Pathophysiology of acute pancreatitis

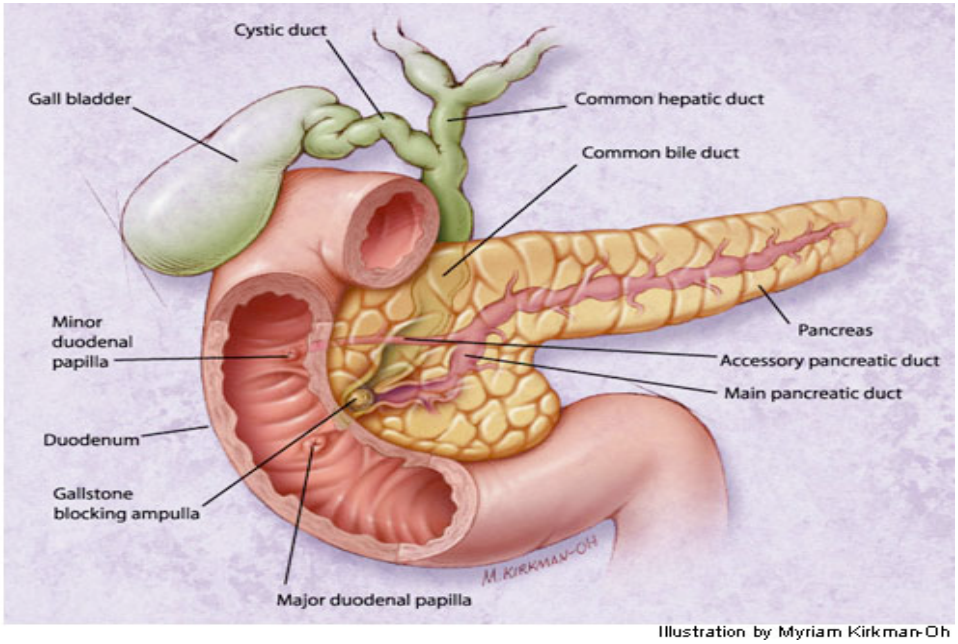


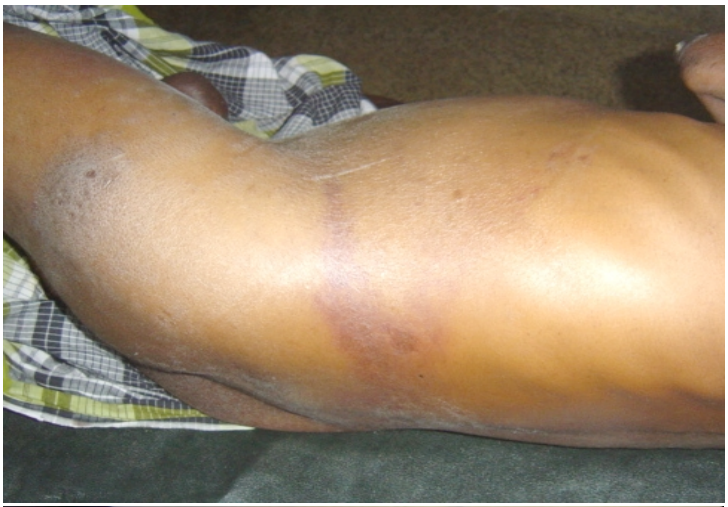
Illustration by Myriam Kirkman-Oh

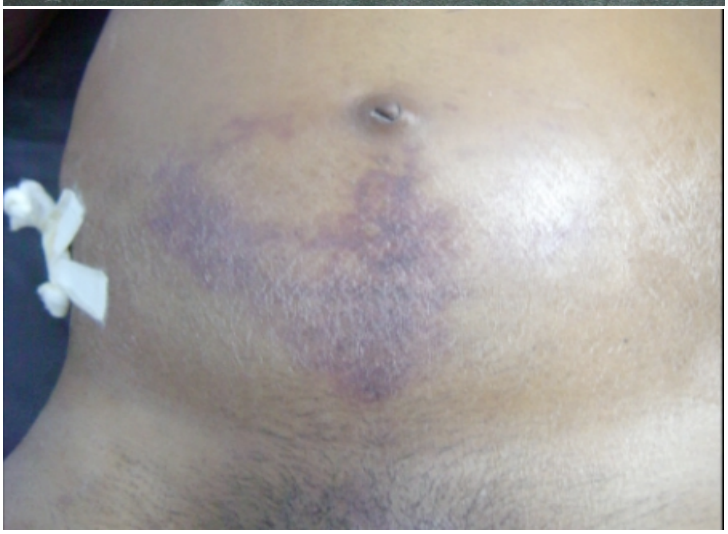
Acute pancreatitis may occur when factors involved in maintaining cellular homeostasis are out of balance. The initiating event may be anything that injures the acinar cell and impairs the secretion of zymogen granules, such as alcohol use, gallstones, and certain drugs. In addition, acute pancreatitis can develop when ductal cell injury leads to delayed or absent enzymatic secretion, such as with the *CFTR* gene mutation. The mechanisms by which alcohol or gallstones cause destruction to pancreatic acinar cells are not currently known.

Once a cellular injury pattern has been initiated, cellular membrane trafficking becomes chaotic, with the following deleterious effects: (1) lysosomal and zymogen granule compartments fuse, enabling activation of trypsinogen to trypsin; (2) intracellular trypsin triggers the entire zymogen activation cascade; and (3) secretory vesicles are extruded across the basolateral membrane into the interstitium, where molecular fragments act as chemoattractants for inflammatory cells. Activated neutrophils then exacerbate the problem by releasing superoxide (the respiratory burst) or proteolytic enzymes (cathepsins B, D, and G; collagenase; and elastase). Finally, macrophages release cytokines that further mediate local (and, in severe cases, systemic) inflammatory responses. The early mediators defined to date are tumor necrosis factor–alpha, interleukin-6, and interleukin-8.

These mediators of inflammation cause an increase pancreatic vascular permeability, leading to **hemorrhage, edema**, and eventually pancreatic **necrosis**. As the mediators are excreted into the circulation, **systemic complications** can arise, such as bacteremia due to gut flora translocation, acute respiratory distress syndrome, pleural

effusions, gastrointestinal hemorrhage, and renal failure. Eventually, the mediators of inflammation can become so overwhelming to the body that hemodynamic instability and death ensue.





Complications of acute pancreatitis

Most complications of acute pancreatitis and subsequent deaths occur within two weeks of onset of pain. Secondary pancreatic infection is the most common cause of death in acute pancreatitis, accounting for 70 to 80 percent of deaths. Complications frequently manifest as necrosis and organ failure, which often includes the cardiovascular, pulmonary and renal systems. Cardiovascular complications may reflect bleeding into the retroperitoneal space and decreased vascular resistance. Pulmonary insufficiency may range from mild atelectasis to life-threatening adult respiratory distress syndrome. Acute renal failure defined as a twofold creatinine rise may ensue secondary to cardiovascular collapse and hypotension, resulting in acute tubular necrosis.

- Acute fluid collections

- These commonly occur early in the course of acute pancreatitis.
- They are primarily detected by imaging studies and not physical examination.
- Because they lack a defined wall and usually regress spontaneously, most acute fluid collections require no specific therapy.

- Pseudocyst
  - This is a collection of pancreatic fluid enclosed by a wall of granulation tissue and requires 4 or more weeks to develop. They occur in 1—8 percent cases
  - While they are sometimes palpable on physical examination, they are usually detected with abdominal ultrasonography or CT scanning.
- Intra-abdominal infections
  - Within the first 1-3 weeks, fluid collections or pancreatic necrosis can become infected and jeopardize clinical outcome. They occur in 1---4 percent cases
  - From 3-6 weeks, pseudocysts may become infected or a pancreatic abscess may develop. A pancreatic abscess is a circumscribed intra-abdominal collection of pus, within or in proximity to the pancreas. It is believed to arise from localized necrosis, with subsequent liquefaction that becomes infected.
  - Intestinal florae are the predominant source of bacteria causing the infection. The usual suspects are *Escherichia coli* (26%), *Pseudomonas* species (16%), *Staphylococcus* species (15%), *Klebsiella* species (10%), *Proteus* species (10%), *Streptococcus* species (4%), *Enterobacter* species (3%), and anaerobic organisms (16%).
  - Fungal superinfections may occur weeks or months into the course of severe necrotizing pancreatitis.
- Pancreatic necrosis
  - This is a nonviable area of pancreatic parenchyma that is often associated with peripancreatic fat necrosis and is principally diagnosed with the aid of dynamic spiral CT scans.
  - Distinguishing between infected and sterile pancreatic necrosis is an ongoing clinical challenge.
  - Sterile pancreatic necrosis is usually treated with aggressive medical management, whereas almost all patients with infected pancreatic necrosis require surgical debridement or percutaneous drainage if they are to survive.

Complications of chronic pancreatitis

Pseudocysts

About 25% of patients with chronic pancreatitis will develop a pseudocyst. Pseudocysts in patients with chronic pancreatitis are less likely to resolve spontaneously than those developing after an acute attack, and patients will require some form of drainage procedure. Simple aspiration guided by ultrasonography is rarely successful in the long term, and most patients require internal drainage. Thin walled pseudocysts bulging into the stomach or duodenum can be drained endoscopically, with surgical drainage reserved for thick walled cysts and those not bulging into the bowel on endoscopy. Occasionally, rupture into the peritoneal cavity causes severe gross ascites or, via pleuroperitoneal connections, a pleural effusion.

Raised amylase activity in the ascitic or pleural fluid (usually [is greater than] 20 000 iu/l) confirms the diagnosis. Patients should be given intravenous or jejunal enteral feeding to rest the bowel and minimise pancreatic stimulation, somatostatin infusion, and repeated aspiration. The cyst resolves in 70% of cases after two to three weeks. Persistent leaks require endoscopic stenting of the pancreatic duct or surgery to drain the site of leakage if it is proximal or resection if distal.

Biliary stricture

Stenosis of the bile duct resulting in persistent jaundice (more than a few weeks) is uncommon and usually secondary to pancreatic fibrosis. The duct should be drained surgically, and this is often done as part of surgery for associated pain or duodenal obstruction. Endoscopic stenting is not a long term solution, and is indicated only for relief of symptoms in high risk cases.

Gastroduodenal obstruction

Gastroduodenal obstruction is rare (1%) and usually due to pancreatic fibrosis in the second part of the duodenum. It is best treated by gastrojejunostomy.

Splenic vein thrombosis

Venous obstruction due to splenic vein thrombosis (segmental or sinistral hypertension) may cause splenomegaly and gastric varices. Most thrombi are asymptomatic but pose a severe risk if surgery is planned. Splenectomy is the best treatment for symptomatic cases.

Gastrointestinal bleeding

Gastrointestinal bleeding may be due to gastric varices, coexisting gastroduodenal disease, or pseudoaneurysms of the splenic artery, which occur in association with pseudocysts. Endoscopy is mandatory in these patients. Pseudoaneurysms are best treated by arterial embolisation or surgical ligation.