Chapter 28: Pancreatitis

INTRODUCTION

- *Acute pancreatitis* (AP) is an inflammatory disorder of the pancreas characterized by upper abdominal pain and pancreatic enzyme elevations.
- *Chronic pancreatitis* (CP) is a progressive disease characterized by long-standing pancreatic inflammation leading to loss of pancreatic exocrine and endocrine function.

ACUTE PANCREATITIS: PATHOPHYSIOLOGY

- Gallstones and alcohol abuse account for most cases in the United States. Diabetes mellitus and autoimmune disorders such as inflammatory bowel disease are also associated with an increase in AP. A cause cannot be identified in some patients (idiopathic pancreatitis).
- Many medications have been implicated (**Table 28-1**), but drug-induced AP is rare. A causal association is difficult to confirm because ethical and practical considerations preclude rechallenge.
- AP is initiated by premature activation of trypsinogen to trypsin within the pancreas, leading to activation of other digestive enzymes and autodigestion of the gland.
- Activated pancreatic enzymes within the pancreas and surrounding tissues produce damage and necrosis to pancreatic tissue, surrounding fat, vascular endothelium, and adjacent structures. Lipase damages fat cells, producing noxious substances that cause further pancreatic and peripancreatic injury.
- Release of cytokines by acinar cells injures those cells and enhances the inflammatory response. Injured acinar cells liberate chemoattractants that attract neutrophils, macrophages, and other cells to the area of inflammation, causing systemic inflammatory response syndrome (SIRS). Vascular damage and ischemia cause release of kinins, which make capillary walls permeable and promote tissue edema.
- Pancreatic infection may result from increased intestinal permeability and translocation of colonic bacteria.
- Local complications in severe AP include acute fluid collection, pancreatic necrosis, infection, abscess, pseudocyst formation, and pancreatic ascites.
- Systemic complications include respiratory failure and cardiovascular, renal, metabolic, hemorrhagic, and CNS abnormalities.

TABLE 28-1

Medications Associated with Acute Pancreatitis

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

CLINICAL PRESENTATION

- Clinical presentation depends on severity of the inflammatory process and whether damage is confined to the pancreas or involves local and systemic complications.
- The initial presentation ranges from moderate abdominal discomfort to excruciating pain, shock, and respiratory distress. Abdominal pain occurs in 95% of patients and is usually epigastric, often radiating to the upper quadrants or back. Onset is usually sudden, and intensity is often described as “knife-like” or “boring.” Pain usually reaches maximum intensity within 30 minutes and may persist for hours or days. Nausea and vomiting occur in 85% of patients and usually follow onset of pain.
- Signs include marked epigastric tenderness on palpation with rebound tenderness and guarding in severe cases. The abdomen is often distended and tympanic with decreased or absent bowel sounds 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 signs of acute respiratory complications.
- Jaundice and altered mental status may be present; other signs of alcoholic liver disease may be present in patients with alcoholic pancreatitis.

DIAGNOSIS

- Diagnosis of AP requires two of the following: (1) upper abdominal pain, (2) serum lipase or amylase at least three times the upper limit of normal, and (3) characteristic findings on imaging studies.
- Transabdominal ultrasound should be performed in all patients to detect dilated biliary ducts and gallstones. Contrast-enhanced computed tomography (CECT) is used if the diagnosis cannot be made from clinical and laboratory findings. Magnetic resonance cholangiopancreatography (MRCP) is used to grade severity of AP, identify bile duct problems not seen on CECT, or if there are contraindications to CECT.
- AP may be associated with leukocytosis, hyperglycemia, and hypoalbuminemia. Hepatic transaminases, alkaline phosphatase, and bilirubin are usually elevated in gallstone pancreatitis and in patients with intrinsic liver disease. Marked hypocalcemia indicates severe necrosis and is a poor prognostic sign.
- Serum amylase usually rises 4–8 hours after symptom onset, peaks at 24 hours, and returns to normal over the next 8–14 days. Concentrations greater than three times the upper limit of normal are highly suggestive of AP.
- Serum lipase is specific to the pancreas, and concentrations are elevated and parallel the serum amylase elevations. Increases persist longer than serum amylase elevations and can be detected after the amylase has returned to normal.
- Hematocrit may be normal, but hemoconcentration results from multiple factors (eg, vomiting). Hematocrit >47% predicts severe AP, and hematocrit <44% predicts mild disease.
- C-reactive protein levels >150 mg/dL at 48–72 hours predict severe AP.
- Thrombocytopenia and increased international normalized ratio (INR) occur in some patients with severe AP and associated liver disease.

TREATMENT (FIG. 28-1)

- Goals of Treatment: Relieve abdominal pain and nausea; replace fluids; correct electrolyte, glucose, and lipid abnormalities; minimize systemic complications; and manage pancreatic necrosis and infection.

FIGURE 28-1

Algorithm of guidelines for evaluation and treatment of acute pancreatitis.

(ERCP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome.)

Nonpharmacologic Therapy

- Endoscopic retrograde cholangiopancreatography (ERCP) may be performed to remove biliary tract stones.
- Patients with alcohol-related pancreatitis should receive abstinence interventions during the inpatient stay.
- Nutritional support is important because AP creates a catabolic state that promotes nutritional depletion. Patients with mild AP can begin oral feeding when pain is decreasing and inflammatory markers are improving. Nutritional support should begin when it is anticipated that oral nutrition will be withheld for longer than 1 week. Enteral nutrition via nasogastric or nasojejunal tube is preferred over parenteral nutrition (PN) in severe AP, if tolerated. If enteral feeding is not possible or is inadequate, PN should be implemented before protein and calorie depletion become advanced.

Pharmacologic Therapy

- Patients with AP often require IV antiemetics for nausea.

- Patients requiring ICU admission should be treated with antisecretory agents if they are at risk of stress-related mucosal bleeding.
- Vasodilation from the inflammatory response, vomiting, and nasogastric suction contribute to hypovolemia and fluid and electrolyte abnormalities, necessitating replacement. Patients should receive aggressive fluid replacement to reduce the risks of persistent SIRS and organ failure. Different guidelines recommend goal-directed IV fluid with either lactated Ringer's at an initial rate of 5–10 mL/kg/hr or crystalloids at a rate of 250–500 mL/hr.
- Intravenous potassium, calcium, and magnesium are used to correct electrolyte deficiency, and insulin is used to treat hyperglycemia.
- Parenteral opioid analgesics are used to control abdominal pain, although high-quality supporting evidence is lacking. Parenteral **morphine** is often used, and patient-controlled analgesia should be considered in patients who require frequent opioid dosing (eg, every 2–3 hours). Nonsteroidal anti-inflammatory agents (NSAIDs) may be sufficient in patients with mild-to-moderate pain if not contraindicated.
- Selective digestive tract decontamination using minimally absorbed antibiotics may be effective in reducing the risk of pancreatic infection, but more studies are needed before this approach can be recommended.
- Prophylactic antibiotics are not recommended in patients with AP without signs or symptoms of infection, including those with necrosis, predicted severe AP, or necrotizing pancreatitis. However, empiric antimicrobial therapy may be considered in patients with necrosis who deteriorate or fail to improve within 7–10 days.
- Patients with known or suspected infected AP should receive broad-spectrum antibiotics that cover the range of enteric aerobic gram-negative bacilli and anaerobic organisms. **Imipenem–cilastatin** (500 mg IV every 8 hours) has been widely used but has been replaced on many formularies by newer carbapenems (eg, **meropenem**). A fluoroquinolone (eg, **ciprofloxacin** or **levofloxacin**) combined with **metronidazole** should be considered for penicillin-allergic patients.
- There are insufficient data to support routine use of somatostatin or octreotide for treatment of AP. Parenteral histamine2-receptor antagonists and proton pump inhibitors do not improve the overall outcome of patients with AP.

EVALUATION OF THERAPEUTIC OUTCOMES

- In patients with mild AP, assess pain control, fluid and electrolyte status, and nutrition periodically depending on the degree of abdominal pain and fluid loss.
- Goals for fluid therapy include one or more of the following: heart rate <120 bpm, mean arterial pressure 65–85 mm Hg, urinary output >0.5–1 mL/kg/hr, invasive measures of stroke volume or intrathoracic blood volume, or hematocrit 35%–44% with blood transfusion.
- Transfer patients with severe AP to an intensive care unit for close monitoring of vital signs, fluid and electrolyte status, white blood cell count, blood glucose, lactate dehydrogenase, aspartate aminotransferase, serum albumin, hematocrit, blood urea nitrogen, serum creatinine, and INR. Continuous hemodynamic and arterial blood gas monitoring is essential. Serum lipase, amylase, and bilirubin require less frequent monitoring. Monitor for signs of infection, relief of abdominal pain, and adequate nutritional status. Assess severity of disease and patient response using evidence-based methods.

CHRONIC PANCREATITIS: PATHOPHYSIOLOGY

- CP results from long-standing pancreatic inflammation and leads to irreversible destruction of pancreatic tissue with fibrin deposition and loss of exocrine and endocrine function.
- Chronic ethanol consumption accounts for about two-thirds of cases in Western society. Most of the remaining cases are idiopathic, and a small percentage is due to rare causes such as autoimmune, hereditary, and tropical pancreatitis.
- The exact pathogenesis is unknown. Activation of pancreatic stellate cells by toxins, oxidative stress, and/or inflammatory mediators appears to be the cause of fibrin deposition.

- Abdominal pain may be caused by abnormal pain processing in the central nervous system and sensitization of visceral nerves. This may explain the hyperalgesia that CP patients often experience with the need for various methods of pain management. Impaired inhibition of somatic and visceral pain pathways may also cause pain in areas distant to the pancreas.

CLINICAL PRESENTATION

- The main features of CP are abdominal pain, malabsorption with steatorrhea, weight loss, and diabetes. Jaundice occurs in ~10% of patients.
- Patients typically report deep, penetrating epigastric or abdominal pain that may radiate to the back. Pain often occurs with meals and at night and may be associated with nausea and vomiting.
- Steatorrhea and azotorrhea occur in most patients. Steatorrhea is often associated with diarrhea and bloating. Weight loss may occur.
- Pancreatic diabetes is a late manifestation commonly associated with pancreatic calcification.

DIAGNOSIS

- Diagnosis is based primarily on clinical presentation and either imaging or pancreatic function studies. Noninvasive imaging includes abdominal ultrasound, CT, and MRCP. Invasive imaging includes endoscopic ultrasonography (EUS) and ERCP.
- Serum amylase and lipase are usually normal or only slightly elevated but may be increased in acute exacerbations.
- Total bilirubin, alkaline phosphatase, and hepatic transaminases may be elevated with ductal obstruction. Serum albumin and calcium may be low with malnutrition.
- Pancreatic function tests include:
    - ✔ Serum trypsinogen (<20 ng/mL 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; stool must be collected for 72 hours)
    - ✔ ^{13}C-mixed triglyceride breath test (not available in the United States)
    - ✔ Secretin stimulation (evaluates duodenal bicarbonate secretion)
    - ✔ Cholecystokinin stimulation (evaluates pancreatic lipase secretion)

TREATMENT

- Goals of Treatment: Major goals for uncomplicated CP are to relieve abdominal pain, treat complications of malabsorption and glucose intolerance, and improve quality of life. Secondary goals are to delay development of complications and treat associated disorders such as depression and malnutrition.

Nonpharmacologic Therapy

- Lifestyle modifications should include abstinence from alcohol and smoking cessation.
- Advise patients with steatorrhea to eat smaller, more frequent meals and reduce dietary fat intake.
- Reduction in dietary fat may be needed if symptoms are uncontrolled with enzyme supplementation. Enteral nutrition via a feeding tube is recommended for patients who cannot consume adequate calories, have continued weight loss, experience complications, or require surgery.

- Invasive procedures and surgery are used primarily to treat uncontrolled pain and the complications of CP.

Pharmacologic Therapy

- Pain may initially be treated with **acetaminophen** (eg, 500–650 mg every 4–6 hours) with or without NSAIDs (eg, **ibuprofen** 200–400 mg every 6–8 hours initially), with adjuvant agents added for inadequate pain relief or as the disease progresses.
- Analgesic regimens should be individualized and start with the lowest effective dose, with titration to maximum recommended or tolerated doses before adding or substituting agents. Schedule analgesics around the clock (rather than as needed) to maximize efficacy. Scheduling short-acting analgesics prior to meals may decrease postprandial pain.
- **Pregabalin** (75 mg twice daily initially; maximum 300 mg twice daily) has the best evidence as an adjuvant agent. Consider selective serotonin reuptake inhibitors (eg, **paroxetine**), serotonin/norepinephrine reuptake inhibitors (eg, **duloxetine**), and tricyclic antidepressants in patients with pain that is difficult to manage.
- **Tramadol** (50–100 mg every 4–6 hours, maximum 400 mg/day) may be tried before adding more potent opioid analgesics.
- Opioids should be reserved for severe or refractory pain:
  - ✔ **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
- Adding pancreatic enzyme supplements or antioxidants for pain control has been studied but is not supported by high-quality evidence and is not recommended in current guidelines.
- Pancreatic enzyme supplementation is required for most patients with malabsorption to achieve adequate nutritional status and reduction in steatorrhea (**Fig. 28-2**). The enzyme dose required to minimize malabsorption is 25,000–50,000 units of lipase administered with each meal initially. Half of the necessary mealtime dose is recommended with snacks. The mealtime dose may be increased to a maximum of 90,000 units. Products containing enteric-coated microspheres are preferred (**Table 28-2**). Ideally, patients should eat 3–5 meals/day, and those who require more than one capsule/tablet per meal should distribute the doses throughout the meal.
- An antisecretory agent (eg, ranitidine, omeprazole) should be added when there is an inadequate response to enzyme therapy alone. The increased gastric and duodenal pH is thought to increase the amount of active enzymes available in the duodenum.
- Adverse effects from pancreatic enzyme supplements are generally benign, but high doses can cause nausea, diarrhea, and intestinal upset. A more serious but uncommon adverse effect is fibrosing colonopathy, which has been reported mostly in children with cystic fibrosis who received high enzyme doses for prolonged periods.
- Assess patients with CP for deficiencies in fat-soluble vitamins and provide supplementation as required.
- Exogenous insulin is the primary means for treating diabetes mellitus associated with CP. Metformin may be initiated in early CP and has the added benefit of reducing the risk of pancreatic cancer.

FIGURE 28-2

Algorithm for the treatment of malabsorption and steatorrhea in chronic pancreatitis.

(H_2RA, histamine$_2$-receptor antagonist; PPI, proton pump inhibitor.)

image

TABLE 28-2

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	16,000	10,000
Zenpep® 5,000 lipase units	5,000	27,000	17,000
Zenpep® 10,000 lipase units	10,000	55,000	34,000
Zenpep® 15,000 lipase units	15,000	82,000	51,000
Zenpep® 20,000 lipase units	20,000	109,000	68,000
Zenpep® 25,000 lipase units	25,000	136,000	85,000
Zenpep® 40,000 lipase units	40,000	218,000	136,000
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® 4,200 lipase units	4,200	17,500	10,000
Pancreaze® 10,500 lipase units	10,500	43,750	25,000
Pancreaze® 16,800 lipase units	16,800	70,000	40,000
Pancreaze® 21,000 lipase units	21,000	61,000	37,000
Ultresa 4,000 lipase units	4,000	8,000	8,000
Ultresa 13,800 lipase units	13,800	27,600	27,600
Ultresa 20,700 lipase units	20,700	41,400	41,400
Ultresa 23,000 lipase units	23,000	46,000	46,000

USP, United States Pharmacopeia.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess the severity and frequency of abdominal pain periodically using a standardized scale to determine analgesic efficacy. Patients receiving opioids should be prescribed laxatives on an as-needed or scheduled basis and be monitored for constipation.
- For patients receiving pancreatic enzymes for malabsorption, monitor body weight and stool frequency and consistency periodically.
- Monitor blood glucose carefully in diabetic patients.

See Chapter 56, Pancreatitis, authored by Scott Bolesta and Patricia A. Montgomery, for a more detailed discussion of this topic.