Acute Pancreatitis:
Review of Contemporary Diagnosis and Management

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INTRODUCTION

Acute pancreatitis describes an acute inflammatory process of the pancreas that rapidly depletes intravascular water and, if unchecked, promotes regional inflammation. The severity spectrum of acute pancreatitis ranges from mild interstitial pancreatitis to a more severe form that includes pancreatic necrosis, which is frequently associated with concomitant multi-organ failure. Mild interstitial pancreatitis has the highest prevalence, and acute pancreatitis is typically rapid in onset. In 2005 and 2007, an estimated 230,000 patients were treated for acute pancreatitis in hospitals in the United States.¹² 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 for acute pancreatitis is $9870.⁵ It 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 had shorter hospital stays and adults aged 45 to 64 years had hospital stays that were 1 day longer, on average.³⁶,⁷ 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.

CLASSIFICATION

A revision of the Atlanta classification schema for acute pancreatitis was recently published.⁶ The revised classification delineates 2 phases of acute pancreatitis: early and late. Severity of pancreatitis can be classified as mild, moderate, or severe. Mild acute pancreatitis is not associated with organ failure or local or systemic complications.
and clinically resolves in 7 days in most patients. Moderately severe acute pancreatitis is defined by the development of transient organ failure as well as complications or exacerbations of comorbid disease. Severe acute pancreatitis is associated with organ failure that persists for more than 48 hours. Local complications of acute pancreatitis include peripancreatic fluid collections, sterile or infected pancreatic and peripancreatic necrosis, pseudocyst formation, or the development of sterile or infected walled-off pancreatic necrosis.8

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 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.9 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.10 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.7 Large stones are more likely to be retained in the gallbladder.

Some data suggests that patients with confirmed gallstone pancreatitis should undergo cholecystectomy during their initial hospitalization (once the acute event has resolved) rather than at a later date, although in practice this can be hard to coordinate in all patients.11 Patients with gallstones and bile duct stones (choledocholithiasis) should undergo cholecystectomy and endoscopic retrograde cholangiopancreatography (ERCP), although the timing of these procedures should be individualized. Some institutions combine cholecystectomy and ERCP into a single procedure, although this can be difficult to do as it requires significant coordination between the gastroenterology and surgical teams.

Caucasians, Hispanics, and American Indians are more likely than African Americans to develop biliary acute pancreatitis.7,9,12 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.13 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.14 Obesity also increases the risk of developing local complications, such as pancreatic fluid collections.12 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.15–17 Elevated alanine aminotransferase (ALT), advancing age, weight gain, female sex, and rapid weight loss are all risk factors associated with the development of biliary acute pancreatitis.7,18 Unsaturated fats, coffee, and moderate alcohol consumption appear to reduce the risk of developing gallstones and, thus, biliary acute pancreatitis.19–21 Elevated 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 between 72% and 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.22 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, although it is thought to propagate an accelerated course in established acute pancreatitis.23 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.6,24 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 in the development of nonbiliary acute pancreatitis.25 Its strength as an independent risk factor in acute pancreatitis appears synergistic with concomitant alcohol use.23 Interventions to reduce alcohol use in patients with acute pancreatitis are critical to help to reduce the development of chronic pancreatitis. Alcohol elimination in patients with chronic pancreatitis can be very difficult and may require multimodality therapy.26

IDIOPATHIC ACUTE PANCREATITIS

Between 10% and 30% of cases of acute pancreatitis may be idiopathic in nature.27 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,28 or the controversial sphincter of Oddi dysfunction, among other possibilities.29

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 the serine protease inhibitor, Kazal type 1 (SPINK1) gene, resulting most often in an autosomal dominant phenotype.30,31 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.32 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.33,34

Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) allele have been
associated with the development of pancreatitis. Mutations in \textit{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 \textit{CFTR} mutations.\textsuperscript{35} Abnormally functioning \textit{CFTR} genes may cause inspissation of pancreatic secretions, leading to pancreatic ductal obstruction and pancreatitis.\textsuperscript{36} \textit{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 \textit{CFTR} mutations.\textsuperscript{37} Recurrent idiopathic pancreatitis that results from \textit{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,\textsuperscript{38} and may represent the third 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.\textsuperscript{39} Women, children, the elderly, and persons with underlying Crohn’s disease, hematologic malignancies, and multiple cancer chemotherapy agents appear to comprise populations with an increased risk of drug-associated acute pancreatitis.\textsuperscript{40} 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 which 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.\textsuperscript{41,42} 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 prevent clinical testing of this—the drug may be reintroduced when it is crucial for the patient’s health, the character of the disease is concerning, and/or when the etiology is not clearly defined.\textsuperscript{43} A commonly encountered difficulty in patients with suspected drug-induced pancreatitis is that the link between the drug and pancreatitis

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobials</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 antiinflammatory</td>
<td>Sulindac, salicylate, indomethacin</td>
</tr>
<tr>
<td>Antiproliferative</td>
<td>Tamoxifen, L-asparaginase</td>
</tr>
<tr>
<td>Other</td>
<td>Estrogen, bethanechol, oral contraceptives, angiotensin-converting enzyme inhibitors, selective serotonin reuptake inhibitors, angiotensin II receptor blockers, statins</td>
</tr>
</tbody>
</table>

**Table.** Medications Implicated in the Development of Drug-Induced Pancreatitis
may be weak, and the patient may have a strong indication to be on the drug (ie, a patient with coronary artery disease who takes a statin or a patient with gastroesophageal reflux disease who takes omeprazole). It can often be problematic to identify a causative agent in patients on multiple agents with a predisposition to causing drug-induced pancreatitis.

**IATROGENIC PANCREATITIS**

Iatrogenic pancreatitis most commonly occurs following ERCP procedures. 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. 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. This is further supported by a contemporary meta-analysis that found that regardless of the severity of PEP, prophylactic stents were beneficial. Furthermore, careful patient selection and minimally traumatic endoscopic techniques appear to offer additional protection against the development of post-ERCP pancreatitis. 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.

**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*. Viruses known to cause acute pancreatitis include mumps, Coxsackie, hepatitis B, *Cytomegalovirus*, and the varicella zoster virus. Only a few bacteria are well established as causes of acute pancreatitis: *Mycoplasma, Legionella, Leptospira*, and *Salmonella*. *Aspergillus* is the only fungus that has been strongly associated with causing acute pancreatitis.

**HYPERTRIGLYCERIDEMIA AND HYPERCALCEMIA**

Elevated triglyceride levels, typically exceeding 500 mg/dL, can be seen in various conditions, including poorly controlled type 2 diabetes, obesity, alcoholism, third trimester pregnancy, renal disease, hypothyroidism, and familial hypertriglyceridemia. Patients should have fasting triglyceride levels checked after their pancreatitis has resolved before diagnosing hypertriglyceridemia, as serum triglycerides can be artificially elevated during an episode of acute pancreatitis. Hypercalcemia is also a recognized etiology of acute pancreatitis. 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. If muscular/myopathic, urologic, or nervous system symptoms coexist with acute pancreatitis, patients should be evaluated for hyperparathyroidism.
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. Autoimmune pancreatitis should be suspected in patients with inflammatory bowel disease. Pediatric acute pancreatitis can also be seen and can be associated with multisystem disease and systemic infection. 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 RECURRENT

If underlying causes are not identified and treated, the risk of recurrent acute pancreatitis can be as high as 40% within 6 years. Gallstone pancreatitis carries a significantly lower risk of recurrence of approximately 10% 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. Most studies report a negative correlation between mortality and recurrent acute pancreatitis.

PATHOPHYSIOLOGY

In pancreatic acinar cells, a primary injury promotes compartmentalization of lysozomal enzymes (eg, cathepsin B and exocrine pancreatic enzymes). Catalytic proteins are then activated with subsequent enzymatic “spilling,” which leads to the typical inflammatory cascade seen in acute pancreatitis. Trypsin activates other proteases like elastase and chymotrypsin, components of the complement and coagulation cascades, and kinins. 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. Tissue breakdown products potentiate vascular injury, with local recruitment of cytokine and arachidonic acid metabolite–secreting leukocytes, with TNF acting as a central mediator. These agents produce edema and reactive oxidation 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. The increase in vascular permeability promotes thrombosis and hemorrhage and can lead to pancreatic ischemia and necrosis. 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.\textsuperscript{72} 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.\textsuperscript{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. On presentation, jaundice or tachycardia may be present, and patients may appear pale and distressed, be febrile, and have a distended abdomen.\textsuperscript{73} 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 necessitate 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 (US). Other clinical findings that can be present in acute pancreatitis include dehydration, which may manifest with elevated blood urea nitrogen and hematocrit and decreased urine output. Findings that may be seen in more severe presentations include 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.\textsuperscript{74,75}

Classification systems are currently being revised, including a 4-tier system with a moderate severe acute pancreatitis category defined as pancreatitis with complications but without multi-organ system dysfunction.\textsuperscript{76}

**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).\textsuperscript{77–79} 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.\textsuperscript{80–82} 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.\textsuperscript{83}
Serum alkaline phosphatase and bilirubin levels are not useful in isolation in the diagnosis of acute biliary pancreatitis, although a 3-fold elevation of ALT has a positive predictive value of 96%, and aspartate transaminase is nearly as useful as ALT according to one meta-analysis. 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 (48 hr after onset) have assumed greater predictive roles in determination of vascular and gastrointestinal complications (see below).

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 quantify 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 is also a useful and economic choice for evaluating patients with suspected gallstone pancreatitis. This study can visualize gallstones in the gallbladder, evidence of acute cholecystitis (gallbladder wall thickening or pericholecystic fluid), and common bile duct dilation (often suggestive of an obstructing common bile duct stone) and in some cases can directly visualize choledocholithiasis. Bowel gas and the pancreas’ retroperitoneal location may obscure the organ on ultrasound imaging. 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 an 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. The degree of necrosis is also an excellent prognostic factor. Small areas of necrosis can still be missed via contrast CT imaging.
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. MRI has a greater sensitivity for detecting mild acute pancreatitis as compared with CT scan. 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. Cost and accessibility limit the availability and use of MRI in rural areas.

Endoscopic ultrasound (EUS) has a defined role in AP—it is useful to evaluate the common bile duct for the presence of stones if gallstone pancreatitis with choledocholithiasis is suspected. EUS can be followed by therapeutic ERCP if a common bile duct stone is identified (to remove said stone). ERCP can also be used to place a stent if biliary obstruction is seen (due to a mass, edema). In biliary pancreatitis, the best timing of when to use EUS versus ERCP is controversial. Current evidence is showing a trend of early EUS imaging over ERCP due to better cost-benefit ratios (especially in severe biliary pancreatitis), improved diagnoses (positive predictive value), and outcomes (according to a recent meta-analysis). ERCP should be used before (or in place of) EUS 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. EUS has some additional diagnostic advantages over CT and transabdominal US: it may show the presence of microlithiasis, occult malignancies of the pancreas, and pancreas divisum.

If stones are seen via EUS, ERCP can typically be performed at the same time. A meta-analysis designed to compare the accuracy of MRCP and EUS in detecting choledocholithiasis showed the 2 modalities are equivalent in this regard (Figure 2). Additionally, there is some prognostic potential for the early prediction of severe acute pancreatitis when peripancreatic edema is seen on EUS. If a neoplasm is suspected, EUS (possibly with concomitant ERCP) is the preferred diagnostic imaging modality; 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. Due to these methodologic flaws, no single biomarker has been accepted into wide clinical practice. 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.\textsuperscript{100–102} 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,\textsuperscript{103–105} although it is 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.\textsuperscript{101} Generally, renal failure, respiratory failure, multi-organ system failure, fluid collections, necrosis, increased ICU length of stay, and shock are all poor prognostic factors.\textsuperscript{106} 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.\textsuperscript{107}

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,\textsuperscript{108} but not in all studies.\textsuperscript{109} 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.\textsuperscript{75} Hemoconcentration markers have a sensitivity of 94% for detecting necrotizing pancreatitis and a negative predictive value of 96%.\textsuperscript{75} 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 hemoconcentration in prognosis of acute pancreatitis.\textsuperscript{110–112} Blood urea nitrogen (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 in 1 retrospective study.\textsuperscript{113} 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 scoring systems.\textsuperscript{114,115} The harmless acute pancreatitis score (HAPS) measures only creatinine, hematocrit, and signs of peritonitis and appears to be the simplest of the scoring systems while maintaining accuracy in detecting mild pancreatitis, though it has not yet undergone vigorous validation.

**MANAGEMENT**

**TREATMENT**

**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.\textsuperscript{75} 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.\textsuperscript{116,117} 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 (defined as receiving $\geq$ one-third of the total 72-hour fluid volume within 24 hours of presentation) promotes lower rates of SIRS, organ failure, and ICU admissions and shorter hospitalizations in patients with interstitial acute pancreatitis.\textsuperscript{118} 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.\textsuperscript{119}

**Nutrition**

Nutrition, as defined by total parenteral nutrition (TPN) and enteral nutrition, plays a critical and 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.\textsuperscript{120,121} 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.\textsuperscript{122} One recent randomized control trial comparing nasogastric versus nasojejunal feeding did not demonstrate inferiority of nasogastric feeding.\textsuperscript{123} Although clinical guidelines are available, practice greatly depends upon regional, institutional, and provider preferences and tailoring to individual patients.\textsuperscript{124} 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.\textsuperscript{120,125} If the patient has not tolerated oral intake by day 7, one may consider beginning nasojejunal feeding.

Aggressive pain management and intravenous fluid replacement are recommended.\textsuperscript{126} Vital signs and urine output should be monitored every few hours for the first 24 to 48 hours by a multidisciplinary team.

**Antibiotics**

A strong preventative measure for reducing infections in pancreatic necrosis is to avoid intravenous nutrition and use enteral nutrition.\textsuperscript{127} The risk of developing infected pancreatic necrosis rises as the proportion of the involved/necrotic pancreas increases.\textsuperscript{119} The presence of physiologic organ failure may be a more important prognostic factor than the presence of sterile or infected necrosis.\textsuperscript{128} 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 and endoscopic drainage and minimally invasive retroperitoneal necrosectomy applied in a stepwise methodology in patients with infected pancreatic necrosis have shown efficacy while reducing
complication rates, although these procedures are not widely performed.129 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.130 Multiple surgeries may be required to fully debride necrotic pancreatic tissue.131 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.132 Patients with known or suspected infected necrosis often undergo needle aspiration to confirm infection, which can be performed via CT- or ultrasound-guided biopsies.133,134 In rare cases, patients with infected necrosis can be treated conservatively with aggressive antibiotics and avoid or significantly delay surgical intervention.135 The use of prophylactic antibiotics in patients with pancreatic necrosis (in an attempt to avoid infection) has been and remains controversial. Some studies have demonstrated benefit in this regard, while others have not shown an advantage, and prevailing opinion on this topic has changed several times in the past 10 to 15 years.136–141 Imipenem, meropenem, and fluorquinolones are commonly used in this setting as these agents have a high degree of pancreatic penetrance. Antibiotic prophylaxis cannot be universally recommended in the setting of acute pancreatitis. Guidelines 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 C-reactive protein with evidence of pancreatic or extrapancreatic infection.142 In general, the current thinking does not favor the use of prophylactic antibiotics in patients with severe acute pancreatitis.

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.143 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.76,77 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.144 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.145–147 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. In general, small pseudocysts are treated via observation. Large cysts, cysts that become infected, or cysts that compress the stomach or bowel (causing gastric outlet obstruction) or the bile duct (causing jaundice) are more likely to warrant drainage by endoscopic, surgical, or interventional radiology approaches.\textsuperscript{148,149} Surgical approaches can be performed in an open or laparoscopic manner. From an endoscopic point of view, transmural (through the stomach or the bowel wall) and transampullary (through the pancreatic duct) approaches are available to drain pancreatic pseudocysts.

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.\textsuperscript{150} Outcomes were defined in terms of lower total costs, resources utilized, length of stay, long-term and major complications, and death.

**CONCLUSION**

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.

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