PANCREAPEDIA
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Introduction to Pancreatic Disease: Acute Pancreatitis

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Version 1.0, December 16, 2014 [DOI: 10.3998/panc.2014.14]

What is acute pancreatitis?

Acute pancreatitis is inflammation of the pancreas. The pancreas is a gland that sits just behind the stomach (**Figure 1**). It has two roles: 1) To secrete digestive juices into the small bowel to digest food and neutralize gastric acid secretion and 2) to release insulin to regulate the glucose levels in the blood. There are three types of cells: 1) acinar cells, which produce pancreatic digestive enzymes; 2) ductal cells lining pancreatic ducts, which secrete a watery fluid to carry the digestive enzymes into the intestine; and 3) endocrine cells present in the islets of Langerhans, which secrete insulin and other hormones (**Figure 2**). Because acinar and ductal cells secrete into a duct this portion is called the exocrine pancreas. Pancreatic digestive enzymes are made as inactive precursors and carried to the small bowel where there are additional enzymatic processes that convert the inactive digestive enzymes to actives ones that digest our food. When pancreatic enzymes are prematurely activated in the pancreas, they attack the pancreas itself instead of digesting food and cause pancreatitis.

Acute pancreatitis is the most common reason for hospitalization for a gastrointestinal related disease in the United States. In 2009, there were 275,000 admissions for acute pancreatitis, and a direct annual cost of $2.6 billion (1). Worldwide, the incidence of acute pancreatitis is between 4.9 and 73.4 cases per 100,000 (2, 3). There is an increasing incidence of acute pancreatitis in the United States. The risk of acute pancreatitis increases with age. Both men and women are at risk for pancreatitis; however gender difference is determined by the cause of acute pancreatitis. For example, acute pancreatitis due to alcohol is more likely in men than in women, which reflects more use of alcohol in men. In contrast, acute pancreatitis due to gallstones is more common in women. More than 60% of the cases of acute pancreatitis occur in adults (4). However, acute pancreatitis in children and adolescents has become more recognized. Pancreatitis is 2 to 3 times higher in African Americans when compared to Caucasians (5).

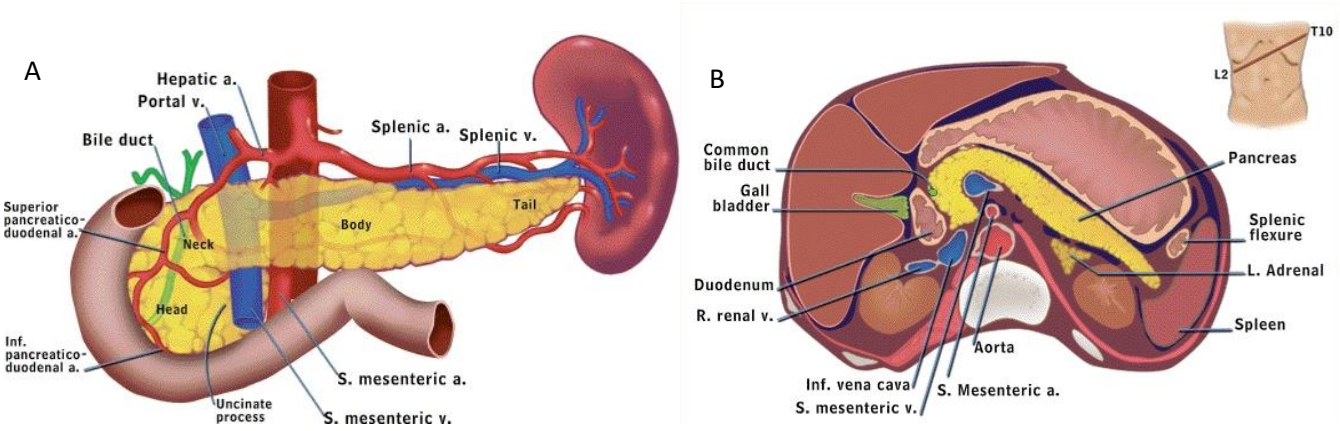

Figure 1. The pancreas. The pancreas has 4 parts: the head, neck, body and tail. Figure 1A is an anatomical drawing showing the vascular supply of the pancreas. Figure 1b shows a cross sectional image of the pancreas obtained from a normal human. Clinically such an image can be obtained by computed Tomography (CT). The pancreas lies behind the stomach which has been removed to visualize the pancreas. Part of the colon and loops of small bowel are also anterior to the pancreas. Behind the pancreas lie a number of large blood vessels including the portal vein, inferior vena cava, aorta, superior mesenteric artery and vein, kidneys and vertebrae. The distal common bile duct passes through the head of the pancreas. Adapted from Gorelick F, Pandol, SJ, Topazian M. *Pancreatic physiology, pathophysiology, acute and chronic pancreatitis*. Gastrointestinal Teaching Project, American Gastroenterologic Association. 2003.

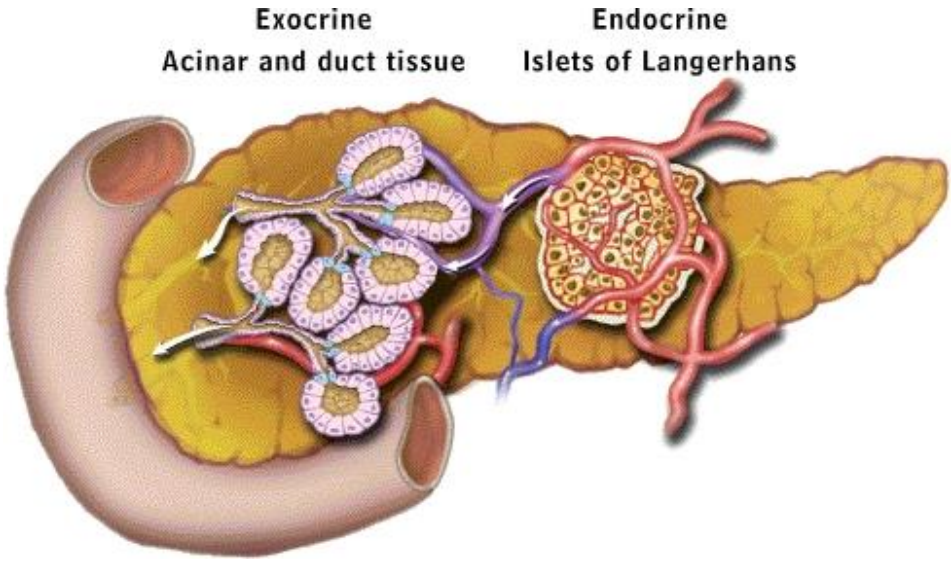

Figure 2. Cells of the pancreas. The pancreas has two types of glandular cells: exocrine cells which include acinar and ductal cells: and endocrine cells present in the islets of Langerhans. The exocrine portion of the pancreas makes up 85% of the pancreas. Adapted from Gorelick F, Pandol, SJ, Topazian M. *Pancreatic physiology, pathophysiology, acute and chronic pancreatitis*. Gastrointestinal Teaching Project, American Gastroenterologic Association. 2003.

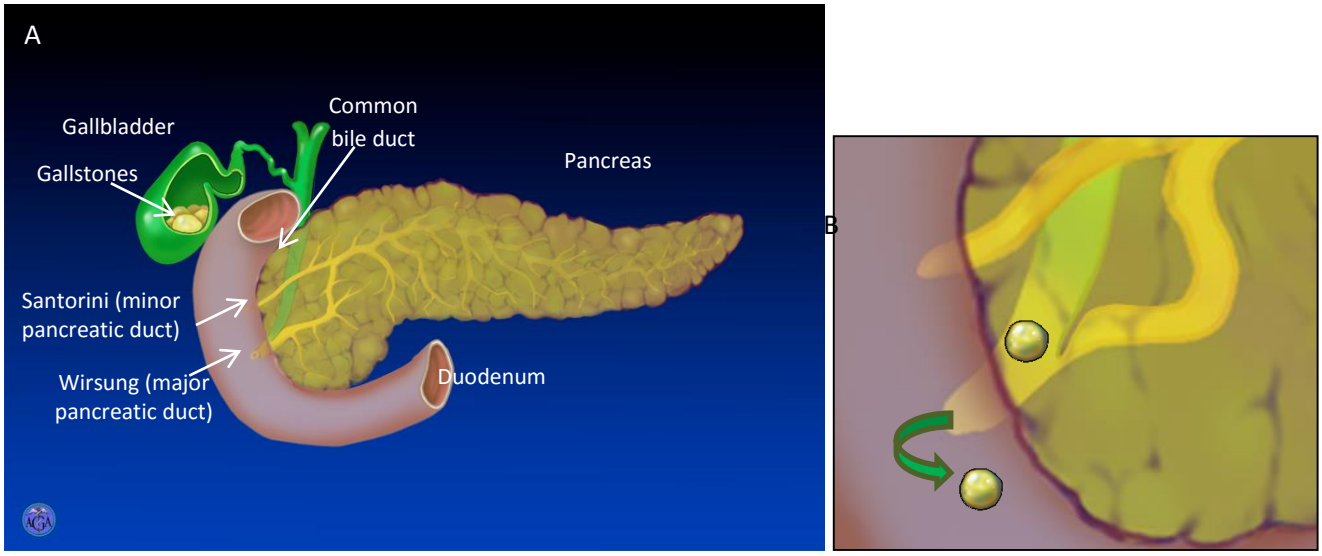

Figure 3. The ductal anatomy. The common bile duct joins the pancreatic duct and empties into the duodenum through the duct of Wirsung. Stones in the gallbladder may fall into the common bile duct, causing obstruction as seen in panel B. Adapted from Adapted from Gorelick F, Pandol, SJ, Topazian M. *Pancreatic physiology, pathophysiology, acute and chronic pancreatitis*. 2003.

What causes acute pancreatitis?

There are many causes of acute pancreatitis. The most common cause in the United States is due to gallstones. Gallstones are tiny rocks that are formed in the gallbladder. They are made of cholesterol or bile material that clump together to form a solid mass. Gallstones may pass into the common bile duct from the gallbladder and obstruct the pancreatic duct, causing the pancreatic fluids to collect in the pancreatic duct leading to inflammation of the pancreas as shown the **Figure 3**. Gallstones are more common in women than men. It can occur in all age groups but has a higher frequency in older patients.

The second most common cause of acute pancreatitis in the United States is alcohol abuse induced acute pancreatitis. This is the most common cause of acute pancreatitis in countries outside of the United States, specifically in European countries where there has been a rise in alcohol consumption. Alcoholic pancreatitis is more likely in middle age population, with a peak incidence at 45-55 years (6). Alcohol has toxic and metabolic effects on the pancreatic acinar cells (7). It can cause small duct obstruction, premature activation of the enzymes, abnormal blood flow to the pancreas, abnormalities in the sphincter of Oddi motility, and stimulation of cholecystokinin (CCK) and secretin releases which activate pancreatic secretion. See **Figure 4** below. The risk of pancreatitis increases with the amount of alcohol consumed. The relationship between alcohol and pancreatitis is not fully understood as only a small fraction of binge drinking leads to pancreatitis. Currently there is interest in identifying genetic variation that may predispose to acute pancreatitis

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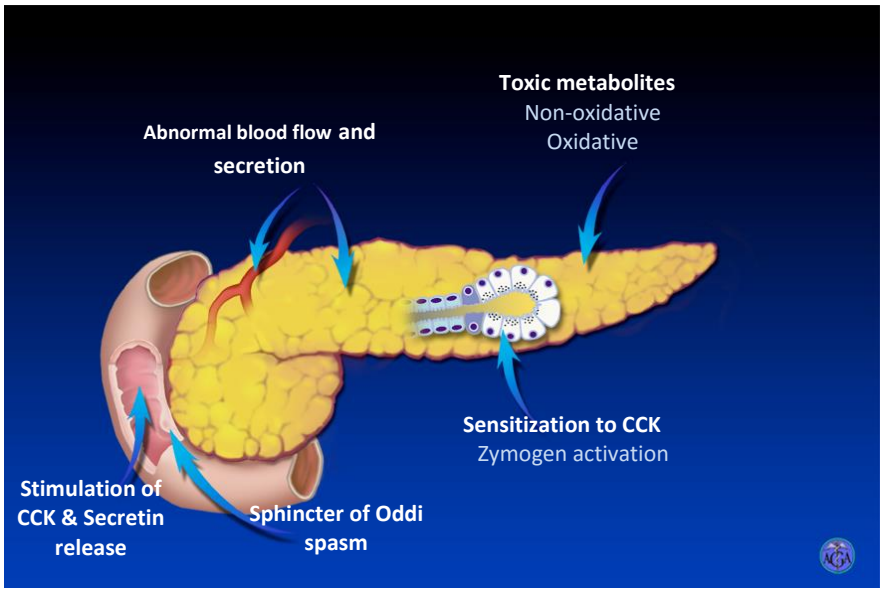

Figure 4. Effects of alcohol on the pancreas. Changes in pancreatic blood flow, coupled with the generation of free radicals from ethanol metabolism, may cause free radical damage. Stimulation of pancreatic secretion coupled with spasm of the sphincter of Oddi could lead to an acute obstructive injury. Adapted from Gorelick F, Pandol, SJ, Topazian M. *Pancreatic physiology, pathophysiology, acute and chronic pancreatitis*. 2003.

Recently, cigarette smoking has emerged as a potential cause of acute pancreatitis. Previously, this was linked to alcohol intake. However, a recent systematic review and analysis of multiple data sets pooled together (meta-analysis) showed that cigarette smoking is an independent risk factor for the development of acute pancreatitis (8).

Elevated triglycerides can also cause acute pancreatitis. Serum triglyceride concentrations above 1000 mg/dL can lead to acute pancreatitis. The exact mechanism is not clearly understood although it is thought to be due to the deleterious effects of hydrolysis of the triglycerides into short-chain fatty acids, which can be toxic to the pancreas. Elevated levels of triglycerides are usually indicative of dietary intake; however familial hypertriglyceridemic diseases can occur with a primary genetic abnormality. Also patients with diabetes will also have a risk for having elevated levels of triglycerides.

Drug induced acute pancreatitis is another important cause, accounting for 3 to 5% of all cases (9). This is the most challenging for physicians. Nearly 240 million Americans take at least one medication weekly (10). There have been more than 100 medications that have been associated with acute pancreatitis in case reports, but these studies have suffered from inappropriate diagnosis of acute pancreatitis and have failed to show a rechallenge with the medication or rule out other potential causes of pancreatitis. In addition, there have been inconsistencies with the time of initiating the drug to the development of acute pancreatitis, also known as latency. There are 4 classes of drugs that have been identified. Class 1 drugs include drugs for which there are at least 1 case report that describes a recurrence of acute pancreatitis with a rechallenge of the drug. This class is further broken down into Class 1a and 1b drugs; Class 1 a refers to drugs for which there is at least 1 case report with positive rechallenge test and exclusion of all other potential causes of acute pancreatitis, whereas in Class 1b other causes of acute pancreatitis were not ruled out. Class 1 drugs have the best level of evidence. Class 2 refers to drugs for which there have been at least 4 case reports and consistent latency of more than 75%.

Class 3 and 4 drugs refer to those with lesser evidence. The table below lists the Class 1a and b medications that have been associated with acute pancreatitis (11). Recently, there has been increased publicity about the use of glucagon-like peptide-1 (GLP-1) receptor agonists, such as exenatide, and dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin and acute pancreatitis. Exenatide, also known as Byetta, as approved by the Food and Drug Administration (FDA) in 2005 for improved glycemic control in patients with type 2 diabetes mellitus. Shortly after its release here was a case report of acute pancreatitis that was published (12), and then 48 others have been recorded since (13). The same occurred for sitagliptin, also known as Januvia, which was approved by the FDA in 2006. However other causes of acute pancreatitis were not ruled out, including gallstones and hypertriglyceridemia, which are prevalent in the diabetic population. A recent literature has revealed that the evidence of the incidence of pancreatitis is low among patients on these medications, and there may be no increase in risk of pancreatitis (14, 15).

Table 1. Class 1a and Class 1b drugs associated with acute pancreatitis.

Class 1a	Class 1b
Bezafibrate	α-methyldopa
Cannabis	All-trans-retinoic acid
Carbimazole	Amiodarone
Cytosine Arabinoside	Azathioprine/ 6 mercaptopurine
Azodisalicylate	Clomiphene
Codeine	Dexamethasone/ Hydrocortisone
Enalipril	Dapsone
Ifosfamide	Estrogen products
Isoniazide	Furosemide
Mesalamine	Lamivudine
Metronidazole	Losartan
Pravastatin	Methimazole
Premarin	Meglumine
Procainamide	Pentamidine
Pyrintol	Trimethoprimsulfamethazole
Simvastatin	
Sulfamethoxazole	
Stibogluconate	
Sulindac	
Tetracycline	
Valproic acid	

Acute pancreatitis may also be a complication of diagnostic procedures such as endoscopic retrograde cholangiopancreatography (ERCP) and can occur in up to 30% of patients undergoing ERCP. A diagnosis is generally made if the patient has persistent post procedural abdominal pain, nausea and vomiting, with an elevation in pancreatic enzymes and/or imaging that is consistent with pancreatic inflammation.

Other rare causes include

- Elevated levels of calcium
- Infections, including mumps and viral hepatitis
- Abdominal surgery
- Direct trauma to the abdomen, including injuries from sports, car accidents and falls
- Hereditary gene mutations
- Malignancy

However despite all known causes, more than one third of cases of acute pancreatitis are idiopathic, meaning that the underlying etiology is unknown (16, 17).

In children, the cause of pancreatitis is typically related to medications, infections (such as mumps, measles, Epstein-barr virus), blunt trauma to the abdomen, congenital defects of the pancreas, and systemic diseases such as hemolytic uremic syndrome, cystic fibrosis, and Reye syndrome (18).

What are the symptoms of acute pancreatitis?

Symptoms of acute pancreatitis includes sudden onset of severe pain in the upper part of the abdomen which can be simultaneously experienced in the back along with nausea, vomiting, and bloating. The pain is worse after eating. The patient may also be jaundiced, which would indicate an obstruction of the bile duct. The patient may also have fever, shortness of breath, fast or slow heart rate or kidney problems if the symptoms are severe. Abdominal pain is also the early sign of acute pancreatitis in older children. However, in younger children, vomiting may be the initial symptom.

How is acute pancreatitis diagnosed?

In addition to the symptoms above, blood work will show elevated levels of the pancreatic digestive enzymes lipase and amylase. These levels are typically more than 3 times the upper limit of normal levels. A computed tomography (CT) scan will show if the pancreas is swollen, which will indicate inflammation. It may also show areas of hypoenhancement which may indicate necrotizing pancreatitis. In addition, it may show other complications of acute pancreatitis, including pseudocyst, and unorganized fluid collections. A transabdominal ultrasound of the abdomen may be performed to detect gallstones and other obstructions of the ductal system. Certain blood tests will also be obtained to look for the etiology of the pancreatitis, such as triglyceride and calcium levels. A history of alcoholism and/or smoking points to these as a cause. If no cause is found with these approaches, then an endoscopic ultrasound may be recommended to evaluate the pancreatic gland and duct to determine if there tumors or other abnormalities that were not seen on the CT or transabdominal ultrasound. Endoscopic ultrasound is an ultrasound probe on a flexible endoscope. It is passed into the stomach and the duodenum and is able to better visualize the pancreas since the pancreas sits posterior to the stomach.

How is acute pancreatitis treated?

Acute pancreatitis can be stratified into various severities. Approximately 85% of the cases are mild (also called acute interstitial pancreatitis, AIP), which indicates an uneventful course. In approximately 15% of cases, patient can develop

severe pancreatitis with tissue damage (also called acute necrotizing pancreatitis (ANP), in which he or she will have a complicated recovery with systemic complications. There is a risk of death associated with ANP.

In the mild cases of acute pancreatitis, patients may or may not need to be hospitalized. In some cases, they can be treated at home by taking pain medications, and clear liquids. In situations when the patient is unable to hold down liquids or oral medications, he or she is admitted to the hospital for a few days and given intravenous fluids and pain medication. In cases of severe pancreatitis, the patient will be admitted to the intensive care unit for closer monitoring.

If the acute pancreatitis is due to gallstones then the patient may undergo a procedure known as endoscopic retrograde cholangiopancreatography (ERCP) to remove the stones in the bile duct and relieve the obstruction. An ERCP is a flexible tube that is inserted through the patient's mouth and into the duodenum. It is specifically designed to gain access to the bile duct. It can show the pancreatic and biliary anatomy, including any strictures or cysts that may have caused obstruction. Patients with gallstone pancreatitis will have a 30% risk of developing acute pancreatitis again in the next year, unless the gallbladder is removed (19).

What are the complications of acute pancreatitis?

1. *AIP and ANP:* Most cases of pancreatitis are AIP and do not lead to complications, and only about 20% of cases are ANP which have a complication rate of about 45% (20). The complications include failure of other organs such as lungs, vascular system and the kidneys. Death can occur in up to 30% of these cases (19, 20). ANP usually develops due to reduced blood flow to the gland which results in dead and devitalized tissue. Previously, the tendency was for early surgical treatment for patients with ANP to remove damaged portions of the gland because they were thought to contribute to failure of the other organs and provide a place for infections to develop. However, a large multi-center randomized controlled trial from the Netherlands changed the movement away from early intervention and let the patient use his/her own tissue recovery system. If there was no clinical improvement in 72 hours from admission or the patient begins to deteriorate, a "step up" approach would take place. The step-up approach which involved placement of percutaneous drains and other minimally invasive procedures as compared to open necrosectomy (surgery to remove damaged tissue), with a median time to intervention of 30 days, and this was shown to have reduced morbidity and mortality (21, 22).

2. *Pseudocyst:* A pseudocyst is a collection of fluid that occurs outside of the pancreatic duct due to leakage from the duct. Most cases resolve spontaneously while a small percentage will require intervention. Intervention includes decompression by endoscopic placement of a drainage tube to connect the cyst to the stomach so that the cyst is drained into the stomach internally without surgery that opens the abdomen.

3. *Extrapancreatic infections:* Extrapancreatic infection occurs in approximately 20% of patients with acute pancreatitis (23, 24). Extrapancreatic infections include bloodstream infection, urinary tract infections, and pneumonias.

How can acute pancreatitis be prevented?

At this time, there is no way of screening patients do determine who is at risk for acute pancreatitis so that primary prevention can be instituted.

Secondary prevention of acute pancreatitis depends on the etiology. Cholecystectomy will prevent further causes of gallstone pancreatitis. Control of triglycerides will prevent further episodes of hypertriglyceridemia induced pancreatitis. Avoiding alcohol consumption and cigarette smoking can decrease the chance of recurrent episodes in patients.

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