data suggest the superiority of a patient-controlled analgesia (PCA) pump with the agent meperidine instead of morphine in this setting as morphine may increase sphincter of Oddi pressure [141]. If the underlying cause of the episode of acute pancreatitis is amenable to correction (eg, choledocholithiasis), therapeutic interventions such as ERCP with biliary sphincterotomy and duct clearance and/or cholecystectomy may be indicated (Figure 3). Other important etiologies that may be correctable are alcohol use/abuse, hypercalcemia, hypertriglyceridemia, and drug-induced pancreatitis. There is little to be gained from daily monitoring of serum amylase and lipase [79,80]. Patients can be gradually returned to oral intake as abdominal pain recedes and hunger returns. Over the course of mild acute pancreatitis, most laboratory abnormalities should show improvement and resolution without further intervention within 3 to 7 days [142].

Patients with more severe acute pancreatitis, manifested as the development of peripancreatic fluid collection, pancreatic pseudocysts, pancreatic necrosis, and/or the development of respiratory, renal, or circulatory compromise, require more aggressive management, and ICU admission is often warranted (Figure 4). In general, a multidisciplinary approach with both medical and surgical teams is generally beneficial. Renal failure may warrant hemodialysis, and patients with respiratory failure may require mechanical ventilation [143–145]. Most acute fluid collections and/or pseudocysts do not require interventions unless they become infected or cause
significant extrinsic compression of other organs. The management of chronic fluid collections such as pseudocysts is complex and controversial. A full discussion of the management of chronic fluid collections that result from an episode of acute pancreatitis is beyond the scope of this manuscript, but a variety of surgical, endoscopic, and percutaneous drainage procedures can be performed.

One Dutch multicenter, randomized controlled trial demonstrated that in patients with infected pancreatic necrosis, endoscopic or percutaneous drainage of infected fluid collections followed by minimally invasive retroperitoneal necrosectomy achieved superior outcomes as compared to traditional open necrosectomy alone [146]. Outcomes were defined in terms of lower total costs, resources utilized, length of stay, long term and major complications and death.

**CONCLUSION**

As we noted in our previous review of this topic [147], which this paper updates, acute pancreatitis remains a significant cause of morbidity and mortality. Most patients with mild acute pancreatitis will recover with conservative measures, although patients who develop more severe pancreatitis, especially those with pancreatic necrosis, require aggressive management and can still have a poor outcome. A multidisciplinary approach is warranted in patients with severe pancreatitis as input from intensivists, gastroenterologists, surgeons, and radiologists and other specialists are usually required. Treatable causes of pancreatitis should be identified and managed appropriately. Despite investigations, a cause of pancreatitis may not be identified in all patients.

Corresponding author: Douglas G. Adler, MD, Univ. of Utah School of Medicine, 30 N. 1900 E, 4R118, Salt Lake City, UT 84132, douglas.adler@hsc.utah.edu.

Financial disclosures: None.

**REFERENCES**


103. Forsmark CE, Baillie J; AGA Institute Clinical Practice and Economics Committee; AGA Institute Governing Board. AGA Institute technical review on acute pancreatitis. Gastroenterology 2007;132:2022–44.


Acute Pancreatitis


Copyright 2012 by Turner White Communications Inc., Wayne, PA. All rights reserved.