

Acute Pancreatitis – The Current Concept in Etiopathogenesis, Morphology and Complications

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1. Introduction

This chapter is a comprehensive approach on etiology, patho-physiological and complications of acute pancreatitis and its review will aid in evaluation of acute pancreatitis in-toto. Pancreatitis is the inflammation of the exocrine pancreas which results from injury to the acinar cells. It may be classified as either acute or chronic. Acute pancreatitis is the reversible injury to the pancreatic parenchyma associated with inflammation and is characterized by a recurrent episode of abdominal pain and elevated serum amylase and lipase levels.

2. Etiopathogenesis of acute pancreatitis

2.1 Etiology

Acute pancreatitis is relatively common. Among the numerous causes, two factors which account for about 70 -80% of cases of acute pancreatitis are **biliary tract disease** and **alcoholism**. The male-to-female ratio is 1: 3 in the group with biliary tract disease and 6: 1 in those with alcoholism.

2.1.1 Important causes are

Alcohol and pancreatitis: Alcohol-induced acute pancreatitis usually develops in patients who consume large quantities of alcohol for 5-10 years before the first attack. However, it may occur with the consumption of a small quantity of alcohol also (two drinks/day). Environmental factors like smoking and high-fat diet may also contribute to the

development of acute pancreatitis in alcoholics. There are three possible different mechanisms of alcoholic pancreatitis.

- **Obstruction of small ductules by proteinaceous plugs:** Chronic alcohol ingestion results in the **secretion of protein-rich pancreatic fluid**, which may result in **inspissated** protein plugs and obstruction of small pancreatic ducts.
- **Abnormal spasm sphincter of Oddi:** Alcohol transiently increases pancreatic exocrine secretion and abnormal **contraction of the sphincter of Oddi** (the muscle at the ampulla of Vater),
- **Direct toxic effects:** Metabolic byproducts of alcohol have **direct toxic effects** on the acinar cells.

METABOLIC FACTORS
<ul style="list-style-type: none"> • Alcoholism • Hyperlipoproteinemia/hypertriglyceridemia • Hyperparathyroidism • Hypercalcemia • Drugs (e.g., furosemide, azathioprine, cyclosporine, tacrolimus)
GENETIC
Mutations in the cationic trypsinogen (<i>PRSS1</i>) and trypsin inhibitor (<i>SPINK1</i>) genes
MECHANICAL
<ul style="list-style-type: none"> • Gallstones • Trauma and injury <ul style="list-style-type: none"> • Blunt abdominal trauma • Iatrogenic injury • Operative injury: Endoscopic procedures with dye injection (retrograde cholangiopancreatography) • Obstruction of the pancreatic duct <ul style="list-style-type: none"> • Periapillary neoplasms (e.g., carcinoma of pancreas) • Parasites (e.g., <i>ascaris lumbricoides</i> and <i>clonorchis sinensis</i>)
VASCULAR/ISCHEMIC INJURY
<ul style="list-style-type: none"> • Shock • Atheroembolism • Vasculitis
INFECTIONS
<ul style="list-style-type: none"> • Mumps

Table 1. Etiologic Factors in Acute Pancreatitis

Gallstones and pancreatitis

- The frequency of acute pancreatitis is inversely proportional to the size of gallstones. Persistence of stones in the bile duct or the ampulla of vater is associated with more severe disease. An impacted gallstone may allow the reflux of bile into the pancreatic duct or occlude the duct's orifice.

Pancreatic Obstruction

- It is a less common cause of acute pancreatitis. Sphincter of Oddi dysfunction and carcinoma of the pancreas are associated with acute pancreatitis and is usually of the mild type.

Genetic Factors

- About 10% to 20% of patients with acute pancreatitis have no known associated etiological processes. Though these are termed idiopathic, the evidence suggests that some may have a genetic basis.
- Hereditary pancreatitis is characterized by recurrent attacks of severe pancreatitis usually developing in childhood. Most of these are caused by germline (inherited) mutations in the cationic trypsinogen gene (also known as PRSS1). In patients with these mutations, trypsin is inappropriately activated in the pancreas, which in turn activates other digestive proenzymes.
- The serine protease inhibitor Kazal type 1 (SPINK1) gene codes for a pancreatic secretory trypsin inhibitor. This inhibits trypsin activity and prevents autodigestion of the pancreas by activated trypsin. Mutation in the SPINK1 gene leads to loss of function of the inhibitor gene and causes pancreatitis.

The other etiological factors for acute pancreatitis are shown in the Table.1.

2.2 Pathogenesis

The changes of acute pancreatitis are due to autodigestion of the pancreatic substance by inappropriately activated pancreatic enzymes.

2.2.1 Mechanism of activation of pancreatic enzymes (Figure.1)

- *Pancreatic duct obstruction:* Any lesion which narrows the lumen of pancreatic ducts or impairs the flow of exocrine secretions can increase intraductal pressure and cause back-diffusion. This results in the accumulation of enzyme-rich fluid in the interstitium and inappropriate activation of proenzymes. Gallstones is one of the main cause of pancreatic duct obstruction.
- *Defective intracellular transport of proenzymes within acinar cells:* In normal acinar cells, the proenzymes and lysosomal hydrolases are transported in separate pathways. Inappropriate delivery of pancreatic proenzymes to the intracellular compartment containing lysosomal hydrolases may activate proenzymes. This mechanism may be responsible for injury due to alcohol or duct obstruction.
- *Primary acinar cell injury:* Acinar cells may be directly damaged by certain viruses (e.g., mumps), drugs, alcohol, trauma to the pancreas, ischemia and shock.
- *Hyperstimulation of pancreas:* This may be seen in association with consumption of alcohol or fat diet.
- *Reflux of bile:* Infected bile or duodenal content may regurgitate into the pancreatic duct due to disruption of sphincter Oddi (e.g., gallstones).

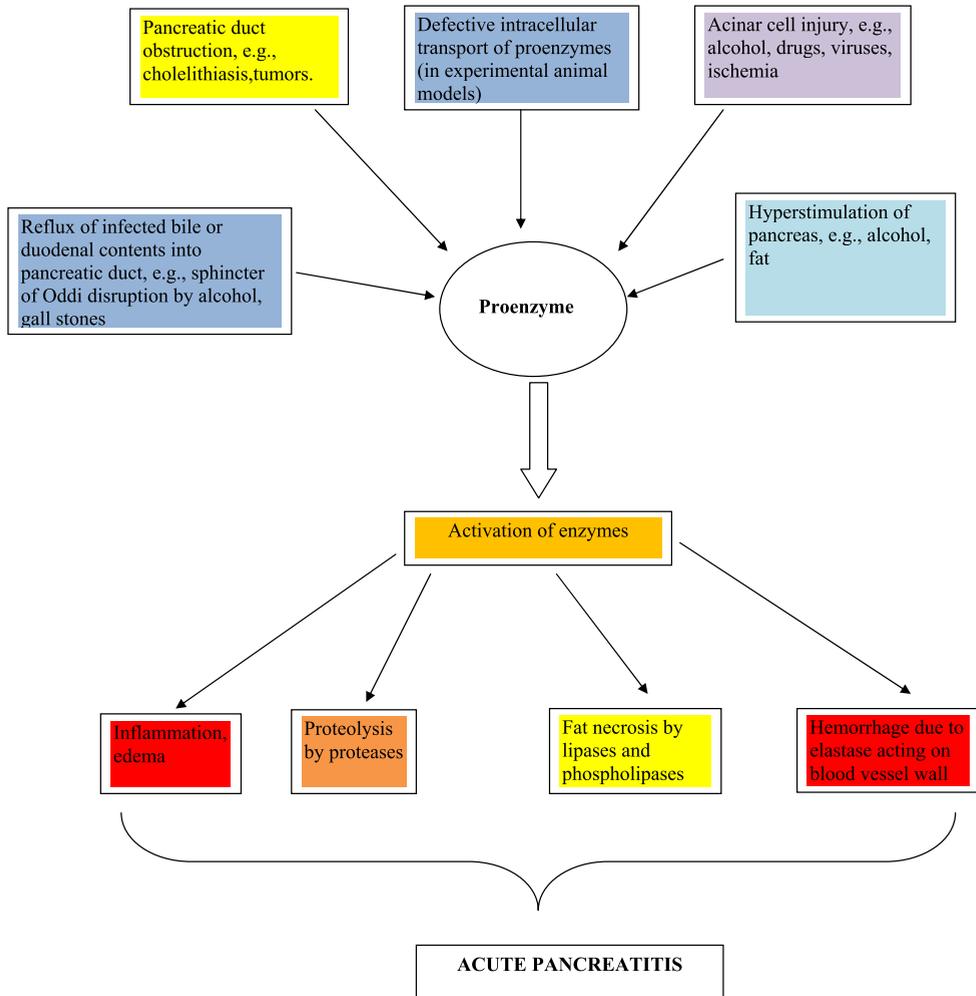


Fig. 1. Diagram Of Mechanism Of Activation Of Pancreatic Enzymes

2.2.2 Pancreatitis evolves in three phases

- Initial phase:** It is characterised by premature activation of zymogen granules releasing active enzymes which cause acinar cell injury, digestion of the pancreas and surrounding tissue. The hyperstimulation of the pancreas may result in the fusion of lysosome and zymogens within large vacuoles. Lysosomal hydrolase namely cathepsin B, is capable of activating trypsinogen to trypsin.
 - Inappropriate activation of trypsinogen:* The inappropriate activation of trypsinogen is an important triggering event in acute pancreatitis. Pancreatic enzymes (including trypsin) are synthesized in an inactive proenzyme form. When trypsin is inappropriately activated, it in turn activates other proenzymes like

prophospholipase and proelastase into active forms. The activated enzyme lipase degrades fat cells and elastase damages the elastic fibers of blood vessels. Trypsin also activates the kinin system, Hageman factor (factor XII), coagulation and complement systems.

- **Second phase:** It involves the activation, chemoattraction and sequestration of neutrophils into the pancreas, resulting in an intrapancreatic inflammatory reaction of variable severity. Leukocyte release cytokines which is responsible for local inflammation and interstitial edema. Edema may decrease the local blood flow and cause further ischemic damage to acinar cells
- **Third phase:** It is due to the effects of activated proteolytic enzymes and cytokines, released by the inflamed pancreas, on distant organs. Activated proteolytic enzymes, especially trypsin, not only digest pancreatic and peripancreatic tissues but also activate other enzymes such as elastase and phospholipase. The active enzymes protease digest cellular membranes and cause parenchymal cell necrosis. The activated lipase causes fat necrosis and the elastase disrupts the vessel wall leading to hemorrhage. Cell injury and death result in the liberation of bradykinin, vasoactive substances and histamine which produce vasodilation, increased vascular permeability, and edema with effects on many organs. Thus it may lead to systemic inflammatory response syndrome (SIRS) and acute respiratory distress syndrome (ARDS) as well as multiorgan failure.

2.2.3 Safety mechanism

The pancreas has many safety mechanisms to prevent autoactivation of zymogens. One of the known mechanisms is the pancreatic secretory trypsin inhibitor (PSTI), which is found in secretory granules. It inhibits trypsin activity.

2.3 Morphology

The normal pancreas has a poorly developed capsule and lies close to adjacent structures, which includes the common bile duct, duodenum, splenic vein and transverse colon. Due to this, in acute pancreatitis these are also commonly involved in the inflammatory process. The morphological features of acute pancreatitis vary from minimal inflammation and edema to severe extensive necrosis and hemorrhage. [Figure.2]

2.3.1 Microscopic features: Important features of acute pancreatitis are

- **Leakage of blood vessels causing edema:** Microvascular leakage results in leakage of plasma into the interstitium of pancreas resulting in edema.
- **Acute inflammation:** Leukocytes are seen in the interstitial connective tissue of pancreas along with inflammatory fluid exudates.
- **Enzymatic fat necrosis:** It is produced due to the action of lipolytic enzymes-lipase.
- **Proteolytic destruction of pancreatic parenchyma:** It is brought out by the action of protease.
- **Destruction of blood vessels:** The elastase causes destruction of blood vessels and subsequent interstitial hemorrhage.

Depending on the extent of severity of inflammatory reaction, acute pancreatitis -

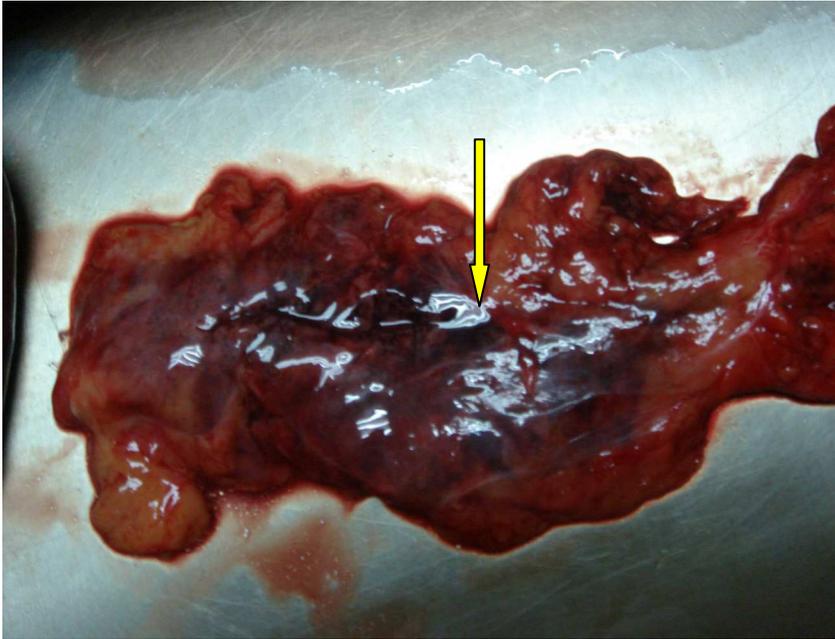


Fig. 2. The Morphological Feature Of Acute Pancreatitis

2.3.2 They are classified into three types

2.3.2.1 Acute interstitial or edematous pancreatitis:

It is a mild and reversible form of acute pancreatitis. It is usually managed medically.

Microscopy: It shows interstitial edema and mild infiltration of polymorphonuclear leukocytes, without any necrosis or hemorrhage. There may be focal areas of fat necrosis in the substance of the pancreas and in peripancreatic fat. Fat necrosis is due to the action of lipase on triglycerides which releases fatty acids from the fat cells. These fatty acids combine with calcium and form insoluble salts and this process is known as saponification. The insoluble salts impart a granular blue appearance to the involved fat cells.

2.3.2.2 Acute necrotizing pancreatitis

It is the severe form of **acute pancreatitis** in which the acinar, ductal tissues and islets of Langerhans show necrotic changes [Figure.2.]

Hemorrhage: Vascular injury due to the enzyme elastase can lead to hemorrhage into the parenchyma of the pancreas, which shows areas of red-black areas of hemorrhage in the substance of pancreas.

Fat necrosis: Foci of fat necrosis is seen both in the pancreatic and extra-pancreatic fat. The extra pancreatic tissue which may show fat necrosis includes: omentum, mesentery of the bowel and outside the abdominal cavity (subcutaneous fat). As a result of deposition of

calcium in the area of fat necrosis (saponification), the blood calcium level may be decreased, sometimes to the level of causing neuromuscular irritability.

Peritoneal cavity: In majority of cases, the peritoneal cavity contains a serous, slightly turbid, brown-tinged fluid in which globules of fat (derived from the action of enzymes on adipose tissue) can be seen [Figure.3].

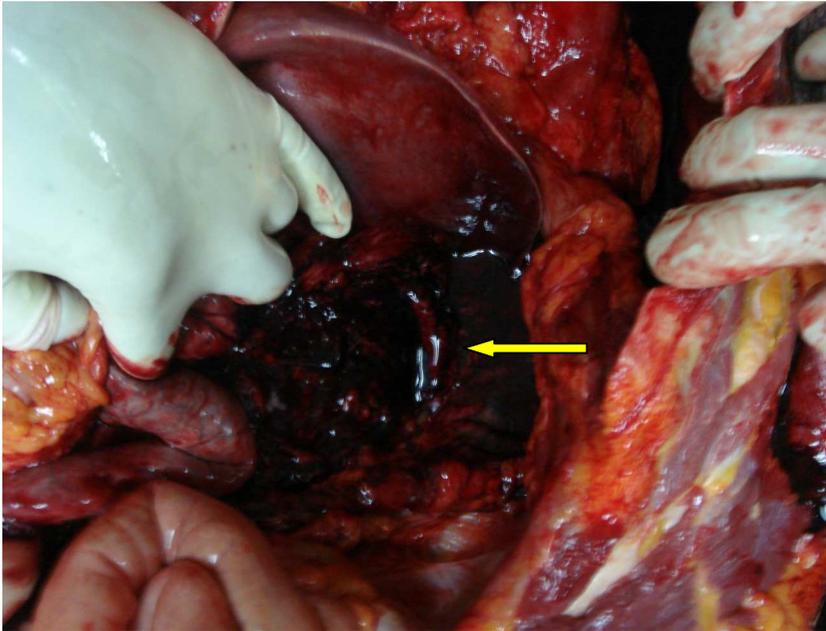


Fig. 3. Peritoneal Cavity In Acute Pancreatitis

- Microscopy:
 - Edema: It is due to leakage through microvasculature.
 - Acute inflammation
 - Enzymatic fat necrosis: It appears granular blue with ghost outlines.
 - Proteolytic destruction of pancreatic parenchyma: Acinar and ductal tissues as well as the islets of Langerhans are necrotic.
 - Destruction of blood vessels (elastase) and subsequent interstitial hemorrhage.

2.3.2.3 Acute hemorrhagic pancreatitis

It is the most severe form of acute **pancreatitis**. It usually occurs in the **middle aged** and is associated with **high morbidity and mortality**. Microscopically, it shows **extensive parenchymal necrosis** accompanied by **hemorrhage** within the pancreas.

The above features linked with the clinical features, laboratory findings and recent investigative procedures help in diagnosing acute pancreatitis with ease. The effective treatment modalities in recent years will insist on efficient interpretation of pathophysiology in acute pancreatitis so as to ensure a speedy recovery from the cause.

2.4 Clinical features

Abdominal pain is the major manifestation of acute pancreatitis. The pain may vary from mild and tolerable to severe, constant and incapacitating distress. Characteristically, the pain is steady and intense, located in the epigastrium and periumbilical region. It often radiates to the upper back as well as to the chest, flanks, and lower abdomen. Anorexia, nausea, vomiting and abdominal distention due to gastric and intestinal hypomotility and chemical peritonitis also frequently accompany the pain.

Full-blown acute pancreatitis usually present with sudden calamitous onset of an “acute abdomen” and is a medical emergency. Many of the systemic features of severe acute pancreatitis are due to release of toxic enzymes, cytokines, and other mediators into the circulation and activation of the systemic inflammatory response. These mediators result in leukocytosis, hemolysis, disseminated intravascular coagulation, fluid sequestration, acute respiratory distress syndrome, and diffuse fat necrosis. Peripheral vascular collapse and shock with acute renal tubular necrosis may also occur.

2.5 Laboratory findings

Marked elevation of serum amylase levels during the first 24 hours, followed within 72 to 96 hours by a rising serum lipase level.

Hyperglycemia is common and is due to multiple factors, including decreased insulin release, increased glucagon release, and an increased output of adrenal glucocorticoids and catecholamines. Glycosuria occurs in 10% of cases.

Hypocalcemia may result from precipitation of calcium soaps in necrotic fat; if persistent, it is a poor prognostic sign.

Hypertriglyceridemia occurs in 15 to 20% of patients, and serum amylase and lipase levels in these individuals are often spuriously normal.

Direct visualization of the enlarged inflamed pancreas by radiography is useful in the diagnosis of pancreatitis.

2.6 Complications of pancreatitis

Complication	Mechanism
Local pancreatic complications	
Necrosis	Inflammation
Abscess	Localised collection of necrotic material
Pseudocyst	Disruption of pancreatic ducts
Pancreatic ascites	Disruption of pancreatic ducts
Systemic complications	
Acute respiratory distress syndrome (ARDS)	Hypoxia due to microthrombi in the pulmonary vessels.
Hypocalcemia	Sequestration of calcium in fat necrosis
Hyperglycemia	Disruption of islets of Langerhans with altered insulin/glucagon release
Gastrointestinal complications	
Upper GI bleeding	Gastric / duodenal erosions
Duodenal obstruction	Compression by pancreatic mass/pseudocyst
Obstructive jaundice	Compression by pancreatic mass/pseudocyst

2.7 Treatment

In the majority of patients (85–90%) acute pancreatitis is self-limited and subsides spontaneously, usually within 3–7 days after treatment is started. About 5% with severe acute pancreatitis die from shock during the first week. Acute respiratory distress syndrome and acute renal failure are dangerous complications

The key to the management of acute pancreatitis is “resting” the pancreas by total restriction of oral intake and by supportive therapy. Conventional mode of treatment include

1. Analgesics for pain,
2. Intravenous fluids and colloids to maintain normal intravascular volume, and
3. No oral alimentation.

The nasogastric suction has no clear-cut advantages in the treatment of mild to moderately severe acute pancreatitis. Therefore, it must be considered elective rather than mandatory. The drugs which block pancreatic secretion have not found to be of any benefit. For this and other reasons, anticholinergic drugs are not indicated in acute pancreatitis.

Role of antibiotics: The benefit of antibiotic prophylaxis in the treatment of necrotizing acute pancreatitis remains controversial. It was observed that there is no benefit of antibiotic prophylaxis with regard to the risk of developing infected pancreatic necrosis.

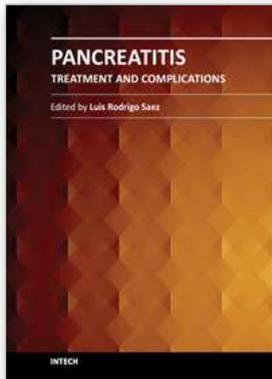
3. Conclusion

These features linked with the clinical features, laboratory findings and recent investigative procedures will help in diagnosing acute pancreatitis with ease. The effective treatment modalities in recent years will insist on efficient interpretation of patho-physiology in acute pancreatitis so as to ensure a speedy recovery from the cause.

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Pancreatitis may be acute or chronic. Although they can be caused by similar aetiologies, they tend to follow distinct natural histories. Around 80% of acute pancreatitis (AP) diagnoses occur as secondary to gallstone disease and alcohol misuse. This disease is commonly associated with the sudden onset of upper abdominal that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10 to 25% of AP episodes are classified as severe, leading to an associated mortality rate of 7 to 30%. Treatment is conservative and consists of general medical support performed by experienced teams, sometimes in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has significant prognostic importance. Necrosis, hemorrhage, and infection convey rates of up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudoaneurysm formation, or venous thrombosis increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

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