

Current approaches to acute and chronic pancreatitis

Key points

- Acute pancreatitis presents with severe abdominal pain and raised serum amylase or lipase levels; the most common cause is gallstone disease.
- Chronic pancreatitis leads to chronic pain, maldigestion and diabetes; the most common cause is prolonged alcohol misuse, but genetic, autoimmune and other forms also occur.
- The most useful diagnostic imaging techniques are abdominal ultrasonography and CT for acute pancreatitis, and magnetic resonance cholangiopancreatography for chronic pancreatitis.
- Mild acute pancreatitis usually requires supportive care only, but severe cases require intensive care and combined medical, surgical and endoscopic treatment.
- Mainstays of treatment of chronic pancreatitis are pain control, pancreatic enzyme supplementation and diabetes control with insulin and diet.

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Acute pancreatitis is painful but usually self-limiting, and typically caused by gallstones. Chronic pancreatitis can lead to persistent pain and pancreatic insufficiency, and often follows prolonged alcohol misuse although other causes are now recognised.

Pancreatitis is a necroinflammatory disease of the pancreas that is believed to result from inappropriate activation of digestive enzymes within the gland. It can be acute or chronic. Acute pancreatitis is usually self-limiting, with a return to normal structure and function on recovery. 'Chronic' implies progressive loss of structure and function over time; chronic pancreatitis is thought to develop with repeated attacks of necroinflammation – the so-called necrosis–fibrosis sequence.

The most common cause of acute pancreatitis in western society is gallstone disease. As shown in Figure 1, when gallstones migrate

from the gallbladder into the duodenum they can transiently obstruct the pancreatic duct, leading to autodigestion. In contrast, the most common cause of chronic pancreatitis in western society is prolonged excessive consumption of alcohol. Excess alcohol is thought to initiate pancreatic injury through direct toxic effects on the pancreatic acinar cell, leading to autodigestion.

Other causes of acute and chronic pancreatitis are listed in the box on page 35. There have been recent breakthroughs in our understanding of the genetics of pancreatitis and also of autoimmune pancreatitis (see the boxes on page 36).¹⁻³

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CAUSES OF PANCREATITIS

Acute pancreatitis

- Gallstones (most common)
- Drugs
 - azathioprine
 - thiazide diuretics
 - oestrogens
 - frusemide
 - sulfonamides
 - tetracyclines
 - valproic acid
 - pentamidine
- Endoscopic retrograde cholangiopancreatography (ERCP)
- Hyperparathyroidism
- Hypertriglyceridaemia
- Infections
 - viral infections: mumps, viral hepatitis, Coxsackie virus and echovirus
 - ascariasis
 - *Mycoplasma* infection
- Obstruction of ampulla of Vater
- Penetrating peptic ulcer
- Surgery, particularly (but not exclusively) near the pancreas or sphincter of Oddi
- Trauma, typically blunt abdominal trauma
- Vasculitis

Chronic pancreatitis

- Alcohol (most common)
- Autoimmune pancreatitis
- Cystic fibrosis
- Hereditary pancreatitis
- Hyperparathyroidism
- Idiopathic pancreatitis
- Protein–energy malnutrition
- Trauma, typically blunt abdominal trauma that damages the pancreas, leading to scarring of the pancreatic duct system
- Tropical pancreatitis

CLINICAL FEATURES

Acute pancreatitis

The cardinal feature of acute pancreatitis is abdominal pain, usually epigastric with radiation to both upper quadrants and the back.

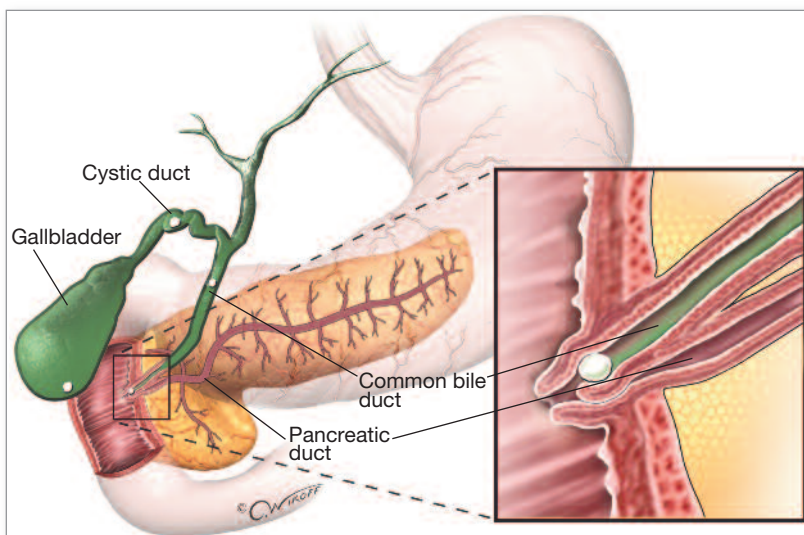


Figure 1. Mechanism of gallstone pancreatitis. Gallstones can intermittently migrate from the gallbladder into the cystic duct and common bile duct and then through the choledochoduodenal junction into the duodenum. While passing through the junction (inset), gallstones can transiently obstruct the pancreatic duct, increasing hydrostatic pressure within the duct, blocking pancreatic secretion and leading to activation of pancreatic enzymes within the pancreas. Gallstones can also become impacted at the junction, causing persistent obstruction.

The pain is usually severe, of gradual onset and commonly accompanied by nausea, vomiting and sweating. Physical examination reveals a distressed patient, but the degree of abdominal tenderness and guarding may be less than expected from the patient's overall demeanour. The patient may be febrile and tachycardic.

In most patients, acute pancreatitis is mild and self-limiting. Around 20% of patients develop severe disease, with local complications, organ failure or sepsis. Severe acute pancreatitis has a mortality of around 30%.

Chronic pancreatitis

Patients with chronic pancreatitis have abdominal pain and pancreatic insufficiency, leading to diabetes mellitus, steatorrhoea, weight loss and malnutrition. Pain, either constant or in prolonged episodes, dominates in the early stages and may lead to depression and opiate dependence. After some years, the severity of pain may decrease while the features of pancreatic insufficiency become more evident.

GENETICS OF CHRONIC PANCREATITIS¹

A major breakthrough in our understanding of the pathogenesis of chronic pancreatitis came in 1996 with the report of a gain-of-function mutation in the cationic trypsinogen gene (*PRSS1*) in a family with hereditary pancreatitis. Several other mutations in the trypsinogen gene have since been described.

A mutation in the serine protease inhibitor *SPINK1* gene, which may increase propensity for autodigestion, has been associated with idiopathic, tropical and autoimmune pancreatitis. This mutation is thought not to be a primary cause but to modify the disease.

A variety of cystic fibrosis transmembrane regulator (*CFTR*) mutations have been described in patients with idiopathic pancreatitis. Affected individuals do not have classic cystic fibrosis. They usually possess two copies of 'mild' *CFTR* mutations or one 'severe' copy and one 'mild' copy.

AUTOIMMUNE PANCREATITIS^{2,3}

Autoimmune pancreatitis is a recently described, rare condition. It typically presents as segmental or total pancreatic enlargement causing obstructive jaundice, commonly in older men. Autoimmune pancreatitis can also present as acute pancreatitis, but this is much less common. The main differential diagnosis is pancreatic cancer.

Histologically, there is diffuse periductal lymphoplasmacytic infiltration and fibrosis of the pancreas. Serum IgG4 levels are raised in 70 to 80% of patients. Other organs and tissues can also be affected by lymphoplasmacytic infiltration and fibrosis, including salivary glands, bile ducts, kidneys and the retroperitoneum.

A second type of autoimmune pancreatitis with a distinct histological appearance has been described. There is less involvement of other organs and an association with inflammatory bowel disease. In this type, serum IgG4 levels are not raised.

INVESTIGATIONS AND DIAGNOSIS**Acute pancreatitis**

The diagnosis of acute pancreatitis is based on findings of raised pancreatic enzyme levels in a patient with abdominal pain and corroborative imaging results as detailed below.

NONPANCREATIC CAUSES OF A HIGH SERUM LIPASE LEVEL

- Gastrointestinal mucosal disease
 - perforated or penetrating peptic ulcer
 - obstructed, perforated, inflamed or infarcted bowel
 - coeliac disease
- Acute cholecystitis
- Renal failure
- Diabetic ketoacidosis
- Macrolipasaemia
- HIV infection
- Drugs (e.g. cholinergic agents, frusemide, indomethacin, methylprednisolone, narcotics, oral contraceptives, thiazide diuretics, valproic acid)

Pancreatic enzyme tests

In acute pancreatitis, serum amylase and/or lipase levels are usually raised to more than three times the upper limit of normal. Serum lipase level is a more specific test for acute pancreatitis than serum amylase level, and elevations in serum lipase level are generally longer lasting, permitting diagnosis when presentation is delayed. However, high levels of lipase may also occur in certain nonpancreatic conditions (see the box on this page). In some of these conditions, the underlying mechanism appears to be a breach in intestinal mucosal integrity, facilitating movement of intestinal enzymes into serum, but in other conditions the mechanism is unclear. Serum amylase level may be elevated in salivary gland conditions, acute pelvic inflammation and the presence of some solid neoplasms of other organs.

Diagnostic imaging

Abdominal ultrasonography is the initial imaging modality of choice in patients with acute pancreatitis. Its main value is in detecting gallbladder disease (stones and a thickened gallbladder wall), but it may also detect pancreatic enlargement

and fluid collections. Demonstration of a normal-diameter common bile duct (less than 7 mm) is useful, but the sensitivity for choledocholithiasis is only 55 to 75%, and bile duct dilatation alone may be secondary to pancreatic swelling. Ultrasonography is operator-dependent, and the pancreas can be obscured by small bowel ileus and gas accumulation.

CT of the abdomen is not operator-dependent and is better than ultrasonography for defining pancreatic size and shape and fluid collections. A finding of peripancreatic fat stranding (a result of necrosis) strongly supports the diagnosis of acute pancreatitis (Figure 2). Some centres delay abdominal CT until later in the course of the illness, especially if severe acute pancreatitis is suspected, to reduce the risk of renal damage and because it often takes several days for focal areas of necrosis to become evident.

Chronic pancreatitis

The most useful diagnostic test for chronic pancreatitis is an imaging technique that can demonstrate structural damage to the pancreas.

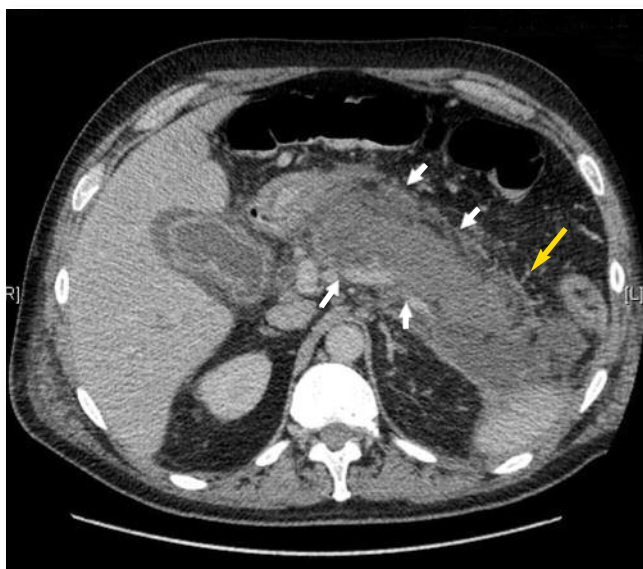


Figure 2. Abdominal CT in a patient with acute pancreatitis, showing a diffusely enlarged pancreas (small white arrows) with peripancreatic fat stranding (large yellow arrow).

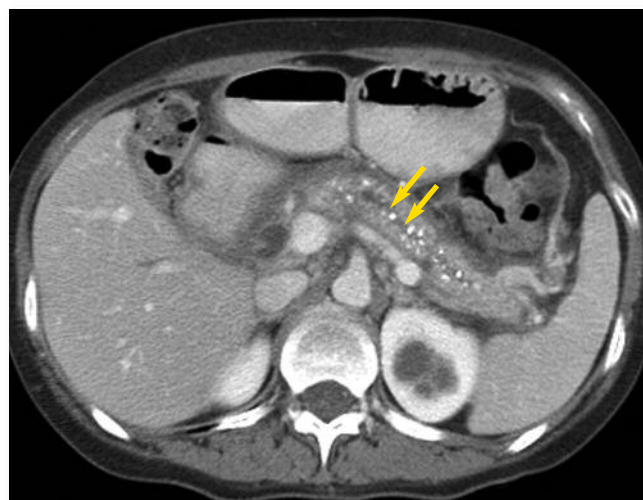


Figure 3. Abdominal CT in a patient with chronic pancreatitis showing typical changes in pancreatic architecture, including atrophy, extensive calcification and a dilated, irregular pancreatic duct (arrows).

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Diagnostic imaging

Abdominal CT is highly reliable for demonstrating key pathological features in chronic pancreatitis such as atrophy, calcification, dilatation and strictures of intrapancreatic ducts and intraductal calculi (Figure 3).

Magnetic resonance cholangiopancreatography (MRCP) has the advantages of better demonstrating ductal morphology (Figures 4a and b) and avoiding ionising radiation, but its availability may be limited.

Abdominal ultrasonography is especially useful for revealing fluid collections in chronic pancreatitis but often does not show important structural changes as well as do abdominal CT and MRCP.

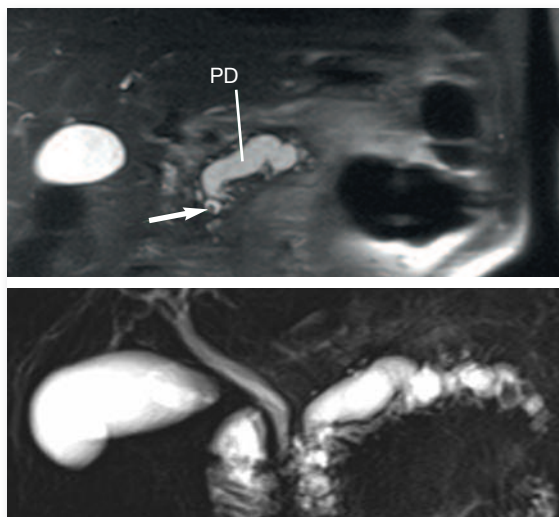
Plain abdominal x-ray is of limited value unless it reveals pancreatic calcification in the presence of steatorrhoea, which may be sufficient to diagnose chronic pancreatitis.

Endoscopic retrograde cholangiopancreatography (ERCP) is the most sensitive method for outlining ductal morphology but is invasive with a risk of post-ERCP

pancreatitis of about 5%. Therefore, it is generally reserved for patients who may need therapeutic intervention, such as removal of an intraductal stone, correction of a stricture or insertion of a stent. Cytological examination of samples of pancreatic juice or ductal brushings obtained at ERCP has limited diagnostic value for excluding malignancy.

Endoscopic ultrasonography (EUS),

available only in specialist centres, is emerging as a useful modality for diagnosing early chronic pancreatitis (Figure 5). Pancreatic biopsy can be performed at the same time, thus providing a quick diagnosis of neoplasia in some cases. However, even with the aid of ERCP and EUS, the exclusion of malignancy in a fibrotic pancreas remains a major diagnostic challenge.



Figures 4a and b. Magnetic resonance cholangiopancreatography (MRCP) in a patient with chronic pancreatitis. a (top). A dilated pancreatic duct (PD) containing a calculus (arrow). b (bottom). A dilated duct with multiple strictures and stones, resulting in a 'chain of lakes' appearance.

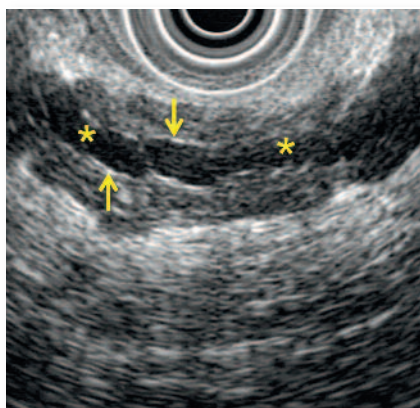


Figure 5. Endoscopic ultrasound examination of the pancreas in a patient with chronic pancreatitis, showing characteristic features: hyperechogenic duct walls (arrows) and an irregular and dilated main duct (asterisks).

Other investigations

Faecal fat determination is valuable for confirming the presence of steatorrhoea. However, its use has decreased because the need to collect stool over three days is inconvenient for the patient and the test is onerous for the laboratory. Nevertheless, it remains a valuable adjunct for diagnosing well-established chronic pancreatitis and assessing response to enzyme replacement therapy.

Many indirect tests of pancreatic function have been proposed over the years, including breath tests (for hydrogen gas or breakdown products of radioactively labelled substrates), stool microscopy with fat staining and measurement of pancreatic enzymes in faeces, but their reliability to determine pancreatic insufficiency accurately is limited. Serum enzyme measurements are of no value in confirming the presence of chronic pancreatitis.

Serum IgG4 levels can be raised in some forms of autoimmune pancreatitis.³ Serum IgG4 measurements are best reserved for patients with an unexplained pancreatic mass or unexplained chronic pancreatitis.

MANAGEMENT

Acute pancreatitis

Most cases of acute pancreatitis are mild and can be managed with analgesia, a nil-by-mouth regimen and intravenous fluid replacement.⁴ In contrast, severe acute pancreatitis requires management by an experienced team of surgeons, physicians and intensivists. As noted earlier, mortality in severe acute pancreatitis is around 30% and can occur either:

- early – around one to two weeks after onset, caused by systemic inflammatory response syndrome and respiratory or renal failure or
- late – three to four weeks after onset, usually caused by sepsis.

Considerable effort has been made trying to predict which cases of acute pancreatitis will become severe so as to institute treatment as soon as possible. Various predictive scoring systems have been devised, based on counting disturbances in physiological and pathological parameters, including vital signs, acid–base balance, renal function, consciousness, haematological parameters and the presence of other illnesses. There is broad international consensus that the APACHE II score is the most reliable predictor.⁵

Patients with severe acute pancreatitis require intensive care support with adequate oxygenation, fluid replacement, nutritional support and antibiotics. Early ERCP with biliary drainage and extraction of stones from the common bile duct is indicated if severe acute gallstone pancreatitis is predicted.

There is evidence that early enteral nutrition may be superior to parenteral nutrition in severe pancreatitis, probably because it helps maintain the integrity of the intestinal mucosal barrier, preventing bacterial translocation and subsequent sepsis. The role of prophylactic antibiotics in cases of predicted severe acute pancreatitis is controversial.

Infection of necrotic tissue or pseudocysts requires intervention, usually by open surgery, although endoscopic,

radiological and laparoscopic techniques are being introduced into clinical practice.

Chronic pancreatitis

The management of a patient with chronic pancreatitis requires a multidisciplinary team. This should comprise a surgeon or gastroenterologist, a pain specialist, a specialist in addiction medicine, a dietitian and an endocrinologist, as well as the GP.

Pain control

Pain is the predominant clinical problem in chronic pancreatitis. A graduated approach to analgesia is recommended, commencing with paracetamol or NSAIDs, but most patients eventually require opioid analgesics. It is important to control pain adequately, and this can require a high level of clinical discernment because of the association of chronic pancreatitis with alcohol misuse and addictive behaviour.

Several operative and endoscopic interventions have been recommended in the past to relieve pain, but none have been trialled against medical therapy alone. Nevertheless, most major centres favour intervention for patients with intractable pain in whom alcohol abstinence appears possible. A widely held view is that pain is related to high pancreatic intraductal and interstitial pressure. Thus the most favoured intervention is some form of drainage, either surgical or by endoscopic insertion of a stent into the pancreatic duct. Surgical excision of the pancreas itself has generally produced poor results. Disappointingly, relatively simple neurolytic (nerve block) techniques have not produced consistent lasting pain relief.

Two forms of medical therapy have been recommended: antioxidant therapy (e.g. selenium, beta-carotene, methionine, vitamins C and E) and pancreatic enzyme replacement therapy (PERT; preparations contain lipase, protease and amylase). Neither have convincing support from large-scale controlled studies but both are relatively safe and can be withdrawn

easily. Antioxidant therapy is based on the belief that oxidant stress has a prominent role in the pathogenesis of pancreatitis. The rationale for PERT is that it can inhibit pancreatic secretion via a negative feedback loop, thereby decreasing pancreatic intraductal and interstitial pressure. PERT showed benefit in some trials but meta-analyses failed to demonstrate an effect.⁶

Management of steatorrhoea and malnutrition

Steatorrhoea is a late symptom of chronic pancreatitis, occurring when more than 90% of the secretory capacity of the gland has been lost. It is managed by PERT. There is no proven benefit of any one pancreatic enzyme formulation over another, although minimicrosphere preparations have a theoretical advantage as they avoid the need for gastric acid suppression and facilitate release in the intestine. Sufficient lipase must be given; the recommended initial dose in adults is 25,000 units of lipase per meal, titrating up to a dose of 80,000 units per meal. PERT should be taken with meals to ensure adequate mixing with chyme. Dietary fat restriction is not recommended for patients with steatorrhoea.

Treatment is ideally monitored by faecal fat determination. This is particularly important in children. However, in most adults with chronic pancreatitis, treatment efficacy is determined by clinical history and monitoring of nutritional status.

An inadequate response to PERT is managed by increasing the dose of pancreatic enzymes and adding a proton pump inhibitor to the regimen (to inhibit secretion of gastric acid, which degrades pancreatic enzymes). If steatorrhoea persists then other causes should be considered, such as small bowel bacterial overgrowth.

It is uncommon for PERT to reverse steatorrhoea completely. Therefore, nutritional status should be monitored, particularly levels of fat-soluble vitamins. Mineral and vitamin supplements should be considered, depending on baseline measurements of serum vitamin D, calcium and

magnesium levels, INR and bone mineral density.

Management of diabetes

Diabetes caused by pancreatitis is managed similarly to diabetes from other causes, that is, with insulin and diet. Patients with chronic pancreatitis are prone to hypoglycaemia because of the concomitant loss of counter-regulatory hormones such as glucagon. The use of insulin in a patient with chronic pancreatitis who continues to misuse alcohol can be a particular challenge.

CONCLUSION

In acute pancreatitis, diagnosis is based on the presence of compatible clinical features with a more than threefold elevation in serum amylase or lipase level and radiological evidence of peripancreatic inflammation. Mainstays of treatment are analgesia, fasting, intravenous fluid replacement and exclusion of acute gallstone obstruction.

In chronic pancreatitis, management requires a multidisciplinary approach, drawing on the expertise of a surgeon or gastroenterologist, pain expert, dietitian and endocrinologist. It can be difficult to exclude the rarer potential causes, although an elevated serum IgG4 level is a simple indicator of autoimmune pancreatitis. Nutritional advice and pancreatic enzyme replacement are commonly required. Adequate pain control is important, with attention to the high risk of addiction when opioids are used. The most favoured approach for resistant pain is endoscopic or surgical drainage of the pancreatic duct. **MT**

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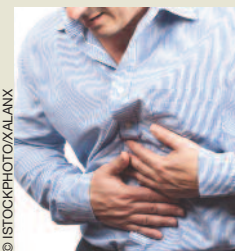
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