Chapter 57: Pancreatitis

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UPDATE SUMMARY

Update Summary

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The following sections, tables, and figures were updated:

- Treatment, Acute Pancreatitis, Pharmacologic Therapy, Fluid resuscitation: minor updates based on new studies
- Table 57-2: added mirtazapine

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 28, Pancreatitis.

KEY CONCEPTS

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ACUTE PANCREATITIS

1. Factors that can contribute to acute pancreatitis should be identified and corrected, including discontinuation of medications that could be potential causes.
2. Patients with acute pancreatitis should receive goal-directed fluid management to reduce the risks of persistent systemic inflammatory response syndrome (SIRS) and organ failure.
3. Parenteral opioid analgesics are used to control abdominal pain associated with acute pancreatitis despite a lack of high-quality evidence to support the practice.
4. Use of prophylactic antibiotics is not recommended in patients with acute pancreatitis without signs or symptoms of infection, including those with predicted severe acute pancreatitis or necrotizing pancreatitis.

CHRONIC PANCREATITIS

5. Chronic pain, malabsorption with resultant steatorrhea, and diabetes mellitus are the hallmark symptoms and complications of chronic pancreatitis.
6. Pain from chronic pancreatitis may initially be treated with nonopioid analgesics, but adjuvant agents may be necessary as the disease progresses.
7. Pancreatic enzyme and fat-soluble vitamin supplementation are the primary treatments for malabsorption due to chronic pancreatitis.
8. Enteric-coated pancreatic enzyme supplements are the preferred dosage form in the treatment of malabsorption and steatorrhea due to chronic pancreatitis.
9. The addition of a histamine-2 receptor antagonist or proton pump inhibitor to pancreatic enzyme supplementation may increase the effectiveness of enzyme therapy for malabsorption and steatorrhea due to chronic pancreatitis.

BEYOND THE BOOK

BEYOND THE BOOK

1. Robert Whipple is a 48-year-old man admitted to the intensive care unit (ICU) for acute pancreatitis. He weighs 89 kg. He has no signs or symptoms of infection. Which resuscitation fluid would you recommend for Mr. Whipple and why? What volume and rate of infusion would you recommend for his resuscitation fluid? What are the endpoints you recommend monitoring to determine adequate fluid resuscitation? These are the key decisions regarding the assess, plan, implement, and monitor aspects of the Pharmacist Patient Care Process concerning fluid resuscitation in patients with acute pancreatitis.
2. Using available resources, determine the monthly cash prescription payment for a patient with exocrine pancreatic insufficiency from chronic pancreatitis who requires 60,000 USP units of lipase with each meal; the patient eats five meals a day, along with three snacks. Do this for all Food and Drug Administration (FDA)-approved pancrelipase products available in the United States. How would this information affect your recommendation of a pancrelipase product for this patient? Now locate the online formulary of a third-party prescription plan in your area. Determine if the plan's coverage of the same pancrelipase products alters your decision in any way. This activity is to make you aware of not only the pill burden of patients with exocrine pancreatic insufficiency but also the cost related to these medications.

INTRODUCTION

Pancreatitis is inflammation of the pancreas with variable involvement of regional tissues or remote organ systems.[1,2] Acute pancreatitis is characterized by severe pain in the upper abdomen and elevations of pancreatic enzymes in the blood.[3,4] In the majority of patients, acute pancreatitis is a self-limiting disease that resolves spontaneously without complications. Approximately 20% of adults with acute pancreatitis have a severe course.[3] While the overall mortality of acute pancreatitis is low, severe pancreatitis is associated with a mortality as high as 40%.[3,5,6] The risk for progression to chronic pancreatitis after an initial episode of acute pancreatitis is related to the etiology. Patients with acute pancreatitis due to gallstone disease have little risk for progression to chronic disease, whereas patients with alcohol-related acute pancreatitis have a risk of 13% to 38% based on whether or not they continue to consume alcohol.[7]

Chronic pancreatitis is characterized by long-standing inflammation that eventually leads to a loss of pancreatic exocrine and endocrine functions.[8–11] It is a progressive disease that often goes unnoticed for many years. The usual initial presentation is complaints of chronic abdominal pain. Later in the disease process malabsorption with resultant steatorrhea occurs. This leads to malnutrition and weight loss. Finally, patients develop diabetes mellitus due to a loss of pancreatic endocrine function.[8,9,11]

EPIDEMIOLOGY

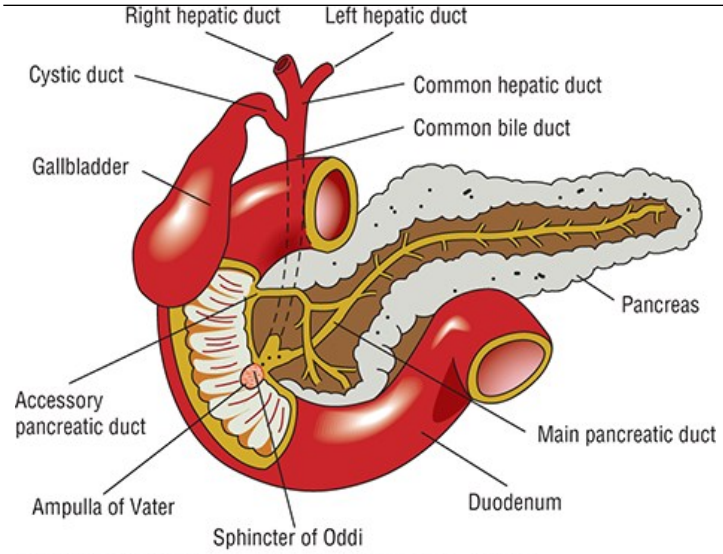
Acute pancreatitis is one of the most common gastrointestinal disorders causing hospitalization in the United States with admission rates of approximately 13 to 45 per 100,000 per year.[3,5,7] The incidence of hospitalization has increased with a 13.3% rise occurring within the first decade of the century.[12] The risk for acute pancreatitis varies widely with geographic, etiologic (eg, alcohol consumption and smoking), environmental, and genetic factors. In adults and children, the increase in acute pancreatitis is often attributed to rising rates of obesity.[4,13] The annual incidence of chronic pancreatitis in the United States is 5 to 14 per 100,000, and the prevalence is 42 to75 per 100,000.[8,10,11] The prevalence increases with age, with an average onset in the fifth to sixth decade of life, and it is 4.5 times more common in males than females.[8,10,11] Also, the prevalence of chronic pancreatitis varies widely based on geographic location.[9] There is also racial disparity with the disease, with Black patients having two to three times the risk than White patients, and being more than twice as likely to be hospitalized.[8,10,11]

PANCREATIC EXOCRINE PHYSIOLOGY

The pancreas possesses both endocrine and exocrine functions. The islets of Langerhans, which contain the cells of the endocrine pancreas, secrete insulin, glucagon, somatostatin, and other polypeptide hormones. The exocrine pancreas is composed of acini and ductules that secrete about 2.5 L/day of isotonic fluid that contains water, electrolytes, and pancreatic enzymes necessary for digestion. Bicarbonate and other electrolytes are secreted primarily by the centroacinar (ductular) cells in order to neutralize gastric acid. Pancreatic juice is delivered to the duodenum via the pancreatic ducts (Fig. 57-1) where the alkaline secretion neutralizes gastric acid and provides an appropriate pH for maintaining the activity of pancreatic enzymes.[14]

FIGURE 57-1

Anatomic structure of the pancreas and biliary tract.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The major pancreatic exocrine enzyme groups are as follows:

1. Amylolytic: α-amylase
2. Lipolytic: lipase, procolipase, prophospholipase A2, and carboxylesterase
3. Proteolytic: trypsinogens, chymotrypsinogen, procarboxypeptidase A and B, proelastase and mesotrypsin
4. Nucleolytic: ribonuclease and deoxyribonuclease
5. Other: trypsin inhibitor

Amylase is responsible for digestion of starches and glycogen through hydrolysis. The lipolytic enzymes break down triglycerides, cholesterol, and other fats in the digestive tract. Specifically, lipase hydrolyzes triglycerides into fatty acids and monoglycerides. Colipase and bile acids facilitate this process by allowing lipase to act on the hydrophobic surface of fat droplets in the mainly hydrophilic environment. Phospholipase A2 and carboxylesterase continue to break down fatty acids, cholesterol, monoglycerides, and other products of fat digestion. Proteolytic enzymes digest proteins into oligopeptides and free amino acids, while nucleases break down nucleic acids.[14]

The production of proteolytic enzymes in the pancreas occurs in a manner that prevents self-digestion of the pancreas. These enzymes are synthesized within the acinar cells, stored in vacuoles, and secreted into the duodenum as zymogens (inactive enzymes). Enterokinase secreted by the duodenal mucosa converts trypsinogen to trypsin, which then activates all other proteolytic zymogens along with procolipase and prophospholipase A2. Thus, two important mechanisms protect the pancreas from the potential degradative action of its own digestive enzymes. First, the synthesis of proteolytic enzymes as zymogens requires extrapancreatic activation by trypsin. Second, pancreatic juice contains a low concentration of trypsin inhibitor, which inactivates any autocatalytically formed trypsin within the pancreas. Proteolytic activity of trypsin in the intestinal lumen is not inhibited because the concentration of trypsin inhibitor is minimal. Lipase, amylase, ribonuclease, and deoxyribonuclease are secreted by the acinar cells in their active form.[14]

The regulation of exocrine pancreatic secretion is a complex interplay of neurohormonal feedback with three distinct phases. The first phase is the cephalic phase where the sight, smell, and taste of food cause pancreatic enzyme secretion through stimulus of the vagus nerve. Vasoactive intestinal peptide (VIP) and gastrin-releasing peptide released from efferent vagus nerve terminals bind to receptors on the acinar cells stimulating enzyme release.[14] Water and bicarbonate are also released from ductal cells due to VIP stimulation. The gastric phase occurs due to gastric distension from food entering the stomach. This results primarily in secretion of digestive enzymes from the pancreas. Once chyme enters the duodenum, the intestinal phase begins. The chyme causes secretin to be released from the duodenal mucosa when its pH is less than 4.5. Secretin results in water and

bicarbonate secretion from the pancreas to increase intestinal pH for stable lipolytic enzyme activity. Digestive enzymes are released from the pancreas due to the presence of fatty acids, peptides, amino acids, and glucose in the duodenum.[14]

The feedback mechanism for continued release of pancreatic enzymes involves the hormone cholecystokinin (CCK). When products of fat, protein, and starch digestion enter the upper small intestine, they stimulate the release of CCK from I cells into the blood. Elevated levels of CCK in the serum activate a vasovagal reflex causing further release of VIP and gastrin-releasing peptide, leading to enhanced pancreatic enzyme secretion. Inhibition of this feedback loop is thought to be due to trypsin. After digestion is complete, unoccupied trypsin is thought to inhibit the release of CCK.[14] A more in-depth discussion of pancreatic physiology can be found elsewhere.[14]

ACUTE PANCREATITIS

Acute pancreatitis may be mild or may be associated with complications including organ failure and pancreatic necrosis. Prognosis and management vary according to the severity of the disease. There are several causes of acute pancreatitis, but the most common are obstruction due to gallstones and alcohol-induced pancreatitis. Patients generally present with abdominal pain and other gastrointestinal symptoms with diagnosis being made based on presenting signs and symptoms, lab abnormalities, and imaging studies as necessary. Treatment focuses on providing fluid resuscitation and treating the pain and complications associated with acute pancreatitis.

Etiology

Table 57-1 lists the etiologic risk factors associated with acute pancreatitis. Obstruction caused by gallstones is the most common cause of acute pancreatitis in the United States, with alcohol misuse being the second most common. Abdominal obesity increases the risk for both gallstone- and nongallstone-related acute pancreatitis. Moderate elevations in lipid levels are associated with nonalcohol-related pancreatitis, and smoking has emerged as a strong risk.[4,7,12,13,15] There is also an autoimmune form of pancreatitis.[3,7] Diabetes mellitus is also associated with an increase in acute pancreatitis as are autoimmune disorders such as inflammatory bowel disease.[3,7,13,16,17] Most remaining cases are classified as idiopathic.[4,13] Acute pancreatitis can occur as a result of undergoing an endoscopic retrograde cholangiopancreatography (ERCP) with overall rates up to 5%.[4,7] Pregnancy is not considered a cause of acute pancreatitis; however, pregnant women develop pancreatitis as a result of a coincident process, most commonly cholelithiasis.[18] The reported incidence of acute pancreatitis in children has increased in recent years, and the common etiologies are biliary disease, systemic illness, medications, trauma, and idiopathic.[19,20]

TABLE 57-1

Etiologic Risk Factors Associated with Acute Pancreatitis

Structural	Gallstone disease, sphincter of Oddi dysfunction, pancreas divisum, pancreatic tumors
Toxins	Alcohol (ethanol) consumption, scorpion bite, organophosphate insecticides
Infectious	Bacterial, viral (including HIV and H1N1 influenza), parasitic
Metabolic	Hypertriglyceridemia, chronic hypercalcemia
Genetic	Cystic fibrosis, α1-antitrypsin deficiency, hereditary (trypsinogen gene mutations)
Medications	See Table 57-2 for specific drugs
Iatrogenic	Abdominal surgery, ERCP
Kidney disease	Chronic kidney disease, dialysis-related
Trauma	Blunt abdominal trauma
Vascular	Vasculitis, atherosclerosis, cholesterol emboli, coronary artery bypass surgery
Other etiologies	Congenital, Crohn's disease, autoimmune, tropical, solid organ transplantation (eg, liver, kidney, heart), refeeding syndrome
Idiopathic	Undetermined cause

HIV, human immunodeficiency virus; ERCP, endoscopic retrograde cholangiopancreatography.

Data from References 3, 4, 7, and 13.

TABLE 57-2

Medications Associated with Acute Pancreatitis

Well-Supported Association	Probable Association	Possible Association	
5-Aminosalicylic acid	Acetaminophen	Aldesleukin	Indinavir
Asparaginase	Hydrochlorothiazide	Amiodarone	Indomethacin
Azathioprine	Itraaconazole	Atorvastatin	Infliximab
Bortezomib	Ifosfamide	Calcium	Ketoprofen
Carbamazepine	Interferon α2b	Ceftriaxone	Ketorolac
Cimetidine	Maprotiline	Capecitabine	Lipid emulsion
Corticosteroids	Methyldopa	Carboplatin	Liraglutide
Cisplatin	Oxaliplatin	Celecoxib	Lisinopril
Cytarabine		Clozapine	Mefenamic acid
Didanosine		Cholestyramine	Metformin
Enalapril		Ciprofloxacin	Metolazone
Erythromycin		Clarithromycin	Metronidazole
Estrogens		Clonidine	Mirtazapine
Furosemide		Cyclosporine	Nitrofurantoin
Lamivudine		Danazol	Omeprazole
Mercaptopurine		Diazoxide	Ondansetron
Mesalamine		Etanercept	Paclitaxel
Octreotide		Ethacrynic acid	Pravastatin
Olsalazine		Exenatide	Propofol
Opiates		Famciclovir	Propoxyphene
Pentamidine		Glyburide	Rifampin
Pentavalent antimonials		Gold therapy	Sertraline
Sulfasalazine		Granisetron	Simvastatin
Sulfamethoxazole and trimethoprim		Ibuprofen	Sitagliptin
Tamoxifen		Imatinib	Sorafenib
Tetracyclines			Sulindac
Valproic acid/salts			Zalcitabine

Data from References 4, 7, 13, 21, 22, and 23.

Medications

1 Factors that can contribute to acute pancreatitis should be identified and corrected, including discontinuation of medications that could be potential causes. Drug-induced acute pancreatitis should be considered when other causes have been excluded and there is a temporal relationship with the initiation of a medication that has been implicated as a cause. Most experts consider drug-induced pancreatitis to be rare, although some reports include higher estimates.[4,7,13] The difficulty in diagnosing drug-induced pancreatitis has led to an underestimation of the rate.[13] Most information on drug-induced acute pancreatitis is obtained from case reports, which do not provide reliable information on incidence. The most convincing case reports involve recurrence on rechallenge; however, rechallenge is rare, occurring only when alternative therapy is not available. Further complicating the evaluation of some reports is the use of medications associated with pancreatitis in patient populations with an increased risk of pancreatitis.[13] Adverse events attributed to newly introduced medications may be reported more frequently.[21] Many medications have been frequently reported to cause acute pancreatitis. Patients with human immunodeficiency virus (HIV) have an increased risk of pancreatitis and there are

many reports of pancreatitis attributed to antiretroviral agents.[4,7,13,21] Pancreatitis due to azathioprine is reported more frequently in patients with Crohn's disease than in patients taking the medication for other indications, suggesting an interaction between the disease and medication. Patients with Crohn's disease often take other medications that can cause pancreatitis, including 5-aminosalycilates, corticosteroids, and sulfasalazine.[24] Patients with type 2 diabetes mellitus have an increased risk of acute pancreatitis. Case reports and some observational studies have linked antihyperglycemic agents, including metformin, sulfonylureas, and incretin mimetics, with pancreatitis. There is no increase in pancreatitis with incretin mimetics compared to sulfonylureas, metformin, or insulin.[25,26] Mixed results have been reported in meta-analyses evaluating the risk of pancreatitis from dipeptidyl peptidase-4 inhibitors.[26,27] Complicating comparisons between agents used to treat diabetes mellitus is that the medications are often used in obese patients and patients with different durations of disease, both of which may also influence disease-associated pancreatitis.[28] Polypharmacy is associated with an increased risk of acute pancreatitis.[29]

The onset of drug-induced pancreatitis after initiation of medications ranges from a few months to several years, with a median of 5 weeks; onset after rechallenge can occur within hours. The onset may differ according to the mechanism. Clinicians should be especially suspicious of a drug as a cause of acute pancreatitis in high-risk patients, such as those receiving immunomodulating drugs or who have HIV infection, the elderly, or those with diabetes mellitus.[23]

Mechanisms of drug-induced pancreatitis have been proposed for some medications but remain poorly defined. Possible mechanisms include direct toxic effects of the drug or its metabolites, hypersensitivity, drug-induced hypertriglyceridemia, and alterations of cellular function in the pancreas and pancreatic duct.[22] Ultimately, drug-induced pancreatitis causes damage to the pancreas, which produces a response similar to other causes of pancreatitis. It is prudent to withdraw a medication when an association is suspected.

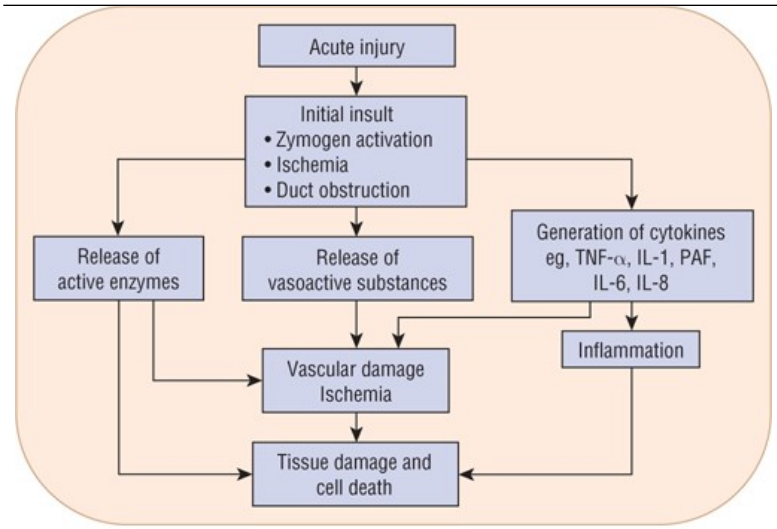
Numerous drugs are believed to cause acute pancreatitis, but ethical and practical considerations often prevent rechallenge with suspected agents. Table 57-2 lists specific agents associated with acute pancreatitis. Classification schemes consider rechallenge, the number of case reports, consistency with respect to the onset of symptoms following initiation of the suspect medication, and exclusion of other causes.

Pathophysiology

The pathophysiology of acute pancreatitis is based on events that initiate injury and secondary events that establish and perpetuate the injury (Fig. 57-2). Gallstones, alcohol misuse, and other causes of pancreatitis produce different initial insults to the pancreas. However, the resulting pathophysiologic process may be similar and include autodigestion, abnormal acinar calcium signaling, and inflammatory response. In acinar cells, the separation of zymogens and lysosomes can be disrupted, resulting in exposure of trypsinogen to lysosomal enzymes such as cathepsin B. The premature activation of trypsinogen to trypsin within the pancreas leads to activation of other digestive enzymes and autodigestion of the gland.[4,7]

FIGURE 57-2

Pathophysiology of acute pancreatitis: initiating and secondary events. (IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8, interleukin-8; PAF, platelet-activating factor; TNF-α, tumor necrosis factor-α.)



In addition to activation of digestive enzymes within the pancreas, enzymes are also released into surrounding fat, vascular endothelium, and other surrounding tissues and structures causing further damage and necrosis. Lipase damages fat cells, producing noxious substances that cause further pancreatic and peripancreatic injury. There may be an independent response from intra-acinar activation of inflammatory factors. The release of cytokines by acinar cells directly causes their injury and enhances the inflammatory response.[30] Injured acinar cells liberate chemoattractants that recruit neutrophils, macrophages, and other cells to the area of inflammation. These immune responses cause a systemic inflammatory response syndrome (SIRS). Vascular damage and ischemia causes the release of kinins, which makes capillary walls permeable and promotes tissue edema. Finally, pancreatic infection may result from increased intestinal permeability and translocation of colonic bacteria.[30]

Clinical Presentation

Signs and Symptoms

The clinical presentation of acute pancreatitis varies depending on the severity of the inflammatory process and whether damage is confined to the pancreas or involves local and systemic complications (Table 57-3).[7]

TABLE 57-3

Presentation and Diagnosis of Acute Pancreatitis

General • The patient may have acute mild symptoms or present with a severe acute attack with life-threatening complications.
Symptoms • The patient may present initially with moderate abdominal discomfort to excruciating pain, nausea, shock, and respiratory distress. • Abdominal pain occurs in 95% of patients. The pain is usually epigastric and radiates to either of the upper quadrants or the back in two-thirds of patients. In gallstone pancreatitis, the pain is typically sudden and quite severe and the intensity is often described as "knife-like" or "boring." The pain usually reaches its maximum intensity within 30 minutes and may persist for hours or days. Repositioning the patient relieves very little of the pain. In alcohol misuse and other cases, the onset of pain may be less abrupt and poorly localized. Pain may not be the dominant symptom if it is masked by multiorgan failure. • Nausea and vomiting occur in 85% of patients and usually follow the onset of abdominal pain. Vomiting does not provide relief of the abdominal pain.

Signs

- Marked epigastric or diffuse tenderness on palpation with rebound tenderness and guarding in severe cases. The abdomen is often distended and tympanic, with bowel sounds decreased or absent in severe disease.
- Vital signs may be normal, but hypotension, tachycardia, and low-grade fever are often observed, especially with widespread pancreatic inflammation and necrosis.
- Dyspnea and tachypnea are often signs of acute respiratory complications. Jaundice and altered mental status may be present and have multiple causes. Other signs of alcohol-induced liver disease may be present in patients with alcohol-induced pancreatitis.

Laboratory tests

- Leukocytosis is frequently present; hyperglycemia or hypoalbuminemia may be present. Liver transaminases, alkaline phosphatase, and bilirubin are usually elevated in gallstone pancreatitis and in patients with intrinsic liver disease. Elevated serum triglycerides may also be a possible etiology.
- The hematocrit may be normal, but hemoconcentration results from multiple factors (eg, vomiting). In patients with third-space fluid loss, hemoconcentration is present and a reasonably accurate marker of severe disease. A hematocrit of greater than 44% predicts severe acute pancreatitis. Further, failure to reverse hemoconcentration has been associated with pancreatic necrosis.
- Blood urea nitrogen (BUN) that is elevated (greater than 20 mg/dL [7.1 mmol/L]) or rising over the first 24 hours has been associated with increased mortality.
- The total serum calcium is usually normal initially, but hypocalcemia disproportionate to the hypoalbuminemia may develop. Marked hypocalcemia is an indication of severe necrosis and a poor prognostic sign.
- The serum amylase concentration usually rises within 4-8 hours of the initial attack, peaks at 24 hours, and returns to normal over the next 8-14 days. Serum amylase concentrations greater than three times the upper limit of normal are highly suggestive of acute pancreatitis. Persistent elevations suggest extensive pancreatic necrosis and related complications. Normal concentrations may be observed if testing is delayed (ie, amylase may have returned to normal) or in patients with hyperlipidemic pancreatitis (ie, marked triglyceride elevations may interfere with amylase assay). In addition, many nonpancreatic diseases may be associated with hyperamylasemia, including salivary, kidney, hepatobiliary, metabolic, female reproductive tract, and neoplastic diseases.
- Serum lipase is specific to the pancreas and concentrations are elevated and parallel the elevations in serum amylase. Levels remain elevated with pancreatic inflammation and return to normal when the inflammatory process resolves. Because of its longer half-life, elevations of serum lipase can be detected after the serum amylase has returned to normal.
- Additional biomarkers: C-reactive protein is a widely available test and levels greater than 190 mg/L at 48 hours predict severe acute pancreatitis.

Abdominal imaging

- Transabdominal ultrasound should be performed in all patients to detect dilated biliary ducts and stones in the gallbladder.
- CECT is used if the diagnosis cannot be made from clinical and laboratory findings. It is less accurate for evaluating the gallbladder and biliary ducts. The test distinguishes interstitial from necrotizing pancreatitis, but does not distinguish between fat necrosis and acute fluid collection. Tests that are performed in the first few days may miss necrosis. Tests should be performed at least 72-96 hours after symptom onset; tests performed too early may result in unnecessary exposure to risk and increased cost.
- Magnetic resonance imaging is used to grade the severity of acute pancreatitis, identify biliary duct problems that are not seen on CT, or if there are contraindications to CECT. Patients over the age of 40 with pancreatitis of an unknown etiology should be evaluated for pancreatic malignancy with CT or endoscopic ultrasonography.

APACHE, Acute Physiology and Chronic Health Evaluation; CECT, contrast-enhanced computed tomography; CT, computed tomography.

Data from References 4, 7, 13, and 30.

Diagnosis

The diagnosis of acute pancreatitis requires two of the following three: upper abdominal pain, a serum lipase or amylase concentration at least three times greater than the upper limit of normal, or characteristic findings on imaging studies.[3,4,13] Lipase is more sensitive and specific than amylase and

is the preferred laboratory test. Although used in the diagnosis of acute pancreatitis, the degree of amylase and lipase elevations is not predictive of patient outcome. Imaging studies are not necessary for diagnosis if the other two findings are positive. Contrast-enhanced computed tomography (CECT) of the abdomen may be used to confirm the diagnosis in patients with amylase or lipase that is not three times the upper limit of normal, or in sedated patients. Patients should be monitored for SIRS organ failure for the first 48 hours.[3,13] For further information on laboratory tests and abdominal imaging, refer to Table 57-3. Pertinent history includes previous history of pancreatitis, gallstone disease, alcohol use, medication use, recent surgery or ERCP, hyperlipidemia, recent infections, trauma, and family history. Magnetic resonance cholangiopancreatography (MRCP) is useful for detecting retained common bile duct stones. Laboratory tests should include liver enzymes, triglycerides, and calcium. Transabdominal ultrasound of the right upper quadrant is recommended to assess for gallstones.[3,4,7,13]

Acute pancreatitis is categorized according to the revised Atlanta classification. The revised Atlanta Classification defines acute pancreatitis as mild disease (not associated with organ failure, local complications, or systemic complications), moderately severe (transient organ failure, local complications or systemic complications), and severe (persistent organ failure).[3,7,13,31] An alternative classification system was proposed by an international multidisciplinary group using factors that have a causal association with severity (ie, distant organ failure or pancreatic necrosis) rather than events that may be associated with severity.[3,7,13,32] This determinant-based classification includes mild (no organ dysfunction or necrosis), moderate (sterile necrosis or transient organ dysfunction or both), severe (either infected necrosis or persistent organ dysfunction), and critical (infected necrosis and persistent organ dysfunction).

Prediction of severity of acute pancreatitis is useful for decisions involving the need for aggressive treatment, including admission to an ICU.[2,4,13] Multiple scoring systems have been developed to predict which patients with acute pancreatitis are at greatest risk for persistent organ failure.[2,4,13] Validated systems include the Acute Physiologic and Chronic Health Evaluation II (APACHEII) system, Bedside Index of Severity in Acute Pancreatitis, Harmless Acute Pancreatitis Score, the Ranson criteria, Japanese Severity Score, Pancreatitis Outcome Prediction, and Modified Glasgow Acute Pancreatitis Severity Score. They are used in determining aggressiveness of initial therapy as well as in developing clinical trials of interventions. However, development and validation of such systems remain an ongoing area of research. BISAP and APACHE II were similar in predicting severity of pancreatitis, organ failure and mortality.[33,34] Despite this, many are too complicated for bedside use or rely on measurements that are not widely available.[4] Also, some scoring systems have not been validated in prospective trials or have poor predictive ability.[3,13] The American Gastroenterological Association guidelines note a lack of demonstrated clinical benefit from the scoring systems and supports the use of a combination of clinical judgment and a variety of scoring tools.[2]

Clinical Course and Prognosis

The clinical course of acute pancreatitis varies from a mild transitory disorder to severe necrotizing disease. Mild acute pancreatitis is self-limiting and subsides spontaneously within 3 to 5 days. Mortality is influenced by etiology, as idiopathic and postoperative acute pancreatitis have higher rates than gallstone- or alcohol-related disease. First and second occurrences also carry a higher mortality than subsequent episodes. Mortality increases with unfavorable early prognostic signs, local complications, and organ failure. Persistent organ failure is a greater risk than transient organ failure.[6] Severe pancreatitis with either organ failure or infected necrosis is associated with a mortality of approximately 30%, and increases when both are present.[3,4,6,7,13]

Complications

Early complications are a result of SIRS and organ failure. The most common systemic complication of acute pancreatitis is respiratory failure.[4,13,21] In addition, patients may experience systemic complications due to exacerbation of preexisting renal, lung, or heart disease.[13,31] A second phase occurs in patients with moderately severe or severe disease. These patients have persistent organ failure and may have local complications including interstitial pancreatitis (acute peripancreatic fluid collection and pancreatic pseudocysts) and collection of necrosis. These develop approximately 3 to 4 weeks after the initial attack.[3,4,13] Long-term complications include recurrence of acute pancreatitis, development of pancreatic exocrine and endocrine insufficiency, and progression to chronic pancreatitis.[3,4,13,35] Exocrine and endocrine insufficiency develops in approximately 20% to 30% of patients following acute pancreatitis, with about one-third of those patients progressing to chronic pancreatitis.[3,4,13,36] Some patients with peripancreatic necrosis will develop secondary infections that usually require invasive intervention.[3,13]

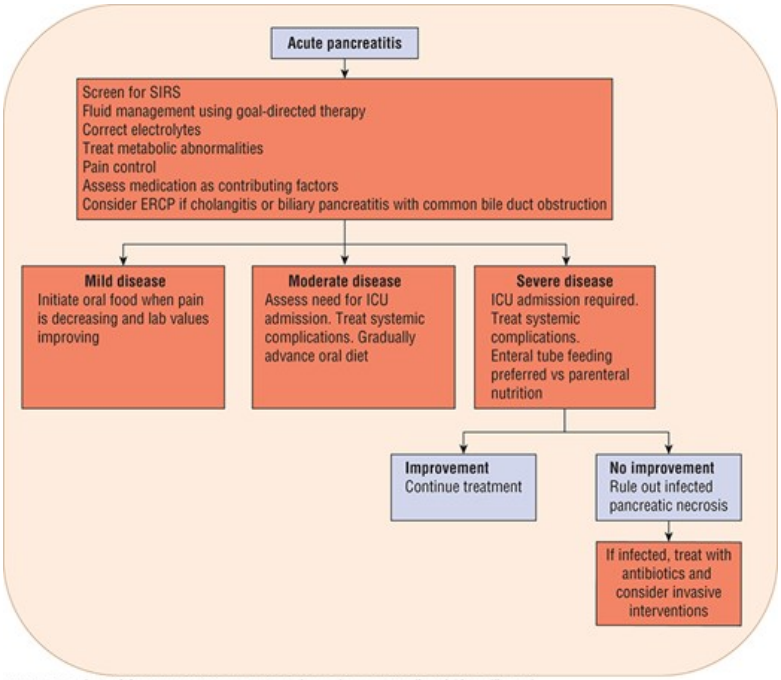
TREATMENT

Desired Outcome

Treatment of acute pancreatitis is aimed at relieving abdominal pain and nausea, replacing fluids, correcting electrolyte, glucose, and lipid abnormalities, minimizing systemic complications, and managing pancreatic necrosis and infection. Management varies depending on the severity of the attack (Fig. 57-3). Patients with mild acute pancreatitis respond very well to the initiation of supportive care. Patients with severe acute pancreatitis should be treated aggressively and monitored closely.

FIGURE 57-3

Algorithm of guidelines for evaluation and treatment of acute pancreatitis. (SIRS, systemic inflammatory response syndrome; ERCP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit.)



General Approach to Treatment

All patients with acute pancreatitis should receive supportive care, including IV fluid resuscitation, adequate nutrition, and effective relief of pain and nausea. Patients should be evaluated for admission to the ICU. Patients predicted to follow a severe course may require treatment of systemic complications.[3,4] Fluid therapy is recommended and may help prevent organ failure.[1,2] Patients with pancreatitis and SIRS should be treated according to SIRS guidelines. IV potassium, calcium, and magnesium are used to correct electrolyte deficiency states. Insulin is used to treat hyperglycemia. Local complications resolve as the inflammatory process subsides. However, patients with necrotizing pancreatitis may require procedural intervention.[37] Medications listed in Table 57-2 should be reviewed and discontinued if other etiologies are unlikely.

Nonpharmacologic Therapy

Nonpharmacologic therapy includes ERCP for removal of any underlying biliary tract stones, procedural interventions, and nutritional support. The need for admission to an ICU should be addressed. Advances in minimally invasive surgical techniques are changing practice with respect to timing and approach to managing infected necrotizing pancreatitis, and may help lower the risk of mortality in the most critical patients.[2,37] Patients with alcohol-related pancreatitis should receive abstinence interventions during the inpatient stay.[1]

Nutrition and Probiotics

Nutritional support plays an important role in the management of patients with mild or severe disease as acute pancreatitis creates a catabolic state that promotes nutritional depletion. This can impair recovery, increase the risk of complications, and prolong hospitalization.[38] Enteral nutrition results in decreased multiple organ failure, complications, duration of hospitalization, mortality, and need for surgical intervention compared with parenteral nutrition.[38,39] Possible mechanisms for this include protection of the gut barrier and prevention of colonization with pathogenic bacteria, both of which may prevent translocation of bacteria and subsequent infection.[3,4] Patients with mild to moderate acute pancreatitis should begin oral feeding as soon as clinically tolerated regardless of serum lipase concentrations, usually within 24 hours of admission.[1,38,40] In severe or complicated disease, nutritional deficits develop rapidly and are complicated by tissue necrosis, organ failure, and surgery. Despite this guideline, recommendations support beginning oral or enteral nutrition within 24 to 72 hours of admission.[38,40,41] If the enteral route is used due to intolerance of an oral diet, based on guidelines make preference for nasogastric feeding tube placement over nasojejunal.[1,38,42] If enteral feeding is not possible or if the patient is unable to obtain sufficient nutrients, total parenteral nutrition should be implemented before protein and calorie depletion become advanced.[1,2,38]

Probiotics have mixed results in several randomized controlled trials for the treatment of severe acute pancreatitis. A meta-analysis, however, did not support the use of probiotics in the treatment of acute pancreatitis, as they have no benefit.[43] Therefore, use of probiotic agents for acute pancreatitis is not recommended by guidelines.[38]

Pharmacologic Therapy

Patients with acute pancreatitis often require IV antiemetics for nausea. Those requiring ICU admission should be treated with antisecretory agents (such as famotidine or pantoprazole) if they are at risk of stress-related mucosal bleeding. Patients also require appropriate fluid resuscitation and pain management, but there is controversy surrounding both of these therapies (see Fig. 57-3). Clinical trials have also failed to identify a group of patients that benefit from prophylactic antibiotics.

Fluid Resuscitation

2 Vasodilation from the inflammatory response, vomiting, and nasogastric suction contributes to hypovolemia and fluid and electrolyte abnormalities, thus necessitating replacement. Patients with acute pancreatitis should receive goal-directed fluid management to reduce the risks of persistent SIRS and organ failure.[1] Recommendations regarding the volume of fluid differ, with anywhere from 250 to 500 mL/hr to 5 to 10 mL/kg/hr in the first 12 to 24 hours.[3,4,13] Goals for fluid therapy in the management of acute pancreatitis are not well-defined but include one or more of the following: heart rate less than 120/min, mean arterial pressure 65 to 85 mm Hg, urinary output greater than 0.5 to 1 mL/kg/hr, or hematocrit 35% to 44% (0.35-0.44) with transfusion of blood.[3,4]

Studies completed to date have been of low quality and have somewhat conflicting results. Observational studies have identified both benefit (decreased mortality and markers of organ failure) and harm (abdominal compartment syndrome) associated with early aggressive fluid administration.[1,2] Mortality was lower in patients with severe acute pancreatitis who received 6 L or more of resuscitation fluid in the first 24 hours.[44] In contrast, there is no benefit to or increased mortality, and a greater risk of acute kidney injury, pancreatic necrosis, and acute respiratory failure in patients who received aggressive fluid therapy.[2,45–48] Patients with sepsis should be resuscitated according to sepsis guidelines.[49]

In addition to questions about the rate and volume of fluid that should be administered to patients with acute pancreatitis, there is also debate regarding which fluid is most appropriate. There is no difference in mortality between saline and lactated Ringer's, but did find a lower odds of SIRS at 24 hours with lactated Ringer's.[50] Lactated Ringer's was associated with a shorter length of hospitalization.[51] Guidelines differ regarding which fluid is preferred with most recommending lactated Ringer's in adult patients.[4] The American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis also recommends against the use of hydroxyethyl starch solutions because there are no benefits beyond saline and lactated Ringer's, and an association with an increase in multiple organ failure.[1]

Relief of Abdominal Pain

3 Parenteral opioid analgesics are used to control abdominal pain associated with acute pancreatitis despite a lack of high-quality evidence to support the practice. Pentazocine led to lower rescue analgesic use and a longer pain-free period compared to parenteral diclofenac.[52]

NSAIDs, however, may be sufficient in patients with mild or moderate pain due to acute pancreatitis and can be used if not otherwise contraindicated.[53] Parenteral morphine is often recommended for pain control because it provides a longer duration of pain relief than other opioids. Although morphine increases biliary pressure, it is contraindicated for use in acute pancreatitis. Patient-controlled analgesia should be considered in patients who require frequent opioid dosing (eg, every 2-3 hours). There was a reduction in 30-day mortality in patients with acute pancreatitis who received thoracic epidural analgesia compared to those who received a standard approach to pain management.[54]

Antimicrobial Use in Acute Pancreatitis

4 Use of prophylactic antibiotics is not recommended in patients with acute pancreatitis without signs or symptoms of infection, including those predicted to develop acute pancreatitis or necrotizing pancreatitis.[1,2] Several small, randomized clinical trials have compared antibiotic prophylaxis with no prophylaxis in patients with severe acute and necrotizing pancreatitis with varying results. Prophylactic antibiotics do not reduce infected necrosis or mortality.[2,55] In addition, overuse of antibiotics increases microbial resistance.

Because the source of bacterial contamination is most likely translocation of organisms from the colon, the antibiotic regimen for patients with known or suspected infected pancreatitis should be broad-spectrum, covering the range of enteric aerobic gram-negative bacilli and anaerobic microorganisms. Imipenem–cilastatin (500 mg IV every 8 hours) has been widely used because of its good penetration into the pancreas and one positive prophylaxis study.[56] However, it has been replaced on many hospital formularies by one of the newer carbapenems (eg, meropenem). Fluoroquinolones, such as ciprofloxacin or levofloxacin, combined with metronidazole should be considered for penicillin-allergic patients.[57] Patients with infected necrotic pancreatitis are generally treated with a combination of invasive interventions and antibiotics. Antibiotics alone may be sufficient in some cases or at least delay the need for an invasive procedure long enough for the necrotic areas to be walled off.[3]

Post-ERCP Pancreatitis

The clinical characteristics of post-ERCP pancreatitis are similar to those of acute pancreatitis from other causes. In most cases, the disease course is mild and resolves in several days. The incidence of post-ERCP pancreatitis has decreased in recent decades, most likely due to better patient selection. Several classes of medications have been studied for prevention of post-ERCP pancreatitis. The best data are with nonsteroidal anti-inflammatory drugs (NSAIDs) administered rectally prior to or immediately following the procedure.[58] The most common beneficial NSAIDs are indomethacin and diclofenac. The combination of rectal diclofenac and sublingual isosorbide dinitrate was superior to diclofenac alone in prevention of post-ERCP pancreatitis, but this finding needs to be validated in additional studies.[59] Another agent that reduced post-ERCP pancreatitis is gabexate mesilate; however, this agent is not approved in the United States.[60] In addition to NSAIDs more aggressive peri-procedural hydration with intravenous crystalloids may reduce the occurrence of post-ERCP pancreatitis.[61–64]

CHRONIC PANCREATITIS

Chronic pancreatitis results from long-standing pancreatic inflammation resulting in irreversible destruction of pancreatic tissue with fibrin deposition, leading to a loss of exocrine and endocrine functions.[5–11] It has four different stages beginning with a preclinical inflammatory stage where patients remain asymptomatic or have indistinguishable symptoms.[9] In the second-stage patients present with acute attacks that often resemble those of acute pancreatitis. The third stage consists of episodes of intermittent or constant abdominal pain. Finally, in the burnout stage patients present with diminished or absent pain, but develop malabsorption syndrome due to loss of pancreatic exocrine function and may develop diabetes mellitus from loss of endocrine function.

Etiology

Chronic alcohol consumption remains the leading cause of chronic pancreatitis in Western society, accounting for up to two-thirds of cases.[10,11,65,66]

The consumption of 40 g/day or more of alcohol poses a significant risk of chronic pancreatitis.[66] Most of the remaining cases can be classified as idiopathic, while a small percentage of cases are due to rare causes, such as autoimmune, hereditary, and tropical pancreatitis.[10,11,67] Various genetic alterations have also been associated with the occurrence of chronic pancreatitis, including mutations of the following genes: protease serine 1 (trypsin 1) (*PRSS1*), serine peptidase inhibitor Kazal type 1 (*SPINK1*), cystic fibrosis transmembrane conductance regulator (*CFTR*), chymotrypsin C, chymotrypsin B1/B2, carboxypeptidase A1, and carboxyl ester lipase (CEL).[8,10,11,65,68,69] There is also a risk of chronic pancreatitis with cigarette smoking that appears to be dose-dependent and may contribute to mortality from chronic pancreatitis.[8,11,15,65,67,70] There are two classification systems for chronic pancreatitis that take into account the various risk factors associated with the disease (Table 57-4).[65]

TABLE 57-4

Classification of Etiology and Risk Factors for Chronic Pancreatitis

M-ANNHEIM	
Multiple	Risk factors
Alcohol	Excessive consumption (>80 g/day), increased consumption (20-80 g/day), moderate consumption (<20 g/day)
Nicotine	Quantitated in pack-years for current smokers
Nutritional factors	High-fat and protein diet, hyperlipidemia (especially hypertriglyceridemia)
Hereditary factors	Hereditary pancreatitis, familial pancreatitis, early and late-onset idiopathic pancreatitis, tropical pancreatitis, possible gene mutations (eg, *PRSS1*, *SPINK1*, and *CFTR*)
Efferent duct factors	Pancreas divisum, annular pancreas/congenital abnormalities, pancreatic duct obstruction (eg, tumors), posttraumatic pancreatic duct scars, sphincter of Oddi dysfunction
Immunologic factors	Autoimmune pancreatitis
Miscellaneous and rare factors	Hypercalcemia and hyperparathyroidism, chronic kidney disease, medications, toxins
TIGAR-O	
Toxic-metabolic	Alcohol, tobacco smoking, hypercalcemia, hyperlipidemia, chronic kidney disease, medications, toxins
Idiopathic	Early onset, late-onset, tropical pancreatitis
Genetic mutations	*PRSS1, CFTR, SPINK1*, others
Autoimmune	Isolated, syndromic
Recurrent and severe associated acute pancreatitis	Postnecrotic (severe acute pancreatitis), vascular disease/ischemic, postirradiation
Obstructive	Pancreas divisum, sphincter of Oddi dysfunction, pancreatic duct obstruction (eg, tumor), posttraumatic pancreatic duct scars

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Pathophysiology

Although the exact mechanism for the pathogenesis of chronic pancreatitis is unknown, several theories have been proposed. One of the main theories is that repeated episodes of acute pancreatitis lead to the occurrence of chronic pancreatitis.[10,11,65,71] Repeated episodes of acute pancreatitis initiate inflammation and necrosis that leads to ductal scarring and fibrosis. This leads to ductal obstruction and eventually results in acinar atrophy and fibrin deposition.

Regardless of the pathophysiologic mechanism, activation of pancreatic stellate cells is the cause of fibrin deposition in chronic pancreatitis. Various

toxins, oxidative stress, and inflammatory mediators activate pancreatic stellate cells.[10,11,67,71] Activated pancreatic stellate cells then initiate fibrinogenesis. Other mediators generated by the stellate cells themselves perpetuate continued stellate cell activation.

The pathogenesis of pain in chronic pancreatitis has long been thought to be the result of increased pancreatic parenchymal pressure from obstruction, inflammation, and necrosis.[10] However, there is a neurogenic origin of pain. There is abnormal pain processing in the central nervous system of patients with chronic pancreatitis, with functional reorganization of the insular cortex.[10,67] Also, visceral nerves in these patients are sensitized. This may explain the hyperalgesia often experienced by these patients, and the need for various methods of pain management.[11] Patients with chronic pancreatitis may also experience pain in areas distant to the pancreas due to impaired inhibition of somatic and visceral pain pathways.

5 Chronic pain, malabsorption with resultant steatorrhea, and diabetes mellitus are the hallmark symptoms and complications of chronic pancreatitis. Although abdominal pain is the most common symptom at any stage, patients may present with various signs and symptoms depending on the stage of the disease. A more comprehensive list of the common signs and symptoms is presented in Table 57-5.

TABLE 57-5

Signs, Symptoms, and Diagnosis of Chronic Pancreatitis

Signs

- Malnutrition (especially in chronic alcohol misuse)
- Abdominal mass (may indicate a pancreatic pseudocyst)
- Jaundice may be seen
- Splenomegaly (rare)

Symptoms

- Abdominal pain
  - Commonly in epigastric area
  - May radiate to the back
  - Described as deep and penetrating
  - May be relieved by bending/leaning forward or bringing knees to the chest
  - Often occurs with meals and at night
  - May be associated with nausea and vomiting
- Steatorrhea
  - Patients describe bulky or foul-smelling stools often with obvious oil droplets
  - Usually have an average of three to four stools per day
  - May be associated with deficiencies in fat-soluble vitamins
  - Watery diarrhea, excess gas, and abdominal cramps are uncommon
- Pancreatic diabetes mellitus
- Diarrhea (associated with steatorrhea)
- Weight loss
  - May be due to severe malabsorption or acute/chronic pain
  - Substantial loss may be due to associated or unrelated malignancy
- Osteopenia/Osteoporosis (from vitamin D malabsorption and increased bone resorption)
- Bone fractures
- Dyspepsia

Laboratory studies

- CBC to rule out infection (ie, infected pseudocyst)
- Serum amylase and lipase
  - Low specificity for chronic pancreatitis

- May be elevated in acute exacerbations
- Usually are normal or only slightly elevated

- Total bilirubin, alkaline phosphatase, and hepatic transaminases may be elevated with ductal obstruction
- Fasting serum glucose or hemoglobin A_{1c}
- Screening for fat-soluble vitamin (ie, A, D, E, and K) and mineral (ie, magnesium, iron, selenium, and zinc) deficiency
- Pancreatic function tests
  - Indirect
    - Serum trypsinogen (<20 ng/mL [mcg/L] is abnormal)
    - Fecal elastase (<200 mcg/g of stool is abnormal)
    - Fecal chymotrypsin (<3 units/g of stool is abnormal)
    - Fecal fat estimation (>7 g/day is abnormal; need to collect 72 hours of stool)
    - ^{13}C-mixed triglyceride breath test (conducted over 6 hours; not available in the United States)
  - Direct
    - Secretin stimulation (evaluates duodenal bicarbonate secretion)
    - Cholecystokinin stimulation (evaluates pancreatic lipase secretion)
  - Serum albumin (may be low with malnutrition)
  - Serum calcium (may be low with malnutrition)

Imaging studies

- Noninvasive
  - Abdominal ultrasound
  - Computed tomography (CT)
  - Magnetic resonance imaging (MRI)
  - Secretin-enhanced magnetic resonance cholangiopancreatography
- Invasive
  - Endoscopic ultrasonography (EUS)
  - Endoscopic retrograde cholangiopancreatography (ERCP)
- Dual-energy X-ray absorptiometry to assess for osteopenia and osteoporosis

CBC, complete blood count.

Data from References 8–11, 23, 38, 69, 72, 73, and 74.

Diagnosis

The diagnosis of chronic pancreatitis is based primarily on presenting signs and symptoms in combination with either imaging, pancreatic function studies, or histological examination (see Table 57-5). Although histology would be the best diagnostic test, it is recommended only in high-risk patients with strong clinical and functional evidence, but inconclusive imaging studies.[67,69] Therefore, testing usually begins with noninvasive or invasive imaging studies. Abdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging may be used first, but are limited in their ability to produce detailed imaging of pancreatic ductal abnormalities.[8,11,69,75] Invasive studies, such as endoscopic ultrasonography (EUS), are recommended when noninvasive studies are inconclusive.[8,11,69] Secretin-enhanced magnetic resonance cholangiopancreatography produces more detailed images of the pancreatic ducts, and is recommended if all other imaging studies cannot confirm a diagnosis and clinical suspicion remains high.[8,11,65,69,75,76] While ERCP is the gold standard invasive study, it is rarely used due to inter- and intra-observer variability, the risk of post-ERCP pancreatitis, and lack of high-quality evidence comparing it to other imaging studies such as CT, MRI, and EUS.[65,69,75,76] In addition to imagining studies, pancreatic function tests are used when imagining is inconclusive, as adjunctive diagnostic studies or to quantify the degree of exocrine insufficiency.[69,75] The most sensitive studies are the secretin and CCK stimulation tests.[65,75,76] However, these are not widely available and are

uncomfortable for patients. Indirect studies of pancreatic function are most sensitive during late chronic pancreatitis.[65]

Clinical Course and Prognosis

The clinical course of chronic pancreatitis depends on the etiology. Exocrine insufficiency occurs when lipase secretion is less than 10% of normal.[9,69,76] Patients with hereditary chronic pancreatitis typically have exocrine insufficiency occur at an early age, while those with alcohol-induced disease have exocrine insufficiency occur about 5 years after disease onset, with "burnout" of the pancreas in about 10 to 20 years.[76,77] Patients with early-onset idiopathic chronic pancreatitis have delayed progression to exocrine insufficiency compared to those with alcohol-induced or late-onset idiopathic disease.[72] Diabetes mellitus occurs later than exocrine insufficiency and has a reported prevalence of 25% to 80%.[8,78]

The median survival of patients with chronic pancreatitis is estimated to be 15 to 20 years after diagnosis.[11] One of the most significant complications of long-standing disease is pancreatic cancer. Patients with chronic pancreatitis have a 16-fold increased risk of pancreatic cancer.[79] This risk increases depending on the etiology, with patients who smoke having twice the risk.[76]

Treatment

Desired Outcome

The major goals in the treatment of uncomplicated chronic pancreatitis are relief of abdominal pain, treatment of any associated complications such as malabsorption and diabetes mellitus, and improvement in quality of life. Secondary goals include delaying development of complications and treating associated disorders such as depression and malnutrition.

General Approach to Treatment

Treatment of chronic pancreatitis and its complications involves various nonpharmacologic and pharmacologic interventions. Lifestyle modifications should include abstinence from alcohol and smoking cessation.[8,11,69,75,76] In addition, patients with steatorrhea may need to eat smaller, more frequent meals and reduce dietary fat intake.[9,38,69,76] The majority of patients require analgesics and pancreatic enzyme replacement therapy (PERT).[8,11,38,69,75,76] Pain can initially be controlled with medications, but may require more aggressive medical and surgical therapies as the disease progresses. Patients with malabsorption require pancreatic enzymes to reduce steatorrhea and maintain adequate nutrient absorption.[8,11,38,69,75,76] An antisecretory agent may be added to the regimen when enzymes alone provide an inadequate reduction in steatorrhea.[8–10,38,69,76]

Nonpharmacologic Therapy

In addition to medical management, the treatment of chronic pancreatitis includes both lifestyle and dietary modifications. Patients should be counseled to abstain from alcohol use, and smoking cessation should be advocated. Cessation of alcohol use may reduce pain in patients with alcohol-induced chronic pancreatitis, and hastens disease progression and reduces the risk of developing pancreatic cancer.[8,9,11,69,75,76] Smoking has been associated with pain relapses and progression of disease, so cessation should be advocated.[8,11,69] Patients with steatorrhea should be counseled to eat small and frequent meals.[38,69,76] A reduction in dietary fat is not needed routinely, but may be needed in those whose symptoms are uncontrolled with enzyme PERT.[38,75,80] Enteral nutrition via a feeding tube is recommended for patients with malnutrition who do not have an adequate response to oral nutrition support.[38] For patients with chronic pancreatitis requiring tube feeding, use of a jejunal feeding tube is recommended.[38,72]

Invasive procedures and surgery are primarily used to treat uncontrolled pain and the associated complications of chronic pancreatitis. Stents placed via ERCP may be used to treat pancreatic duct strictures in order to relieve parenchymal pressure and reduce pain.[8,69,75,81] Extracorporeal shock wave lithotripsy can be used to break up pancreatic stones with ultrasonic vibration prior to removal by ERCP.[8,11,81,82] Blockade of pain signals through the celiac plexus may be achieved utilizing EUS.[11,69,75,81] The various complications of chronic pancreatitis that can be treated endoscopically include common bile duct strictures, duodenal obstructions, and pancreatic pseudocysts.[8,11,69,75,81] Various surgical techniques including total pancreatectomy may also be used to relieve pain associated with chronic pancreatitis.[23,73,83] Surgery is more effective at relieving pain than endoscopic procedures, but is usually reserved when endoscopic therapy fails.[8,11,69,75,83,84] Finally, total pancreatectomy with transplantation of

pancreatic islet cells to reduce the need for exogenous insulin is recommended as a last-line option for the treatment of pain due to chronic pancreatitis.[8,11,69,75]

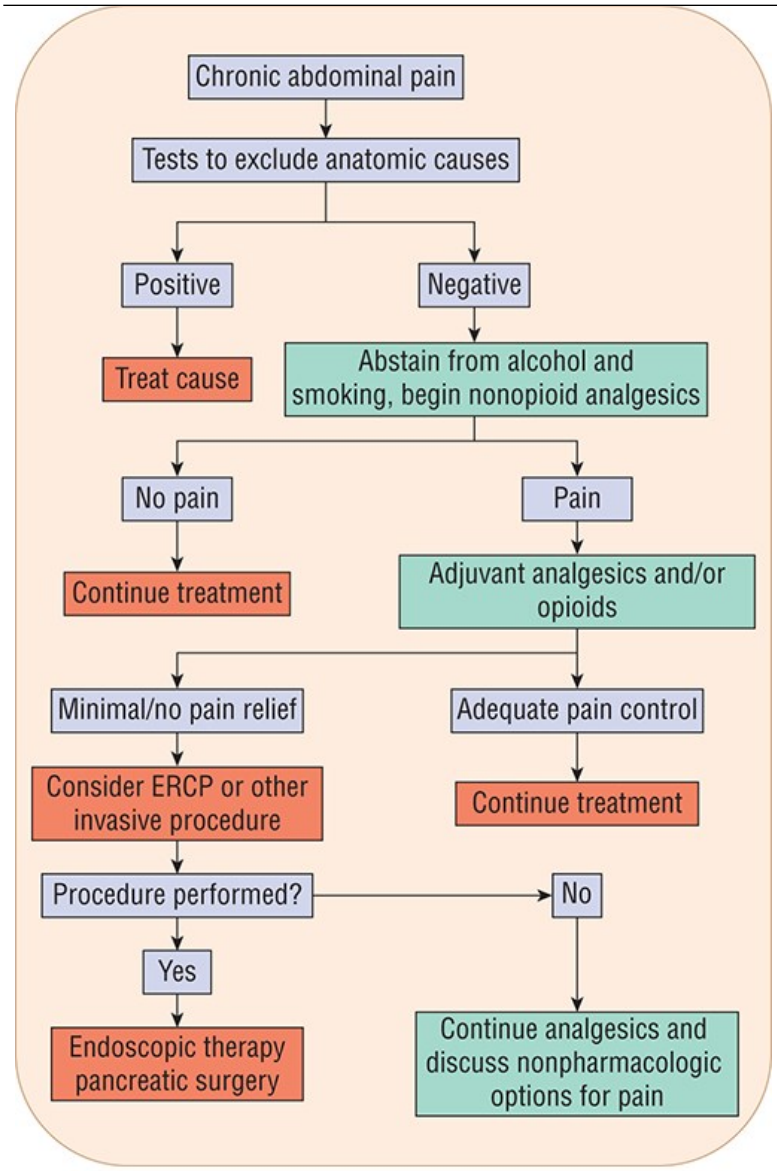
Pharmacologic Therapy

General Recommendations

Pharmacologic therapy of chronic pancreatitis is aimed at controlling pain, treating malabsorption and associated steatorrhea, and controlling diabetes mellitus. Once other causes have been excluded, acetaminophen with or without NSAIDs should be tried initially for pain management (Fig. 57-4).[8,11,67,71,72] Patients with inadequate relief from these agents should have adjuvant agents added to their regimen, with opioid analgesics reserved for patients with refractory pain.[8,11,71,72,75,76] The addition of pancreatic enzyme supplements for pain control has been studied, but is not recommended based on available evidence.[8,9,11,67,69,71,75,76] Antioxidants are recommended for relief of pain due to chronic pancreatitis based on some trials.[8,11,69]

FIGURE 57-4

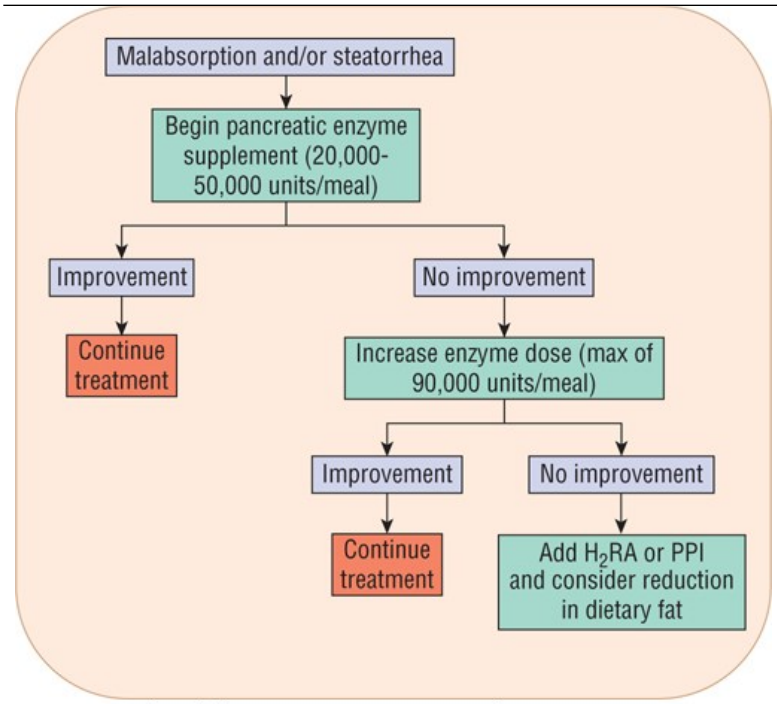
Algorithm for the treatment of abdominal pain in chronic pancreatitis. (ERCP, endoscopic retrograde cholangiopancreatography.)



Most patients with malabsorption will require pancreatic enzyme supplementation in order to achieve adequate nutritional status and reduction in steatorrhea (Fig. 57-5). An antisecretory agent (ie, histamine-2 receptor antagonist or proton pump inhibitor) should be added to the regimen when there is an inadequate response to enzyme therapy alone.[8,38,69,75,76,80] If these measures are ineffective, documentation of the diagnosis and exclusion of other diseases should be undertaken. Exogenous insulin is the primary pharmacologic agent used in the treatment of diabetes mellitus associated with chronic pancreatitis.[8,9,67,71] Metformin may be initiated in early chronic pancreatitis, and has the added benefit of significantly reducing the risk of pancreatic cancer.[8,67,71]

FIGURE 57-5

Algorithm for the treatment of malabsorption and steatorrhea in chronic pancreatitis. (H_2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.)



Relief of Chronic Abdominal Pain

Analgesics

6 Pain from chronic pancreatitis may initially be treated with nonopioid analgesics, but adjuvant agents may be necessary as the disease progresses. Regimens should be individualized and should begin with the lowest effective dose. The dosage regimen should be maximized before adding or substituting agents. Analgesics should be scheduled around the clock rather than as needed in order to maximize efficacy. Scheduling short-acting analgesics prior to meals should help decrease postprandial pain. Following the World Health Organization pain ladder, acetaminophen or NSAIDs should be used initially.[8,11,67,71–73] As the response diminishes to adequate doses of nonopioid analgesics, adjuvant agents should be added to the regimen.[8,11,67,71,73] Tramadol may also be effective and could be tried before adding opioid analgesics.[11,73] Opioids are used last as other agents become ineffective or patients have intolerance (Table 57-6).[8,11,67,69,71,72,80]

TABLE 57-6

Recommendations for the Pharmacologic Treatment of Chronic Pancreatitis

Treatment of chronic pain (oral drug regimens)

Nonopioid analgesics

- Begin with acetaminophen at doses of 500-650 mg per dose every 4-6 hours following product labeling for maximum daily dose; caution for patients also receiving acetaminophen from other combination analgesics, and in those with liver disease
- Can also start with NSAIDs at low doses (ie, 200-400 mg ibuprofen every 6-8 hours) and titrate to maximum recommended doses as needed; caution in patients with cardiovascular disease or high disease risk, and in patients with kidney impairment or disease

Adjuvant agents

- Pregabalin has the best evidence; begin with 75 mg twice daily; maximum dose of 300 mg twice daily
- Consider use of selective serotonin reuptake inhibitors (eg, paroxetine), serotonin/norepinephrine reuptake inhibitors (eg, duloxetine) and tricyclic antidepressants in patients with difficult-to-manage pain

Opioids

- Tramadol: 50-100 mg every 4-6 hours, not to exceed 400 mg/day; has opioid-like effect; contraindicated in alcohol or hypnotic intoxication; be aware of drug interactions; expensive
- Codeine 30-60 mg every 6 hours; hydrocodone 5-10 mg every 4-6 hours; morphine sulfate (extended-release) 30-60 mg every 8-12 hours; oxycodone 5-10 mg every 6 hours; methadone 2.5-10 mg every 8-12 hours; hydromorphone 0.5-1 mg every 4-6 hours; fentanyl patch 25-100 mcg/hr every 72 hours
- Risk of potentiation with alcohol; impaired respiration; constipation; hypotension; allergy
- Dosing is usually based on providing continuous pain relief; consider combining with acetaminophen; opioid dependence is common; abuse is a concern in patients who misuse alcohol; tolerance may develop

Treatment of malabsorption and steatorrhea

- Start with pancreatic enzymes containing 20,000-50,000 USP units of lipase with each meal of a preferred product (see Table 57-7); administer dose during meals; administer multiple capsules/tablets throughout the meal; use half the mealtime dose with snacks
- Increase dose to a maximum of 90,000 USP units of lipase per meal
- Products containing enteric-coated microspheres may be more effective than other dose forms

Acid-suppression agents

- May improve efficacy of enzyme therapy for malabsorption and steatorrhea
- Preferred for use with nonenteric-coated dose forms

USP, United States Pharmacopeia.

Data from References 8, 9, 11, 67, 69, 72, 75, 76, 80, and 74.

Pancreatic Enzymes

Although pancreatic enzymes are primarily used to treat malabsorption associated with chronic pancreatitis, they have also been used to treat pain from the disease. Relief of pain using pancreatic enzymes is thought to be due to their ability to break down CCK.[9,72,75] Release of CCK is normally inhibited by trypsin, but patients with chronic pancreatitis have decreased trypsin production. The proteases in pancreatic enzyme supplements are thought to act as substitutes for endogenous trypsin, leading to a decrease in CCK release. However, there are mixed results from trials investigating pancreatic enzyme supplements for the treatment of pain from chronic pancreatitis. This may be due to the differences between the various enzyme formulations used in the trials as well as the small number of subjects enrolled.[9,11,69,75,76] However, trials that used nonenteric-coated enzyme formulations have a benefit in the treatment of pain.[71,72,74] Enteric-coated formulations may not release enough proteases in the duodenum to inhibit

CCK release. Despite their intuitive mechanism current guidelines do not recommend the use of pancreatic enzyme therapy for the treatment of pain from chronic pancreatitis due to lack of beneficial outcomes.[69,80]

Other Agents

Various adjuvant agents are also used in patients experiencing pain from chronic pancreatitis. Selective serotonin reuptake inhibitors and tricyclic antidepressants are used both for treating the concomitant depression that often occurs in patients with chronic pancreatitis and for their potential effects on pain (see Table 57-6).[8,9,11,67,71] Gabapentin and pregabalin are effective adjunct analgesics.[8,9,11,67,85] Patients with chronic pancreatitis have increased oxidative stress, and the use of antioxidants, such as selenium, vitamins C and E, and β-carotene, has some benefit in relieving pain and improving quality of life in these patients.[11,69,86–88] The details of their benefit remains variable, but due to their low cost and relative safety, the American College of Gastroenterology guidelines for chronic pancreatitis considers their use for treatment of pain.[69]

Treatment of Malabsorption

7 Pancreatic enzyme and fat-soluble vitamin supplementation are the primary treatments for malabsorption due to chronic pancreatitis. Treatment should begin when steatorrhea is documented and persistent weight loss occurs despite any dietary modifications. The utilization of pancreatic enzymes enhances the patient's nutritional status and reduces steatorrhea and resultant abdominal symptoms. Malabsorption is minimized if the concentration of lipase delivered to the duodenum with supplementation is about 10% of normal pancreatic output.[9] This requires that 20,000 to 50,000 units of lipase be administered with each meal to start (see Table 57-6).[38,67,75,80,89,90] Half of the necessary mealtime dose is recommended with snacks.[38,80,89] In many cases the lipase dose will need to be increased due to insufficient lipolytic activity, but doses greater than 90,000 units per meal are not recommended. In addition to enzyme replacement therapy, patients with chronic pancreatitis have deficiencies in fat-soluble vitamins.[38,69,91] Thus, they should be assessed for vitamin deficiencies and provided necessary supplementation as required.[9,38,69,76,80,89]

8 There is little evidence regarding the optimal dosage form and administration of pancreatic enzyme supplements. Most studies have compared them with placebo rather than other enzyme products, and used quantitation of fat absorption or elimination as a primary measure of efficacy rather than weight gain.[69,92] While they may not completely eliminate steatorrhea, they improve nutritional parameters and quality of life of patients with chronic pancreatitis.[8,11,69,76] Since most exogenous lipase is rapidly and irreversibly destroyed at low intragastric pH, enteric-coated products are preferred for the treatment of malabsorption and steatorrhea. The enteric coating only dissolves at a pH greater than 5.5, which allows a sufficient quantity of enzymes to remain intact until dissolution of the coating in the duodenum.[38,76] However, enzymes must also be emptied from the stomach into the duodenum at the same rate and time as ingested food. The size of the enteric-coated enzyme preparation influences the rate of enzyme delivery to the duodenum.[9] Likewise, the administration time relevant to a meal influences the timing of enzyme delivery. Products containing enzymes in small enteric-coated microspheres are preferred, and they should be administered with meals.[38,67,76,80,90] Ideally, patients should eat five to six small meals per day, and if patients need to take more than one capsule/tablet per meal, the doses should be distributed throughout the meal.[38,67,80]

Despite enzyme therapy, patients may continue to have steatorrhea and fail to have improvement in nutritional parameters. Adherence should be assessed in these patients as the number of capsules required with each meal can lead to reduced adherence. Alternative products with higher lipase content can be tried in order to reduce the number of capsules needed. If this fails, the dose of lipase should be increased. Finally, addition of an antisecretory agent (ie, histamine-2 receptor antagonist or proton pump inhibitor) may be tried to increase the availability of active enzymes in the duodenum.[8,38,76,80,89,90]

Pancreatic Enzyme Supplements

Five pancreatic enzyme products are approved by the FDA, but only two of these products are specifically approved for exocrine pancreatic insufficiency associated with chronic pancreatitis.[93,94] Dosage forms of approved products include regular-release tablets, enteric-coated beads, bicarbonate-buffered enteric-coated microspheres, enteric-coated microspheres, and enteric-coated minitablets or microtablets encased in a cellulose or gelatin capsule (Table 57-7). Enzymes are easily administered to patients who are able to swallow the capsules or their contents. However, administration to patients with enteral feeding tubes presents a challenge. Products containing microspheres may be administered through feeding

tubes in food or solutions with a pH of 4.5 or less.[38,90] Clinicians must be aware, however, that available products are not equivalent and should consider this before substituting products in patients who require administration through a nonoral route. Careful consideration should also be given to this issue in patient care facilities with limited formularies.

TABLE 57-7

Commercially Available Pancreatic Enzyme (Pancrelipase) Preparations

	Enzyme Content Per Unit Dose (USP Units)		
Product	**Lipase**	**Amylase**	**Protease**
Tablets			
Viokace™ 10,440 lipase units	10,440	39,150	39,150
Viokace™ 20,880 lipase units	20,880	78,300	78,300
Enteric-coated beads			
Zenpep® 3,000 lipase units	3,000	14,000	10,000
Zenpep® 5,000 lipase units	5,000	24,000	17,000
Zenpep® 10,000 lipase units	10,000	42,000	32,000
Zenpep® 15,000 lipase units	15,000	63,000	47,000
Zenpep® 20,000 lipase units	20,000	84,000	38,000
Zenpep® 25,000 lipase units	25,000	105,000	79,000
Zenpep® 40,000 lipase units	40,000	168,000	126,000
Enteric-coated microspheres with bicarbonate buffer			
Pertzye 4,000 lipase units	4,000	15,125	14,375
Pertzye 8,000 lipase units	8,000	30,250	28,750
Pertzye 16,000 lipase units	16,000	60,500	57,500
Enteric-coated microspheres			
Creon® 3,000 lipase units	3,000	15,000	9,500
Creon® 6,000 lipase units	6,000	30,000	19,000
Creon® 12,000 lipase units	12,000	60,000	38,000
Creon® 24,000 lipase units	24,000	120,000	76,000

Creon® 36,000 lipase units	36,000	180,000	114,000
Enteric-coated minitablets/microtablets			
Pancreaze® 2,600 lipase units	2,600	10,850	6,200
Pancreaze® 4,200 lipase units	4,200	24,600	14,200
Pancreaze® 10,500 lipase units	10,500	61,500	35,500
Pancreaze® 16,800 lipase units	16,800	98,400	56,800
Pancreaze® 21,000 lipase units	21,000	83,900	54,700

USP, United States Pharmacopeia.

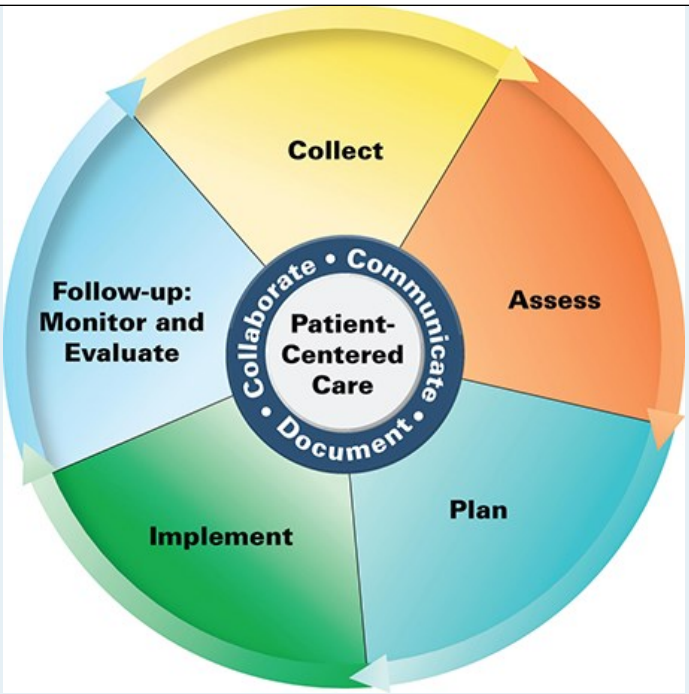
Adverse reactions from pancreatic enzyme supplements are generally benign. High doses can lead to nausea, diarrhea, and intestinal upset.[76] One of the more serious adverse effects of these products is fibrosing colonopathy. It occurs when the enzymes cause deposition of fibrin in the colon leading to colonic stricture. This reaction is uncommon and has been reported mostly in children with cystic fibrosis who received high doses of enzymes for prolonged periods.[38,76] Another concern with pancreatic enzymes is the risk of possible viral infection due to contamination of these porcine-derived products.[76]

Adjuncts to Enzyme Therapy

9 The addition of a histamine-2 receptor antagonist or proton pump inhibitor to pancreatic enzyme supplementation may increase the effectiveness of enzyme therapy for malabsorption and steatorrhea. The beneficial effects of these agents result from an increase in gastric and duodenal pH.[38,76,90] This results in an increase in the amount of active enzymes available in the duodenum. Their use has been mainly recommended with nonenteric-coated enzyme products.[9,75,80,89] In fact, the only nonenteric-coated formulation approved by the FDA is indicated for administration with a proton pump inhibitor.[94]

PATIENT CARE PROCESS

Patient Care Process for Pancreatitis



Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient history (past medical—hyperlipidemia, recent surgery, gallstone disease or ERCP; social—dietary habits, alcohol use, tobacco use)
- Current and recent (for acute pancreatitis; see Table 57-2) medications
- Medication allergies
- Review of systems for the abdomen and gastrointestinal system (eg, abdominal pain, nausea and vomiting, stool frequency and consistency for chronic pancreatitis; see Tables 57-3 and 57-5)
- Objective data
  - Acute pancreatitis (see Table 57-3)

    Vital signs (eg, BP, heart rate, temperature, respiratory rate)

    Labs (eg, CBC, Chem-7, calcium, albumin, amylase, lipase, transaminases, bilirubin, triglycerides)

    Microbiology results

    Intake/output
  - Chronic pancreatitis (see Table 57-5)

    Physical exam (eg, weight; assessment for neuropathy, nephropathy, and retinopathy with diabetes)

    Labs (eg, fasting serum glucose, bilirubin, transaminases, pancreatic function tests, fat-soluble vitamins, zinc, magnesium, calcium, albumin)

Assess

- Acute pancreatitis
  - Causative medications (see Table 57-2)
  - Nutrition and fluid status
  - Abdominal pain: location, radiation, severity, onset
  - Infectious etiologies
  - Continuous hemodynamic monitoring
- Chronic pancreatitis
  - Alcohol and tobacco use
  - Abdominal pain
  - Trends in weight, nutrition status, serum glucose, and stool consistency and frequency (assess for constipation if patient is taking opioids)

Plan*

- Acute pancreatitis
  - Fluid support including choice and dose
  - Discontinue suspected causal medications
  - Nutrition support including route and caloric requirements
  - Pain management with specific medication choice, route, and dose
  - Antimicrobial therapy regimen for suspected or identified infection(s)
- Chronic pancreatitis
  - Tailored lifestyle modifications (eg, abstinence from alcohol, smoking cessation; see Fig. 57-4)
  - Nutrition support and dietetic counseling
  - Therapy for abdominal pain (see Fig. 57-4) with analgesics (see Table 57-6) and pancreatic enzymes (see Table 57-7), including the need for treatment of constipation if opioids are utilized
  - Therapy for malabsorption (see Fig. 57-5, and Tables 57-6 and 57-7)
  - Treatment of concomitant diabetes mellitus if present

Implement

- Consultation with additional providers as necessary (eg, dietician, pain management specialist, infectious diseases, gastroenterology, endocrinology) and consider transfer to a specialty center if severe disease
- Pain therapy with clearly identified goals for both the provider and patient
- Fluid and nutrition support as appropriate
- Necessary lifestyle modifications (eg, alcohol and smoking cessation)

- For patients with acute pancreatitis consider antimicrobial therapy if suspected or known infection and narrow coverage based on cultures and sensitivities
- For patients with malabsorption due to chronic pancreatitis initiate appropriate pancreatic enzyme therapy

Follow-up: Monitor and Evaluate

- Pain control and constipation if opioids utilized
- Acute pancreatitis
  - Fluid and electrolytes along with kidney and liver function (eg, serum creatinine, BUN, bilirubin, transaminases)
  - Signs and symptoms of infection along with microbiology culture and sensitivity results
  - Hemodynamic parameters for signs of decreased intravascular volume and shock
  - Nutrition status and support (eg, prealbumin, albumin, changes in caloric requirements and delivery route)
  - Discontinuation of causative medication(s) on discharge and identification of necessary therapeutic alternative(s)
  - Brief alcohol cessation intervention prior to discharge for alcohol-related acute pancreatitis
- Chronic pancreatitis
  - Alcohol intake and smoking status utilizing motivational interviewing
  - Weight and effects of diet on abdominal pain and malabsorption symptoms
  - Efficacy of pancreatic enzymes on symptoms of malabsorption (see Fig. 57-5)
  - Serum blood glucose along with signs and symptoms of diabetes mellitus

**Collaborate with patients, caregivers, and other healthcare professionals.*

EVALUATION OF THERAPEUTIC OUTCOMES

Acute Pancreatitis

Hydration status, serum electrolytes, pain control, and nutritional status should be assessed periodically in patients with mild acute pancreatitis, depending on the degree of abdominal pain and fluid loss. Patients with severe acute pancreatitis should receive intensive care and close monitoring of vital signs, fluid and electrolyte status, white blood cell count, blood glucose, lactate dehydrogenase, aspartate aminotransferase, serum albumin, hematocrit, BUN, serum creatinine, and international normalized ratio. Continuous hemodynamic and arterial blood gas monitoring is essential. Serum lipase, amylase, and bilirubin require less frequent monitoring. The patient should also be monitored for signs of infection, relief of abdominal pain, and adequate nutritional status. Severity of disease and patient response should be assessed using an evidence-based method.

Chronic Pancreatitis

The severity and frequency of abdominal pain should be assessed periodically in patients with chronic pancreatitis using a standardized scale in order to determine the efficacy of pain therapy. Patients receiving opioids should be prescribed laxatives on an as-needed or scheduled basis and be monitored for constipation. Patients receiving pancreatic enzymes for malabsorption should have their weight and stool frequency and consistency monitored periodically. More objective assessments of fecal fat content, such as the ^{13}C-mixed triglyceride breath test, can be utilized, but are usually unnecessary and impractical in general clinical practice.[9,38,76] Blood glucose must be closely monitored in patients with diabetes mellitus, and those with long-standing disease should receive appropriate monitoring for nephropathy, retinopathy, and neuropathy.[9]

ABBREVIATIONS

APACHE	Acute Physiology and Chronic Health Evaluation
BISAP	besdside index of severity in acute pancreatitis
BUN	blood urea nitrogen
CCK	cholecystokinin
CECT	contrast-enhanced computed tomography
CEL	carboxyl ester lipase
CFTR	cystic fibrosis transmembrane conductance regulator gene
CT	computed tomography
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasonography
HIV	human immunodeficiency virus
ICU	intensive care unit
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
NSAID	nonsteroidal anti-inflammatory drug
PERT	pancreatic enzyme replacement therapy
PRSS1	protease serine 1 (trypsin 1) gene
SIRS	systemic inflammatory response syndrome
SPINK1	serine peptidase inhibitor Kazal type 1 gene
VIP	vasoactive intestinal peptide

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SELF-ASSESSMENT QUESTIONS

1. Which of the following etiologies of acute pancreatitis is the most common in the United States?
   A. Gallstones
   B. Medications
   C. Alcohol
   D. ERCP
2. Which of the following medications has a probable association as a cause of acute pancreatitis?
   A. Pravastatin
   B. Opiates
   C. Hydrochlorothiazide
   D. Bactrim
3. Which of the following is correct concerning the course of acute pancreatitis?
   A. About half of patients have a severe course with a mortality rate over 50%.
   B. The gold standard for identifying patients at risk for a severe course is serum lipase.
   C. There is no role for CECT in the diagnosis or staging of acute pancreatitis.
   D. Scoring systems combine multiple factors to predict the clinical course of acute pancreatitis.
4. Which of the following is correct regarding fluid replacement in acute pancreatitis?
   A. Patients at risk for renal or cardiovascular complications should be fluid restricted.
   B. Fluid and electrolyte requirements are minimal in patients with mild disease.
   C. Guidelines recommend 5-10 mL/kg/hr of initial fluid replacement.
   D. Sequestered fluid in the peritoneal or retroperitoneal space should not be replaced.

5. Which of the following is the best nutrition therapy for a patient who is on hospital day 5 with slowly resolving severe acute pancreatitis?

   A. Oral nutrition with a low-fat diet

   B. Enteral nutrition support via the nasogastric route

   C. Total parenteral nutrition

   D. Combined enteral and parenteral nutrition

6. Which of the following is correct with respect to the use of opioid analgesics for pain associated with acute pancreatitis?

   A. Avoid agents that cause spasm of the sphincter of Oddi.

   B. Morphine is often used due to longer duration of action.

   C. Synthetic opioids are the preferred agents.

   D. Merperidine is the agent of choice.

7. Which is of the following is correct regarding studies evaluating the use of prophylactic antibiotics in acute pancreatitis?

   A. No benefit is present in acute pancreatitis without infection.

   B. Studies using carbapenems show a decrease in pancreatic infection.

   C. The largest studies have the greatest benefit.

   D. Studies enrolling patients without necrosis show a decrease in mortality.

8. Which of the following cell types are thought to be a primary cause of the pathogenesis of chronic pancreatitis?

   A. B cells

   B. Macrophages

   C. T cells

   D. Stellate

9. Which of the following imaging studies should be used first along with clinical signs and symptoms in the diagnosis of chronic pancreatitis?

   A. CT

   B. MRCP

   C. EUS

   D. ERCP

10. Which of the following is the best recommendation for a 47-year-old man with chronic pancreatitis who smokes and still has steatorrhea despite maximum pancreatic enzyme supplementation?

    A. Begin a histamine-2 receptor antagonist.

    B. Quit smoking and begin fat-soluble vitamin supplementation.

    C. Begin a proton pump inhibitor, quit smoking, and reduce fat intake.

D. Switch enzyme supplement and maintain current fat intake.

11. Which of the following is the best therapy for treating pain from chronic pancreatitis in a 51-year-old woman with a past medical history of a bleeding gastric ulcer who is no longer getting relief from acetaminophen 650 mg orally four times daily?

A. Fentanyl 25 mcg/hr transdermal patch every 72 hours

B. Hydrocodone/acetaminophen 5/500 mg orally four times daily

C. Ibuprofen 400 mg orally three times daily

D. Tramadol 50 mg orally four times daily

12. Which of the following patients with chronic pancreatitis is the best candidate for pancreatic enzyme supplementation?

A. Steatorrhea with persistent weight loss

B. Steatorrhea without weight loss

C. Fecal fat estimation of 2 g/day

D. Worsening pain despite opioids

13. Which of the following pancreatic enzyme supplement dose forms could be administered through an enteral feeding tube in an acidic solution?

A. Minitablets

B. Enteric-coated beads

C. Microspheres

D. Microtablets

14. Which of the following is the best option for a patient with persistent steatorrhea who has not gained weight despite receiving the maximum dose of microsphere enzyme supplements administered during meals?

A. Change to minitablets

B. Add an antisecretory agent

C. Administer supplements before meals

D. Administer supplements with applesauce

15. Which of the following should regularly be assessed in a patient receiving opioids for pain associated with chronic pancreatitis?

A. Steatorrhea

B. Weight loss

C. Respiratory depression

D. Constipation

SELF-ASSESSMENT QUESTIONS-ANSWERS

1. **A.** Obstruction due to gallstones is the leading cause of acute pancreatitis in the United States, with alcohol misuse being the second most common

cause. Although medications and ERCP can cause acute pancreatitis, they are infrequent causes compared to gallstones and alcohol misuse. See Table 57-1 for other etiologies of acute pancreatitis.

2. **C.** Hydrochlorothiazide is classified as having a probable cause of acute pancreatitis. A list of other medications associated with the occurrence of acute pancreatitis and their classification as a likely cause can be found inTable 57-2.

3. **D.** Several scoring systems have been developed to predict the clinical course of acute pancreatitis. They all use multiple pieces of information that usually makes them difficult to use at the bedside.

4. **C.** Guidelines recommend anywhere from 250 to 500 mL/hr to 5 to 10 mL/kg/hr of intravenous fluid for the first 12 to 24 hours during resuscitation in patients with acute pancreatitis.

5. **B.** Current guidelines recommend beginning oral or enteral nutrition within the first 24 to 72 hours of admission in patients with severe acute pancreatitis. If the patient cannot tolerate an oral diet enteral nutrition delivered via the nasogastric route is recommended.

6. **B.** When the utilization of opioids is necessary for pain control in patients with acute pancreatitis, morphine is preferred due to its longer duration of action.

7. **A.** Large studies and meta-analyses show no benefit with prophylactic antimicrobial use in patients with severe acute or necrotizing pancreatitis in patients without signs or symptoms of infection. When infected pancreatitis is suspected, carbapenems is beneficial.

8. **D.** Activation of pancreatic stellate cells is thought to be the primary pathophysiologic mechanism for the development of chronic pancreatitis. Their activation by various mediators leads to fibrin deposition that causes pancreatic duct obstruction.

9. **A.** CT and MRI are recommended first along with clinical signs and symptoms for the diagnosis of chronic pancreatitis. More invasive imaging studies, such as MRCP, EUS and ERCP are recommended when noninvasive studies are inconclusive.

10. **C.** Smoking is strongly associated with the occurrence and risk of chronic pancreatitis, as well as worsening progression of the disease, so smoking cessation should be implemented for this patient. In addition, patients who fail to respond to maximum doses of pancreatic enzyme supplementation should reduce fat intake and have an antisecretory agent, either a histamine-2 receptor antagonist or proton pump inhibitor, added to their medication therapy regimen.

11. **D.** While NSAIDs and acetaminophen are the first-line analgesics recommended for the treatment of pain from chronic pancreatitis, NSAIDs would be contraindicated in this patient with a history of a bleeding gastric ulcer. Tramadol is effective in the treatment of pain from chronic pancreatitis and is recommended before implementation of opioids.

12. **A.** While laboratory studies may be used to assess the effectiveness and guide the dosage of pancreatic enzyme supplementation, clinical signs and symptoms of malabsorption, along with indicators of malnutrition such as weight loss, are used in determining when supplementation should be initiated.

13. **C.** Products composed of microspheres are recommended for administration through enteral feeding tubes when suspended in an acidic solution. This is because they have the smallest particle size compared to products composed of microbeads or mini- or microtablets.

14. **B.** The addition of a histamine-2 receptor antagonist or proton pump inhibitor is recommended when patients with exocrine pancreatic insufficiency fail to show an adequate response to maximum tolerated enzyme supplementation. The increase in gastric pH provided by the use of these agents allows more enzymes to survive the generally acid gastric contents until they reach the duodenum.

15. **D.** Patients prescribed opioids for the pain due to chronic pancreatitis should be assessed regularly for constipation. In addition, they should be prescribed laxatives on as-needed or scheduled basis for episodes of constipation.