

# V DISEASES OF THE PANCREAS

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## Definitions of Disease Presentations

### ACUTE AND CHRONIC PANCREATITIS

Acute pancreatitis has traditionally been defined as an acute inflammatory process of the pancreas that (1) is associated with abdominal pain and elevations in serum levels of pancreatic enzymes and (2) disrupts normal pancreatic architecture and function only until the illness resolves. Chronic pancreatitis, on the other hand, is traditionally described as associated with permanent and irreversible damage to the gland. These definitions, which were developed at a series of international meetings, have limited applicability for clinicians. For example, some patients with severe acute pancreatitis develop substantial necrosis of the gland during the acute attack and sustain permanent abnormalities of both pancreatic architecture and pancreatic function. Likewise, many patients with an acute attack of alcoholic pancreatitis have already developed histologic changes of chronic pancreatitis at the onset of symptoms. Both types of patient are at risk for the complications of acute pancreatitis and are best managed as having acute pancreatitis, although they do not fit the traditional classification schemes.

In addressing these problems, the most recent consensus conference, the International Symposium on Acute Pancreatitis,<sup>1</sup> defined acute pancreatitis in a more clinically useful manner—that is, as an acute inflammatory process of the pancreas with variable involvement of regional tissues and remote organ systems. Because it may not be possible at the time of the attack to determine whether permanent architectural or functional changes are present or will develop, the disease may subsequently be reclassified, on the basis of additional clinical information, as chronic pancreatitis or as an acute exacerbation of chronic pancreatitis.

The International Symposium on Acute Pancreatitis also defined severe acute pancreatitis as the presence of organ failure (e.g., shock, pulmonary insufficiency, renal failure, or gastrointestinal bleeding) or pancreatic or peripancreatic complications (e.g., necrosis, abscess, or pseudocyst), or both, along with unfavorable early prognostic signs (e.g., using the Ranson criteria or the APACHE II score) [*see Determining Disease Severity, below*]. Although not perfect, these clinical definitions more closely fit the approach to management.

### COMPLICATIONS OF PANCREATITIS

As part of the consensus conference on acute pancreatitis,<sup>1</sup> more precise definitions were developed to describe the local and systemic complications of acute pancreatitis. An acute fluid collection was defined as a collection of fluid occurring in or around the pancreas early in the course of acute pancreatitis. This collection of fluid is composed of both pancreatic juice and inflammatory fluid; it is poorly circumscribed and lacks a visible wall of fibrosis or granulation tissue. On computed tomography, these collections are seen as low-attenuation areas without a visible capsule. They are quite common in acute pancreatitis, occurring in 30% to 50% of cases.<sup>2</sup> Many of these acute fluid collections

resolve, but some may persist and develop a visible capsule, at which time they are termed pseudocysts.

Pseudocysts are defined as collections of fluid (pancreatic juice) surrounded by a fibrous capsule. It takes at least 4 to 6 weeks for an acute fluid collection to develop a capsule and become a pseudocyst. Pseudocysts may remain sterile or may become secondarily infected.

Pancreatic necrosis is a pathologic finding but is clinically defined on contrast-enhanced CT (CECT) as areas of pancreatic parenchyma that show no enhancement with the infusion of intravenous contrast. Acute necrotizing pancreatitis (i.e., CECT findings of pancreatic necrosis) may be subclassified as sterile necrosis or infected necrosis on the basis of the presence or absence of bacteria in an aspiration or surgical sample. Acute interstitial pancreatitis is defined by the absence of CECT findings of necrosis. Finally, pancreatic abscess is defined as a circumscribed collection of pus containing little necrotic tissue. What formerly was called infected pseudocyst is now referred to as a pancreatic abscess. The term phlegmon was omitted from the report because there was no consensus on its definition.

## Acute Pancreatitis

### EPIDEMIOLOGY

Estimates of the incidence of acute pancreatitis range from about 5 to 25 cases per 100,000 population. In the United States, between 166,000 and 224,000 patients are admitted each year with a primary diagnosis of acute pancreatitis.<sup>3</sup> The number of patients discharged from hospitals with a diagnosis of acute pancreatitis has steadily increased over the past 20 years.<sup>4,5</sup> Similar trends have been seen in other developed countries.<sup>6</sup> The reason for the increased incidence of acute pancreatitis in the United States is unclear, but the increase may be related to the increased incidence of gallstones (one of the major causes of acute pancreatitis)<sup>5</sup> in association with the epidemic of obesity.<sup>7</sup> In large series from referral hospitals, the mortality associated with acute pancreatitis has ranged from 5% to 10%; however, this range is probably high because of referral patterns, as recent estimates using more comprehensive hospital databases have documented an overall mortality of about 2%.<sup>8</sup> Mortality varies with etiology, the development of complications or necrosis, and the number and severity of comorbid medical conditions.<sup>9,10</sup> The cost of care is substantial, with estimates of total direct and indirect costs ranging from \$3.6 billion to \$6 billion annually.<sup>1,5,8</sup>

### ETIOLOGY

Many factors have been implicated as causes of acute pancreatitis [*see Table 1*]. Together, gallstone disease and alcohol abuse account for 70% to 80% of all cases of acute pancreatitis.<sup>1</sup> The prevalence of acute pancreatitis varies from population to population, depending on the relative prevalence of alcohol abuse and gallstone disease.

#### *Gallstone Disease*

The exact mechanism by which gallstone disease causes acute pancreatitis is not completely understood. It is clear that the pas-

sage of a gallstone through the ampulla of Vater is an important initiating event for gallstone pancreatitis, most likely by the gallstone's causing transient obstruction of the pancreatic duct or by edema resulting after stone passage. The association between obesity and gallstone disease is well established,<sup>4</sup> but abdominal obesity may be a more specific risk factor. A large prospective study indicated that abdominal adiposity in men carries a relative risk of gallstone disease of 2.29.<sup>11</sup>

#### Alcohol Abuse

The mechanism by which alcohol consumption produces acute (and chronic) pancreatitis remains obscure. In most patients, long-standing abuse of alcohol is required, and in such patients, histologic chronic pancreatitis is usually present at the onset of a clinically apparent acute attack.<sup>12</sup> In a minority of patients, a large alcoholic binge is the initiating event for acute pancreatitis, and no evidence is found of preexisting chronic damage to the gland.

#### Obstruction of the Pancreatic Duct

A number of disorders appear to cause acute pancreatitis by a process that obstructs the pancreatic duct. The most common of these is the presence of gallstones (see above). The other conditions are relatively uncommon. One such condition is sphincter of Oddi dysfunction, in which elevations of basal pancreatic sphincter pressure (more than 40 mm Hg above duodenal baseline pressures) produce pancreatic duct obstruction and acute pancreatitis. In addition, both benign and malignant strictures of the pancreatic duct can produce acute pancreatitis, as can malignancy of the ampulla of Vater. Given this, a search for underlying pancreatic or ampullary malignancy is warranted in patients at higher risk for malignancy (e.g., those older than 40 to 45 years) with unexplained pancreatitis. Less common causes of pancreatic duct obstruction and acute pancreatitis include choledochal cysts, periampullary duodenal diverticula, and worms migrating through the ampulla (*Ascaris lumbricoides*, *Clonorchis sinensis*).

Pancreas divisum, which occurs in 5% to 7% of the population, is a rare cause of acute pancreatitis.<sup>13,14</sup> In this congenital condition, the fetal dorsal and ventral pancreatic buds fail to fuse, and the majority of pancreatic secretions enter the duodenum through the smaller minor papilla. In a small subset of patients with pancreas divisum, the minor papilla may be inadequate to allow free drainage of pancreatic juice, creating a blockage that may lead to acute or chronic pancreatitis.<sup>13-15</sup>

#### Drugs and Toxins

Drug-induced acute pancreatitis is a relatively rare event and is usually idiosyncratic.<sup>16,17</sup> The antimetabolites 6-mercaptopurine and azathioprine have the highest attack rate, causing acute pancreatitis in up to 4% of patients who take these drugs. Many additional drugs have been reported to cause acute pancreatitis, the most common being pentamidine, didanosine, sulfonamides, valproic acid, furosemide, and aminosaliclates. In addition to ethyl alcohol [see Alcohol Abuse, above], a number of toxins may injure the pancreas and cause acute pancreatitis; these include methyl alcohol, organophosphate insecticides, and the venom from certain Central and South American scorpions. Scorpion venom and insecticides appear to cause acute pancreatitis by hyperstimulating pancreatic secretion via a cholinergic mechanism.

**Table 1 Causes of Acute Pancreatitis**

Gallstones and microlithiasis
Alcohol abuse
Obstruction of pancreatic duct
Sphincter of Oddi dysfunction
Pancreas divisum with stenotic minor papilla
Ampullary or pancreatic tumors
Trauma
Post-ERCP trauma
Blunt or penetrating trauma
Toxins
Methyl alcohol
Scorpion venom
Organophosphate insecticides
Drugs
Azathioprine
6-Mercaptopurine (6-MP)
Pentamidine
Didanosine
Sulfonamides
Valproic acid
Furosemide
Aminosaliclates
Infections
Viral (mumps, rubella, coxsackie B, cytomegalovirus, HIV)
Bacterial ( <i>Klebsiella</i> , <i>Escherichia coli</i> )
Fungal ( <i>Candida</i> )
Hypertriglyceridemia
Genetic mutation
Hereditary pancreatitis
Cystic fibrosis
Surgery

ERCP—endoscopic retrograde cholangiopancreatography

#### Infection

A number of infections have been reported to cause acute pancreatitis; among them are a variety of viral infections such as cytomegalovirus, mumps, rubella, and coxsackie B. Patients with AIDS commonly have increased serum amylase levels in the absence of acute pancreatitis and less commonly develop acute pancreatitis secondary to opportunistic infections (e.g., cytomegalovirus, *Cryptosporidium*, or *Mycobacterium* infections) or as a side effect of a medication.<sup>18</sup>

#### Metabolic Factors

Metabolic causes of acute pancreatitis include hypertriglyceridemia and hypercalcemia. Serum triglycerides generally need to be in excess of 1,000 mg/dl to produce acute pancreatitis.<sup>19</sup> Serum triglyceride levels in excess of 1,000 mg/dl are most commonly seen in type V hyperlipoproteinemia and are usually associated with diabetes mellitus. Acute pancreatitis can itself raise triglyceride levels but not to this degree. The use of estrogens in postmenopausal women with underlying hypertriglyceridemia is associated with increased levels of triglyceride and the induction of pancreatitis, particularly if the fasting triglyceride level before initiating estrogen treatment is more than 750 mg/dl.<sup>20</sup> Hypercalcemia, usually associated with hyperparathyroidism, is a very rare metabolic cause of acute pancreatitis.

#### Trauma

Trauma to the pancreas or pancreatic duct may cause acute

pancreatitis. Blunt trauma to the abdomen may cause contusion, laceration, or complete transection of the gland. In most cases of major trauma affecting the pancreas, damage occurs at the mid-body of the pancreas, where the pancreas is crushed against the vertebral bodies; acute pancreatitis develops rapidly in most of these patients. Patients with less extensive injuries may experience a delayed onset of symptoms up to several months or even longer after the trauma. Iatrogenic trauma during endoscopic retrograde cholangiopancreatography (ERCP) causes acute pancreatitis in about 3% to 5% of cases, although in certain subgroups (e.g., those suspected of having sphincter of Oddi dysfunction), the risk may be as high as 20% to 25%.<sup>21</sup> ERCP appears to cause pancreatitis as a consequence of obstruction, inflammation, and edema of the pancreatic duct orifice and by barotrauma to the acinar cells. Ischemic injury to the pancreas may occur in the setting of many surgical procedures, because the pancreatic vasculature has very limited ability for vasodilatation. In such cases, postoperative pancreatitis is often quite severe and most commonly occurs after cardiac surgery or cardiopulmonary bypass.

#### *Genetic Factors*

A number of mutations have been described in association with acute and chronic pancreatitis. These include mutations in the cationic trypsinogen (*PRSS1*), cystic fibrosis transmembrane conductance regulator (*CFTR*), and secretory trypsin inhibitor (or serine protease inhibitor Kazal type 1 [*SPINK1*]) genes.<sup>22</sup> These conditions are most commonly associated with chronic pancreatitis [see Chronic Pancreatitis, Etiology, below] but in some cases may also produce acute flares. A number of studies have examined polymorphisms in cytokines involved in the inflammatory response to determine whether such polymorphisms might be predictors of the severity of acute pancreatitis. To date, these studies have been unrevealing.

#### *Autoimmune Pancreatitis*

Autoimmune pancreatitis is a benign disease characterized by irregular narrowing of the pancreatic duct, swelling of the parenchyma, and lymphoplasmacytic infiltration and fibrosis. Autoimmune pancreatitis can present clinically as an attack of acute pancreatitis. Patients with autoimmune pancreatitis may have high antinuclear antibody and serum IgG4 concentrations, providing a useful means of distinguishing this disorder from other diseases of the pancreas or biliary tract.<sup>23,24</sup> Patients with autoimmune pancreatitis generally have a favorable response to corticosteroid treatment.

#### *Undetermined Causes*

After evaluation, about 25% of all patients with acute pancreatitis do not have a specific definable etiology. In fact, after gallstones and alcohol, idiopathic acute pancreatitis is the most common diagnosis. Some of these patients may be surreptitious alcoholics, but many more appear to have a forme fruste of gallstone disease. Two series have documented the presence of microscopic gallstones (so-called microlithiasis) in two thirds to three fourths of patients with apparent idiopathic acute pancreatitis.<sup>25,26</sup> The importance of microlithiasis is underscored by the fact that cholecystectomy, ERCP with sphincterotomy, and agents used to dissolve gallstones (e.g., ursodeoxycholic acid) all reduced the frequency of recurrent attacks of acute pancreatitis in patients participating in these studies. Unfortunately, there is as yet no standardized method to determine the presence of microlithiasis.

## PATHOGENESIS

The pathophysiology of acute pancreatitis, irrespective of cause, remains poorly understood. All etiologies appear to converge on a final common pathway that allows the premature activation of digestive enzymes within the pancreas.<sup>27,28</sup> The conversion of the inactive proenzyme trypsinogen to its active form trypsin appears to be a critical early step because trypsin can then activate most of the other digestive proenzymes. The release of activated digestive enzymes into the pancreas and surrounding tissues can produce tissue damage and necrosis of the pancreas, its surrounding fat, and adjacent structures. This chemical "burn" of the retroperitoneum leads to substantial fluid loss into this area—so-called third-space fluid losses. Not all patients with acute pancreatitis develop necrosis of the pancreas itself; necrosis is most commonly seen in severe attacks of acute pancreatitis. Substantial pancreatic necrosis (acute necrotizing pancreatitis) is usually distinguished from the milder form in which necrosis is absent (interstitial pancreatitis).

The release of activated digestive enzymes into the systemic circulation can overwhelm normal protective mechanisms (e.g., antiproteases) and cause direct damage to distant organs and other systemic enzyme systems (e.g., complement and kinin systems). Finally, a number of inflammatory mediators and cytokines can be released from inflammatory cells to produce a systemic immune response syndrome (SIRS) or sepsislike syndrome.<sup>29,30</sup> The combination of activated digestive enzymes in the systemic circulation, the activation of other enzyme systems, and the release of inflammatory cytokines can produce the severe systemic complications associated with severe acute pancreatitis [see Table 2]. Recognition of the role of these inflammatory mediators has not only improved our understanding of the pathophysiology of acute pancreatitis but also provided potential new targets for therapy.

## DIAGNOSIS

### *Clinical Findings*

The diagnosis of acute pancreatitis is usually suspected on the basis of compatible signs and symptoms and confirmed by laboratory tests and radiographic imaging. Pain is the most common symptom of acute pancreatitis, occurring in up to 95% of patients. The pain of acute pancreatitis is most commonly felt in the epigastrium and radiates to the back in up to two thirds of patients. Pain may be felt more diffusely across the abdomen. The pain is usually quite severe, reaches its maximum intensity within 30 minutes, and lasts hours to days. In some cases, pain may not be the dominant symptom, particularly if it is masked by multiorgan failure, delirium, or coma; in rare cases, pain may be absent altogether. Nausea and vomiting are commonly associated with the pain of pancreatitis. No relief of the abdominal pain is achieved by vomiting.

The physical examination usually reveals epigastric or diffuse tenderness on palpation, with rebound tenderness and guarding present in the most severe cases. The abdomen is often distended and tympanic, and bowel sounds may be decreased or absent. Vital signs may be normal; more commonly, tachycardia, hypotension, tachypnea, and low-grade fever are noted. Orthostatic hypotension, tachycardia, and shock early in the course of acute pancreatitis are markers for substantial third-space fluid losses and indicate both a poor prognosis and probable need for admission to an intensive care unit. Dyspnea or tachypnea may occur because of muscular splinting secondary to abdominal

pain, pleural effusions, or a pulmonary capillary leak syndrome (i.e., acute respiratory distress syndrome [ARDS]). Generally, the presence of tachypnea, dyspnea, or oxygen desaturation merits ICU admission. Rare physical findings include ecchymoses of the flank (Grey Turner sign) and umbilicus (Cullen sign) and eruptive xanthomas in patients with hyperlipidemic pancreatitis; signs of alcoholic liver disease may be present in patients with alcoholic pancreatitis. Altered mental status may be present and usually has multiple causes (alcohol withdrawal, hypotension, electrolyte imbalance, and hypoxemia). Jaundice may be present, either from obstruction of the bile duct by a gallstone or from extrinsic compression of the bile duct by a large peripancreatic fluid collection. Purtscher retinopathy presenting as retinal hemorrhage is a very rare complication of acute pancreatitis.

#### Laboratory Tests

A history and physical examination suggestive of acute pancreatitis may be seen in a wide variety of intra-abdominal diseases. Therefore, the diagnosis is usually confirmed with a combination of laboratory tests and imaging studies.

**Serum amylase** The serum amylase level has long been the most widely used confirmatory laboratory measurement for acute pancreatitis. At least 75% of patients with acute pancreatitis will have increased levels of serum amylase at the time of initial evaluation.<sup>31</sup> Levels greater than three times the upper limit of normal are highly suggestive of acute pancreatitis. Amylase is cleared by the kidney; in patients with renal failure, a higher threshold of five times the upper limit of normal should be used. Normal levels of serum amylase, however, do not rule out the presence of pancreatitis. Serum amylase levels may be normal in some patients with acute alcoholic pancreatitis and in patients with hyperlipidemic pancreatitis (marked elevations in triglyceride levels can interfere with the laboratory assay for amylase). More generally, elevated levels of serum amylase may have already returned to normal if testing is delayed until several days after the onset of symptoms. In several large series of fatal pancreatitis, 10% to 30% of patients who died of acute pancreatitis were undiagnosed before autopsy.<sup>32</sup> The diagnosis of acute pancreatitis is generally missed in such patients for one of two reasons: serum amylase levels are normal (or are not measured) or the presenting symptoms are atypical (e.g., coma or multiorgan failure rather than abdominal pain). The true sensitivity of the serum amylase measurement as a diagnostic test for acute pancreatitis is therefore difficult to determine.

Elevations of the serum amylase level are not specific for acute pancreatitis and may be associated with a very wide variety of nonpancreatic conditions [see Table 3]. Although many of these other conditions would not be mistaken for acute pancreatitis, a number of intra-abdominal conditions can produce increased serum amylase levels and mimic both the signs and the symptoms of acute pancreatitis. Such disorders include intestinal ischemia and perforation, bowel obstruction, choledocholithiasis, cholelithiasis with cholecystitis, tubo-ovarian disease (ectopic pregnancy, acute salpingitis), and acute appendicitis.

**Serum lipase** The serum lipase level is often used as an adjunct to or in place of serum amylase testing as a confirmatory test for acute pancreatitis. Accurate measurement of serum lipase was difficult in the past, but new methods provide high levels of precision. The lipase level is in fact slightly more sensitive and somewhat more specific for acute pancreatitis than the amy-

**Table 2** Complications of Acute Pancreatitis

Local complications
Peripancreatic fluid collection
Pseudocyst
Pancreatic necrosis (sterile or infected)
Abscess
Duodenal obstruction
Biliary obstruction
Systemic complications
Cardiovascular
Hypotension and shock
Pericardial effusion and tamponade
ECG changes
Pulmonary
Hypoxia
Atelectasis, pneumonia
Pleural effusion
Acute respiratory distress syndrome
Metabolic
Hypocalcemia
Hypertriglyceridemia
Hyperglycemia
Renal
Oliguria and azotemia
Acute tubular necrosis
Hematologic
Disseminated intravascular coagulation (DIC)
Vascular thrombosis (particularly splenic vein)
Gastrointestinal bleeding
Other
Encephalopathy
Distant fat necrosis
Retinopathy

lase level.<sup>31</sup> In addition, serum lipase stays elevated longer and can confirm a diagnosis of acute pancreatitis up to 5 to 10 days after the onset of symptoms, by which time amylase levels have generally returned to normal. Like amylase, lipase may be elevated in other intra-abdominal conditions (with the exception of tubo-ovarian disease) and may be elevated in renal failure. Elevations that are more than three times the upper limit of normal have the greatest diagnostic sensitivity and specificity, but again, this threshold may need to be increased to five times the upper limit of normal in patients with renal failure. Lipase is probably preferable to amylase as a confirmatory test because in addition to its greater specificity, it is no more costly and, in most hospitals, has equally rapid availability.

**Other tests** Leukocytosis is frequently present in acute pancreatitis. The hematocrit may be normal, but in patients with severe pancreatitis and substantial third-space fluid loss, hemoconcentration is present. There are a number of methods to gauge the severity of pancreatitis, but the presence of hemoconcentration is a reasonably accurate marker of severe pancreatitis.<sup>33</sup> Hyperglycemia and hypocalcemia may also be present. Tetany is rare because ionized calcium levels are usually normal in pancreatitis despite the presence of hypocalcemia. Liver chemistries may be elevated in persons with gallstone pancreatitis or with intrinsic liver disease (e.g., alcoholic hepatitis). Elevations of alanine aminotransferase levels to three times the normal level strongly suggest gallstone disease as the etiology; however, any significant abnormality of liver chemistries should raise the suspicion of gall-

stone pancreatitis, particularly if the abnormalities rapidly return to the normal range over the course of a few days.<sup>34</sup> The differentiation of gallstone pancreatitis from other forms of pancreatitis is important because specific therapy may be required [see Removal of Common Bile Duct Stones, *below*].

### Imaging Studies

Imaging studies, particularly ultrasound and CT, can be useful in confirming a diagnosis of acute pancreatitis, determining etiology, and assessing the severity of the attack.

**Radiology** Plain abdominal radiographs may help in the evaluation of acute abdominal pain by documenting the presence of conditions (e.g., an ileus or free intraperitoneal air) that cause acute pain, but the findings are never specific enough to confirm a diagnosis of acute pancreatitis. Similarly, barium or water-soluble contrast studies of the upper gastrointestinal tract are not helpful in confirming a diagnosis of acute pancreatitis.

**Ultrasonography** Abdominal ultrasonography (US) is a highly useful test in the evaluation of suspected acute pancreatitis. Diagnostic abnormalities of the pancreas, including pancreatic enlargement, changes in echotexture, and peripancreatic fluid collections, can be seen in up to two thirds of patients; in the remaining third, overlying bowel gas limits the ability of sound transmission, thus preventing adequate visualization of the pancreas.

US is the most sensitive test for detecting stones in the gallbladder in patients with gallstone pancreatitis. The presence of gallstones or a dilated bile duct visualized on US is highly predictive of gallstone disease as the etiology of acute pancreatitis. If the gallbladder and biliary tree cannot be imaged on initial ultra-

sonography, a repeat ultrasound several days later may prove diagnostic of gallstone pancreatitis.

**Computed tomography** Computed tomography is much more accurate than US in confirming the presence of acute pancreatitis, although CT is less accurate in evaluating the biliary tree and gallbladder for stones.<sup>35-37</sup> The two tests are therefore often used together in patients with acute pancreatitis. CT results may be normal in a small subset of patients with very mild acute pancreatitis (10% of patients), but the test is reliably diagnostic in moderate or severe disease. CT is also quite useful in assessing conditions that mimic severe acute pancreatitis. In addition, CT plays a very important role in determining severity of the attack [see CT Findings, *below*].

The use of a rapid bolus of intravenous contrast coupled with rapid scanning of the pancreas by use of CECT can provide a diagnosis of acute pancreatitis and, very importantly, assess the severity of disease and the extent of pancreatic necrosis. As visualized on CECT, viable pancreatic parenchyma is enhanced by uptake of the contrast medium, and necrotic areas of the gland are unenhanced. The extent of necrosis is a very important indicator of prognosis.<sup>35-37</sup>

CT scans are not required in every patient with acute pancreatitis, but they should be performed in patients with a first attack of pancreatitis, with moderate or severe symptoms, with systemic complications, in whom there is a suspicion of a complication (e.g., pancreatic pseudocyst), with smoldering pancreatitis that is slow to improve, or when the diagnosis is unclear.

**Magnetic resonance imaging** Gadolinium-enhanced dynamic magnetic resonance imaging can be used to grade the severity of acute pancreatitis if there are contraindications to intravenous contrast-enhanced CT, such as renal failure or iodine sensitivity.<sup>38</sup> Furthermore, magnetic resonance cholangiopancreatography (MRCP) is an accurate way to test for the presence of common bile duct stones.<sup>39</sup> It may be difficult, however, to perform MRI or MRCP in very sick patients.

**Endoscopy** ERCP and endoscopic ultrasonography (EUS) are not used as diagnostic tests for acute pancreatitis, although they may be useful in determining etiology. ERCP is accurate in evaluating many of the less common causes of acute pancreatitis, including microlithiasis, sphincter of Oddi dysfunction, pancreas divisum, and pancreatic duct strictures (benign and malignant). As a diagnostic test, ERCP is generally reserved for patients who have experienced a second attack of unexplained pancreatitis, although use of ERCP may be considered as a diagnostic option after a single attack of unexplained pancreatitis in patients at risk for malignant pancreatic duct strictures (e.g., those older than 40 to 45 years). ERCP certainly has value as a therapeutic tool (e.g., for finding and removing common bile duct stones in patients with gallstone pancreatitis).

EUS is also useful in the documentation of gallstones, microlithiasis, pancreatic tumors, and pancreas divisum. Although it is used less frequently than ERCP in patients with acute pancreatitis (primarily because it is not widely available), EUS has a significantly lower risk of complications. EUS is highly accurate in both documenting stones and visualizing tumors (more sensitive than ERCP) and will be used more commonly in the future [see Figure 1].

**Table 3** Nonpancreatic Causes of Elevated Amylase and Lipase Levels

<i>Amylase</i>	<i>Lipase</i>
Biliary disease Common bile duct obstruction Acute cholecystitis	Biliary disease Common bile duct obstruction Acute cholecystitis
Intestinal ischemia, obstruction, or perforation	Intestinal ischemia, obstruction, or perforation
Acute appendicitis	Acute appendicitis
Gynecologic conditions Ectopic pregnancy Acute salpingitis Ovarian cysts and malignancies	Renal insufficiency
Renal insufficiency	
Macroamylasemia	
Salivary gland disease, including mumps	
Miscellaneous causes Anorexia nervosa Diabetic ketoacidosis Lung cancer Head trauma	



**Figure 1** An endoscopic ultrasound image of a pancreatic mass in a patient with unexplained acute pancreatitis. The mass is labeled and sits on the splenic vein (SV). The mass was not visible on computed tomography.

### Determining Disease Severity

Three quarters of patients with acute pancreatitis have a benign course and recover rapidly. The highest morbidity and mortality are in patients with necrotizing pancreatitis. The mortality associated with acute pancreatitis is 2% to 10%, with the lower estimates of mortality coming from database analyses and the higher estimates coming from more selected or referral populations. Mortality within the first week of the illness is most commonly from ARDS, multiorgan failure, or a sepsislike syndrome. Patients with persisting organ failure are at greatest risk of mortality; transient organ failure is generally not associated with mortality. Mortality after the first or second week is most commonly caused by infection of pancreatic tissue (i.e., pancreatic abscess or infected necrosis).

After making a diagnosis of acute pancreatitis, the clinician's next goal is to estimate prognosis and severity of disease. The accurate assessment of prognosis and severity allows more accurate decision making regarding ICU admission, measurement of central venous pressure or pulmonary capillary wedge pressure, and administration of prophylactic antibiotics. The assessment of severity of acute pancreatitis may be based on clinical features, laboratory tests, or imaging studies or a combination of the three. Frequently, careful evaluation by an experienced clinician is a very helpful method of gauging severity and detecting complications. The presence of delirium or coma, hypoxia, or features suggestive of massive third-space fluid loss (i.e., hypotension, tachycardia, oliguria, azotemia, or hemoconcentration) within the first 24 hours suggests a severe attack and the need for ICU admission.<sup>40</sup> Many patients will not develop such a dramatic illness, and a number of multiple-factor scoring systems are available to assist the clinician in determining severity and estimating prognosis.

**Multiple-factor scoring systems** Several multiple-factor scoring systems have been developed that use a combination of clinical and laboratory features to determine disease severity; these include the Ranson criteria [see Table 4], modified Glasgow criteria, and APACHE II criteria [see Table 5]. The most widely quoted system developed by Ranson utilizes two systems: one for gallstone pancreatitis and one for nongallstone (alcoholic) pancreatitis. In the Ranson system, the presence of one or two criteria is very specific, though not sensitive, for clinically mild pancreatitis.<sup>40,41</sup> The presence of three or four risk factors is associated with a mortality of 15%, although many patients with three or four criteria also recover rapidly without sequelae. The presence of a high number of criteria (e.g., six or seven Ranson criteria) is associated with a high likelihood of substantial morbidity and mortality (> 50% mortality).<sup>40,41</sup> All of the multiple-factor scoring systems suffer from the limitation of a high false positive rate; in other words, the presence of a moderate number of criteria is generally associated with moderate risk of morbidity and mortality, but the scoring systems do not identify whether that individual patient is likely to suffer morbidity or mortality. The APACHE II system has an advantage over the Ranson and Glasgow systems in that it can be applied at any point in the clinical illness; the Ranson and Glasgow scores require up to 48 hours before they can be calculated. Three or more Ranson criteria or eight or more APACHE II points are commonly considered an indication of an unfavorable prognosis.

**CT findings** CT is a useful adjunct for estimating disease severity. The initial scoring systems correlated the severity of the pancreatic and peripancreatic inflammatory processes with the prognosis. Subsequently, CT was combined with a rapidly administered bolus of intravenous contrast (CECT) to define the presence and extent of pancreatic necrosis; this technique has become widely used.<sup>36,37,41</sup> The lack of vascular contrast enhancement of the pancreas on CECT corresponds in a general way to the presence of necrosis. Pancreatic necrosis complicates about 25% of all cases of acute pancreatitis and is generally associated with more clinically severe disease; it is particularly associated with the development of the late complications of pancreatic abscess and infected necrosis.<sup>37,41,42</sup>

As with all systems used in assessing severity, CECT produces a significant number of false positive results, in that many patients who have evidence of necrosis on dynamic CT scanning have a mild clinical course.<sup>43</sup> Despite that, the presence of substantial pancreatic necrosis (more than one third of the gland) is a useful marker of severity because nearly all patients with a clinically severe course have necrosis and almost all cases of serious pancreatic infection occurs in this group.<sup>42,43</sup>

At the International Symposium on Acute Pancreatitis, an attempt was made to consolidate the various methods for determining disease severity into a unified approach.<sup>1</sup> The resulting system defines severe pancreatitis by a combination of clinical features (organ failure), multiple-factor scoring systems, and the presence of local pancreatic complications [see Table 6]. This system is useful in that it consolidates the various methods, but it does not replace frequent and experienced clinical observation.

### MANAGEMENT

The treatment of acute pancreatitis has four goals: (1) provide supportive care; (2) minimize or reduce the local necrosis and the systemic inflammatory process; (3) recognize and treat complications; and (4) prevent subsequent attacks.

## Supportive Care

**Mild acute pancreatitis** The foundations of supportive care include making the patient nil per os (NPO); providing relief from pain and nausea; replacing fluid losses; providing nutrition, if needed; and monitoring for the development of complications. This is relatively straightforward in patients with mild pancreatitis, because fluid losses are modest and complications are rare. Pain and nausea can usually be controlled by the use of moderate dosages of intravenous analgesics and antiemetics. Even in mild pancreatitis, fluid losses may be significant because of third-space fluid losses, vomiting, and insensible losses; appropriate fluid resuscitation is critical in minimizing complications. Patients can generally be fed when bowel sounds have returned and pain has resolved.

**Severe acute pancreatitis** When pancreatitis is severe or is predicted to be severe (based on CT or CECT findings, multiple-factor scoring systems, early evidence of significant third-space fluid losses, or early respiratory insufficiency), supportive care is more challenging and usually requires the resources of an ICU. Prompt and vigorous fluid replacement is critical in the early phases of severe acute pancreatitis and can minimize or prevent early complications, including renal failure and cardiovascular collapse.<sup>44</sup> The pancreas itself is prone to ischemic injury in the setting of intravascular fluid volume depletion. The pancreatic microcirculation has little capacity to respond to diminished blood supply, and intravascular volume depletion may worsen the degree of pancreatic necrosis. For all these reasons, early and vigorous fluid resuscitation is important in the management of severe pancreatitis.<sup>40,44</sup>

Hemoconcentration is a common and readily available marker of substantial third-space fluid losses. Measurement of central venous pressure or, if required, pulmonary capillary wedge pressure allows accurate assessment of fluid needs. Fluid needs of 5 to 10 L/day are not uncommon. Treatment with crystalloid solutions is usually appropriate, although colloid solutions (albumin or blood) may be appropriate when albumin levels are extremely low (< 2.0 mg/dl) or when the hematocrit is below 25%.

Admission to an ICU, in addition to facilitating the monitoring of fluid resuscitation, allows for intensive monitoring of respiratory and metabolic complications. Pulmonary capillary leak syndrome (i.e., ARDS) is one of the most serious complications

of severe pancreatitis. Hypoxia and dyspnea are usually noted, but ARDS must be distinguished from fluid overload or congestive heart failure. This is best done with the use of a Swan-Ganz catheter. A variety of early metabolic complications (e.g., hyperglycemia, hypocalcemia, hypertriglyceridemia, and hypomagnesemia) are also most easily managed in an ICU setting.

Nutritional support is useful for patients with severe pancreatitis and for those with milder pancreatitis who nonetheless are unable to eat for more than 5 to 7 days. The preferred route of providing exogenous nutrients has changed. For years, total parenteral nutrition (TPN) has been the standard practice. Accumulating evidence suggests that enteral feeding is comparable or superior to TPN.<sup>45-47</sup> Prospective, randomized trials have demonstrated that enteral feeding infused distal to the ligament of Treitz is associated with fewer complications (infection and hyperglycemia) and is cheaper than TPN.<sup>45</sup> Although the evidence is not definitive,<sup>47</sup> the accumulating data supporting this method of enteral feeding have led to a shift in the preferred method of providing nutrition to patients with acute pancreatitis. The main practical challenge in using enteral jejunal feeding is placing and maintaining position of the nasojejunal tube.

### Treatment of Necrosis and Inflammation

**Pancreatic rest** No treatment has been proved to interrupt the inflammatory process effectively. Many early studies focused on strategies that were thought to "rest" the pancreas beyond the rest associated with maintaining the patient NPO. These have included nasogastric suction, H<sub>2</sub> receptor antagonists, atropine, somatostatin and its analogue octreotide, glucagon, and even fluorouracil. None of these approaches appear to have any benefit on the outcome of acute pancreatitis, although meta-analyses of somatostatin and octreotide suggest a slight trend toward benefit.<sup>48</sup> That is not to say that nasogastric suction is not useful if the patient has substantial nausea and vomiting or that administration of H<sub>2</sub> receptor antagonists does not prevent stress erosions and ulcers; however, neither of these therapies improves the overall outcome of the acute pancreatitis itself.

**Protease removal or inhibition** A second strategy to interrupt the inflammatory process is to remove proteases by peritoneal lavage or inhibit circulating proteases by administration of antiproteases (e.g., aprotinin or gabexate). However, neither method of protease control has been shown to be of benefit in acute pancreatitis. One potential reason for lack of efficacy is that these therapies can generally be administered only after the initiation of acute pancreatitis. In animal models, these therapies have been administered before the initiation of pancreatitis and have been shown to be nearly uniformly beneficial.<sup>49</sup> Pancreatitis induced by ERCP offers a unique opportunity to administer therapy in humans before the onset of acute pancreatitis. Although the data are inconclusive, meta-analyses have identified a reduction in post-ERCP pancreatitis in patients receiving the protease inhibitor gabexate or the antisecretory hormone somatostatin (but not, interestingly, its analogue octreotide).<sup>50,51</sup> The effect of these agents is only modest, and they are not available for clinical use in the United States. The effect of other methods, particularly the use of temporary pancreatic duct stents, appears to be far superior.

**Anticytokine therapy** Some studies have focused on control of the systemic immune response through the modulation of inflammatory cytokines. Because this cytokine cascade is felt to

**Table 4 Ranson Prognostic Scoring System for Pancreatitis**

Type	On Admission	Within 48 Hours
Nongallstone pancreatitis	Age > 55 yr WBC count > 16,000/mm <sup>3</sup> Glucose > 200 mg/dl LDH > 350 IU/L AST > 250 U/L	Decrease in Hct > 10 points Increase in BUN > 5 mg/dl Serum calcium < 8 mg/dl P <sub>a</sub> O <sub>2</sub> < 60 mm Hg Base deficit > 4 mmol/L Fluid deficit > 6 L
Gallstone pancreatitis	Age > 70 yr WBC count > 18,000/mm <sup>3</sup> Glucose > 220 mg/dl LDH > 400 IU/L AST > 500 U/L	Decrease in Hct > 10 points Increase in BUN > 2 mg/dl Serum calcium < 8 mg/dl Base deficit > 5 mmol/L Fluid deficit > 4 L

AST—aspartate aminotransferase BUN—blood urea nitrogen Hct—hematocrit  
LDH—lactate dehydrogenase P<sub>a</sub>O<sub>2</sub>—arterial oxygen tension WBC—white blood cell

Table 5 APACHE II Severity of Disease Classification System\*

Physiologic Variable	Physiologic Points								
	Range								
Rectal temperature (°C)	≥ 41°	39.0°–40.9°	—	38.5°–38.9°	36.0°–38.4°	34.0°–35.9°	32.0°–31.9°	30.0°–31.9°	≤ 29.9°
Mean arterial pressure (mm Hg)	≥ 160	130–159	110–129	—	70–109	—	50–69	—	≤ 49
Heart rate (ventricular response)	≥ 180	140–179	110–139	—	70–109	—	55–69	40–54	≥ 39
Respiratory rate (nonventilated or ventilated)	≥ 50	35–49	—	25–34	12–24	10–11	6–9	—	≤ 5
A-aPo <sub>2</sub> (mm Hg)									
F <sub>I</sub> O <sub>2</sub> ≥ 0.5 (record A-aPo <sub>2</sub> )	≥ 500	350–499	200–349	—	< 200	—	—	—	—
F <sub>I</sub> O <sub>2</sub> < 0.5 (record only P <sub>a</sub> O <sub>2</sub> )	—	—	—	—	Po <sub>2</sub> > 70	Po <sub>2</sub> 61–70	—	Po <sub>2</sub> 55–60	Po <sub>2</sub> < 55
Arterial pH	≥ 7.7	7.6–7.69	—	7.5–7.59	7.33–7.49	—	7.25–7.32	7.15–7.24	< 7.15
Serum sodium (mmol/L)	≥ 180	160–179	155–159	150–154	130–149	—	120–129	111–119	< 110
Serum potassium (mmol/L)	≥ 7.0	6.0–6.9	—	5.5–5.9	3.5–5.4	3.0–3.4	2.5–2.9	—	< 2.5
Serum creatinine (mg/dl) <sup>†</sup>	≥ 3.5	2.0–3.4	1.5–1.9	—	0.6–1.4	—	< 0.6	—	—
Hematocrit (%)	≥ 60	—	50.0–59.9	46.0–49.9	30.0–45.9	—	20.0–29.9	—	< 20
White blood cell count 1,000/mm <sup>3</sup>	≥ 40	—	20.0–39.9	15–19.9	3.0–14.9	—	1.0–2.9	—	< 1
Serum HCO <sub>3</sub> (mmol/L) <sup>‡</sup>	≥ 52	41.0–51.9	—	32.0–40.9	22.0–31.9	—	18.0–21.9	14.0–17.9	< 15
Individual variable points	+4	+3	+2	+1	0	+1	+2	+3	+4

Total acute physiology score = sum of the individual variable points for all 12 variables.

\*APACHE II Score = Physiologic points + Glasgow Coma points + Age points + Chronic Health points.

(continued)

underlie the development of multiorgan failure, cytokines are attractive targets for therapy. Platelet-activating factor (PAF) has been considered to be a major proinflammatory cytokine, and several small randomized trials using an antagonist of PAF have suggested that this agent may reduce the severity of pancreatitis if administered early in the disease course. The results of these small trials, however, have not been confirmed in a large randomized trial.<sup>52</sup> PAF antagonists have also been tested as therapies to prevent post-ERCP pancreatitis but have not shown significant benefit. It is likely that interfering with the cytokine cascade will require multiple agents, and further testing of these and similar therapies will clarify the role they play in the treatment of severe acute pancreatitis.

**Removal of common bile duct stones** A therapy that has been tested as a strategy to reduce local or systemic inflammation is the removal of common bile duct stones in patients with gallstone pancreatitis. In the vast majority of patients with gallstone pancreatitis, the offending bile duct stone has already passed into the duodenum at the onset of disease. Evaluation of the common bile duct for stones early in the clinical course of gallstone pancreatitis detects the presence of stones in up to 78% of patients. This level drops to between 3% and 33% if the evaluation is undertaken later in the clinical course.<sup>53</sup> The vast majority of patients thus pass the stone spontaneously; however, in a small subset of patients, a persistent common bile duct stone remains, and anecdotal observations suggest that these patients seem to be at risk for more severe pancreatitis (e.g., more organ failure and a greater degree of necrosis) and concomitant cholangitis. It is well established that cholangitis complicates up to 10% of cases of gallstone pancreatitis. Furthermore, it may be difficult

in some patients to distinguish the presence of concomitant cholangitis from severe pancreatitis, because the two diseases may present similar features (e.g., fever, leukocytosis, abdominal pain, and abnormal liver chemistries). Therefore, the strategy was proposed to remove common bile duct stones in patients with gallstone pancreatitis as a means to reduce severity of disease and to prevent or treat concomitant cholangitis.

Early attempts to remove persistent common bile duct stones by surgery were associated with a mortality higher than that associated with conservative management. Subsequently, endoscopic techniques (e.g., ERCP) were used to remove stones. Three randomized trials assessed the utility of early ERCP and stone removal in patients with suspected gallstone pancreatitis.<sup>54-56</sup>

The initial study reported that the morbidity in patients with gallstone pancreatitis who underwent ERCP and stone removal within 72 hours was lower than the morbidity in a group of patients managed conservatively.<sup>54</sup> This benefit included a reduction in complications (organ failure and others) and a trend (not statistically significant) toward lower mortality. These benefits were restricted to a subgroup of patients who were predicted to have a severe attack. The second randomized trial noted a reduction in biliary sepsis but no reduction in organ failure or other complications associated with severe gallstone pancreatitis.<sup>55</sup> One of the two studies therefore suggested that early ERCP reduced the severity of pancreatitis, whereas the other study found that ERCP had no effect on the severity of pancreatitis but merely prevented or treated concomitant cholangitis caused by common bile duct stones. A third randomized trial attempted to reconcile these results by excluding patients with cholangitis or those at high risk for cholangitis (i.e., patients with jaundice). This study demonstrated no re-

Table 5 (continued)

Glasgow Coma Points		
	Response	Points
Eyes open	Spontaneous	+4
	To voice	+3
	To pain	+2
	None	+1
Verbal response	Oriented	+5
	Confused conversation	+4
	Inappropriate words	+3
	Incomprehensible sounds	+2
	None	+1
Best motor response	Obeys commands	+6
	Localizes pain	+5
	Flexion-withdrawal to pain	+4
	Abnormal flexion (decorticate)	+3
	Abnormal extension (decerebrate)	+2
	None/flaccid	+1

Total Glasgow Coma points = 15 - Glasgow Coma score.

Age Points	
Age (yr)	Points
< 44	0
45-54	2
55-64	3
65-74	5
≥ 75	6

duction in morbidity or mortality in patients with gallstone pancreatitis but without jaundice.<sup>56</sup>

Taken together, these three studies suggest that early ERCP is indicated in patients with evidence of biliary sepsis (i.e., fever, jaundice, and right upper quadrant pain) and in those with a high likelihood of developing biliary sepsis. High risk of biliary sepsis might be clinically defined as findings highly suggestive of a persistent obstructing common bile duct stone and could be defined by the presence of a stone in the common bile duct as visualized on radiographic imaging; by persistently abnormal liver chemistries; or by radiographic evidence of a persistently dilated bile duct. Early ERCP may also be considered in patients with early and progressive organ system failure, in whom it may be difficult to determine whether the downhill course is caused by severe pancreatitis or by associated cholangitis. Undertaking ERCP in this situation can be challenging, and sedating these critically ill individuals is not without risk.

#### Treatment of Complications

**Systemic complications** Systemic complications of acute pancreatitis can occur in a wide variety of organ systems [see Table 2].<sup>44,57</sup> Systemic complications, particularly shock, ARDS, and multiorgan failure, are the most common causes of death from acute pancreatitis within the first week of the illness. In patients with severe pancreatitis, fluid losses into the retroperitoneum can be massive and can produce intravascular volume depletion, hypotension and shock, and renal failure. The development of renal failure, shock, or massive volume depletion is an indication of severe disease and is associated with increased

Chronic Health Points	
Hepatic	Biopsy-proven cirrhosis and documented portal hypertension; past episodes of upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure, encephalopathy, or coma
Cardiovascular	New York Heart Association class IV status
Respiratory	Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (e.g., unable to climb stairs or perform household duties) or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (> 40 mm Hg), or respirator dependency
Renal	Recurring long-term dialysis
Immunocompromised	The patient has received therapy that suppresses resistance to infection (e.g., immunosuppression, chemotherapy, radiation, long-term or recent high-dose steroids) or has a disease that is sufficiently advanced to suppress resistance to infection (e.g., leukemia, lymphoma, or AIDS) If the patient has a history of severe organ system insufficiency <sup>§</sup> or is immunocompromised, <sup>§</sup> assign points as follows: Nonoperative or emergency postoperative patients, 5 points Elective postoperative patients, 2 points

<sup>†</sup>Double point score for acute renal failure.

<sup>‡</sup>Venous; not preferred use if there are no arterial blood gases.

<sup>§</sup>Organ insufficiency or immunocompromised state must have been evident before hospital admission.

A-aPO<sub>2</sub>—alveolar-arterial oxygen tension difference F<sub>I</sub>O<sub>2</sub>—fraction of inspired oxygen  
P<sub>a</sub>O<sub>2</sub>—arterial oxygen tension

mortality. Most substantial fluid losses occur early in the course of acute pancreatitis; hence, attention must be paid to adequate and aggressive fluid resuscitation early in the disease course.<sup>44</sup>

**Hypoxia** Hypoxia is not uncommon during the initial stages of acute pancreatitis. A subset of patients will develop more substantial or prolonged hypoxia and go on to develop ARDS. Thus, it is reasonable to monitor patients with acute pancreatitis, especially those with severe acute pancreatitis, by means of pulse oximetry to detect the development of hypox-

Table 6 Atlanta Criteria for Severity

- Organ failure
  - Shock (supine systolic blood pressure < 90 mm Hg)
  - Pulmonary insufficiency (P<sub>a</sub>O<sub>2</sub> < 60 mm Hg)
  - Renal failure (serum creatinine > 2 mg/dl)
  - Gastrointestinal tract bleeding (> 500 ml in 24 hr)
- and/or
- Local complications
  - Necrosis
  - Abscess
  - Pseudocysts
- and/or
- Unfavorable prognostic signs
  - Ranson score > 3
  - APACHE II score > 8

emia. Because patients who develop hypoxia are also at risk for MOF, persistent hypoxemia merits ICU admission. Fluid management in these patients can be difficult and is best done with monitoring of pulmonary capillary wedge pressure. Mechanical ventilation, usually with positive end-expiratory pressure (PEEP), is often necessary.

**Cardiac complications** A variety of cardiac complications may occur in severe acute pancreatitis, including congestive heart failure, myocardial infarction, cardiac arrhythmias, and cardiogenic shock. Hypotension is most commonly caused by third-space fluid losses and intravascular volume depletion. Cardiac dysfunction may, however, occur as part of SIRS seen in severe acute pancreatitis, which is characterized by high cardiac output and low systemic vascular resistance. Hypotension that is not responsive to fluid resuscitation may require the use of pressor agents.

**Metabolic complications** A number of metabolic complications may also occur in acute pancreatitis, including hypocalcemia, hyperglycemia, and hyperlipidemia. Hypocalcemia is most commonly the result of hypoalbuminemia and is uncommonly associated with a reduction in ionized calcium or symptoms of hypocalcemia. Calcium replacement is usually not needed in the absence of decreased ionized calcium or signs of neuromuscular instability (e.g., tetany, the Chvostek sign, and the Trousseau sign). Calcium should, nonetheless, be monitored carefully, as it can be a marker of severe pancreatitis.

Hyperglycemia, like hypocalcemia, is one of the Ranson criteria indicating a poor prognosis. Treatment of mild hyperglycemia is not necessary, but significant increases in blood glucose levels (i.e., levels > 200 mg/dl) should be treated with sliding-scale insulin to minimize associated fluid losses caused by glycosuria and to prevent any detrimental effect on white cell function.

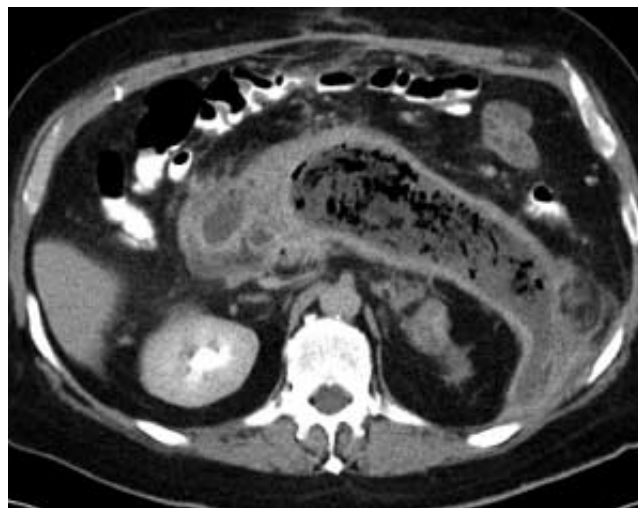
Hyperlipidemia is associated with acute pancreatitis, both as an etiologic factor and as a consequence. Many patients with acute pancreatitis may develop a modest elevation in serum triglyceride levels (i.e., levels > 300 to 400 mg/dl) as a consequence of acute pancreatitis. These elevations in triglyceride levels are usually short-lived and do not require therapy. Levels above 1,000 mg/dl indicate hypertriglyceridemia as the cause, rather than a consequence, of acute pancreatitis. These levels will usually drop rapidly while the patient is NPO. Marked elevations in triglyceride levels (> 10,000 mg/dl) or failure of triglyceride levels to drop as expected may occasionally necessitate the use of plasmapheresis to rapidly clear triglycerides from the serum. After recovery from pancreatitis, patients with hyperlipidemic pancreatitis should be started on appropriate medications and dietary therapy to control lipids.

**Gastrointestinal bleeding** Gastrointestinal bleeding may complicate acute pancreatitis and is a marker of a severe attack.<sup>57,58</sup> Bleeding may occur from stress erosions, peptic ulceration, pseudoaneurysm, or varices developing as a consequence of splenic vein thrombosis. Splenic vein thrombosis, which may occur as a consequence of inflammatory and neoplastic pancreatic diseases, causes a left-sided portal hypertension characterized by gastric varices out of proportion to esophageal varices. These varices may bleed and, if they do, may be managed by splenectomy, which is curative. Bleeding from a pseudoaneurysm is usually associated with a pseudocyst [see Chronic Pancreatitis, Treatment of Other Complications, *below*].

**Other systemic complications** Rare complications of acute pancreatitis include other vascular thromboses, disseminated intravascular coagulation, distant fat necrosis in the skin (resembling erythema nodosum), encephalopathy, and sudden blindness.

**Pancreatic infection and abscess** Infected pancreatic necrosis, the most serious form of pancreatic infection, occurs in about 1% to 4% of patients overall with pancreatic infection and in 15% to 30% of those with pancreatic necrosis.<sup>42,59,60</sup> The mortality of necrotizing pancreatitis is about 10%, but this rate triples when infection supervenes. Most commonly, infection occurs during the second and third weeks of an attack of severe pancreatitis. The patient develops fever (often, temperatures > 102° F [38.9° C]), leukocytosis, and recurrent or worsening abdominal pain. The infecting organisms usually seed the necrotic area from the gut and are most commonly gram-negative rods (e.g., *Klebsiella* or *Escherichia coli*) and *Staphylococcus aureus*. *Candida*, *Enterococcus*, and anaerobic organisms are seen less commonly as causal agents of pancreatic infection. When infection is suspected, a CT scan should be obtained to evaluate the extent of necrosis and identify optimal locations for percutaneous sampling.<sup>40,42,61</sup> The finding of gas within the pancreatic parenchyma is highly specific but quite insensitive for serious pancreatic infection [see Figure 2]. However, a clinical suspicion of infection together with a finding of necrosis is an indication for percutaneous aspiration of suspicious areas, and a Gram stain and a culture of the collected tissue should be done. Experience over the past 15 years has demonstrated that percutaneous aspiration is both highly accurate and safe.<sup>40,42,59,60</sup> If pancreatic infection is demonstrated on percutaneous aspiration, the therapy of choice is prompt surgical debridement. Successful management of necrotic collections by percutaneous or endoscopic catheterization has also been reported,<sup>62</sup> but these techniques require further study because it is difficult to remove the necrotic tissue through catheters and, hence, difficult to cure the infection by this means.

Pancreatic abscess may also complicate severe acute pancreatitis, usually as a consequence of superinfection of a preexisting fluid collection or pseudocyst. Less commonly, an abscess develops secondary to superinfection of necrotic sites in the pancreas. The clinical presentation of pancreatic abscess is indistinguishable from that of infected necrosis, although therapy may differ.



**Figure 2** A CT scan demonstrating a large amount of air within the necrotic pancreas in a patient with infected pancreatic necrosis.

Therapy for pancreatic abscess usually consists of antibiotics and drainage. Unlike infected necrosis, which is typically treated by surgical debridement, pancreatic abscess may allow treatment by percutaneous or endoscopic tube drainage, because typically there is little solid necrotic tissue in the abscess cavity. The decision whether to treat with tube drainage or surgical exploration depends on whether the collections contain solid necrotic tissue (indicating infected necrosis, which typically necessitates open surgical drainage) or primarily pus (indicating abscess, which may allow drainage by endoscopic or percutaneous tube). However, distinguishing infected necrosis from pus may be difficult, and the most accurate picture of the collection contents is probably provided by MRI and EUS. EUS in particular is valuable because the collection not only can be assessed for the character of its contents but also can be drained safely in the same setting if appropriate. If doubt exists, it is better to err on the side of caution and opt for open surgical drainage.

Because the consequences of abscess and infected pancreatic necrosis are often severe, numerous studies have been directed toward identifying effective measures to prevent these infections. Currently, however, the role of antibiotics in the prevention of pancreatic infection is controversial. Early studies using prophylactic ampicillin demonstrated no reduction in pancreatic infections; it was later demonstrated that ampicillin does not penetrate the necrotic pancreas at adequate concentrations. More recent studies have identified agents that have adequate penetration of the necrotic pancreas; effective therapies include imipenem,<sup>63,64</sup> cefuroxime,<sup>65</sup> ofloxacin and metronidazole,<sup>66</sup> and ciprofloxacin and metronidazole.<sup>67</sup> A Cochrane Database review concluded that intravenous prophylactic antibiotic therapy for 10 to 14 days reduced the risk of superinfection of pancreatic necrosis and mortality.<sup>68</sup> This analysis, however, did not include the only relevant double-blind, randomized trial,<sup>67</sup> which demonstrated that there was no benefit with the use of prophylactic antibiotics for necrotic pancreatitis. These divergent findings have led to a difference of opinion on the overall utility of prophylactic antibiotics.

Generally, antibiotic use should be limited to patients at risk for serious pancreatic infection (i.e., if more than 30% of the gland appears necrotic on CT), and the selected antibiotic should be one that penetrates the necrotic tissue (i.e., imipenem or a fluoroquinolone plus metronidazole). Treatment should be continued for a maximum of 10 to 14 days. Patients receiving these broad-spectrum antibiotics are at risk for infection with resistant bacteria and fungal superinfection. Some researchers have advocated the concomitant use of antifungal agents such as fluconazole to reduce the risk of fungal infection, but the effectiveness of this strategy is unproved.

**Fluid collections and pseudocysts** Fluid collections in and around the pancreas occur commonly in patients with acute pancreatitis. Peripancreatic fluid collections are generally amorphous and not encapsulated. Most fluid collections resolve spontaneously, but some develop into pseudocysts.<sup>57,69,70</sup> A pseudocyst is a rounded collection of pancreatic fluid enclosed by a wall of fibrous or granulation tissue that can usually be seen on a CT scan. Most collections occur in the lesser sac or pararenal spaces, but they may develop anywhere and may even penetrate adjacent solid organs (e.g., the liver or spleen). Pseudocysts complicate 1% to 8% of all cases of acute pancreatitis.<sup>69,70</sup> Pseudocysts may persist, resolve, be asymptomatic, or be associated with symptoms or complications. The most common symptom asso-

ciated with a pseudocyst is abdominal pain; however, other symptoms may develop if the pseudocyst obstructs an adjacent hollow viscus. For example, obstruction of the duodenum causes nausea and vomiting, whereas obstruction of the bile duct causes jaundice. Up to two thirds of all pseudocysts ultimately resolve, but spontaneous resolution is unlikely to occur with pseudocysts that are larger than 5 to 6 cm or are present for more than 6 weeks. In addition, pseudocysts larger than 6 cm are somewhat more likely to produce complications, including obstruction of an adjacent hollow viscus (e.g., duodenum or bile duct), infection, bleeding, or rupture. Infection of a pseudocyst (i.e., a pancreatic abscess) is usually relatively easy to manage with antibiotics and endoscopic or percutaneous catheter drainage; however, pseudocysts characterized by bleeding and rupture are associated with much greater morbidity and mortality. Bleeding may occur from a large artery that has formed a pseudoaneurysm from the pressure exerted by a contiguous pseudocyst, and the resulting blood flow can reach the gut through the pancreatic duct or can enter the peritoneum through a rupture of the pseudocyst. An initial bleed may be self-limited, but any unexplained drop in hemoglobin or change in pain pattern in a patient with a pseudocyst is an indication for an emergency CT scan. If any evidence of bleeding is found, emergency angiography with embolization can be lifesaving.<sup>58</sup>

Asymptomatic pseudocysts generally pose little risk of complications, even if they are large.<sup>70</sup> Symptomatic or complicated pseudocysts require therapy, and emergency surgery is required when bleeding or rupture is detected. Otherwise, elective surgical, percutaneous, or endoscopic techniques can be successful, depending on the location of the pseudocyst and the availability of expertise in these modalities. In the past, endoscopic drainage could be applied only to pseudocysts that produced a visible bulging impression in the lumen of the stomach or duodenum. Today, endoscopic pseudocyst drainage can be accomplished by using real-time endoscopic ultrasound guidance without the need of visually observing a bulge.<sup>71</sup> Percutaneous tube drainage can also treat pseudocysts that are farther from the gut lumen; however, tube drainage can produce a chronically draining external pancreatic fistula. Surgical treatment of pseudocysts probably has the best long-term results, but it also carries the most significant morbidity. Endoscopic ultrasound-guided transmural pseudocyst drainage appears to offer the best risk-to-benefit ratio for pseudocysts in anatomically amenable locations, but studies directly comparing surgical, endoscopic, and percutaneous drainage are lacking.

#### *Prevention of Subsequent Attacks*

Preventing subsequent attacks of acute pancreatitis requires elimination of the cause of the disease. In patients with acute alcoholic pancreatitis, cessation of alcohol consumption appears to have some benefit in reducing relapse, although unfortunately, the disease may continue to progress to symptomatic chronic pancreatitis despite abstinence. In patients with gallstone pancreatitis, cholecystectomy virtually eliminates recurrence. Similarly, the detection of microlithiasis followed by appropriate therapy (i.e., cholecystectomy, endoscopic biliary sphincterotomy, and possibly the use of ursodeoxycholic acid) can prevent recurrent pancreatitis. Aggressive control of serum lipid levels can prevent recurrent attacks of hyperlipidemic pancreatitis. In patients with a disorder that obstructs the pancreatic duct (e.g., benign or malignant pancreatic duct stricture, pancreas divisum, sphincter of Oddi dysfunction, and ampullary tumor), removal

of the obstruction by surgical or endoscopic means is generally effective in preventing relapse.

## Chronic Pancreatitis

Chronic pancreatitis is characterized by irreversible damage to the pancreas and the development of histologic evidence of fibrosis and destruction of exocrine (acinar cell) and endocrine (islets of Langerhans) tissue. As with acute pancreatitis, the definition of chronic pancreatitis was developed at international symposia.<sup>72</sup> Several variants of chronic pancreatitis were defined, including chronic calcified pancreatitis (the most common form, which is commonly caused by excessive alcohol intake), chronic obstructive pancreatitis (caused by long-standing pancreatic duct obstruction), and chronic inflammatory pancreatitis (associated with inflammatory and, particularly, autoimmune diseases). Unfortunately, it is often not possible to make the distinction between these variants on the basis of clinical findings or imaging studies, and the distinctions are not very useful to clinicians. Recent classification schemes have focused more on etiology and are somewhat more useful to clinicians.<sup>22</sup>

### EPIDEMIOLOGY

The prevalence of chronic pancreatitis varies with the population. Estimates of annual incidence in several studies range from three to nine cases per 100,000 population.<sup>5,73</sup> One study estimated an overall prevalence of 27.4 per 100,000 population. In nonfederal hospitals in the United States, this accounts for 122,000 outpatient visits and more than 20,000 hospitalizations annually.<sup>34</sup> The natural history can be quite variable and is clearly affected by the presence of ongoing alcoholism in persons with chronic alcoholic pancreatitis. In one large multicenter study,<sup>74</sup> the standardized mortality ratio was 3.6 (those with a diagnosis of chronic pancreatitis died at 3.6 times the rate of age-matched control subjects). Older persons and those with alcoholic chronic pancreatitis have the lowest survival. Overall, 10-year survival for patients with chronic pancreatitis has been shown to be about 70%, and 20-year survival about 45%.<sup>5,74</sup> Chronic pancreatitis is a strong risk factor for pancreatic adenocarcinoma, which partly explains the increased mortality associated with chronic pancreatitis.

### ETIOLOGY

#### *Alcohol Abuse*

Alcohol is the cause of chronic pancreatitis in 70% to 90% of all cases. In general, at least 5 years of alcohol intake exceeding 150 g/day is required to develop symptomatic chronic pancreatitis, although some patients develop chronic pancreatitis with less alcohol intake. Only 5% to 15% of heavy drinkers ultimately develop chronic pancreatitis, suggesting that cofactors play an important role in pathogenesis.<sup>12</sup> Predisposing factors may include genetic abnormalities and a diet high in fat and protein. The mechanism by which alcohol causes chronic pancreatitis remains undefined, but it may be related to a change in pancreatic secretion leading to (1) protein plug formation in the pancreatic duct, (2) a direct toxic effect of alcohol or its metabolites, or (3) repeated attacks of acute alcoholic pancreatitis that eventually produce chronic irreversible damage. It has been observed that the vast majority of patients who develop an acute attack of alcoholic pancreatitis already have preexisting chronic damage to the gland.

#### *Tropical Pancreatitis*

Tropical pancreatitis is seen in certain areas of Indonesia, India, and Africa. The disease typically presents in childhood, with diabetes, abdominal pain, steatorrhea, malnutrition, and diffuse pancreatic calcifications. Malnutrition appears to be an important cofactor in this disease, as may be the presence of toxic metabolites of the dietary staple cassava. Studies also suggest a strong genetic component, with mutations in the *SPINK1* gene occurring in more than one third of patients.<sup>75</sup>

#### *Genetic Factors*

Hereditary pancreatitis is an autosomal dominant disease that typically presents in childhood or early adulthood and frequently is accompanied by steatorrhea, diabetes mellitus, and diffuse pancreatic calcifications. Pain and acute episodes of pancreatitis flares may also occur but are somewhat less common in hereditary pancreatitis than in alcoholic chronic pancreatitis. The initially identified genetic abnormality is a defect in the *PRSS1* gene on chromosome 7.<sup>22,76</sup> Multiple mutations have been described, but two are more common.<sup>76</sup> The two more common mutations appear to produce a trypsinogen that, once activated, is difficult or impossible to inactivate. The activated enzyme, trypsin, can in turn activate all the other pancreatic enzymes. Chronic pancreatitis appears to be caused in this situation by prolonged low-grade pancreatic injury from the activated proteases. Pancreatic adenocarcinoma frequently complicates the condition; patients with chronic pancreatitis have a 30% risk of developing pancreatic adenocarcinoma by age 70.<sup>77</sup> The risk may be substantially higher in patients with paternal inheritance.

Mutation of the *SPINK1* gene increases the propensity to develop chronic pancreatitis,<sup>22,75</sup> although mutation of this gene appears to act as a cofactor. Increased frequency of mutations in *SPINK1* is seen in patients with pancreatitis of different etiologies—namely, tropical pancreatitis (> 33% of patients), alcoholic chronic pancreatitis (about 6% of patients), hereditary pancreatitis (in a few kindreds in addition to their *PRSS1* mutation), and idiopathic chronic pancreatitis (sometimes in association with additional mutations in the *CFTR* gene). Mutations in *SPINK1* are common in the general population, but in most cases, pancreatic disease does not occur in these individuals; therefore, these mutations provide only a predisposition to chronic pancreatitis and are only some of the many factors contributing to formation of the disease.

*CFTR* mutations are also associated with chronic pancreatitis. Patients with classic cystic fibrosis commonly develop pancreatic insufficiency that requires supplementation of pancreatic enzyme. Several studies have also suggested that less common cystic fibrosis gene mutations, particularly when they occur as a mixed heterozygote (different mutations on the two alleles), are associated with relapsing pancreatitis and chronic pancreatitis in the absence of obvious sinopulmonary disease.<sup>22,78</sup> Patients with both *CFTR* and *SPINK1* mutations are at exceedingly high risk for chronic pancreatitis.

#### *Undetermined Causes*

Some patients may be misdiagnosed as having idiopathic pancreatitis if appropriate genetic studies are not performed or if a careful history of alcohol use is not obtained. Even if genetic studies are done, not all mutations may be identified (e.g., many commercially available screens look for only a few hundred of the more than 1,200 known *CFTR* mutations), and many identified *CFTR* and *SPINK1* mutations produce only a predisposition

to disease (unlike *PRSS1* mutations, which cause disease). Previous studies of patients with so-called idiopathic chronic pancreatitis that did not assess for the presence of genetic mutations appeared to identify two forms: early-onset and late-onset idiopathic chronic pancreatitis. The early-onset form presents just before or during the second decade, and it is typically associated with severe pain in the absence of diabetes, steatorrhea, or pancreatic calcification.<sup>79</sup> The late-onset form presents at a mean age of 56 years and is more commonly associated with exocrine or endocrine insufficiency and less commonly associated with severe pain.<sup>79</sup> The relative role of genetic influences on these two phenotypic variations remains to be determined.

#### PATHOGENESIS

The pathophysiology of chronic pancreatitis remains poorly understood. The events that occur in hereditary chronic pancreatitis suggest that one common underlying theme may be multiple subclinical episodes of acute injury that ultimately produce chronic pancreatitis.<sup>80</sup> A recent hypothesis (the so-called sentinel acute pancreatitis event [SAPE] hypothesis)<sup>81</sup> suggests that in a patient with an underlying susceptibility (e.g., genetic background), a sentinel event (e.g., alcohol exposure) can trigger the disease process, producing acute inflammation and infiltration of inflammatory cells. The acute pancreatitis may heal or, with repeated episodes, may lead to activation of pancreatic stellate cells and the development of fibrosis (i.e., chronic pancreatitis). This hypothesis, while attractive, is as yet unproved.

#### DIAGNOSIS

##### *Clinical Findings*

The diagnosis of chronic pancreatitis is suspected on the basis of suggestive signs and symptoms and confirmed by further tests of pancreatic structure or function. The disease is usually suspected on the basis of the presence of abdominal pain.

The vast majority of patients with chronic pancreatitis will experience pain at some point during their illness.<sup>73,79</sup> The pain tends to be episodic initially, but it may become more constant or continuous as the disease progresses. During acute attacks, the patient may be thought to have acute pancreatitis until the diagnosis of chronic pancreatitis can ultimately be established. Although there is no pathognomonic character of the pain, it is most commonly felt in the epigastrium, with radiation to the back. In severe episodes, nausea and vomiting are common. The natural history of the pain is quite variable, and it may worsen, stabilize, or even resolve over time. In some patients, the onset is gradual and evolves into constant abdominal pain. However, a minority of patients with chronic pancreatitis have no pain. In these patients, the disease may be suspected on the basis of the development of exocrine insufficiency (steatorrhea, weight loss, and malnutrition) or endocrine insufficiency (diabetes mellitus).

##### *Laboratory Tests*

The clinical features suggestive of chronic pancreatitis (e.g., abdominal pain, steatorrhea, weight loss, and malnutrition) are not specific for chronic pancreatitis; the diagnosis requires confirmatory tests. Diagnostic tests are usually separated into tests that detect abnormalities of pancreatic function and tests that detect abnormalities of pancreatic structure [see Table 7]. Chronic pancreatitis is a slowly progressive disease, and the abnormalities of pancreatic structure or function may take years to develop or may not develop at all. Hence, all of the diagnostic tests are

**Table 7 Diagnostic Tests for Chronic Pancreatitis\***

<i>Structural Tests</i>	<i>Functional Tests</i>
Endoscopic ultrasonography	Direct hormonal stimulation test (secretin or secretin-CCK test)
Endoscopic retrograde pancreatography	Fecal elastase
Computed tomography	Serum trypsin
Magnetic resonance imaging/magnetic resonance cholangiopancreatography	Fecal fat
Abdominal ultrasound	Serum glucose
Plain abdominal radiograph	—

\*Ranked in approximate order of decreasing sensitivity.  
CCK—cholecystokinin

most accurate in far-advanced disease, when obvious structural or functional abnormalities have developed.

Structural abnormalities that can be diagnostic of chronic pancreatitis include changes in the main pancreatic duct (dilatation, strictures, irregularity, and pancreatic duct stones), side branches of the pancreatic duct (dilatation and irregularity), or pancreatic parenchyma (diffuse pancreatic calcifications). These findings can be visualized utilizing the diagnostic tests that evaluate pancreatic structure [see Table 7].

Functional abnormalities in chronic pancreatitis include a decrease in stimulated secretory capacity, exocrine insufficiency (malabsorption and steatorrhea), and endocrine insufficiency (diabetes mellitus).<sup>82</sup> Patients with alcoholic chronic pancreatitis, hereditary chronic pancreatitis, tropical pancreatitis, and late-onset idiopathic chronic pancreatitis are most likely to develop these abnormalities, although the course of development may take many years. Patients with early-onset idiopathic chronic pancreatitis may not develop these abnormalities at all. This observation has led to a general classification of chronic pancreatitis as either big-duct or small-duct disease [see Imaging Studies, Disease Classification, *below*].

**Serum tests** Serum amylase or lipase levels may be elevated during acute exacerbations of chronic pancreatitis, but these elevations are usually only modest and are neither routinely present nor diagnostic for chronic pancreatitis. Serum trypsinogen (often called serum trypsin) can also be measured. Low levels of serum trypsinogen (< 20 ng/ml) are highly specific for chronic pancreatitis,<sup>73,83</sup> but such low levels occur only in advanced disease (in the presence of steatorrhea). Very low levels of serum trypsinogen may also be seen occasionally in patients with pancreatic adenocarcinoma. Serum trypsinogen levels are in the normal range in most patients with less advanced chronic pancreatitis.

**Stool tests** A 72-hour stool collection for fat is the gold standard to detect steatorrhea but is cumbersome and unpleasant to perform. Steatorrhea is seen only in far-advanced chronic pancreatitis. More than 7 g of fat in the stool per 24 hours is considered abnormal. Of note, the patient has to be placed on a diet containing 100 g of fat a day for the results of the stool collection to be valid. At least 90% of the pancreatic enzyme secretory capacity needs to be lost before steatorrhea will develop.<sup>84</sup> Qualitative stool stains for fat (e.g., Sudan III) are far less accurate than a

72-hour collection but are easily performed. They should also be performed only while the patient is on a high-fat diet. Fecal levels of elastase and chymotrypsin may be reduced in patients with chronic pancreatitis, but only in cases of more advanced chronic pancreatitis.<sup>82</sup> Measurement of fecal elastase in a random stool sample is of reasonable accuracy<sup>83,85</sup> in these patients and is now available from reference laboratories in the United States. Values of fecal elastase of less than 200 µg/g of stool are seen in patients with more advanced chronic pancreatitis.

**Direct pancreatic function tests** The direct pancreatic function tests involve placing a tube into the duodenum to collect pancreatic juice and are complex and cumbersome. These tests directly measure pancreatic output of enzymes or bicarbonate after stimulation with a secretagogue (e.g., secretin or cholecystokinin or its analogue). Although these tests are able to detect severe decreases in pancreatic secretory output, their strength is in detecting moderate decreases in maximal stimulated secretory capacity. This decrease in maximal stimulated secretory capacity occurs before secretory failure (exocrine insufficiency) in chronic pancreatitis, and the direct function tests are felt to be the most sensitive tests available to detect chronic pancreatitis at an early stage (earlier than any other test).<sup>73,82,86</sup> They are particularly useful in making the diagnosis in patients with small-duct chronic pancreatitis, in whom alternative diagnostic tests (e.g., CT, ERCP) are likely to miss the diagnosis. Unfortunately, direct pancreatic function tests are available only at a few referral centers in the United States. Alternatives to cumbersome traditional pancreatic function testing have been studied. The collection of pure pancreatic juice for 15 minutes at the time of ERCP—the so-called intraductal secretin test—proved to be an inaccurate way to evaluate pancreatic function.<sup>87</sup> Another alternative involves administering a secretagogue (secretin) and collecting pancreatic secretions through an endoscope during upper endoscopy with sedation. Although accurate, the 1-hour collection of pancreatic secretions after secretin stimulation at the time of upper endoscopy appears to be perhaps too impractical for widespread application.<sup>88</sup> It is hoped that refinements will eventually allow these more sensitive tests to be used in a wider population of patients.

### Imaging Studies

**Radiology** Simple plain abdominal radiographs may detect diffuse pancreatic calcification in very far advanced chronic pancreatitis [see Figure 3]. This finding is highly specific but quite insensitive.

**Ultrasonography** Abdominal US is most likely to detect advanced abnormalities of pancreatic structure; however, US is diagnostic in only 60% of patients.<sup>73</sup> The pancreas is often not well visualized on transabdominal US. New techniques of contrast-enhanced US and tissue harmonic imaging may provide better diagnostic accuracy.<sup>89</sup>

**Computed tomography** CT is much more sensitive than US (CT, 75% to 90%) because of its capacity to detect more focal abnormalities, such as calcification, a dilated pancreatic duct, fluid collections, and focal enlargements. CT may also demonstrate gland atrophy, which is seen in patients of advanced age in the absence of chronic pancreatitis. The use of multislice CT produces images of exceptional quality; this imaging technique should improve diagnostic accuracy, although it has not been



**Figure 3** A plain film of the abdomen demonstrating multiple calcified stones in the pancreatic duct in a patient with advanced chronic pancreatitis.

adequately studied.<sup>90</sup> Like US, CT can be falsely negative in early or less advanced chronic pancreatitis.

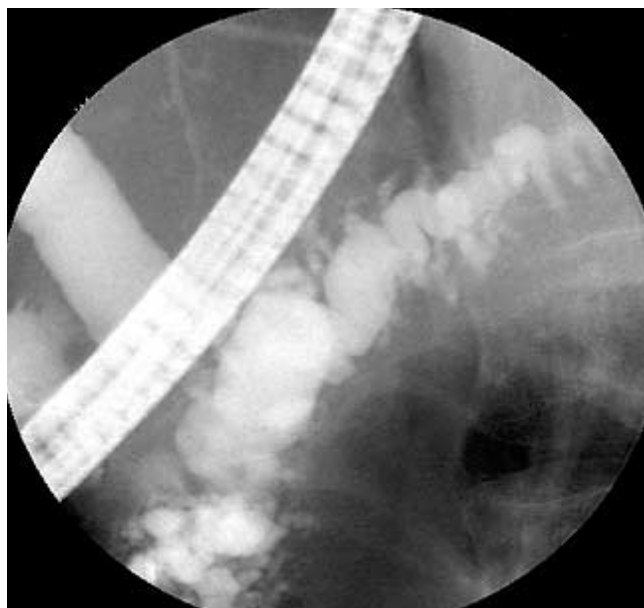
**Magnetic resonance imaging** An improvement in magnetic resonance technology has allowed more accurate imaging of both the pancreatic parenchyma and the pancreatic duct with MRCP. It is not clear whether MRI and MRCP are superior to CT, but they do appear to be at least equivalent to CT in overall accuracy.<sup>90</sup> The use of secretin before MRCP allows improved imaging of the pancreatic duct and, theoretically, calculation of pancreatic secretory volume.<sup>91</sup> Secretin-stimulated MRCP is being used at a number of centers and may improve overall accuracy of MRI for chronic pancreatitis.

**Endoscopy** Two endoscopic tests are used to diagnose chronic pancreatitis: ERCP and EUS. ERCP has a reported sensitivity of 75% to 90%.<sup>73,86</sup> With ERCP, radiographic contrast is injected into the pancreatic duct. Changes in the pancreatic duct consistent with chronic pancreatitis include ductal dilatation, strictures, irregularity, and filling defects (stones) in the pancreatic duct [see Figures 4 and 5]. The changes associated with chronic pancreatitis that are seen on ERCP are not specific, as they can also be seen in other clinical presentations—namely, (1) in elderly patients with pancreatic duct dilatation caused by aging, (2) in patients with resolving acute pancreatitis, (3) in some patients with pancreatic carcinoma, and (4) in patients who have previously undergone pancreatic duct stenting.<sup>86</sup> In addition to its diagnostic ability, ERCP may have therapeutic application in a subset of patients [see Management, Endoscopic and Surgical Therapy, below].

EUS, which allows a highly detailed examination of the pancreatic parenchyma and pancreatic duct, routinely detects abnormalities in patients with chronic pancreatitis (high sensitivity). The test is interpreted on the basis of documented changes in both the pancreatic duct and pancreatic parenchyma; a system of

grading EUS findings usually assesses nine specific features.<sup>92,93</sup> In addition, a normal EUS examination essentially rules out chronic pancreatitis. The specificity of the test requires some further study in that many patients without clinical chronic pancreatitis may have modest numbers of abnormalities on EUS [see Figure 6].<sup>92,93</sup>

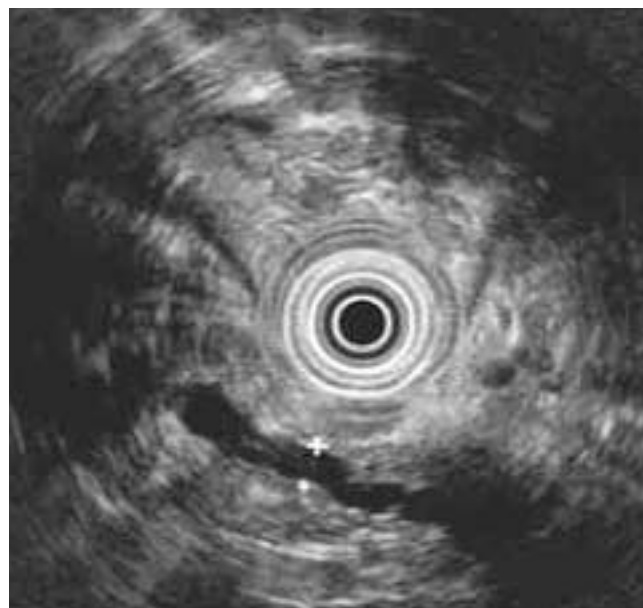
**Disease classification** Depending on the findings on imaging studies, patients may be classified as having so-called big-duct or small-duct chronic pancreatitis. This distinction has both diagnostic and therapeutic implications. Big-duct disease implies substantial abnormalities of the pancreatic duct (gener-



*Figure 4* An endoscopic retrograde cholangiopancreatography image demonstrating massive pancreatic duct dilatation in a patient with big-duct chronic pancreatitis.



*Figure 5* An endoscopic retrograde cholangiopancreatography image demonstrating minimal pancreatic duct abnormalities in a patient with painful small-duct chronic pancreatitis.



*Figure 6* An endoscopic ultrasound image demonstrating a dilated pancreatic duct (markers) in a patient with advanced chronic pancreatitis.

ally, dilatation visible on US, CT, ERCP, or EUS, often with pancreatic calcifications), and small-duct disease implies the absence of these findings (e.g., a normal or near-normal US, CT, or ERCP) [see Figures 4 and 5]. The diagnosis of big-duct disease is much simpler; the disease usually results from alcohol abuse, and the therapeutic options include treatments aimed at decompressing the dilated pancreatic duct. The diagnosis and management of small-duct disease may prove to be more difficult than those of big-duct disease because with small-duct disease, imaging studies may be normal, disease is more commonly idiopathic, and treatment options focus on medical therapy rather than surgical or endoscopic attempts to decompress the pancreatic duct.

#### *Diagnostic Approach*

The diagnostic approach to chronic pancreatitis should begin with tests that are safe, inexpensive, and able to detect relatively far advanced disease. Diagnostic tests that fit in this category include serum trypsinogen, fecal elastase, and abdominal US. If these tests do not lead to a diagnosis, riskier or more expensive tests will generally need to be employed (e.g., MRI/MRCP, CT, ERCP, or EUS). Direct pancreatic function testing, if available, logically should be used after the initial tests and before the more expensive or invasive tests, because direct pancreatic function tests are the most sensitive tests available and are lower in cost and less risky than the other options. Because most clinicians do not have access to pancreatic function testing, the riskier, more expensive tests are usually performed, starting with a good-quality CT using pancreatic protocol.

#### MANAGEMENT

##### *Abdominal Pain*

Pain is the most common symptom of chronic pancreatitis requiring medical care. There are a number of potential causes of pain in chronic pancreatitis, including inflammation of pan-

creatic nerves, pancreatic tissue ischemia, increased pressure in the gland or an associated pseudocyst, obstruction of a surrounding hollow viscus (e.g., duodenum or bile duct), and co-existent pancreatic carcinoma. The initial evaluation should focus on identifying conditions for which specific therapy exists. These conditions include pancreatic pseudocyst, duodenal or bile duct compression, and superimposed pancreatic carcinoma. This evaluation is most commonly done by performing a high-quality CT scan of the abdomen. If such a condition is identified, specific therapy is required [see Treatment of Other Complications, *below*].

**Analgesia and cessation of alcohol use** Nonspecific measures to reduce pain in chronic pancreatitis include cessation of alcohol consumption and use of analgesics. Cessation of alcohol consumption can reduce pain in some patients with alcoholic chronic pancreatitis and may prolong life by preventing other alcohol-induced diseases. Unfortunately, abstinence will not halt the progression of chronic pancreatitis, although it may slow it. Analgesics are generally needed, but it is important to start with the least potent agents first (e.g., propoxyphene napsulate or tramadol) because narcotic addiction can occur in up to 30% of patients. Many patients will require more potent narcotics. Adding an antidepressant (a selective serotonin reuptake inhibitor or a tricyclic) may allow potentiation of the narcotic effect. If these simple measures fail, further therapy utilizing medical, endoscopic, or surgical techniques can be considered.

**Administration of pancreatic enzymes** Several controlled trials have attempted to delineate the effectiveness of orally administered pancreatic enzymes to decrease pain. The concept behind this therapy is that proteases that are present in the duodenum may reduce the stimulus for pancreatic secretion by a negative-feedback mechanism. Only conventional (non-enteric-coated) preparations of pancreatic enzymes can deliver proteases to the duodenum; enteric-coated enzyme preparations deliver proteases too far distally to achieve a negative-feedback effect. Two studies utilizing non-enteric-coated enzymes at high dosages (8 tablets total, in four divided doses with meals and at night, coupled with an agent to suppress gastric acid to prevent premature inactivation of the enzymes) demonstrated a reduction in pain. Four other studies utilizing enteric-coated enzymes showed no effect. A meta-analysis of these studies suggested enzymes are of no benefit in treating pain.<sup>94</sup> In the two studies that demonstrated effectiveness, it appears that persons with less advanced disease (small-duct chronic pancreatitis) respond best, and females with idiopathic chronic pancreatitis seem to have the highest response rate. The role of enzymes in treating pain is controversial, although a consensus review advocated their use.<sup>95</sup> Non-enteric-coated enzyme preparations are of modest effectiveness, but they may be worth a trial in patients with less advanced disease in whom other simple medical measures have failed. A trial of enzymes for pain is generally pointless in patients with advanced or big-duct chronic pancreatitis (mainly alcoholic chronic pancreatitis). These enzyme products are inactivated by gastric acid; thus, concomitant therapy with an agent to reduce gastric acid (H<sub>2</sub> receptor antagonist or proton pump inhibitor) is needed.

**Neurolysis** Neurolysis via a celiac plexus block or thoracoscopic splanchnicectomy has been evaluated in a number of small studies. The use of percutaneous celiac plexus block has largely been abandoned in patients with chronic pancreatitis be-

cause of its transitory effectiveness. EUS-guided celiac plexus block is simpler and safer than percutaneous techniques and appears to last longer.<sup>96</sup> Thoracoscopic splanchnicectomy involves sectioning the splanchnic nerves at thoracoscopy. The short-term response is good (60% to 80% response), but the long-term response has been disappointing.<sup>97</sup>

**Endoscopic and surgical therapy** Endoscopic therapy and surgical therapy are most useful in patients with advanced or big-duct chronic pancreatitis. Endoscopic therapy has a general goal of relieving obstruction in the pancreatic duct by dilating or stenting a stricture or by removing an obstructing stone. Only a subset of patients with chronic pancreatitis are candidates for such therapy; generally, endoscopic therapy may be considered an option in patients with a dilated pancreatic duct (big-duct chronic pancreatitis) and an obstructing stricture or stone in the head of the gland. The results of large case series indicate that endoscopic therapy may improve pain in 70% to 80% of carefully selected patients.<sup>73,95,98,99</sup> The only randomized, controlled trial that compared endoscopic therapy with surgery showed that the two therapies provide equivalent short-term pain relief, but surgery provided better long-term pain relief.<sup>100</sup> Even if endoscopic therapy is not possible, however, an ERCP may provide useful information for planning surgical therapy.

Surgical procedures that are commonly used to treat pain include decompression of the main pancreatic duct, with or without resection of a portion of the pancreas. Surgery may also be indicated for treatment of a complication such as a pseudocyst, duodenal or common bile duct obstruction, or pancreatic fistula. For patients with intractable pain and a dilated duct, the most commonly performed procedure is the lateral pancreaticojejunostomy (i.e., modified Puestow procedure), in which the pancreatic duct is widely incised along its length and overlaid with a defunctionalized loop of small intestine for drainage of pancreatic juice directly into the small bowel. In some patients, resection of a portion of the pancreatic head may also be needed to decompress smaller-duct branches in the pancreatic head and uncinate process. Substantial pain relief is obtained in 65% to 85% of patients and appears to be relatively long lasting (in some studies, pain relief was sustained for more than 7 years); over time, the response declines to about 50%.<sup>95,101</sup> Mortality for these procedures is about 3% in experienced hands.

**Table 8 Enzyme Supplements for Chronic Pancreatitis**

<i>Preparation</i>	<i>Units of Lipase per Tablet or Capsule</i>
Nonenteric-coated (conventional) preparations	—
Viokase 8, 16	8,000 and 16,000, respectively
Kuzyme-HP	8,000
Generic pancrealipase	8,000
Enteric-coated preparations	—
Creon 10, 20	10,000 and 20,000, respectively
Pancrease MT 4, 10, 16	4,000, 10,000, and 16,000, respectively
Ultrase MT 6, 12, 18, 20	6,000, 12,000, 18,000, and 20,000, respectively

## Steatorrhea

The pancreas possesses a 90% functional reserve for the secretion of digestive enzymes.<sup>84</sup> Hence, only 10% of normal maximal output of enzymes is needed to prevent malabsorption of nutrients. Steatorrhea is therefore a late complication of chronic pancreatitis requiring the presence of substantial pancreatic damage. Steatorrhea takes, on average, 13 and 26 years to develop after a diagnosis of alcoholic and idiopathic chronic pancreatitis, respectively.<sup>79</sup> Fat malabsorption tends to occur earlier than protein or carbohydrate malabsorption. Steatorrhea is most precisely established by measuring fecal fat excretion over 72 hours while the patient is on a diet that contains 100 g of fat a day. This test, however, is cumbersome to perform and unpleasant for both patient and staff. In practice, steatorrhea is more commonly diagnosed by identification of clinical features of oily or floating stool, diarrhea, and weight loss and is confirmed by the response to pancreatic enzyme supplementation. Unlike for the treatment of pain, enteric-coated enzyme preparations are commonly selected over non-enteric-coated preparations for the treatment of steatorrhea because of the higher potency and the need for fewer pills with the enteric-coated agents. However, non-enteric-coated enzyme preparations can be used effectively to treat steatorrhea if they are administered in sufficient doses and coadministered with an agent that reduces gastric acid. At least 30,000 units of lipase must be delivered to the small intestine during the prandial and postprandial period to reduce steatorrhea to a manageable level [see Table 8]. The clinical goal of this enzyme replacement therapy is to reduce the diarrhea and the losses in stool of fat, protein, and carbohydrate, thereby allowing maintenance or improvement of weight and nutritional status. In patients who do not achieve these end points, explanations for therapeutic failure need to be considered. Such explanations include patient noncompliance, inadequate dosage of enzyme therapy, destruction of exogenous enzymes by gastric acid (if non-enteric-coated preparations were prescribed), poor diet (particularly in chronic alcoholics), and the presence of a second disease causing malabsorption (e.g., small bowel bacterial overgrowth).<sup>102</sup>

## Endocrine Insufficiency

Diabetes mellitus, like steatorrhea, is a late complication of chronic pancreatitis. Progressive destruction of the islets of Langerhans can destroy both insulin- and glucagon-secreting cells. The inadequate glucagon reserves predispose patients with this disorder to treatment-induced hypoglycemia. Complications of diabetes such as neuropathy, retinopathy, and nephropathy occur at the same rate as in other patients with diabetes mellitus.<sup>103</sup> Therapy is usually directed at controlling urinary losses of glucose rather than at maintaining tight control of blood glucose levels. Overvigorous attempts at tight control of blood glucose levels are often associated with disastrous complications of treatment-induced hypoglycemia.<sup>104</sup> However, attempts at tight control of blood glucose levels are indicated in patients with hyperlipidemic pancreatitis because in this group, the diabetes is usually a primary illness and tight control of blood glucose levels makes control of serum lipid levels possible.

## Other Complications

**Pancreatic pseudocyst** In chronic pancreatitis, as in acute pancreatitis [see Acute Pancreatitis, Treatment of Complications, *above*], asymptomatic pseudocysts less than 6 cm can be safely observed. However, unlike in acute pancreatitis, most pseudocysts that occur in the setting of chronic pancreatitis are general-

ly mature at the time of their diagnosis, and therapy therefore need not be delayed if therapy is indicated. Symptomatic, complicated, or enlarging pseudocysts require therapy by percutaneous, endoscopic, or surgical techniques. Surgical therapy usually involves cyst decompression into a loop of small bowel, and this is often coupled with a pancreatic duct drainage procedure (e.g., modified Puestow procedure). Surgical therapy has a long-term success rate of more than 90%, with an operative mortality of less than 3%.<sup>69,70,73</sup> Percutaneous tube drainage of pseudocysts is also a management option and is immediately successful in 95% of patients. The long-term success rate of percutaneous drainage is still unknown, but it is certainly less than that of surgical techniques. Endoscopic therapy has short-term success rates greater than 90%.<sup>69,70</sup> The limited number of studies that have evaluated the long-term success rate of endoscopic drainage suggest excellent results, with complete resolution of the pseudocyst observed in 90% of patients.<sup>69,70,105</sup>

Complicated pseudocysts may require specific types of therapy. An infected pseudocyst (pancreatic abscess) generally responds to antibiotics and drainage (e.g., endoscopic, percutaneous, or surgical). Bleeding from a pseudocyst may occur in small vessels in its wall or from an associated large arterial pseudoaneurysm. Bleeding from a pseudoaneurysm requires urgent angiography with embolization, sometimes followed by surgical therapy.<sup>58</sup> If no pseudoaneurysm is present on angiography, surgical therapy remains the best choice of therapy for bleeding pseudocysts. Some pseudocysts may rupture and produce a pancreatic fistula that drains into the peritoneal cavity (producing pancreatic ascites) or into the pleural space (producing a pancreatic pleural effusion). In such cases, patients may not complain of symptoms of chronic pancreatitis but may instead note abdominal distention or shortness of breath. The diagnosis can be established by documenting high levels of amylase in the leaked fluid, typically more than 4,000 U/L.<sup>73,106</sup> Treatment may require surgery, and ERCP is used preoperatively to delineate the location of the leak. In many patients, endoscopic therapy and placement of a stent across the fistula site will prove curative.

**Other cystic lesions** A number of other cystic lesions may occur in the pancreas, including true cysts and cystic neoplasms. Serous cystic neoplasms are benign, but mucin-producing cystic neoplasms may follow a more malignant course. Mucinous cystic neoplasms present as large cystic collections (cystadenomas and cystadenocarcinomas) and may be relatively asymptomatic. Most cystic neoplasms occur in middle-aged patients, particularly in women.<sup>107</sup> They are often mistaken for pseudocysts and inappropriately treated as such. These cystic neoplasms may follow an initially benign course; but when they undergo malignant degeneration, they have poor outcomes equivalent to those of standard adenocarcinoma.

The presence of a pancreatic cystic collection in a middle-aged person (particularly female) without a previous history of pancreatitis should immediately suggest a cystic neoplasm, not a pseudocyst. The diagnosis of a cystic neoplasm requires histologic evidence of epithelial or neoplastic tissue in the cyst wall. Analysis of the cyst fluid obtained by EUS is becoming a highly useful method of differentiating pseudocysts from cystic neoplasms.<sup>108</sup> When these cystic collections are mistaken for pseudocysts, they are treated with drainage, and no tissue is obtained to allow differentiation of a cystic neoplasm from a pseudocyst. Therefore, the therapy of choice for cystic neoplasms is surgical resection, not drainage.

Intraductal papillary mucinous tumors (IPMT, formerly called mucinous ductal ectasia) are characterized by superficially spreading neoplastic tissue along the wall of the pancreatic duct. This neoplastic tissue produces mucin, and patients usually present with a markedly dilated pancreatic duct filled with gelatinous mucin. The appearance is often pathognomonic on ERCP but is occasionally mistaken for chronic pancreatitis. The natural history of the lesions is variable. In general, resection is attempted if the patient is a fit surgical candidate. Depending on the extent of the neoplastic tissue along the pancreatic duct, extensive resection may be needed to eliminate the lesion.<sup>109</sup>

**Pancreatic cancer** Chronic pancreatitis is a risk factor for pancreatic carcinoma, and the two diseases can be difficult to distinguish in some patients. The risk is about 4% after 20 years of disease.<sup>110</sup> The cancer risk may be as high as 40% in patients with hereditary chronic pancreatitis.<sup>7</sup> There is no effective method of surveillance in these patients and no absolutely reliable method to distinguish cancer from chronic pancreatitis. EUS with directed biopsy, ERCP with cytologic brushings, CT scan, and tumor markers such as CA19-9 are most commonly used.

**Common bile duct or duodenal obstruction** Fibrosis and inflammation in the head of the pancreas may compress surrounding hollow structures, particularly the common bile duct and duodenum. Compression of the common bile duct produces jaundice, and duodenal compression produces symptoms similar to those of gastric outlet obstruction. Both duodenal compression and gastric outlet obstruction generally require surgical repair with a biliary bypass or gastrojejunostomy, respectively.

*Peter Draganov, M.D., has no commercial relationships with manufacturers of products or providers of services discussed in this chapter.*

*Chris E. Forsmark, M.D., F.A.C.P., has received grants for clinical research from AstraZeneca Pharmaceuticals LP and TAP Pharmaceutical Products, Inc., and has received grants for educational activities from Cook Endoscopy and the Olympus Corporation.*

*Octreotide acetate and pancreatic enzymes discussed in this chapter have not been approved by the FDA for use in the treatment of chronic pancreatic pain.*

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