

Acute Pancreatitis: Etiology, Clinical Presentation, Diagnosis, and Therapy

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A clinical review of acute pancreatitis is important and timely. First, acute pancreatitis is a common disease that causes significant morbidity and mortality. More than 300,000 patients are admitted per year for pancreatitis [1], and about 20,000 die from this disease per year in the United States [2]. Second the clinician needs to be educated about major recent advances in this field. For example, new insights have been developed into the pathophysiology and clinical presentation of autoimmune pancreatitis and genetic forms of pancreatitis. Third, clinicians may underdiagnose pancreatitis at the extremes of the clinical spectrum of very mild and very severe disease [3,4]. Missed mild disease can result in failed opportunities to prevent recurrent attacks, whereas failure to recognize a fulminant attack can result in otherwise preventable mortality. This article provides a comprehensive review of this subject with a focus on the clinical management of acute pancreatitis, including new insights into the pathophysiology, diagnosis, and therapy.

Clinical presentation

Symptoms

Abdominal pain is the cardinal symptom. It occurs in about 95% of cases. Typically it is generalized to the upper abdomen, but it may be more localized to the right upper quadrant, epigastric area, or, occasionally, left upper quadrant. The pain typically occurs acutely, without a prodrome, and rapidly reaches maximum intensity. It tends to be moderately to intensely severe and tends to last for several days. The pain typically is boring and deep because of the retroperitoneal location of the pancreas.

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It often radiates in a bandlike manner to the lower thoracic region of the back. The pain tends to be steady but is exacerbated by eating or drinking, especially the drinking of alcohol. Patients may lean forward or even curl up in a knee-to-chest (fetal position) to decrease the pain by decreasing the stretch of the pancreas. With biliary pancreatitis, the pain may be more localized to the right upper quadrant, more gradual in onset, and more variable in intensity over time because of the contribution of biliary colic. Although patients who have gastrointestinal perforation tend to be motionless, patients who have acute pancreatitis may be restless and agitated. About 90% of patients have nausea and vomiting, which can be severe and unremitting. The vomiting is related to peripancreatic inflammation extending to the posterior gastric wall and a localized or generalized ileus.

Physical examination

The severity of the physical findings depends on the severity of the attack. Mild disease presents with only mild abdominal tenderness. Severe disease presents with severe abdominal tenderness and guarding, generally localized to the upper abdomen. Rebound tenderness is unusual. Hypoactive bowel sounds, accompanied by epigastric distention, may be caused by peripancreatic spread of the inflammatory process that produces a generalized ileus, localized spread of the inflammation to the adjacent small intestine that produces a sentinel loop, or localized spread of the inflammation to the adjacent transverse colon that produces a colon cut-off sign. Tachycardia and mild hypotension may result from hypovolemia from sequestration of fluid in the pancreatic bed. About 60% of patients develop low-grade pyrexia from peripancreatic inflammation without evident infection. Patients may have shallow, rapid respirations from diaphragmatic inflammation, pleural effusions, and respiratory compromise.

Uncommon physical findings reflect specific complications. Unilateral dullness to percussion and decreased breath sounds at a lung base indicate a pleural effusion. Subcutaneous fat necrosis, or panniculitis, typically presents as tender, palpable, subcutaneous, red nodules that are 0.5 to 2 cm in diameter and most commonly occur along the distal extremities. Ecchymoses in the flanks, called "Gray-Turner's sign," indicate retroperitoneal hemorrhage from hemorrhagic pancreatitis, whereas ecchymoses in the periumbilical region, called "Cullen's sign," indicate intra-abdominal hemorrhage [5]. Jaundice suggests choledochal obstruction from gallstone pancreatitis.

Laboratory tests

Leukocytosis is common because of a systemic inflammatory response. Mild hyperglycemia is common because of decreased insulin secretion and increased glucagon levels. The serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels sometimes are mildly elevated

in alcoholic pancreatitis but frequently are significantly elevated in biliary pancreatitis. An ALT level higher than 150 IU/L (approximately threefold or more above normal) therefore suggests biliary rather than alcoholic pancreatitis. In a meta-analysis, a serum ALT level higher than 150 IU/L had a positive predictive value of 95% in diagnosing acute gallstone pancreatitis [6].

Serum lipase

The serum lipase level generally is the primary diagnostic marker for acute pancreatitis because of high sensitivity and specificity. The serum lipase assay has become more reliable with the recent incorporation of colipase. Serum lipase now is more than 90% sensitive for acute pancreatitis [7]. The serum lipase level rises early in pancreatitis and remains elevated for several days. It may increase up to twofold above normal with renal failure, however, because of decreased renal excretion and increase up to threefold with intestinal inflammation or perforation because of leakage of lipase from the intestine.

Serum amylase

The serum amylase level was the traditional, standard diagnostic blood test. The serum amylase level increases during acute pancreatitis from leakage from the inflamed pancreas into the bloodstream and from decreased renal excretion. Although serum amylase is a very sensitive diagnostic test, hyperamylasemia has insufficient specificity. Many disorders cause mild to moderate hyperamylasemia (Table 1), but an amylase level more than three times above normal is highly specific for pancreatitis. The serum amylase level is insensitive in three uncommon situations: in delayed clinical presentation, because the serum amylase normalizes after several days of pancreatitis; in pancreatitis resulting from hypertriglyceridemia, which typically produces minimally or mildly elevated serum amylase levels, possibly because of the dilutional effects of the lipemia; and in acute-on-chronic alcoholic pancreatitis in which the amylase level rises only modestly because of pre-existing pancreatic injury [8]. Macroamylasemia produces hyperamylasemia without clinical pancreatitis because of large multimers of amylase complexed with immunoglobulin A. These large molecules are not filtered and excreted by the kidney, so the urinary amylase level and fractional excretion of amylase is low.

Other serum tests

Other pancreatic enzymes that leak from the pancreas during pancreatitis and accumulate in the serum include phospholipase A, trypsin, trypsinogen-2, and carboxyl ester lipase. The acutely inflamed pancreas also overproduces pancreatitis-associated protein and trypsinogen activation peptide [9]. These laboratory tests are experimental and are not used routinely for diagnosis because of the excellent sensitivity and specificity of the standard serum lipase test [10].

Table 1
Causes of hyperamylasemia aside from acute pancreatitis

Other disorders	Cause	Differentiating characteristics
Macroamylasemia	The high molecular weight polymer of amylase in macroamylasemia is not excreted by the kidneys, resulting in a very high serum amylase level.	With macroamylasemia, the amylase-to-creatinine renal clearance is less than 1% because of minimal renal clearance of macroamylase.
Renal failure	Amylase accumulates in serum because of the lack of renal clearance.	An amylase level more than three times normal is relatively specific for pancreatitis even in the presence of renal insufficiency.
Mumps parotitis	Salivary amylase increases because of inflammation of the salivary glands.	Can fractionate serum amylase into the salivary and pancreatic portions; in practice, the serum lipase is used to diagnose acute pancreatitis when mumps is in the differential.
ERCP-induced hyperamylasemia	Hyperamylasemia very common after ERCP because of pancreatic trauma.	Pancreatitis is diagnosed only by the presence of significant abdominal pain and hyperamylasemia after ERCP.
Esophageal perforation	Extra-esophageal leakage of salivary amylase with esophageal perforation	Interpret an elevated amylase level in conjunction with the clinical presentation; hyperamylasemia may be a valuable clue to esophageal perforation.
Pregnancy	Serum amylase is only mildly increased during pregnancy.	A significantly elevated amylase level retains its diagnostic value during pregnancy.

Abbreviation: ERCP, endoscopic retrograde cholangiopancreatography.

Radiologic tests

Abdominal radiography

Any patient who has unexplained, severe abdominal pain should undergo supine and upright chest and abdominal radiographs or, if available, abdominal CT. Abdominal radiographs are performed mainly to exclude alternative abdominal diseases, such as gastrointestinal perforation, but may indicate findings suggestive of pancreatitis. Intestinal loops may be generally dilated from a generalized ileus. A severe ileus may produce multiple air-fluid levels. In a sentinel loop, bowel is focally dilated proximally because of spasm of distal bowel overlying the inflamed pancreas [11]. Similarly, in the colon cut-off sign the mid-transverse colon is dilated focally because of extension of peripancreatic inflammation and bowel spasm at the splenic flexure [12]. Edema and inflammation of the pancreatic head may manifest as widening of the C-loop (descending duodenum) that frames the medial border of the pancreas. Occasionally, visualization of calcifications in the gallbladder suggests gallstone pancreatitis.

The chest roentgenogram may reveal a pleural effusion that is more common on the left side [13]. Other abnormalities on a chest roentgenogram include elevation of the left hemidiaphragm, basal atelectasis, and pulmonary infiltrates [14].

Abdominal ultrasonography

Abdominal ultrasonography is the primary imaging study for abdominal pain associated with jaundice and for excluding gallstones as the cause of acute pancreatitis. It has the advantages of low cost, ready availability, and easy portability for bedside application in very sick patients. It thus is ubiquitous in the evaluation of pancreatitis. When adequately visualized, an inflamed pancreas is recognized as hypoechoic and enlarged because of parenchymal edema. The pancreas is visualized inadequately in 30% of cases, however, either because of the presence of overlying intestinal gas, particularly with a localized ileus, or because the presence of fat in the abdominal wall limits penetration of the acoustic waves [15]. Abdominal ultrasound is about 95% sensitive for the detection of cholecystolithiasis but is only about 50% sensitive for the detection of choledocholithiasis [16]. Abdominal ultrasound is less accurate than CT in delineating peripancreatic inflammation and detecting intrapancreatic necrosis.

Abdominal CT

Patients who present with severe pancreatitis or who present initially with mild to moderate pancreatitis that does not improve after several days of supportive therapy should undergo abdominal CT. For optimal sensitivity, patients should receive both intravenous and oral contrast. Intravenous contrast is contraindicated in the presence of renal insufficiency. Abdominal CT is highly useful to determine the severity and complications of pancreatitis. Pancreatic inflammation is recognized reliably as pancreatomegaly, a smooth pancreatic margin, parenchymal inhomogeneity, peripancreatic fluid, or peripancreatic inflammation visualized as peripancreatic streakiness or “dirty” fat. Most importantly, dynamic CT demonstrates necrotic or poorly perfused pancreatic parenchyma as areas that fail to enhance, with a density of less than 50 Hounsfield units, after intravenous contrast administration.

The severity of abnormalities on an unenhanced CT is graded quantitatively and is combined with the severity of pancreatic necrosis on an enhanced CT to form the CT severity index (Table 2) [17,18]. This index has important prognostic implications, as described later [19].

Nonstandard imaging tests

MRI has had limited application for diagnostic imaging of acute pancreatitis because it is less available, more cumbersome, and more expensive than CT. It has advantages in selected patients, however, such as those who are pregnant (because of the radiation teratogenicity of CT), those who are allergic to the contrast used for enhanced CT, and those who

Table 2

Quantitative determination of the severity of CT findings based on noncontrast and contrast findings

CT severity index ^a	Points
1. Grade of acute pancreatitis based on noncontrast CT findings	
A Normal pancreas	0
B Focal or diffuse enlargement, including contour irregularities and inhomogeneous parenchymal attenuation	1
C Grade B plus peripancreatic inflammation	2
D Grade C plus a single fluid collection	3
E Grade C plus two or more fluid collections or retroperitoneal gas	4
2. Degree of pancreatic necrosis based on contrast CT findings	
A No pancreatic necrosis	0
B Necrosis of up to one third of pancreas	2
C Necrosis of up to one half of pancreas	4
D Necrosis of more than one half of the pancreas	6

^a CT severity index = 1 (grade points) + 2 (degree of necrosis).

Data from Balthazar EJ, Robinson DL, Megibow AJ, et al. Acute pancreatitis: value of CT in establishing prognosis. *Radiology* 1990;174(2):331-6; and Balthazar EJ, Freeny PC, van Sonnenberg E. Imaging and intervention in acute pancreatitis. *Radiology* 1994;193(2):297-306.

have renal insufficiency that can be exacerbated by the iodinated contrast used for enhanced CT. It has advantages in all patients, in that magnetic resonance cholangiopancreatography (MRCP) delineates the bile and pancreatic ducts better than CT and has a higher sensitivity in detecting choledocholithiasis. In a recent meta-analysis, MRCP had 90% sensitivity and 95% specificity for detecting choledocholithiasis [20]. MRI may prove to be superior to CT in the characterization of pancreatic fluid collections. MRCP is used currently to detect choledocholithiasis before therapeutic endoscopic retrograde cholangiopancreatography (ERCP).

Endoscopic ultrasound is somewhat more sensitive than MRCP in detecting choledocholithiasis. It is useful in patients who are pregnant because of its relative safety during pregnancy and in patients who cannot undergo MRCP, such as patients who have internal metallic devices. ERCP with sphincterotomy is essential for the diagnosis and therapy of symptomatic choledocholithiasis and is valuable for determining the cause of recurrent acute pancreatitis of unknown origin. Cholescintigraphy is highly useful to diagnose acute cholecystitis, where it is the test of choice, but it provides limited information about the bile ducts and is not indicated in the evaluation of suspected choledocholithiasis [21].

Clinical predictors of diseases severity

Determination of the severity of pancreatitis is important for early recognition of pancreatic complications, triage of patients to higher levels of care such as an ICU, therapeutic decisions, and prognostication. The serum lipase and amylase levels are poorly correlated with disease severity and

lack prognostic significance. The experienced clinicians' clinical impression, based on their informal evaluation of the vital signs, respiratory distress, renal insufficiency, other evidence of organ failure, and abnormal laboratory tests, is fairly specific but relatively insensitive in determining disease severity and predicting complications. Laboratory values that suggest severe disease include leukocytosis, elevated C-reactive protein, and elevated trypsinogen activation peptide [22].

Formal clinical scoring systems improve the accuracy of determining disease severity. The Ranson criteria distinguish between mild and severe pancreatitis with about 80% accuracy [23]. The Ranson criteria, however, require evaluation of 11 parameters over 48 hours. The APACHE II scale has advantages in that it can be performed on admission, can be re-evaluated at any time during the patient's hospitalization, and is applicable to any medical illness. It incorporates 11 physiologic variables in addition to the patient's age, organ insufficiency, neurologic status (as determined by the Glasgow coma scale), and postoperative state. It is a fairly reliable indicator of disease severity and is a robust predictor of complications. It is, however, cumbersome to use clinically.

The CT severity index includes findings of inflammation with noncontrast CT and findings of necrosis with contrast CT. It provides important information about the severity of pancreatitis and the prediction of complications and mortality. Gurleyik and colleagues [24] found a sensitivity of 85% and a specificity of 98% in predicting severe pancreatitis based solely on this index. In one study, patients who had a severity index less than three had only a 4% morbidity rate and no mortality, whereas patients who had a severity index of more than six had a 92% morbidity rate and a 17% mortality [17]. In other studies, patients who had a CT severity index greater than five were eight times more likely to die, 17 times more likely to have a prolonged hospital course, and 10 times more likely to require necrosectomy than patients who had a severity index less than five [25–27].

Established causes of pancreatitis

Determining the cause of pancreatitis is an essential component of the diagnostic evaluation. First, the cause vitally affects the therapy. An etiologic diagnosis can result in elimination of the precipitating factor and prevention of disease recurrence. Second, different causes have different natural histories with different complications (eg, alcoholic versus biliary pancreatitis). Third, certain causes of pancreatitis have long-term consequences (eg, pancreatic cancer associated with hereditary pancreatitis).

The causes are listed in **Box 1**. About 75% of all cases are caused by gallstones or alcoholism. The relative rate of gallstones versus alcoholism as the cause critically depends on the age of the patient and the catchment area. With thorough evaluation the cause of pancreatitis can be identified in perhaps another 10% of cases, leaving about 15% of cases as idiopathic.

Box 1. Causes of acute pancreatitis**Well-established causes**

- Gallstones
- Alcoholism
- Hypertriglyceridemia
- Post-endoscopic retrograde cholangiopancreatography
- Drug induced
- Autoimmune
- Genetic
- Abdominal trauma
- Postoperative
- Ischemia
- Infections
- Hypercalcemia and hyperparathyroidism
- Posterior penetrating ulcer
- Scorpion venom
- Pancreas divisum with ductular narrowing on pancreatogram
- Idiopathic

Controversial causes

- Sphincter of Oddi dysfunction
- Pancreas divisum without ductal narrowing on pancreatogram
- Microlithiasis/sludge

Gallstones

Gallstones cause about 40% of cases of pancreatitis [28]. Proposed mechanisms include reflux of noxious bile into the pancreatic duct from transient obstruction of the ampulla during gallstone passage and pancreatic ductal hypertension from either a stone impacted at the ampulla [29] or ampullary trauma caused by stone passage [30]. Gallstone pancreatitis is reviewed extensively in the article by Attasaranya and colleagues in this issue.

Other obstructive causes of pancreatitis

Obstructive causes of pancreatitis, in addition to gallstones, include pancreas divisum, sphincter of Oddi stenosis, periampullary tumors, pancreatic cancer, parasites, and clots [31]. Pancreatic cancer occasionally can cause acute pancreatitis because of temporary duct obstruction by clots within the pancreatic duct and occasionally can mimic chronic pancreatitis because of chronic malignant obstruction of the pancreatic duct [32]. Intraductal papillary mucinous neoplasm is a rare pancreatic tumor characterized by intraductal proliferation of mucin-producing cells that secrete mucin into the ducts. This tumor often presents with recurrent episodes of acute

pancreatitis caused by temporary pancreatic duct obstruction by the excreted highly viscous mucus [33]. Other important obstructive causes are discussed later under their individual headings.

Alcoholism

Alcoholism is responsible for about 35% of cases of acute pancreatitis [28]. The pathophysiology may be multifactorial. Proposed mechanisms include sphincter of Oddi spasm, precipitation of insoluble protein plugs that obstruct the pancreatic ductules, activation of pancreatic proteases, and overstimulation of pancreatic secretion by cholecystokinin [34]. Alcoholic pancreatitis generally requires drinking more than eight alcoholic drinks/day (> 100 g/d) for more than 5 years [34,35].

Only 5% to 10% of alcoholics develop acute pancreatitis [36]. This low rate argues that genetic or environmental cofactors are important in developing alcoholic pancreatitis. Smoking is an important cofactor. For example, in a retrospective study of 129,000 subjects enrolled at Kaiser Permanente, the relative risk of alcoholic pancreatitis was 4.9 (confidence interval [CI], 2.2–11.2; $P < .001$) in smokers compared with nonsmokers [37]. Mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*), *PRSS1*, and *SPINK1* (serine protease inhibitor kazal type 1) genes are associated with genetic pancreatitis. Their role as cofactors in the development of alcoholic pancreatitis is controversial, however, because only 10% of patients who have alcoholic pancreatitis have mutations in any of these genes [38]. For example, mutation of the *SPINK1* gene, the most common mutation, occurs in only about 8% of patients who have chronic alcoholic pancreatitis [38–40].

Alcoholic pancreatitis predominantly affects males (male: female ratio = 2.5:1), occurs predominantly in young adults (approximate mean age, 35 years [41]), and occurs more frequently in American blacks than in whites (relative risk, 2.6; 95% CI, 1.8–3.9) [37]. Pain is the predominant symptom of alcoholic pancreatitis [42]. Acute alcoholic pancreatitis, unlike biliary pancreatitis, tends to occur in a pancreas already damaged by prior alcohol-induced pancreatotoxicity and frequently results in the development of chronic pancreatitis. In one study, for example, about 70% of patients developed chronic pancreatitis 10 years after an initial episode of acute alcoholic pancreatitis [43]. Abstinence from alcohol retards the progression to chronic pancreatitis [44].

Hypertriglyceridemia

Hypertriglyceridemia causes about 2% of cases of acute pancreatitis [45]. A serum triglyceride level greater than 1000 mg/dL suggests this possible cause, and a triglyceride level greater than 2000 mg/dL is diagnostic [46]. Alcoholic pancreatitis sometimes is associated with an elevated serum triglyceride level caused by acute alcoholism, but this elevation generally is mild and rarely is higher than 1000 mg/dL [47]. The triglyceride level should be

measured early after clinical presentation with pancreatitis, because this level tends to decline rapidly during the hospitalization due to fasting, insulin therapy, and restoration of fluid and electrolyte balance. The serum in patients who have hypertriglyceridemia may be opalescent because of increased very low density lipoprotein or milky because of hyperchylomicronemia [45].

Free fatty acids produced by triglyceride metabolism are believed to be pancreatotoxic and to cause the pancreatitis. Pancreatitis from hypertriglyceridemia in childhood usually stems from congenital types I, II, and V hyperlipidemia. Adults can develop an acquired hypertriglyceridemia because of alcoholism, obesity, poorly controlled diabetes mellitus, and hypothyroidism in association with a mild form of genetically inherited type I or V hyperlipidemia.

Patients have the typical symptoms of pancreatitis, including abdominal pain and nausea and vomiting. For example, among 70 patients, 100% had abdominal pain, and 91% had nausea and vomiting [45]. Patients typically have only minimal to mild elevations of the serum amylase, possibly because of hemodilution of the amylase in the lactescent serum. For example, among 70 patients, only one half had a serum amylase level more than two times normal, and only two thirds had a serum lipase level more than two times normal [45]. Pancreatitis from hypertriglyceridemia is not more severe than pancreatitis from other causes [45]. Patients who have severe pancreatitis and profound hypertriglyceridemia ($>10,000$ mg/dL) may benefit from plasmapheresis [48,49]. After recovering from this pancreatitis, the patient should be placed on a lipid-lowering regimen including a low-fat diet, regular exercise regimen, tight control of diabetes, avoidance of alcohol, and possibly lipid-lowering drugs such as statins, fibrates, niacin, and fish oil [50,51]. Reducing the serum triglyceride level towards normal prevents recurrent pancreatitis.

Pancreatitis after endoscopic retrograde cholangiopancreatography

About 2% of cases of pancreatitis are caused by ERCP. Pancreatitis is the most common complication of ERCP. Pancreatitis occurs in approximately 5% of ERCPs, with a range from 2% to 7% depending on the criteria for defining the pancreatitis, the type of procedure, and the experience of the endoscopist [52,53]. Although typically mild, 5% to 10% of cases after ERCP are severe, as defined by prolonged hospitalization or development of complications [52]. Pancreatitis is diagnosed reliably after ERCP by abdominal pain that is consistent with pancreatitis, that is associated with an at least a threefold increase in the serum lipase or amylase level, and that requires hospitalization or extending the length of hospitalization in an already hospitalized patient [54]. Mild to moderate elevations of the serum amylase and lipase levels are common after ERCP and do not, by themselves, constitute clinical pancreatitis. For example in a study of 513 patients, 85 patients (16.5%) developed hyperamylasemia after ERCP, but only 17 patients (3.3%) had clinical pancreatitis [55].

Two pathophysiologic theories have been proposed, and the two mechanisms may act synergistically. First, traumatic intubation of the ampulla can cause sphincter spasm, delayed pancreatic drainage, and pancreatic duct hypertension. This theory is supported by the increasing incidence of pancreatitis with increasing number of failed pancreatic duct cannulations, presumably from increased ampullary trauma. For example, in a prospective study of 1223 patients, only 3.3% of patients who had five or fewer attempted cannulations developed pancreatitis, whereas 14.9% of patients who had 20 or more attempted cannulations developed pancreatitis [56]. This theory is also supported by the increased risk of pancreatitis after ERCP, presumably caused by greater ampullary trauma, when gastroenterology fellows are involved in a procedure compared with a procedure performed exclusively by attending physicians [57]. This theory is supported strongly by the dramatic reduction in risk of pancreatitis after ERCP with prophylactic deployment of a transpapillary pancreatic duct stent in high-risk patients. For example, in a meta-analysis of five randomized, prospective trials including 481 patients, only 5.8% of patients who had a prophylactic stent developed pancreatitis, whereas 13.1% of patients who did not receive a stent developed pancreatitis. Moreover, all seven cases of severe pancreatitis in this review occurred in patients who did not receive a prophylactic stent [52].

Second, excessive hydrostatic pressure during contrast injection may injure the pancreatic duct and parenchyma. This theory is supported by the markedly increased risk of postprocedure pancreatitis with acinarization (visualization of the secondary radicles of the pancreatic duct) during contrast injection, presumably caused by excessive hydrostatic forces [52,58], and by the markedly reduced risk of pancreatitis (from 32% to 4% in one study) with the use of aspirating rather than nonaspirating continuous perfusion manometric catheters within the pancreatic duct [59].

The risk of ERCP-induced pancreatitis is reduced by the techniques listed in Box 2 [53,56,57,59–64]. The protease inhibitors gabexate or ulinastatin [65] and the inhibitors of pancreatic secretion somatostatin or octreotide have been proposed as prophylactic agents to prevent pancreatitis after ERCP [66]. The data on these agents are conflicting, and these agents currently are considered as experimental for prophylaxis [52]. The clinical management of this pancreatitis generally is similar to that for pancreatitis of other causes [67].

Drug-induced pancreatitis

Drugs are responsible for about 2% of cases of pancreatitis [68]. Commonly implicated drugs are listed according to their postulated mechanisms of pancreatic injury in Box 3 [69–81]. Drug-induced pancreatitis tends to be mild and self limited. Aside from the general supportive measures, cessation of the offending drug is critical.

Box 2. Techniques to reduce the risk of ERCP-induced pancreatitis*Patient selection*

Avoid solely diagnostic ERCPs. Replace diagnostic ERCPs with less invasive, low-risk tests such as MRCP. Perform ERCP only when therapy is contemplated [60].

Endoscopist selection

Select an experienced endoscopist who performs a high volume of ERCPs [53].

Avoid having a gastroenterology fellow attempt numerous cannulations [57].

Procedure technique

Limit the number of attempted cannulations of the pancreatic duct [53,56].

Limit the number of contrast injections into the pancreatic duct [61].

Limit the force of injection into pancreatic duct (avoid acinarization) [62].

Avoid excessive trauma to the ampulla during cannulation [56].

Use adequate patient sedation (current report).

Specialized procedure considerations

When performing sphincter of Oddi manometry, use a manometry catheter that permits duct aspiration [59].

Avoid precut sphincterotomy unless absolutely necessary [61].

Place a transpapillary pancreatic duct stent in high-risk patients or procedures (eg, manometry for suspected sphincter of Oddi dysfunction) [63].

Avoid balloon sphincterotomy unless absolutely necessary [64].

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

An association between a drug and pancreatitis is strengthened by the number of reported cases, the number of independent reports, and the quality of these individual cases. The strength of an association between a drug and pancreatitis in a specific case is established by the occurrence of pancreatitis during drug exposure, exclusion of other causes, resolution of pancreatitis after drug discontinuation, and recurrence of pancreatitis with drug rechallenge [82]. Rechallenge with a drug that previously caused a hypersensitivity reaction in the pancreas may cause fulminant pancreatitis, however.

Box 3. Drugs commonly implicated as causes of pancreatitis and their postulated mechanisms*Drug-induced hypersensitivity reaction*

5-Aminosalicylic acid/sulfasalazine [69]

Azathioprine [70]

6-Mercaptopurine [71]

Metronidazole [72]

Tetracycline [73]

Toxic metabolite

Pentamidine [74]

Valproic acid [75]

Didanosine [76]

Drug-induced hypertriglyceridemia

Thiazides [77]

Isoretinoin [78]

Tamoxifen [79]

Overdose reaction

Acetaminophen [80]

Erythromycin [81]

Autoimmune pancreatitis

Autoimmune pancreatitis presents with characteristic clinical, pathologic, and radiologic findings. Patients often present with a subacute pancreatitis with jaundice, a lymphoplasmocytic infiltrate on pathologic examination of a pancreatic biopsy, a focal mass in the pancreatic head on CT, and irregular narrowing of the proximal pancreatic duct on ERCP. Patients characteristically have elevated IgG4 levels in the serum and an infiltrate of IgG4-containing plasma cells in the pancreas.

Patients tend to present with findings suggestive of chronic rather than acute pancreatitis. They often have mild abdominal discomfort and mildly elevated serum amylase and lipase levels [83,84]. Pancreatic cancer often is in the differential diagnosis because of frequent findings of a focal mass in the head of the pancreas and narrowing of the proximal pancreatic duct. Corticosteroids are the therapy of choice. They generally produce rapid relief of symptoms, normalize the laboratory parameters, reverse the inflammatory process, and resolve the radiographic abnormalities [85,86].

Genetic causes of pancreatitis

Mutations of several genes can cause pancreatitis. Hereditary pancreatitis is associated with mutations in the trypsinogen gene *PRSS1* that promotes

premature conversion of trypsinogen to active trypsin that causes pancreatic autodigestion. This relatively rare genetic syndrome is characterized clinically by development of pancreatitis at a very young age, subsequent gradual development of chronic pancreatitis, a high risk of developing pancreatic cancer, and a strong family history [87].

Mutations in *SPINK1*, a gene that encodes for a pancreatic trypsin inhibitor, are associated with acute and chronic pancreatitis resulting from an impaired ability to counteract the effects of activated trypsin within pancreatic acinar cells. Patients who have severe *SPINK1* mutations typically develop chronic pancreatitis in childhood [88]. Such mutations are a common cause of chronic pancreatitis in childhood. For example, in a series of 96 children who had chronic pancreatitis, 23% had *SPINK1* mutations [89]. Two percent of healthy adults who do not have pancreatitis do have *SPINK1* mutations, however, suggesting that such mutations predispose a person to the development of, but do not necessarily cause, pancreatitis [90,91].

Severe homozygote mutations of the *CFTR* gene cause cystic fibrosis. Patients who are compound heterozygotes for mild *CFTR* gene mutations have a 40- to 80-fold increased risk of developing chronic pancreatitis compared with the general population [92]. These patients do not develop other manifestations of cystic fibrosis, such as sinopulmonary disease, and have normal sweat chloride testing.

Abdominal trauma

Pancreatic injury occurs in about 0.2% of cases of blunt trauma and in about 1% of penetrating injuries [93,94]. These low rates result from the retroperitoneal location of the pancreas. This pancreatic injury can cause acute pancreatitis. The clinical manifestations of pancreatitis may be subtle. Pancreatitis should be suspected when patients who have experienced trauma over the region of the pancreas present with abdominal pain and nausea and vomiting associated with hyperamylasemia. The main pancreatic duct is vulnerable to disruption from blunt trauma as it crosses over the vertebral column. Duct rupture can cause pancreatic ascites from leakage of pancreatic juice. Less severe ductular injury can cause duct scarring and stenosis that manifests as obstructive pancreatitis distal to the stricture. Ductal rupture may be diagnosed noninvasively by abdominal CT or MR cholangiography and semi-invasively by ERCP. At ERCP, a damaged duct can be stented to prevent duct leakage or stricture [95].

Postoperative pancreatitis

The mechanisms of postoperative pancreatitis include transient intraoperative hypotension or pancreatic trauma caused by intraoperative pancreatic manipulation [96]. Intraoperative or postoperative medications may also cause pancreatitis. Percutaneous pancreatic biopsy [97] and renal lithotripsy [98] may cause traumatic pancreatitis.

Ischemia

Pancreatic ischemia is a rare cause of pancreatitis due to the rich perfusion of the pancreas from the superior and inferior pancreaticoduodenal arterial arcades derived from the celiac axis and the superior mesenteric artery [99]. **Box 4** lists reported causes of ischemic pancreatitis [96,100–113].

Infections

Immunocompetent patients

Mumps and coxsackie B virus are the most common causes of infectious pancreatitis [114–116]. Other viral causes include Hepatitis B, Cytomegalovirus, Herpes simplex, and Varicella zoster. Reported bacterial causes include *Mycoplasma*, *Salmonella typhosa*, *Leptospira*, and *Legionella*. Other infectious agents include *Aspergillus*, *Cryptosporidium*, and *Toxoplasma*. The *Ascaris* worm can produce pancreatitis by obstructing the pancreatic duct [117].

In a review of 32 definite cases of pancreatic infections, 69% of patients presented with clinical symptoms and signs of acute pancreatitis, and 64% presented with pyrexia. In 71% of cases, the patients had clinical findings that were characteristic for the specific infectious agent [115].

Immunosuppressed patients

Hyperamylasemia is common in patients who have AIDS, and most patients who have AIDS with hyperamylasemia do not have acute pancreatitis [118]. Opportunistic infections may involve the pancreas in patients who have AIDS. They often present as a pancreatic infection or abscess

Box 4. Causes of ischemic pancreatitis

Atheromatous embolism [100,101]

Vasculitis

 Systemic lupus erythematosus [102,103]

 Polyarteritis nodosa [104,105]

Hypotension

 Intraoperative hypotension [96]

 Hemorrhagic shock [106]

Drugs

 Ergotamine [107]

 Cocaine [108,109]

Hypercoagulable disorders

 Anticardiolipin (antiphospholipid) antibodies [110]

 Factor V Leiden mutation [111]

Transcatheter arterial embolization for hepatocellular carcinoma [112,113]

and less commonly present as acute pancreatitis. The most common pathogens are Cytomegalovirus [119] and *Mycobacterium avium intracellulare* [120]. Other micro-organisms include *Cryptococcus neoformans*, *Toxoplasma gondii*, *Mycobacterium tuberculosis*, *Pneumocystis carinii*, and *Candida* species [121]. Pancreatic infections often are associated with widespread or disseminated opportunistic infections in patients who have AIDS.

Opportunistic infections of the biliary tree in patients who have AIDS may present with a cholangiopathy that closely resembles idiopathic sclerosing cholangitis [122]. ERCP demonstrates irregular beading and strictures of the biliary tree. Commonly implicated infections include *Cryptosporidium*, *Mycobacterium avium intracellulare*, Cytomegalovirus, *Microsporidium*, and *Isospora* [122]. Drugs used to treat opportunistic infections associated with AIDS, such as trimethoprim or pentamidine [74], and drugs used to treat the HIV infection itself, such as didanosine [76], can cause pancreatitis.

Hypercalcemia

Hypercalcemia and primary hyperparathyroidism are associated with acute pancreatitis. For example, in a retrospective review of 1435 patients undergoing surgery for primary hyperparathyroidism, 40 patients (3.2%) had pancreatitis without any evident cause other than hypercalcemia [123]. Primary hyperparathyroidism causes somewhat less than 0.5% of all cases of pancreatitis. Proposed pathophysiologic mechanisms include calcium deposition within the pancreatic duct or trypsinogen activation induced by calcium [124]. Abrupt elevation of the serum calcium level may increase the risk of pancreatitis because of the conversion of trypsinogen to trypsin [125]. For example, rapid calcium infusion in rats leads to acute pancreatitis in a dose-dependent fashion [124].

Posterior penetrating duodenal ulcer

Rarely a posterior duodenal ulcer can penetrate into the pancreas and thereby cause acute pancreatitis [126]. This complication can produce significant hemorrhage [126]. This cause is rarely reported now because of improved medical therapy for duodenal ulcers.

Scorpion venom

The venom of two species of scorpions found in Trinidad and Brazil can induce pancreatitis after introduction into the bloodstream via a scorpion bite. The mechanism is massive cholinergic stimulation of the pancreas [127].

Controversial causes of pancreatitis

The following three etiologies occasionally definitely cause pancreatitis and are postulated to cause many cases of otherwise idiopathic pancreatitis.

For example, pancreas divisum is a definite cause of pancreatitis when associated with ductal obstruction as demonstrated by a proximally narrowed pancreatic duct and delayed emptying of injected contrast. Its pathophysiologic role is controversial in idiopathic pancreatitis in the 95% of cases of pancreas divisum without demonstrable ductular obstruction.

Pancreas divisum

Pancreas divisum occurs in about 7% of the healthy population [128]. During organogenesis, the proximal dorsal pancreatic duct normally regresses while the rest of the dorsal duct fuses with the ventral pancreatic duct to produce a single, continuous, relatively wide and long pancreatic duct that empties through the major papilla. In pancreas divisum, the normal fusion fails to occur: the dorsal duct drains most of the pancreas through the minor papilla, and the ventral duct drains only the head of the pancreas through the major papilla. Pancreas divisum is diagnosed by pancreatography. Injection of contrast through the major papilla at ERCP opacifies only the proximal ventral duct. Injection of contrast through the minor papilla demonstrates the dorsal pancreatogram. Pancreas divisum increasingly is diagnosed by MR pancreatography.

Pancreas divisum sometimes is associated with pancreatitis because of ductal hypertension from increased resistance to flow through a narrowed dorsal duct at its papillary origin. This mechanism is supported by findings of proximal narrowing and distal dilatation of the dorsal duct at pancreatography and by reports that most patients who have pancreatitis associated with pancreas divisum improve substantially after minor duct sphincterotomy and have lower rates of recurrent pancreatitis than untreated patients [129,130]. This association is controversial, however, because 95% of patients who have pancreas divisum do not suffer from pancreatitis [131]. This low risk of pancreatitis is explained by the relatively infrequency of ductal narrowing with pancreatic divisum.

Sphincter of Oddi dysfunction

The sphincter of Oddi is a segment of circular and longitudinal muscle 6 to 10 mm long that encircles the distal common bile duct and pancreatic duct. The sphincter maintains a resting (basal) pressure to maintain resistance to bile flow that permits the gallbladder to fill during fasting and that prevents retrograde reflux of duodenal contents into the choledochus. Sphincter relaxation permits coordinated release of bile and pancreatic secretions into the duodenum to digest intraluminal food contents and to neutralize the gastric acid conveyed to the duodenal lumen. The sphincter can exhibit stenosis caused by inflammation or fibrosis from pancreatitis, traumatic gallstone passage, or intraoperative trauma. This stenosis manifests at manometry as an elevated basal pressure (>40 mm Hg) that does not decline after administration of smooth muscle relaxants (fixed

stenosis) and at ERCP as delayed emptying of biliary or pancreatic duct contents [132]. "Sphincter of Oddi dyskinesia" refers to sphincter spasm or uncoordinated contractions. Manometric features include an elevated basal sphincter pressure that decreases dramatically with smooth muscle dilators such as glucagon, rapid bursts of sphincter of Oddi contractions, frequent retrograde phasic contractions, and a paradoxical increase in sphincter pressure after administration of cholecystokinin octapeptide [133].

Sphincter of Oddi dysfunction is a controversial cause of acute pancreatitis. In an animal model, transient sphincter contraction induced by local application of carbachol with simultaneous stimulation of pancreatic secretion induced by cholecystokinin/secretin caused pancreatic injury and hyperamylasemia characteristic of acute pancreatitis [134]. Functional pancreatic sphincter of Oddi dysfunction, according to the Rome III criteria, is suspected clinically by recurrent episodes of epigastric or right upper quadrant pain that last 30 minutes or longer, that progressively intensify to a steady level, that interfere with daily activities, that are not relieved by bowel movements or postural change, that are not relieved by antacids, and that are associated with an elevated serum lipase or amylase level [135]. Pancreatic sphincter of Oddi dysfunction in patients who have recurrent episodes of pancreatitis is classified into three types. In type I, patients have (1) serum amylase or lipase levels more than 1.5 times normal in association with abdominal pain, (2) a pancreatic duct that is dilated (>6 mm) in the pancreatic head, and (3) delayed drainage of contrast (>9 minutes) at ERCP. In type II, patients satisfy one or two these criteria. In type III, patients have none of these criteria [136]. Sphincter of Oddi dysfunction is detected at manometry in 92% of patients who have type I pancreatic sphincter of Oddi dysfunction but is detected in only 35% of patients who have type III sphincter of Oddi dysfunction [136].

Calcium-channel blockers, such as nifedipine, and nitrates have been used experimentally to reverse sphincter of Oddi hypertension and to reduce pancreatic symptoms [137,138]. Endoscopic pancreatic sphincterotomy has been used for pancreatitis associated with pancreatic sphincter of Oddi dysfunction proven by ERCP with manometry. In a series of 160 such patients, 64% had complete long-term resolution of symptoms after pancreatic sphincterotomy [139]. Pancreatic sphincterotomy should be undertaken only by expert endoscopists at specialized tertiary centers that frequently deal with this disorder.

Biliary sludge/microlithiasis

Biliary sludge is a viscous suspension of fluid that contains small stones, cholesterol monohydrate crystals, or calcium bilirubinate granules [140]. Sludge appears at ultrasonography as low-amplitude layers in the most dependent part of the gallbladder that shift with positioning and that do not exhibit acoustic shadowing [141]. Most patients who have biliary sludge are asymptomatic. Biliary sludge, however, is detected with increased

frequency in patients who have acute, otherwise idiopathic, pancreatitis. For example, in a series of 31 patients who had idiopathic acute pancreatitis, 23 patients (74%) had biliary sludge detected by ultrasonography or had cholesterol monohydrate or calcium bilirubinate crystals detected by biliary microscopy [142]. These findings have been confirmed in another study of 51 patients who had idiopathic pancreatitis [143]. Although controversial, many authorities recommend cholecystectomy for recurrent episodes of otherwise idiopathic pancreatitis associated with biliary sludge [144].

Therapy

Team approach

A team approach with specialist consultation and referral helps optimize the management of severe and complicated pancreatitis. The intensivist manages the general ICU care including invasive hemodynamic monitoring, aggressive fluid hydration, and management of cardiovascular, pulmonary, or renal failure. The radiologist can grade the severity of the pancreatitis according to the CT severity index. The gastrointestinal endoscopist performs ERCP with sphincterotomy as necessary. The gastrointestinal surgeon performs necrosectomy for infected pancreatic necrosis. An infectious disease specialist is involved in selecting the antibiotics for pancreatic infections. Ideally, a dedicated pancreatologist coordinates and supervises the care of severe pancreatitis at tertiary referral centers.

Triage

Almost all patients who have acute pancreatitis should be hospitalized for supportive therapy and optimal management, especially for the first episode of pancreatitis, in which there is a need to determine the specific cause. Occasionally patients who have chronic pancreatitis may be able to manage a smoldering episode of recurrent pancreatitis at home. Patients exhibiting early signs of organ failure should be monitored in an ICU. The three goals of therapy for acute pancreatitis are general supportive therapy to prevent complications, directed therapy for specific causes of pancreatitis, and early recognition and aggressive treatment of complications.

General supportive therapy

Patients who have acute pancreatitis generally are severely intravascularly depleted on presentation from the profound loss of intravascular fluid into the inflamed pancreas and abdomen. This hypovolemia can manifest clinically as hemoconcentration, hypotension, tachycardia, dry mucous membranes, poor skin turgor, and oliguria. Decreased pancreatic perfusion from hypovolemia can exacerbate pancreatic necrosis and can cause acute tubular necrosis [145]. Patients who have pancreatitis often are relatively

young and do not have cardiac disease. Such patients should be hydrated intravenously aggressively with 250 to 300 cm³/h of crystalloid solutions for the first 48 hours after admission.

The adequacy of the rehydration is monitored (Box 5). The hematocrit may decline mildly with rehydration because of hemodilution [146]. In patients who have mild to moderate pancreatitis, rehydration does not require invasive monitoring. In patients who have severe pancreatitis and unstable vital signs, a Foley catheter should be inserted to monitor urine output, and a central line should be used to monitor central venous pressure. Patients who have borderline cardiac function or respiratory failure may require a Swann-Ganz catheter to monitor fluid balance during aggressive hydration.

Patients without prior diabetes mellitus may experience moderate hyperglycemia during severe pancreatitis. The serum glucose level should be monitored carefully. Insulin should be administered cautiously because of volatility in the serum glucose level, the potential for a blunted pancreatic release of glucagon in response to hypoglycemia, and the frequently transient nature of the serum glucose abnormalities. Hypocalcemia commonly occurs with acute pancreatitis, particularly when the attack is severe [147].

Analgesia is essential. Traditionally, opiates are used because of their potency. Ideally, the administered opiate should not induce sphincter of Oddi hypertension that could exacerbate the pancreatitis. Morphine traditionally has been disfavored for acute pancreatitis because it increases the sphincter of Oddi pressure. For example, in a study of 19 healthy subjects, morphine increased the baseline sphincter pressure by threefold [148]. Meperidine, 50 to 100 mg every 3 hours, has been the traditional opiate regimen of choice because it does not raise the sphincter pressure [149]. For example, in a series of 47 patients evaluated by manometry, intravenous administration of meperidine did not alter the sphincter pressure significantly [150]. Meperidine can be administered safely for a few days but should not be administered long term at high dose (> 100 mg/3 h) because the accumulation of the metabolite normeperidine can cause agitation and,

Box 5. Noninvasive monitoring of the adequacy of rehydration

Blood pressure: hypotension, orthostasis

Pulse: tachycardia, orthostasis

Skin turgor

Moistness of mucous membranes

Azotemia: serum urea nitrogen and creatinine levels

Hematocrit: absence of hemoconcentration

Urine output

Urine sodium concentration

rarely, seizures [151]. Hydromorphone or fentanyl is a useful alternative in this situation [152]. The dose of analgesia should be monitored and titrated to achieve pain relief without somnolence or hypoventilation.

Nasogastric tube aspiration traditionally was used to prevent pancreatic stimulation induced by gastric distention and acid secretion. Multiple clinical trials, however, have demonstrated no benefit from nasogastric aspiration. For example, in a prospective, randomized trial of 60 patients who had mild to moderate pancreatitis, patients receiving nasogastric aspiration tended to resume oral feedings later and remain hospitalized longer than patients not receiving nasogastric aspiration [153]. Nasogastric aspiration is reserved for patients who have a severe ileus pattern on abdominal roentgenograms, severe abdominal distention on abdominal examination, or persistent emesis [154].

The oxygen saturation should be maintained at 95% or higher, with supplemental oxygen administered by nasal cannulae as necessary to maintain pancreatic oxygenation and prevent pancreatic necrosis. An oxygen saturation below 90% may require delivery of supplemental oxygen by a face mask. Endotracheal intubation and assisted ventilation should be performed early if the patient remains hypoxic despite these measures, has severe pulmonary disease, or experiences respiratory fatigue. Hypoxemia in the absence of pre-existing pulmonary disease may be an early sign of the adult respiratory distress syndrome (ARDS) caused by interstitial edema from increased alveolar capillary permeability [155]. The pulmonary venous wedge pressure characteristically is normal with ARDS. Chest roentgenogram may reveal multilobar pulmonary infiltrates. ARDS is treated by endotracheal intubation and mechanically assisted ventilation using high positive end-expiratory pressures.

Patients initially should receive nothing by mouth to rest the pancreas. Patients who have mild to moderate and uncomplicated pancreatitis usually are managed solely by intravenous hydration without initiating parenteral feeding, because they typically can resume oral feedings within several days when the patient has no more abdominal pain, nausea, vomiting, and abdominal distention. The diet is advanced slowly to minimize the risk of postprandial pain and recurrent pancreatitis [156]. The diet initially consists of clear liquids and then is advanced sequentially to full liquids, soft solids, and full solids, as tolerated. The diet initially consists mostly of carbohydrates with some proteins and small amounts of fat added gradually as tolerated. Initially intake is limited to small amounts of kcal/d that are increased gradually as tolerated. Mild to moderate residual elevations of the serum amylase or lipase level are not contraindications to oral feeding, but an amylase or lipase level that is more than threefold above the normal range signals a moderately increased risk of inducing abdominal pain with refeeding [156].

Patients who have severe pancreatitis typically cannot resume oral feedings for many days after presentation because of persistent ileus, abdominal

pain, or unresolved pancreatitis that is exacerbated by eating. These patients, however, particularly benefit from nutritional supplementation for tissue repair after tissue catabolism from pancreatic necrosis and the systemic inflammatory response. Total parenteral nutrition (TPN) was used traditionally for patients who had severe pancreatitis to provide nutrition efficiently without stimulating the pancreas and reactivating the pancreatitis. Prolonged TPN, however, is associated with significant risks of direct complications including line sepsis, local abscess, localized hematomas, pneumothorax, venous thrombosis, and venous air embolism, as well as indirect complications involving the kidneys, bones, liver, and biliary tract from metabolic abnormalities [157]. Clinical studies have shown consistently that TPN has a higher complication rate than either intravenous peripheral nutrition or enteral nutrition. For example, in a randomized, prospective study of 70 patients who had severe pancreatitis, patients receiving TPN had significantly higher rates of pancreatic infectious complications (16 versus 7; $P = .02$), multiorgan failure (17 versus 7; $P = .02$), and mortality (12 versus 2; $P < .01$) than patients receiving total enteral nutrition. TPN also is more than four times more expensive than nasoenteral feeding [158].

Stimulation of pancreatic secretion by the presence of food in the gut only pertains to food within the gastric or duodenal lumen. Feeding via a nasojejunal tube with the distal port in the middle jejunum therefore does not stimulate exocrine pancreatic secretion and does not reactivate the pancreatitis. This finding has been demonstrated in animal studies [159] and human trials [160]. In a meta-analysis of seven randomized, controlled trials, enteral nutrition resulted in significantly fewer infectious complications (risk ratio, 0.46; CI, 0.39–0.74; $P < .001$) and a significantly shorter hospital stay than seen with parenteral nutrition (weighted mean difference, -3.94 days; CI, -5.86 to -2.02 days; $P < .0001$) [161].

Peritoneal lavage to remove toxic necrotic compounds no longer is recommended for severe pancreatitis. In a meta-analysis of eight randomized, prospective clinical trials involving a total of 333 patients, peritoneal lavage did not reduce morbidity or mortality significantly [162].

Prophylactic administration of antibiotics for severe pancreatitis, in the absence of a specific infection, is controversial because of highly variable and contradictory study results. For example, in a double-blind, placebo-controlled, randomized trial of 114 patients who had severe acute pancreatitis, patients receiving antibiotics demonstrated no improvement in outcome, in terms of infected pancreatic necrosis or mortality, when compared with expectant management with antibiotic treatment administered only when local infections or sepsis occurred [163]. In contrast, a meta-analysis of eight controlled trials involving 814 patients (which did not include the aforementioned study) reported a significantly lower mortality in patients administered prophylactic antibiotics than in untreated controls (6.6% versus 13.3%; $P = .016$) [164]. Recent guidelines issued by the American College of Gastroenterology do not recommend antibiotic prophylaxis to

prevent pancreatic infection [165]. Recent guidelines by the American Gastroenterology Association make no recommendations regarding antibiotic prophylaxis but note that antibiotic prophylaxis should be considered when the extent of pancreatic necrosis is 30% or greater on abdominal CT scan [166]. Antibiotics selected for pancreatic infections should be bactericidal and produce adequate therapeutic levels within pancreatic tissue [164]. Such antibiotics include imipenem, third-generation cephalosporins, and piperacillin [167]. Broad-spectrum antibiotic prophylaxis increases the risks of fungal infection [168].

Complications

Complications of acute pancreatitis include pancreatic manifestations, peripancreatic complications, and systemic manifestations. The mechanisms, diagnosis, and treatment of these complications are reviewed in Table 3. The article by Jury and Tariq in this issue discusses many of these complications in detail from the surgical perspective.

Acute pancreatitis during pregnancy

Acute pancreatitis has been reported in about 0.1% or more of pregnancies. Gallstones are the most common cause because of the cholestatic effects of gestational sex hormones, particularly estrogen [169]. Alcohol is a relatively uncommon cause of pancreatitis during pregnancy, presumably because of decreased use of alcohol, a known teratogen [170].

Pregnancy does not alter the clinical presentation of acute pancreatitis significantly. The pain typically is epigastric. The pain may radiate to the back. Nausea, emesis, and pyrexia frequently occur [171]. Signs include mid-abdominal tenderness, abdominal guarding, hypoactive bowel sounds, abdominal distention, and increased tympany [172]. The serum lipase level is not affected by pregnancy and retains its diagnostic usefulness during pregnancy [173]. The serum amylase level is elevated only mildly during a normal pregnancy; a more than threefold elevation of the serum amylase level is relatively specific for acute pancreatitis.

Abdominal ultrasonography is the preferred method to detect cholelithiasis and bile duct dilatation. Abdominal CT usually is avoided during pregnancy because of concerns about radiation teratogenicity [174]. Abdominal ultrasound is useful to gauge the severity of pancreatic inflammation in thin patients, but the pancreas may be poorly visualized in the presence of overlying bowel gas from a localized ileus and because of the presence of the overlying gravid uterus. Abdominal CT typically exposes the fetus to less than 1 rad and can be considered when very strongly indicated [175].

Acute pancreatitis tends to be mild during pregnancy and to respond well to medical therapy, including intravenous fluid administration, analgesia,

Table 3
Complications of acute pancreatitis

Complication	Mechanism	Diagnosis	Treatment
Hypocalcemia	Sequestration of calcium by free fatty acids generated by fat necrosis. Serum calcium level may be artifactually depressed by decreased binding of calcium by albumin caused by hypoalbuminemia.	Serum calcium and albumin levels	Rarely severe or symptomatic. Slowly replete calcium intravenously if unbound (ionized) serum calcium level is decreased.
Disseminated fat necrosis	Lipolysis by pancreatic enzymes released into the bloodstream converts triglycerides to monoglycerides and toxic free fatty acids.	Tender, subcutaneous, erythematous nodules that are 0.5–2.0 cm in diameter along the distal limbs; pyrexia; and eosinophilia	Supportive therapy to control the acute pancreatitis
Adult respiratory distress syndrome	Pulmonary capillary injury resulting in fluid extravasation	Hypoxia, normal pulmonary venous wedge pressure, decreased pulmonary compliance. Chest roentgenogram: diffuse bilateral pulmonary infiltrates	Mechanical ventilation with positive end-expiratory pressure. Pulmonary venous wedge pressure monitoring in an ICU
Renal insufficiency	Prerenal azotemia from hypovolemia from sequestration of fluid in pancreatic bed. Hypotension may cause acute tubular necrosis.	Elevated serum urea nitrogen and creatinine levels; microscopic examination of urinary sediment	Aggressive intravenous hydration with normalization of blood pressure
Sterile pancreatic necrosis	Release of activated pancreatic enzymes that cause pancreatic autodigestion, microvascular injury, and necrosis	CT: focal lack of enhancement with injection of intravenous contrast	Aggressive supportive care, especially intravenous hydration. Supplemental oxygenation as necessary. Monitoring of pulmonary vein wedge pressure by a Swann-Ganz catheter.

Infected pancreatic necrosis	One third or more of patients who have pancreatic necrosis develop infected necrosis from translocation of gut-derived micro-organisms.	Sepsis, persistent pyrexia and leukocytosis. CT with contrast: inhomogeneous, nonenhancing pancreatic lesions, gas in pancreas. CT-guided aspirate: Gram-stain, fungal stain, and cultures	Aggressive percutaneous drainage of pancreatic fluid; antibiotics; necrosectomy
Ascending cholangitis	Stone impacted in choledochus leading to biliary stasis and infection	Charcot's triad: right upper quadrant pain, jaundice, and fever. Persistently elevated liver function tests. Choledocholithiasis diagnosed by endoscopic ultrasound, MRCP, or ERCP	ERCP with sphincterotomy and balloon sweeping of choledochus
Chronic pancreatitis	Long-term chronic injury to pancreatic ducts and parenchyma from duct plugs, autolysis, and inflammation from alcoholism, hypertriglyceridemia, or hereditary pancreatitis	Steatorrhea (abdominal CT or ERCP): pancreatic calcifications, irregular beading of pancreatic ducts ("chain of lakes")	Prevent recurrent acute pancreatitis by reversal of preventable factors: alcohol cessation and control of triglyceride level, pancreatic enzyme therapy. Avoid smoking Pain control: analgesia, celiac ganglion blockade, or Puestow procedure
Splenic artery or gastroduodenal artery pseudoaneurysm	Pancreatic pseudocyst erodes into an adjacent artery to create a pseudoaneurysm.	CT with contrast, MRI, or angiography	Angiographic embolization, surgical ligation of vessel, or broad surgical resection
Pancreatic fistulae	Posterior leakage from pancreatic duct disruption with burrowing of fluid through tissue	Fistula fluid has high protein and amylase level. ERCP to delineate proximal fistula. Fistulogram for external fistula. CT scan for extent of fistula	Stenting of disrupted pancreatic duct; octreotide to decrease pancreatic secretions; or surgical resection

Table 3
(continued)

Complication	Mechanism	Diagnosis	Treatment
Pancreatic pseudocyst	Leakage of pancreatic secretions and liquefaction of necrotic pancreatic tissue with gradual formation of a pseudocapsule	CT: round, fluid-filled, homogeneous cyst in pancreas that is nonenhancing more than 4 weeks after an episode of acute pancreatitis; persistent hyperamylasemia	Asymptomatic, sterile, pseudocyst: monitor by serial abdominal imaging. Symptomatic, enlarging, or infected pseudocyst: internal drainage via endoscopic cyst-gastrostomy, or pancreatic duct stent for a communicating pseudocyst. Surgical drainage
Pancreatic ascites	Pancreatic duct disruption with leakage of ductular secretions	Abdominal imaging: ascites. High amylase and total protein level in ascitic fluid	Endoscopic stent to bridge the ductal disruption; aggressive paracentesis and octreotide therapy to decrease pancreatic secretions; pancreatic surgery
Splenic vein thrombosis	Vascular compression by or spread of inflammation from the nearby enlarged and inflamed pancreas	Contrast CT, MRI, or Doppler ultrasound: splenomegaly, gastric varices, and splenic vein thrombosis	Consider thrombolysis for acute thrombosis. May require splenectomy for isolated bleeding gastric varices.
Cardiovascular shock with hypovolemia	Hypovolemia from sequestration of fluid in pancreatic bed and leaky capillaries. Myocardial depression caused by systemic inflammatory response	Hypotension, tachycardia, low urine sodium concentration. Low pulmonary vein wedge pressure on Swann-Ganz monitoring	Aggressive rehydration with hemodynamic monitoring in an ICU. May require vasopressors.

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

gastric acid suppression, temporarily taking nothing per mouth, and nasogastric tube aspiration in the presence of severe gastric distention, severe emesis, or a marked ileus [176]. Pregnancy should not delay CT-guided aspiration or surgery for severe complications of pancreatitis. Endoscopic sphincterotomy can be performed during pregnancy for symptomatic cholelithiasis with minimal fetal radiation exposure. It generally results in a successful maternal and fetal outcome [177]. For example, in a study of 19 (mostly therapeutic) ERCPs during pregnancy, 17 of the pregnancies (89%) resulted in healthy infants, including 16 born at term (excluding 2 unknown pregnancy outcomes and 2 elective abortions) [178]. ERCP during pregnancy is reviewed in detail in the article on hepatic disorders mildly to moderately affected by pregnancy by Cappell in this issue.

Future directions of research

In terms of etiology, the cofactors necessary for the development of alcoholic pancreatitis need to be elucidated further. The genetics of pancreatitis requires extensive research into the pathophysiology, incidence, and the role of genetic mutations as a cofactor in other forms of pancreatitis, such as alcoholic pancreatitis. An important focus of research is to identify further causes of pancreatitis to reduce the incidence of idiopathic pancreatitis. The roles of pancreas divisum, sphincter of Oddi dysfunction, and biliary sludge in pancreatitis need to be defined better. In particular, the criteria for pancreatitis caused by sphincter of Oddi dysfunction and pancreas divisum should be defined more quantitatively. The role of microlithiasis in idiopathic pancreatitis requires analysis in a large, prospective, controlled trial. The subject of drug-induced pancreatitis merits further analysis, perhaps using a multicenter prospective study funded by the National Institutes of Health, as is being done for drug-induced liver disease (see the article by Fontana in this issue).

New treatments are needed to reduce the extent of pancreatic necrosis and to prevent infection of necrotic pancreatic tissue. In particular, the indications, specific antibiotics, dosage, and protocol for administration of antibiotics must be clarified for severe, sterile, pancreatic necrosis. Novel therapies such as local pancreatic vasodilators or antiinflammatory mediators may help reduce the extent of pancreatic necrosis during an acute attack.

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