PANCREATITIS

The [pancreas](http://www.webmd.com/digestive-disorders/picture-of-the-pancreas) is a large gland behind the [stomach](http://www.webmd.com/digestive-disorders/picture-of-the-stomach) and next to the small intestine. The pancreas does two main things:

1. It releases powerful [digestive enzymes](http://www.webmd.com/drugs/2/drug-673/digestive%2Benzymes%2Boral/details) into the small intestine to aid the digestion of food.
2. It releases the hormones [insulin](http://www.webmd.com/diabetes/guide/diabetes-types-insulin) and glucagon into the bloodstream. These hormones help the body control how it uses food for energy.

[Pancreatitis](http://www.webmd.com/digestive-disorders/digestive-diseases-pancreatitis) is a disease in which the pancreas becomes inflamed. Pancreatic damage happens when the digestive enzymes are activated before they are released into the small intestine and begin attacking the pancreas.

There are two forms of [pancreatitis](http://www.webmd.com/diabetes/rm-quiz-pancreas): acute and chronic.

**Acute pancreatitis.**Acute pancreatitis is a sudden [inflammation](http://www.webmd.com/arthritis/about-inflammation) that lasts for a short time. It may range from mild discomfort to a severe, life-threatening illness. Most people with acute pancreatitis recover completely after getting the right treatment. In severe cases, acute pancreatitis can result in bleeding into the gland, serious tissue damage, infection, and [cyst](http://www.webmd.com/skin-problems-and-treatments/guide/cysts-lumps-bumps) formation. Severe pancreatitis can also harm other vital organs such as the [heart](http://www.webmd.com/heart/picture-of-the-heart), [lungs](http://www.webmd.com/lung/picture-of-the-lungs), and [kidneys](http://www.webmd.com/urinary-incontinence-oab/picture-of-the-kidneys). **Acute**

**aetiologyP**Both acute and chronic pancreatitis are frequently associated with other disease entities collectively referred to as the *etiologies of pancreatitis* ( Box 55-1 ). In developed countries, roughly 70% to 80% of patients with pancreatitis have their pancreatitis in association with either biliary tract stone disease or ethanol abuse. For the most part, biliary tract stone disease is associated with acute pancreatitis, whereas chronic pancreatitis is associated with the intake of large amounts of ethanol over protracted periods. In 10% to 15% of pancreatitis cases, no etiology can be identified, and those individuals are said to have idiopathic pancreatitis. In the remaining 10% to 15% of patients, pancreatitis is associated with one of many possible miscellaneous etiologies. In underdeveloped countries, particularly in Africa and Southeast Asia, pancreatitis is frequently termed either *tropical* or *nutritional.* Recent reports indicate that many patients with tropical pancreatitis have a form of hereditary pancreatitis caused by mutations of the genes that code for pancreatic secretory trypsin inhibitors. Affected individuals often complain of painful attacks, and they frequently develop pancreatic calcifications as well as diabetes. Ketoacidosis is uncommon.

Biliary Tract Stones

The onset of acute pancreatitis is frequently associated with the passage of biliary tract stones through the terminal biliopancreatic duct into the duodenum. Stones can be retrieved from the stools of roughly 90% of patients with stone-induced pancreatitis. There has been much speculation regarding the mechanisms by which such stones might cause pancreatitis. In 1901, Opie, a pathologist at Johns Hopkins University, noted a stone lodged in the terminal biliopancreatic duct of a patient who had died of severe pancreatitis. He suggested that the stone might have caused outflow obstruction from a *common biliopancreatic channel,* allowing bile to reflux into the pancreatic duct.[7] In a second publication based on observations made at another autopsy, Opie suggested that biliary pancreatitis could also occur when a stone, or the edema and inflammation caused by its passage, caused outflow obstruction of the pancreatic duct even in the absence of bile reflux. Although the bile reflux theory, often referred to as the *common channel theory,* was originally favored, subsequent studies have cast doubt on its validity, and most observers now believe that it is stone-induced pancreatic duct obstruction and ductal hypertension, rather than bile reflux, that triggers acute pancreatitis. Recent data derived from experiments using a model of pancreatitis induced in opossums also support the duct obstruction theory. Those experiments indicate that pancreatic duct obstruction, without bile duct obstruction or bile reflux, can cause pancreatitis and that the severity of pancreatitis is not worsened by bile reflux into the pancreatic duct.[8]

Abuse of Ethanol

The most frequent cause of morphologically defined chronic pancreatitis is ethanol abuse, but occasionally ethanol can also induce acute pancreatitis. There is no threshold rate of consumption below which ethanol consumption is not associated with an increased incidence of pancreatitis. The mean ethanol consumption among patients with ethanol-induced pancreatitis is 150 to 175 g/day. The mean duration of ethanol abuse for men is 18 ± 11 years and, for women, 11 ± 8 years. Ethanol-induced pancreatitis, like ethanol abuse itself, is more common in men than in women. Dietary factors, such as consumption of a high-protein diet with either high-fat or low-fat content, may contribute to the development of pancreatitis. Most observers currently believe that the chronic pancreatitis that follows prolonged ethanol abuse reflects repeated, but subclinical, episodes of acute pancreatic injury. These repeated episodes of pancreatic injury with necrosis eventually lead to the fibrosis that characterizes chronic pancreatitis.[9]

Many theories have been advanced to explain the mechanism by which ethanol might cause pancreatic injury. According to one theory, ethanol consumption causes hypertriglyceridemia and the generation of fatty acids as well as their ethyl ester metabolites that can injure the pancreas. Another theory suggests that ethanol ingestion causes intrapancreatic generation of oxygen-derived free radicals that can injure the pancreas. Others believe that ethanol acts directly on pancreatic acinar cells to cause injury or that it promotes secretion of pancreatic juice that is high in proteolytic enzyme content but low in enzyme inhibitor content. Theoretically, enzyme activation could occur under these conditions, and that activation could cause pancreatic injury. Secretion of an enzyme-rich fluid deficient in enzyme inhibitors could also lead to protein precipitation and the formation of intraductal plugs. Those plugs, by causing duct obstruction and ductal hypertension, could subsequently trigger pancreatic injury. Ethanol ingestion has also been reported to cause sphincter of Oddi spasm, and this could also contribute to ethanol-induced pancreatitis if it resulted in ductal hypertension. Each of these various theories has attractive features and its own proponents, but, at present, the actual mechanisms by which ethanol causes pancreatitis remain unclear.

Drugs

Exposure to certain drugs is, perhaps, the third most frequent cause of pancreatitis ( Box 55-2 ), but the mechanisms by which those drugs cause pancreatitis is not known. Although many different drugs have been implicated, the strength of the data supporting a cause-and-effect relationship in pancreatitis varies considerably. Drugs associated with pancreatitis can be divided into the following three groups:

**ancreatitis**

|  |  |  |
| --- | --- | --- |
|  |  | Abuse of ethanol  |
|  |  | Biliary tract stones  |
|  |  | Drugs  |
|  |  | Endoscopic retrograde cholangiopancreatography  |
|  |  | Hypercalcemia  |
|  |  | Hyperlipidemia  |
|  |  | Idiopathic  |
|  |  | Infections  |
|  |  | Ischemia  |
|  |  | Parasites  |
|  |  | Postoperative  |
|  |  | Scorpion sting  |
|  |  | Trauma  |

**Pathophysiology of Acute and Chronic Pancreatitis**

It is generally believed that acute pancreatitis is triggered by obstruction of the pancreatic duct and that the injury begins within pancreatic acinar cells. That injury is believed to include, and possibly be the result of, intra-acinar cell activation of digestive enzyme zymogens, including trypsinogen. Chronic pancreatitis is believed to reflect repeated episodes of subclinical acute pancreatitis with unrecognized pancreatic necrosis evolving into pancreatic fibrosis.

One of the central issues in our understanding of the cellular events leading to acute pancreatitis is how duct obstruction could result in intra-acinar cell enzyme activation. Perhaps one of the most widely accepted theories to explain this coupling is the so-called colocalization hypothesis.[12] This hypothesis is based on a number of studies that have used experimental models of pancreatitis induced in laboratory animals. In those studies, one of the earliest changes noted has been the colocalization of digestive enzyme zymogens such as trypsinogen with lysosomal hydrolases such as cathepsin B inside cytoplasmic vacuoles. Under these conditions, cathepsin B can activate trypsinogen, and trypsin can activate the other zymogens. According to the colocalization hypothesis, cathepsin B–mediated intra-acinar cell activation of the digestive enzymes leads to acinar cell injury and triggers an intrapancreatic inflammatory response. The intensity of that inflammatory response appears to regulate the severity of the pancreatitis and to couple pancreatitis to extrapancreatic events such as lung and renal injury.

**Presentation of an Acute Attack**

The clinical presentation, diagnosis, and management of an acute attack of pancreatitis are similar regardless of whether that attack is *acute* or *chronic* pancreatitis. In fact, many describe patients with chronic pancreatitis who present with acute symptoms as having *acute on chronic* pancreatitis. On the other hand, the long-term management of patients with acute and chronic pancreatitis may differ considerably. The former primarily involves elimination of the inciting cause, whereas for chronic pancreatitis, irreversible changes have usually occurred before diagnosis, and long-term management primarily involves treatment of pain and pancreatic exocrine and endocrine insufficiency. For these reasons, this discussion of clinical presentation focuses on issues relevant to an acute attack and does not make distinctions based on whether that is an attack of acute or chronic pancreatitis.

Symptoms

Abdominal pain, nausea, and vomiting are the dominant symptoms of pancreatitis. Typically, the pain is located in the epigastrium, but it may also involve both upper quadrants, the lower abdomen, or the lower chest. It may have a pleuritic component and be felt in one or both shoulders. Most patients describe the pain as being knifelike and radiating straight through to the mid-central back. It is usually abrupt in onset and slowly increases in magnitude to reach a maximal level. The pain is usually constant, although it may be somewhat relieved by leaning forward or lying on the side with the knees drawn upward. Patients with chronic pancreatitis frequently describe similar prior attacks that are often noted to occur within 12 to 24 hours of ethanol consumption. The nausea and vomiting of pancreatitis usually persists even after the stomach has been emptied. The vomiting may lead to gastroesophageal tears (i.e., Mallory-Weiss syndrome) and upper gastrointestinal bleeding. Although vomiting and retching may be relieved by passage of a nasogastric tube, the pain usually persists even after gastric decompression. Some patients, especially those with postoperative pancreatitis who are already receiving analgesic medications, may not experience abdominal pain, and therefore, the diagnosis of pancreatitis may be particularly difficult.

Physical Findings

Pancreatitis patients are frequently noted to be rolling or moving around in search of a more comfortable position and, in this sense, they are unlike patients with a perforated viscus who often remain motionless because movement worsens their pain. Patients with severe pancreatitis usually appear ill and anxious. Hyperthermia is common and may be explained by the release of proinflammatory factors, including cytokines and chemokines, from the injured pancreas. Tachycardia, tachypnea, and hypotension caused by hypovolemia are common. Hypovolemia can also result in collapsed neck veins, dry skin, dry mucous membranes, and diminished subcutaneous elasticity. Because pleuritic and abdominal pain may make breathing difficult, breath sounds in the lower lung fields are usually diminished, and atelectasis may be present.

A pleural effusion can often be detected on either side, although it is more commonly found on the left. Patients with severe pancreatitis frequently develop an acute lung injury that can clinically present as the adult respiratory distress syndrome (ARDS). Occasionally, patients with pancreatitis have alterations in their mental status as a result of drug or ethanol exposure, hypotension, hypoxemia, or release of circulating toxic agents from the inflamed pancreas. Some degree of jaundice is common. In gallstone-induced acute pancreatitis, the jaundice may reflect distal bile duct obstruction, but jaundice can also occur in nonbiliary pancreatitis either as a result of duct obstruction caused by the inflamed pancreas or as a result of cholestasis induced by the severe illness itself. As a result of ileus, bowel sounds are usually diminished during an attack of pancreatitis, and the abdomen may become distended and tympanitic. Direct, percussion, and rebound abdominal tenderness, as well as both voluntary and involuntary guarding, are common. These findings may be localized to the epigastrium, or they may be diffusely present throughout the abdomen. An epigastric mass, reflecting the inflamed pancreas and surrounding tissues, may be felt in the upper abdomen or left upper quadrant. On rare occasions, flank ecchymoses (Grey Turner's sign) or periumbilical ecchymoses (Cullen's sign), which result from retroperitoneal hemorrhage, can be seen during severe pancreatitis. Occasionally, patients develop areas of tender subcutaneous induration and erythema that resemble erythema nodosum but that, in the case of pancreatitis, are caused by subcutaneous fat necrosis.

 PROGNOSIS

As a result, a number of prognostic schemes have been developed. Among the clinical scoring systems, the most widely used are those developed in New York by Ranson's group[15] ( Table 55-1 ) and, in Glasgow, by Imrie's group.[16] Patients with fewer than three of the prognostic criteria can be expected to have a mild attack with little morbidity and a mortality rate of less than 1%. On the other hand, with the presence of more prognostic factors, increased morbidity and mortality can be expected, so that with three or four of Ranson's criteria, the mortality rate may reach 15%, and 50% of patients may need to be treated in an intensive care unit. Most patients with five or six signs will require intensive care, and with seven or eight of Ranson's signs, the mortality rate may reach 90%.

**Table 55-1** **--** **Ranson's Prognostic Signs**

| **ADMISSION** | **INITIAL 48 HOURS** |
| --- | --- |
| **Gallstone Pancreatitis** |  |
| Age > 70 yr | Hct fall >10 |
| WBC >18,000/mm3 | BUN elevation >2 mg/100 mL |
| Glucose > 220 mg/100 mL | Ca2+ <8 mg/100 mL |
| LDH >400 IU/L | Base deficit >5 mEq/L |
| AST >250U/100 mL | Fluid sequestration >4 L |
| **Nongallstone Pancreatitis** |  |
| Age >55 yr | Hct fall >10 |
| WBC >16,000/mm3 | BUN elevation >5 mg/100 mL |
| Glucose >200 mg/100 mL | Ca2+ <8 mg/100 mL |
| LDH >350 IU/L | Pao2 <55 mm Hg |
| AST >250U/100 mL | Base deficit >4 mEq/L |
|  | Fluid sequestration >6 L |

**Treatment of an Acute Attack**

An acute attack of pancreatitis evolves in two, somewhat overlapping, phases. The initial phase, which lasts for 1 to 2 weeks, involves an acute inflammatory and autodigestive process that takes place within and around the pancreas. It may have systemic effects as well. In patients with severe pancreatitis, this initial phase of pancreatitis seamlessly evolves into a later phase that may last for weeks or months. This later phase of pancreatitis is primarily characterized by the development of local complications that are the result of necrosis, infection, and pancreatic duct rupture.

Initial Treatment

The initial management of patients with pancreatitis focuses on establishing the diagnosis, estimating its severity, addressing the major symptoms (i.e., pain, nausea, vomiting, and hypovolemia), and limiting its progression. Ideally, the diagnosis is established without exploratory surgery because exploration may increase the incidence of later pancreatic infection. On occasion, however, exploration may be required to establish the diagnosis with certainty, especially when the diagnosis is uncertain, and the patient has not responded favorably to aggressive nonoperative treatment. For the most part, patients with predicted severe pancreatitis are treated in an intensive care setting because it is in this group that fluid and respiratory management may be particularly challenging, and both morbidity and mortality are, essentially, confined to this group.

Management of Pain

The pain of pancreatitis may be severe and difficult to control. Most patients require narcotic medications. Meperidine and its analogues are probably preferable to morphine in this setting because morphine can induce spasm of the sphincter of Oddi, which could, at least theoretically, worsen biliary pancreatitis.

Fluid and Electrolyte Management

Aggressive fluid and electrolyte repletion is the most important element in the initial management of pancreatitis. Fluid losses can be enormous and can lead to marked hemoconcentration as well as hypovolemia. Inadequate fluid resuscitation during the early stages of pancreatitis can worsen the severity of an attack and lead to subsequent complications. The fluid depletion that occurs in pancreatitis results from the additive effects of losing fluid both externally and internally. The external fluid losses are caused by repeated episodes of vomiting and worsen by nausea that limits fluid intake. Repeated vomiting can result in a hypochloremic alkalosis. Internal fluid losses, which are usually even greater than the external losses, are caused by fluid sequestration into areas of inflammation (i.e., the peripancreatic retroperitoneum) and into the pulmonary parenchyma and soft tissues elsewhere in the body. These latter losses result from the diffuse capillary leak phenomenon that is triggered by proinflammatory factors released during pancreatitis. Total fluid losses may be so great that they lead to hypovolemia and hypoperfusion, and as a result, a metabolic acidosis can develop. Many of the patients with chronic pancreatitis are alcoholics who, even before the onset of pancreatitis, had hypoalbuminemia and hypomagnesemia. Those problems are exacerbated by the losses of pancreatitis. The measured values for serum albumin may be even further depressed as fluid losses are treated with albumin-free crystalloid solutions. Although hypocalcemia is common particularly during a severe attack, the low total serum calcium is usually attributable to the low levels of circulating albumin, and no treatment is needed when ionized calcium is normal. Occasionally, however, ionized calcium levels may also be depressed, and tetany as well as carpopedal spasm can occur. Under those circumstances, aggressive calcium repletion is indicated.

During the first several days of a severe attack, circulating levels of many proinflammatory factors, including cytokines and chemokines, are elevated. This so-called cytokine storm, in many cases, triggers the systemic immune response syndrome, and as a result, the hemodynamic parameters of these patients may resemble those of sepsis associated with other disease states. Heart rate, cardiac output, and cardiac index usually rise, and total peripheral resistance falls. Hypoxemia can also occur as a result of the combined effects of increased intrapulmonary shunting and a pancreatitis-associated lung injury that closely resembles that seen in other forms of ARDS. Fluid management, although critical, may be particularly difficult when hypovolemia is combined with the respiratory failure of ARDS.

Treatment requires meticulous replacement of fluid and electrolyte losses. A fluid balance flow sheet is helpful, but parameters such as pulse rate, blood pressure, oxygen saturation, and urine output are notoriously unreliable for determining fluid needs in this setting. The hematocrit, however, can be quite useful because increased levels usually are accurate indicators of the magnitude of extracellular fluid loss. However, in a setting of blood loss or hemolysis, hematocrit measurements may lose their value in fluid management. Measurement of central filling pressures, using a Swan-Ganz or central venous pressure catheter, can be helpful in guiding fluid management, particularly when hypovolemia is combined with lung injury.

**Chronic pancreatitis.**Chronic pancreatitis is long-lasting [inflammation](http://www.webmd.com/women/ss/slideshow-what-is-inflammation) of the pancreas. It most often happens after an episode of acute pancreatitis. Heavy alcohol drinking is another big cause. Damage to the pancreas from heavy alcohol use may not cause symptoms for many years, but then the person may suddenly develop severe [pancreatitis symptoms](http://www.webmd.com/digestive-disorders/understanding-pancreatitis-symptoms). **Pathology and Etiology of Chronic Pancreatitis**

Chronic pancreatitis is characterized by irreversible changes, including pancreatic fibrosis and the loss of functional pancreatic exocrine or endocrine tissue. Most patients develop chronic pancreatitis as a result of prolonged ethanol abuse. It is generally believed that, in its earliest stages, chronic pancreatitis is an acute inflammatory process, and repeated episodes of subclinical acute pancreatic injury and necrosis lead to the fibrosis of chronic pancreatitis.

**Diagnosis of Chronic Pancreatitis**

There has been considerable confusion concerning the clinical distinction between chronic and acute pancreatitis. To a great extent, this confusion results from the fact that, from a clinical standpoint, attacks of chronic pancreatitis may be indistinguishable from those of acute pancreatitis. Fortunately, the initial management of acute or chronic pancreatitis attacks is identical, as is the management of complications such as infection, necrosis, and pseudocyst (see Treatment of an Acute Attack section, earlier). On the other hand, the two forms of pancreatitis have natural histories that differ considerably, and the long-term management of chronic pancreatitis presents challenges that are not inherent to the management of acute pancreatitis.

History

Patients with chronic pancreatitis may describe prior episodes of pancreatic-type abdominal pain, and 60% to 80% of patients have a long history of ethanol abuse. There may be a family history of pancreatitis suggestive of the presence of hereditary pancreatitis or a history of autoimmune diseases, including primary sclerosing cholangitis and Sjögren's syndrome, that raise suspicion of pancreatitis on an autoimmune basis. Diabetes mellitus or a history suggestive of malabsorption (i.e., steatorrhea) indicates that significant pancreatic endocrine or exocrine function has been lost, and this is most compatible with the diagnosis of chronic pancreatitis. Typically, patients with chronic pancreatitis have upper abdominal pain radiating to the back. It can be constant or episodic and triggered by drinking alcohol or eating. Repeated use of heating pads or hot water bottles to treat the chronic pain may result in skin lesions (erythema ab igne) that define the distribution of the pain ( Fig. 55-5 ). Some patients experience no pain.

Natural History

Some patients with chronic pancreatitis have a painless disease that remains unrecognized until complications or loss of pancreatic function leads to the diagnosis. Most patients, however, have intermittent or constant pain that may limit lifestyle or mandate repeated hospitalizations. Ammann and Muellhaupt[34] have suggested that the painful pancreatitis experienced by many of these patients evolves into a painless disease as pancreatic function is lost, but the existence of this “burnout” phenomenon is highly controversial. More often, the disease remains painful, addicting doses of narcotics are required, and loss of function results in diabetes, steatorrhea, and profound weight loss.

**Treatment of Pancreatic Malabsorption**

The loss of pancreatic exocrine function in chronic pancreatitis affects the output of all pancreatic digestive enzymes, but it is mostly fat absorption that is abnormal, and it is the delivery of lipolytic enzyme activity to the small intestine that determines the success of treatment. In health, roughly 300,000 IU of lipase is secreted by the pancreas within 4 hours of ingesting a typical meal, but only 10% (30,000 IU) of secreted lipase is needed to allow for normal fat digestion and absorption. Theoretically, pancreatic malabsorption of fat is corrected by oral administration of exogenous lipase. Unfortunately, most orally administered lipase is inactivated as it traverses the acidic environment of the stomach, allowing only 8% to 15% of ingested lipase activity to reach the duodenum. Some of that lipase may be ineffective, either because of low duodenal pH (caused by inadequate pancreatic secretion of bicarbonate) or because the exogenously administered lipase arrives in the duodenum before or after the ingested fat. The use of acid-inhibiting agents (e.g., proton pump inhibitors) and enterically coated microsphere delivery systems can partially compensate for these problems. Thus, treatment involves acid suppression, a low-fat diet, and lipase doses of 90 to 150,000 IU per meal, although control of steatorrhea is often incomplete even with this treatment.

**Treatment of Pain in Chronic Pancreatitis**

Medical Management

Complete abstinence from ethanol is advised for patients with alcohol-induced pancreatitis, but symptoms may persist even after complete abstinence. Attacks of hyperlipidemia-induced pancreatitis can be prevented by normalizing lipid levels with medication or dietary changes. Most patients with autoimmune pancreatitis are cured by administration of steroids. For most patients with pain-ful chronic pancreatitis, intermittent or persistent pain remains a major issue, and analgesics of increasing potency are needed. Toskes[35] noted that some of their patients with painful chronic pancreatitis have diminished pain if pancreatic secretion is reduced either by oral administration of pancreatic enzymes or by administration of the inhibitory hormone somatostatin. However, the clinical results achieved using exogenous pancreatic enzymes to reduce the pain of chronic pancreatitis have been variable, and at this time, the role of enzyme administration for pain relief in these patients is highly controversial.

**What Are the Symptoms of Pancreatitis?**

**Symptoms of acute pancreatitis:**

* Upper [abdominal pain](http://www.webmd.com/pain-management/guide/abdominal-pain-causes-treatments) that radiates into the back; it may be aggravated by eating, especially foods high in fat.
* Swollen and tender [abdomen](http://www.webmd.com/digestive-disorders/picture-of-the-abdomen)
* [Nausea and vomiting](http://www.webmd.com/digestive-disorders/digestive-diseases-nausea-vomiting)
* Fever
* Increased [heart rate](http://www.webmd.com/heart-disease/pulse-measurement)

**Symptoms of chronic pancreatitis:**

The symptoms of chronic pancreatitis are similar to those of acute pancreatitis. Patients frequently feel constant pain in the upper abdomen that radiates to the back. In some patients, the pain may be disabling. Other symptoms are diarrhea and [weight loss](http://www.webmd.com/diet/default.htm) caused by poor absorption (malabsorption) of food. This malabsorption happens because the gland is not releasing enough enzymes to break down food. Also, [diabetes](http://www.webmd.com/diabetes/default.htm) may develop if the [insulin](http://www.webmd.com/diabetes/treat-your-diabetes-17/slideshow-blood-sugar-insulin)-producing cells of the pancreas are damaged.