Acute and chronic pancreatitis

Stephen J N Tattersall, Minoti V Apte and Jeremy S Wilson

THE PANCREAS is a lobulated structure, 10–15 cm long, lying posteriorly in the upper abdomen, draped across the upper lumbar spine (Box 1). It extends from the duodenal loop (head) to the hilum of the spleen (tail). Its close proximity to a number of intra-abdominal structures, including the stomach and duodenum, the transverse colon, the splenic and superior mesenteric vessels, and the spleen, gives rise to the possibility of a number of local complications of pancreatic inflammation.

The exocrine pancreas is the major digestive organ of the body. It secretes up to 20 g of enzyme protein into the duodenum each day. It has a protein synthetic capacity similar to that of the lactating mammary gland.

Pancreatitis

Pancreatitis is a necro-inflammatory condition of the pancreas. There is now experimental and genetic evidence that the disease arises as a result of inappropriate activation of digestive enzymes within the gland.

Acute pancreatitis is generally a mild, self-limiting disease, requiring only conservative medical therapy. A minority of cases are severe (Box 2), with local and/or systemic complications and significant mortality (10%–30%).[1]

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Abstract

- Acute pancreatitis is generally a mild condition that settles spontaneously. A minority of acute pancreatitis cases become severe, with local and distant complications and the need for intensive, and possibly interventional, therapy.
- Chronic pancreatitis is a relatively uncommon condition but one that can significantly impact on quality of life and pose challenges for management.
- This review describes modern advances in the understanding of the pathogenesis of pancreatitis and outlines a recommended approach for diagnosis and therapy.

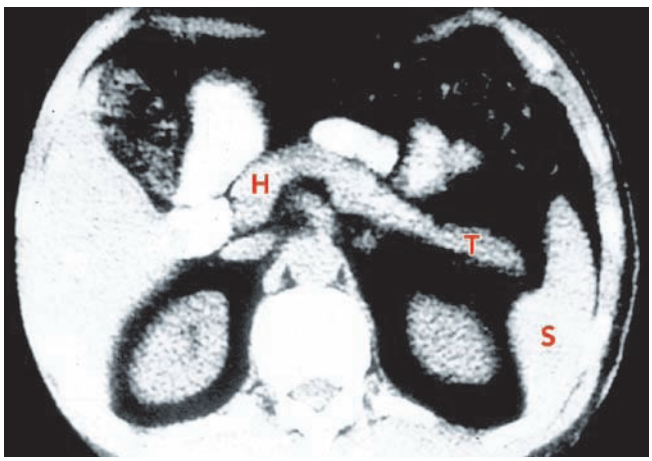
ADF Health 2008; 9: 24-33

Chronic pancreatitis occurs as a result of repeated necro-inflammatory episodes, with progressive loss of normal pancreatic structure and function. Pathologically, chronic pancreatitis is characterised by necro-inflammation, fibrosis, and loss of glandular tissue (atrophy) (Box 3).

Associations of pancreatitis

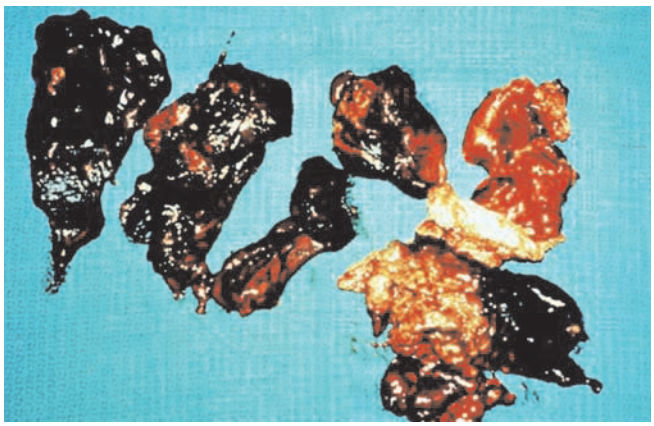
The most common association of acute pancreatitis is gallstone disease, and that of chronic pancreatitis (in Western society) is overuse of alcohol. Other associations of acute and chronic pancreatitis in Western society are listed in Box 4.

1 Gross pancreatic anatomy

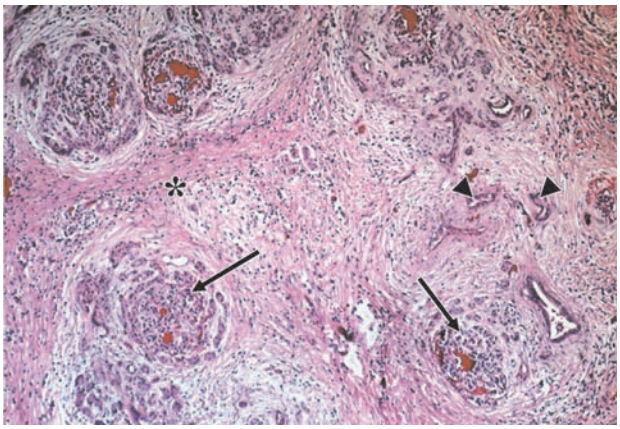


*Contrast-enhanced computed tomography scan showing the pancreas extending from its head (**H**) adjacent to the second part of the duodenum to its tail (**T**) at the hilum of the spleen (**S**). The pancreas is in the retroperitoneum and lies in close proximity to the stomach anteriorly, and a number of major vessels, including the splenic vein.*

2 Necrosis and haemorrhage in pancreatic tissue following severe acute pancreatitis



3 Pathological features of chronic pancreatitis



Pancreatic tissue from a patient with chronic alcoholic pancreatitis, showing broad bands of fibrosis (asterisk), some residual acinar tissue (arrows), an inflammatory cell infiltrate and distorted ducts (arrowheads) (haematoxylin–eosin stain, original magnification × 400). (From the American Gastroenterological Association slide set, with permission.)

Pathogenetic mechanisms

Acute pancreatitis

Gallstone pancreatitis arises from migration of gallstones from the gall bladder to the duodenum, causing a transient obstruction of the adjacent pancreatic duct at the choledocho-duodenal junction, with consequent upstream blockage of pancreatic secretion (Box 5). Exocytosis of zymogen granules (which contain digestive enzymes) from pancreatic acinar cells is blocked, and the zymogen granules coalesce with lysosomes within the acinar cell to form autophagic vacuoles. Within these vacuoles, lysosomal enzymes activate digestive enzymes, with consequent autodigestion of the gland.

Cell injury and death give rise to an inflammatory response, with local release of pro-inflammatory cytokines and other inflammatory mediators. In a minority of cases, the inflammatory response can be severe and systemic, with multiorgan failure.

Local complications can include fluid collections, vascular thrombosis, and sepsis. In severe cases, sepsis appears late (2–4 weeks after the initial event) and results mainly from bacterial translocation from the intestine.

The pathogenetic sequence described for gallstone pancreatitis probably also explains the initiation of a number of other forms of acute pancreatitis (post-endoscopic retrograde cholangiopancreatography [ERCP], duct obstruction, sphincter of Oddi stenosis or spasm, etc). However, not all forms of acute pancreatitis can fit within this pathogenetic schema, including drug-induced, hypercalcaemic, hyperlipaemic, and vasculitis-associated pancreatitis. Other mechanisms must be invoked for these less common entities, and their pathogenesis is not well understood.

4 Causes of pancreatitis

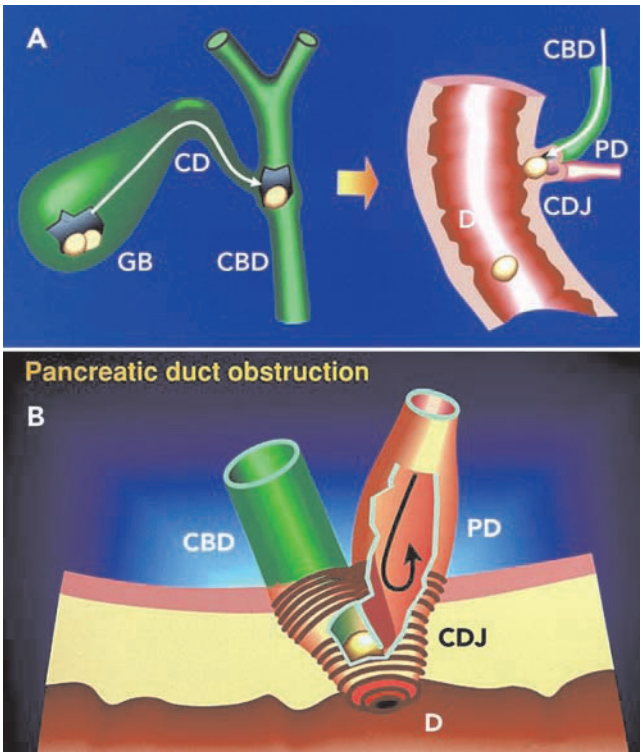
Acute pancreatitis	Chronic pancreatitis
Common	*Common*
■ Gallstones	■ Alcohol consumption
Uncommon	*Uncommon*
■ Hypertriglyceridaemia ■ Hyperparathyroidism ■ Surgery ■ Endoscopic pancreatography ■ Trauma ■ Drugs: azathioprine, thiazide diuretics, oestrogens, frusemide, sulfonamides, tetracyclines, valproic acid, pentamidine ■ Infections: mumps, viral hepatitis, coxsackie, echo virus, ascariasis, mycoplasma ■ Vasculitis ■ Obstruction of ampulla of Vater ■ Penetrating peptic ulcer	■ Idiopathic ■ Trauma ■ Hereditary ■ Hypertriglyceridaemia ■ Hyperparathyroidism ■ Cystic fibrosis ■ Protein energy malnutrition

Chronic pancreatitis

As consumption of alcohol is the most common association of chronic pancreatitis in Western society, most is known about the pathogenesis of alcoholic chronic pancreatitis. Studies in experimental animals have delineated a number of metabolic effects on the pancreas or pancreatic acinar cell which could predispose to autodigestion in the presence of an as yet unidentified trigger factor. These alcohol-induced changes are depicted in Box 6. The end result of repeated episodes of necro-inflammation is a gland characterised by atrophy (loss of both exocrine and endocrine tissue) and fibrosis (the necrosis–fibrosis sequence).

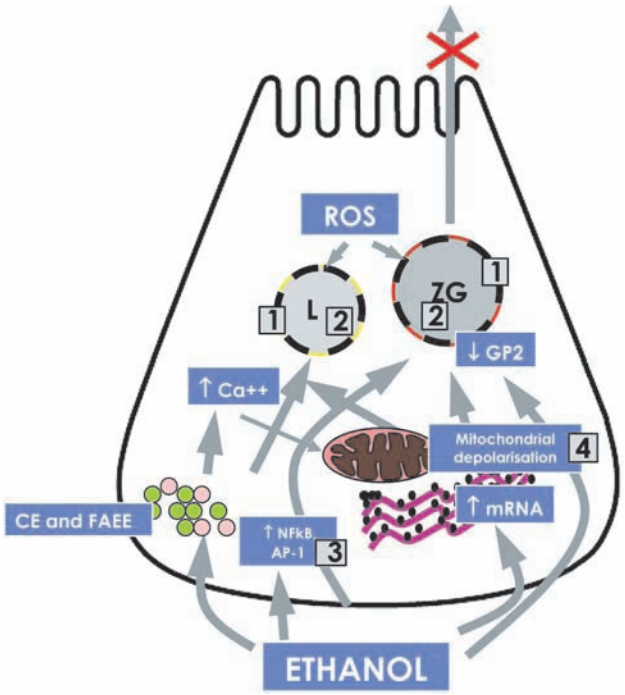
There have been considerable advances over the past decade in our understanding of pancreatic fibrogenesis. The pancreatic stellate cell (PSC) is now established as the principal effector cell in pancreatic fibrosis. This cell responds to a number

5 Mechanisms of gallstone pancreatitis



A: *Gallstones may intermittently migrate out of the gallbladder (GB) via the cystic duct (CD) into the common bile duct (CBD) and then pass through the choledochoduodenal junction (CDJ) into the duodenum (D).*
B: *Gallstones cause transient obstruction of the pancreatic duct (PD) as they pass from the CBD through the CDJ into the duodenum. Obstruction of the PD raises hydrostatic pressure within it, causing blockage of pancreatic secretion and subsequent activation of pancreatic enzymes within the pancreas. This is thought to be the initiating factor in gallstone pancreatitis. Gallstones may also become impacted at the CDJ, causing a persistent obstruction.*

6 Effects of alcohol on the pancreatic acinar cell



The diagram depicts an overall hypothesis for the pathogenesis of alcoholic pancreatitis, based on experimental evidence of molecular effects of alcohol on the pancreatic acinar cell. Alcohol, its metabolites and oxidant stress exert a number of toxic effects on pancreatic acinar cells, which predispose the gland to autodigestive injury, acute necro-inflammation and cell death. These include:

1: *destabilisation of lysosomes (L) and zymogen granules (ZG) (mediated by oxidant stress [reactive oxygen species; ROS], cholesteryl esters [CE], fatty acid ethyl esters [FAEE] and decreased glycoprotein 2 [GP2], a major structural component of zymogen membranes);*

2: *increased digestive and lysosomal enzyme content (due to increased synthesis [increased mRNA] and impaired secretion);*

3: *increased activation of transcription factors (NFkB and AP-1) which regulate cytokine expression;*

4: *a sustained increase in cytoplasmic calcium (Ca++) and mitochondrial calcium overload leading to mitochondrial depolarisation.*

The above changes sensitise the cell such that in the presence of an appropriate trigger or cofactor, injury is initiated.

of stimuli (including alcohol and its metabolites, pro-inflammatory cytokines and oxidant stress) with increased production of extracellular matrix (ECM) proteins. PSCs also produce endogenous cytokines, and this ability may account for the perpetuation of pancreatic fibrosis even after removal of the initial insult. PSCs probably also play a central role in pancreatic regeneration. In health, PSCs most likely regulate ECM homeostasis and maintain the architectural integrity of the pancreas. Knowledge of the biology and pathobiology of PSCs should ultimately allow us to modify their behaviour and thus ameliorate or modulate the course of chronic pancreatitis.

An enigmatic feature of alcoholic pancreatitis is that only about 5% of heavy drinkers develop the disease. This implies the existence of a susceptibility factor, but, to date, none has been conclusively identified (Box 7).

Genetic advances in the pathogenesis of chronic pancreatitis

Over the past decade, there have been considerable advances in elucidating the pathogenesis of chronic pancreatitis traditionally classified as "idiopathic". Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene have been associated with cases of idiopathic pancreatitis. The affected individuals do not have classical cystic fibrosis (CF) and should not be regarded as having CF. They usually possess two copies of "mild" (mild-disease producing) mutations, or one copy of a "severe" (severe-disease producing) mutation and one "mild" copy. The association of CFTR mutations with chronic pancreatitis suggests that dysfunction of pancreatic ducts (where CFTR is expressed and plays a major role in fluid and electrolyte secretion) plays a role in pathogenesis.

Several different mutations in the cationic trypsinogen gene (PRSS1) have been identified in families with hereditary

pancreatitis and occasionally in sporadic cases of idiopathic pancreatitis. Some of these mutations interfere with the inactivation of activated trypsin, whereas others enhance trypsinogen autoactivation — both types of changes predispose to autodigestion.

Naturally occurring protease inhibitors play an important role in the pancreas, protecting against autodigestion. It is therefore of interest that mutations of the serine protease inhibitor Kazal type 1 (SPINK1) gene have been identified in pancreatitis. SPINK1 mutations have been reported in 15%–40% of cases of idiopathic pancreatitis and in about half of patients with tropical pancreatitis. Intriguingly, the functional significance of SPINK1 mutations remains to be elucidated; recombinant mutant protein appears to have normal activity.

7 Possible susceptibility factors in alcoholic pancreatitis

Inherited factors		Lifestyle factors	
HLA	No[2]	Diet	No[14]
α1-antitrypsin deficiency	No[3]	Beverage type	No[14]
Cystic fibrosis genotype	No[4,5]		Yes[15]*
Alcohol metabolising enzymes		Drinking pattern	No[14]
Alcohol dehydrogenase	No[6,7]	Smoking†	Yes[16,17]
Cytochrome P450-2E1	No[6]		No[18]
Cholesteryl ester lipase	Yes[8]		
Trypsinogen gene mutations	No[9]*		
PSTI/SPINK1 mutations	Yes[10]		
Cytokines	No[11]*		
Detoxifying enzymes			
Glutathione *S*-transferase	No[6]		
UDP-glucuronosyl transferase	Yes[12]*		
	No[13]*		

* These studies did not include alcoholics without pancreatitis as controls.
† It appears unlikely that smoking is an initiating factor in alcoholic pancreatitis, as the risk of developing pancreatitis is not increased in heavy drinkers who smoke compared with heavy drinkers who do not smoke. However, it is possible that smoking plays a role in disease progression.

Tropical pancreatitis

Tropical pancreatitis is a form of calcific pancreatitis predominantly affecting young adults in southern India, South-East Asia, and Africa. Patients usually present with symptoms of functional insufficiency, without a prior history of abdominal pain. The cause is not known, although evidence of genetic associations is emerging.

Autoimmune pancreatitis

Autoimmune pancreatitis is a relatively rare, recently characterised disease. Pathologically, the pancreas manifests diffuse lymphocytic and plasma cell infiltration and florid fibrosis. The disease usually affects the entire gland, although segmental forms have been described. There is an association with certain HLA-DR subtypes, and serum immunoglobulin levels (particularly IgG_4) are usually elevated. The disease is associated with other autoimmune conditions and the presence of autoantibodies. Notably, it is steroid responsive. Classically, autoimmune pancreatitis is a disease of older men who present with abdominal pain and obstructive jaundice, with evidence on computed tomography (CT) of a diffusely enlarged pancreas. Pancreatic cancer is the principal differential diagnosis, so it is important to think about an autoimmune aetiology before subjecting the patient to unnecessary surgery.

Clinical features

Acute pancreatitis

Usually the major symptom of acute pancreatitis is severe, constant abdominal pain. This pain is usually epigastric or peri-umbilical. It may radiate to the back and into the chest or flank. Often, the pain is relieved by sitting forward and exacerbated by lying flat. The pain is often associated with nausea and vomiting.

Physical examination usually reveals abdominal tenderness and guarding; however, these signs may be unimpressive when compared with the apparent severity of the pain and the general condition of the patient. Pyrexia, tachycardia and signs of pulmonary decompensation may be present and may be harbingers of severe pancreatitis. Cullen's sign (blue discolouration around the umbilicus) and Grey-Turner's sign (purple discolouration in the flanks) are rarely seen, but indicate severe necrotising pancreatitis.

The differential diagnosis of acute pancreatitis includes both intra-abdominal causes (perforated viscus, mesenteric ischaemia, aortic rupture/dissection, intestinal obstruction and biliary disease) and non-abdominal causes (pneumonia, myocardial infarction, vasculitis and diabetic ketoacidosis).

A major diagnostic and predictive dilemma in the management of acute pancreatitis relates to the detection of patients who will develop severe disease (10%–15% of all cases of pancreatitis). A number of algorithms have been developed to assist clinicians to detect those patients who may require more intensive therapy. However, the clinician responsible for a patient with established acute pancreatitis needs to be aware of danger signs. These include pulmonary insufficiency, renal insufficiency, hypocalcaemia, persistent fever, persistent leukocytosis and glucose intolerance. The diagnosis needs to be constantly reviewed and intensive care services in the hospital notified and engaged.

Chronic pancreatitis

The major features of this disease are abdominal pain (either intermittent or constant) and pancreatic insufficiency resulting in maldigestion (weight loss and steatorrhea) and diabetes. Fibrosis in the pancreas may constrict the distal common bile duct,

8 Ranson's criteria

At admission	
Age	> 55 years
White blood cell count	16.0 × 10^9/L
Blood glucose	11.1 mmol/L
Serum lactate dehydrogenase	> 350 U/L
Aspartate transaminase	> 250 U/L
During initial 48 hours	
Haematocrit	decrease > 10%
Blood urea nitrogen	increase 1.8 mmol/L
Serum calcium	< 2 mmol/L
Base deficit	> 4 mEq/L
Fluid sequestration	> 6000 mL
PaO_2	< 60 mmHg

Scoring: 1 point for each criterion met. Score > 3 predicts severe disease. Adapted from Ranson, 1974.[30]

9 Acute Physiology and Chronic Health Evaluation (APACHE II) scale

Age
Rectal temperature
Mean arterial pressure
Heart rate
PaO_2
Arterial pH
Serum potassium
Serum sodium
Serum creatinine
Haematocrit
White blood cell count
Glasgow Coma Scale score
Chronic health status

Scoring is based on a formula with a score > 8 predicting severe disease.

resulting in jaundice. Concomitant liver disease due to alcohol use may also cause jaundice. Patients with chronic pancreatitis are at an increased risk of developing pancreatic cancer.

Diagnosis of acute pancreatitis

A diagnosis of acute pancreatitis is usually made in the presence of two of the following three criteria:[19]

- Typical abdominal pain
- Elevation in serum levels of amylase or lipase > 3 times the upper limit of normal
- Evidence of inflammation in the pancreas on imaging (CT is the preferred modality)

Elevation of serum levels of amylase or lipase to < 3 times the upper limit of normal in the presence of abdominal pain is suggestive but not diagnostic of acute pancreatitis.

Pancreatic enzyme tests

Both serum amylase and lipase levels are usually elevated during an episode of acute pancreatitis. Lipase is more specific than amylase, as the latter can be elevated in conditions such as parotitis, macroamylasaemia and some malignancies.[20] Lipase persists for longer in serum and its measurement is a more sensitive test than serum amylase;[21] it is therefore considered the preferred test and there is no added value in measuring both enzymes.

The absolute level of either amylase or lipase does not correlate with the severity of pancreatitis, and serial measurements are not helpful in monitoring the course of the disease.[22] Other serum enzyme markers of pancreatitis include carboxypeptidase, trypsin, trypsinogen-2, trypsinogen activation peptide, phospholipase, carboxyl ester lipase and colipase. Assays for these enzymes are rarely available outside major centres and add little further diagnostic information.

Radiological investigations

Contrast-enhanced, thin-slice, multi-detector CT scanning is the imaging investigation of choice for staging the severity of acute pancreatitis (distinguishing between interstitial and necrotising pancreatitis), for identifying major complications and for excluding conditions that may mimic acute pancreatitis. Findings on CT scanning that will support a diagnosis of acute pancreatitis include focal or diffuse enlargement of the gland; non-homogenous enhancement with iodinated contrast medium (indicating necrosis); irregular or indistinct outline of the gland; surrounding oedema or stranding; presence of peripancreatic fluid collections; and presence of gas in the pancreas or retroperitoneum. Other causes of acute abdomen such as visceral perforation and mesenteric ischaemia can usually be excluded. Clues to the underlying cause of pancreatitis such as presence of biliary or pancreatic duct dilatation or stones, presence of pancreatic calcification (indicating chronic pancreatitis), or masses suggestive of malignancy may also be seen. Complications of acute pancreatitis such as splenic vein thrombosis, pancreatic necrosis, pancreatic duct disruption,

10 CT severity index

CT grade		Score
A	Normal pancreas	0 points
B	Oedematous pancreas	1 point
C	B plus mild extrapancreatic changes	2 points
D	Severe extrapancreatic changes plus one fluid collection	3 points
E	Multiple or extensive fluid collections	4 points
Necrosis		
A	None	0 points
B	Less than one-third	2 points
C	Greater than one-third but less than half	4 points
D	More than half	6 points

CT = computed tomography. Scoring: CT grade + necrosis score. Score > 5 predicts severe disease. Adapted from Balthazar, 1990.[31]

ascites and pseudocyst formation may be identified, but may not be evident early in the course of the disease.

Not all patients require a CT scan during admission for acute pancreatitis. For example, an alcoholic patient with recurrent episodes of acute pancreatitis who presents with mild pancreatitis that resolves quickly does not require an abdominal CT scan. The timing of abdominal CT scanning will depend on the indication. Early imaging (within 24 hours) is important when there is diagnostic uncertainty; however, an early CT scan may underestimate the degree of necrosis. For staging severity, the optimal timing of imaging is 48–72 hours after the onset of symptoms, at which time pancreatic necrosis is likely to be evident.[23] Abdominal ultrasonography is often performed and may indicate an enlarged pancreas or dilated common bile duct, but its use is often limited because of excessive bowel gas (due to ileus). It is useful for detecting gallstones, particularly gallbladder stones. Plain x-rays add little value to the diagnosis in the modern era. An erect chest x-ray is useful for excluding perforated viscus.

Magnetic resonance imaging (MRI) is a promising, non-invasive technique for diagnosing acute pancreatitis. MRI correlates well with abdominal CT in acute pancreatitis.[24] MRI may be more sensitive than CT in detecting mild pancreatitis and may be better able to identify and characterise complications such as fluid collections, necrosis, haemorrhage, abscess and pseudocyst.[25] MRI has also been reported to correlate better with Ranson's score for the prediction of severe pancreatitis.[26] Magnetic resonance cholangiopancreatography (MRCP) is similar to ERCP in identifying choledocholithiasis, and superior to both CT and ultrasonography for this indication.[27] The non-invasive nature of MRCP makes it attractive as an initial imaging modality to exclude choledocholithiasis in cases of predicted severe acute pancreatitis.

Once a diagnosis of acute pancreatitis is made, investigations should be aimed at predicting the severity of the pancreatitis and identifying the underlying cause. These will determine the appropriate management strategies and prognosis.

11 Clinical and biochemical predictors of severity

Predictor	Comment
Age > 55 years	Correlates with worse prognosis in most studies
Obesity	Associated with greater local and systemic morbidity but not mortality[32]
Organ failure at admission	Associated with higher mortality. Progression of single organ failure to multiple organ failure predicts worse outcome.[33] Persistence of organ failure beyond 48 hours correlates with higher mortality[34]
Pleural effusion at presentation	Correlates with pancreatic necrosis, organ failure and mortality[35]
Pulmonary infiltrates	Associated with higher mortality[36]
C-reactive protein	Value > 150 mg/L at 48 hours (not at admission) has comparable predictive value to Ranson's criteria and Acute Physiology and Chronic Health Evaluation (APACHE II) score[37]
Haematocrit	Value > 48% or failure of haematocrit to improve at 48 hours after admission predicts pancreatic necrosis[38]

12 Comparison between scoring systems for acute pancreatitis

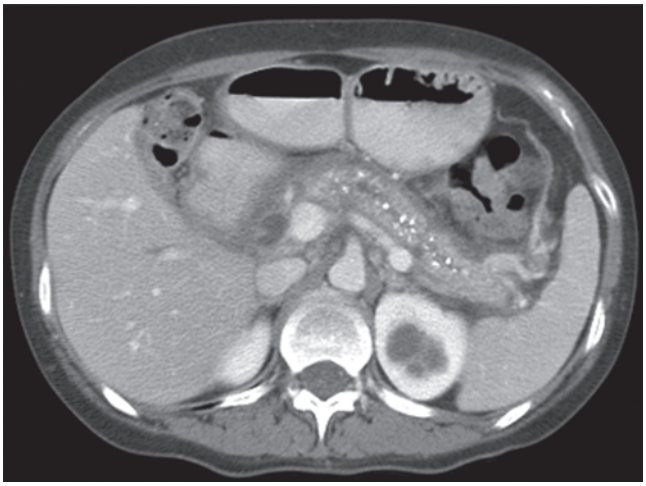
Scoring system	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
On admission					
APACHE II score > 8	68–71%	48–67%	30–40%	84–87%	53–68%
At 24 hours					
APACHE II score > 8	63%	73%	38%	88%	71%
CRP > 150 mg/L	65%	73%	37%	90%	72%
At 48 hours					
APACHE II score > 8	56–78%	52–64%	30–33%	85–88%	58–63%
Ranson's score > 3	75–89%	54–71%	37–49%	91–96%	62–75%
CRP > 150 mg/L	65%	73%	37%	90%	72%

APACHE = Acute Physiology and Chronic Health Evaluation. CRP = C-reactive protein.
Adapted from Whitcomb, 2006.[39]

Predicting severity

Predicting the severity of an episode of pancreatitis at the time of presentation has important implications for the immediate management of the patient and the prognosis. Severe pancreatitis has been defined (according to the Atlanta symposium) by the presence of pancreatic necrosis, the presence of distant organ failure or the development of local complications.[28] Various algorithms for predicting severity exist, but they all suffer from limitations in their application, their predictive accuracy or both.[29] In some studies, clinical assessment is as accurate in predicting severity. There are some emerging tests for systemic inflammation and physiological response that may have comparable value to the scoring systems. The most widely used clinical scoring systems are Ranson's criteria (Box 8), the Acute Physiology and Chronic

13 Computed tomography scan of pancreas in chronic pancreatitis



Changes in pancreatic architecture are visible: there is extensive calcification within the pancreas, atrophy of pancreatic tissue, and the pancreatic duct is dilated and irregular. (From the American Gastroenterological Association slide set, with permission)

Health Evaluation (APACHE II) scale (Box 9) and the CT severity index (Box 10).

APACHE II is the best predictor of severe acute pancreatitis at admission (the other scoring systems are not available until 48 hours), but has a greater degree of complexity than the alternatives. Ranson's score is simpler to compile and may have better accuracy, but cannot be completed until 48 hours after admission. Other clinical and biochemical predictors of severity are outlined in Box 11. Studies comparing the different systems have not convincingly demonstrated the superiority of one system over another, but rather underline the need to use ongoing clinical evaluation as well as these tools in predicting which patients are at risk of local and systemic complications and death (Box 12).

Determining aetiology

Determination of the cause of acute pancreatitis is important for guiding immediate management and for preventing recurrence. History alone will identify the cause in a large proportion of patients. A history of alcohol intake, medication use (see Box 4), abdominal trauma, recent abdominal surgery or procedures (particularly ERCP) will all point to a specific cause of pancreatitis. A sudden onset of symptoms, the presence of fevers, or previous diagnosis of cholelithiasis will suggest a biliary cause. A minority will have a family history or previous episodes.

All patients should have serum calcium and triglyceride levels measured at admission to identify the small proportion in which hypercalcaemia or hypertriglyceridaemia are causative. Elevated liver enzymes may indicate a biliary cause for pancreatitis. Elevated alanine aminotransferase > 150 IU/L has a high specificity (> 96%) for biliary cause but a low sensitivity.[40] If a biliary cause is suspected, abdominal ultrasonography should be performed to identify gallstones or a dilated biliary tree. For patients in whom initial ultrasound is not definitive, further imaging with other modalities in the setting of severe pancreatitis, or repeat scanning after resolution in mild cases, is indicated. Other investigations that may be used when a biliary cause is suspected and intervention is contemplated include MRI/MRCP, endoscopic ultrasound (EUS) and ERCP.

About a quarter of patients will have no identified cause for the first episode of acute pancreatitis. For patients with mild attacks, no further investigations are warranted. Only a minority will have repeat episodes and it is in these patients that further investigations should be undertaken to identify less common causes.

Investigation of recurrent acute pancreatitis

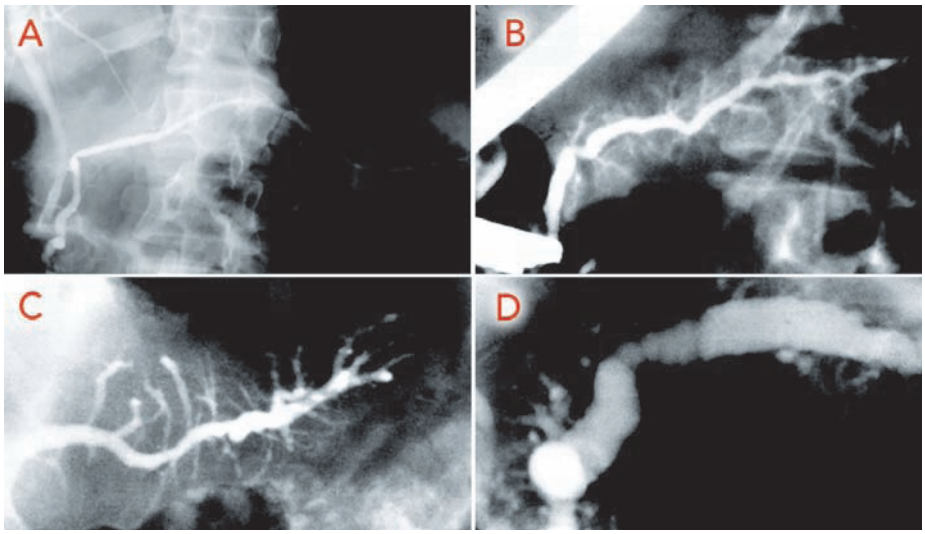
Patients with recurrent attacks of pancreatitis remain a difficult management problem. For those in whom alcohol is a causative factor, the risk of recurrent attacks is increased with continued alcohol consumption. A proportion of patients with recurrent attacks of acute pancreatitis but no identifiable gallstones may have undetected biliary microlithiasis and may benefit from cholecystectomy or endoscopic biliary sphincterotomy. However, before subjecting patients to potentially unnecessary surgery or endoscopic intervention, a rigorous search for gallstones or microlithiasis should be undertaken. This should comprise transabdominal ultrasound examinations, ERCP or MRCP, and EUS. Some international centres use microscopy of bile (searching for crystals) as an indicator of biliary disease; however, this is not a widely practised procedure. For patients with recurrent attacks in whom alcohol use and gallstones are not present, other causes to be considered include hereditary pancreatitis, tropical pancreatitis, autoimmune pancreatitis, ductal obstruction or systemic conditions such as hypertriglyceridaemia and hypercalcaemia. Testing for genetic associations of chronic pancreatitis is not indicated outside of specialist practice, as the results are of uncertain significance.

Diagnosis of chronic pancreatitis

A diagnosis of chronic pancreatitis is made by the association of typical abdominal pain with exocrine insufficiency (maldigestion, steatorrhoea and weight loss) and endocrine insufficiency (diabetes). Radiological evidence of changes in the pancreatic architecture will further support the diagnosis. Abdominal CT is a useful test for defining pancreatic size and architecture (Box 13). ERCP remains the gold standard for diagnosis (Box 14); however, less invasive alternatives such as MRI and EUS are undergoing evaluation. The only accurate test for diagnosing maldigestion is a 3-day faecal fat measurement. However, this test is inconvenient for the patient, unpleasant for the technicians, and not widely available. Given the difficulties of direct testing, several indirect measures, including faecal elastase, faecal chymotrypsin and the bentiromide test, have been developed. Unfortunately, indirect testing is of limited clinical use as it is unreliable in those with mild steatorrhoea (although universally positive in those with

severe, clinically apparent steatorrhoea). Diabetes can be diagnosed with fasting blood sugar levels and confirmed with glucose challenge testing.

14 Pancreatograms demonstrating changes in chronic pancreatitis



A: *Normal pancreas: the duct is smooth, regular and not dilated, with normal side branches.* ***B:*** *Early changes of chronic pancreatitis: pancreatogram shows a mildly dilated, ectatic and somewhat tortuous pancreatic duct with areas of stenosis and dilatation.* ***C:*** *Moderate changes of chronic pancreatitis: pancreatogram shows a markedly dilated, tortuous pancreatic duct with beading and clubbing of side branches.* ***D:*** *Severe chronic pancreatitis: pancreatogram shows severe dilatation and distortion involving the main pancreatic duct and all side branches.*
(From the American Gastroenterological Association slide set, with permission.)

Treatment

Treatment of acute pancreatitis consists of supportive measures, monitoring for complications and symptom control. Historically, measures to "rest" the pancreas have been an important part of management; this strategy is now largely obsolete because the pancreas is metabolically inactive during acute pancreatitis. Despite trials of a number of anti-proteinases and anti-inflammatory agents, no treatment has been shown to alter the course of pancreatitis. Specific treatments for underlying causes are available for a minority of patients.

Nearly all patients with pancreatitis will require hospitalisation. Patients with predicted mild pancreatitis and no organ compromise or significant comorbidities may be safely managed on a general ward. Patients with predicted severe pancreatitis, organ dysfunction or significant comorbidities should be admitted to an intensive care unit. All patients should have fluid resuscitation to address haemodynamic instability, prevent haemoconcentration and optimise hydration. Large volumes of fluid may be sequestered in the pancreatic bed ("third-space" losses) and rapid replenishment may be required. Persistent haemoconcentration at 24 hours because of inadequate fluid replacement is associated with pancreatic necrosis.[41] Delays in correction of organ failure (including renal failure) have also been associated with worse outcomes.[34] Caution should be exercised in those with cardiac failure or renal impairment, and all patients should have strict recording of fluid balance and urine output. Electrolyte and metabolic abnormalities should be rapidly corrected, and oxygen administered to correct hypoxaemia.

Treatment for pain should be administered intravenously (at least initially) and will usually comprise narcotic analgesia. Opiates in general, and morphine specifically, increase sphincter of Oddi pressure, but there is no evidence that this is clinically significant. For patients requiring significant amounts of narcotics, monitoring of oxygen saturations is warranted.

Nutrition

Traditionally, patients have been treated with "bowel rest" to reduce hormonal stimulation of the pancreas. In patients with predicted mild pancreatitis whose symptoms rapidly resolve, it is reasonable to reintroduce oral intake when pain and nausea have subsided. In patients with severe or prolonged pancreatitis, nutrition becomes an important issue. The balance of evidence favours the safety of enteral nutrition in preference to the parenteral route because of lower rates of infection, reduced need for surgical intervention, lower costs and shorter hospital stays.[42,43] Although naso-jejunal feeding has been preferred because of reduced pancreatic stimulation, recent evidence supports the safety of naso-gastric feeding.[44] A proportion of patients will not tolerate adequate enteral nutrition and require supplemental parenteral nutrition.

Antibiotics

In patients with severe pancreatitis (particularly in the presence of pancreatic necrosis), infection is a serious complication. The role of prophylactic antibiotics has been investigated in a number of trials, but remains controversial. The largest trial and the only one with a double-blinded, placebo-controlled protocol did not demonstrate a benefit for the combination of ciprofloxacin and metronidazole.[45] On current evidence, the case for the prophylactic use of antibiotics or antifungals in acute pancreatitis is weak.

Early intervention

Early intervention (within 72 hours) with ERCP and biliary sphincterotomy for patients with biliary pancreatitis has been demonstrated to be beneficial in a subset of patients with predicted severe pancreatitis in the presence of obstructive jaundice, a dilated common bile duct or cholangitis.[46-49] In these patients, early intervention reduces complications by nearly 50%, but has no effect on mortality.

For patients with biliary pancreatitis that resolves, 30%–50% will have a recurrence an average of 3 months after discharge. Early cholecystectomy with intra-operative cholangiogram (during admission or within a month of discharge) is appropriate to avoid recurrent pancreatitis.[19,50-52] Patients who are unfit for operative management may be safely treated with endoscopic biliary sphincterotomy.[53]

Management of pancreatic necrosis and fluid collections

Sterile pancreatic necrosis does not require any specific intervention. Worsening abdominal pain, fever and leukocytosis in the presence of pancreatic necrosis may herald infected necrosis, which is a serious complication with a high mortality rate. In patients with clinical suspicion of infected necrosis, imaging with CT, MRI or EUS and, ultimately, fine-needle aspiration for bacteriological examination should be undertaken. If infected necrosis is confirmed, definitive treatment with antibiotics and surgical debridement of the pancreas is required. Radiological and endoscopic procedures are emerging as alternative methods for pancreatic debridement; however, these approaches are still being evaluated.

Acute fluid collections in the vicinity of the pancreas are common in patients with moderate to severe pancreatitis. About 15% will become encapsulated to form pseudocysts. Uncomplicated pseudocysts usually require no specific therapy. Drainage may be required if pseudocysts cause significant abdominal pain or obstruction of adjacent structures (stomach, duodenum or biliary tree), or become infected or bleed. Surgical, endoscopic and radiological techniques have all been used for complicated pseudocysts; the choice of therapy will depend on the characteristics of the collection, the patient, local resources and expertise.

Management of chronic pancreatitis

Treatment of chronic pancreatitis is mainly symptomatic and supportive, with the goal of improving quality of life. Specific therapies exist for the minority of patients with underlying metabolic conditions. In alcoholic pancreatitis, complete abstinence from alcohol is essential. Abstinence may improve pain control and slow deterioration in pancreatic function. Recognising pancreatic cancer and distinguishing it from benign pancreatic conditions may be a difficult diagnostic problem requiring clinical vigilance, careful use of imaging and early consideration of biopsy.

The pain of chronic pancreatitis is difficult to treat and its pathophysiology is poorly understood. Treatment of pain in patients with chronic pancreatitis may be complicated by issues of opiate dependence and drug-seeking behaviour. Although simple analgesics are first-line therapy, most patients will require long-term narcotic analgesia. Antioxidant therapy may be beneficial in some patients.[54] Pancreatic enzyme supplementation has not been consistently shown to provide benefit for pancreatic pain. Invasive approaches to the treatment of pancreatic pain (including coeliac plexus block, endotherapy of pancreatic strictures and stones, surgical decompression of the pancreatic duct, and pancreatic resection or total pancreatectomy) are used in some specialist centres with the relevant expertise, but trial data to support these techniques are lacking. Interventional therapy has a role in the treatment of complications such as pseudocyst, biliary stenosis and duodenal stenosis.

Maldigestion, steatorrhoea and weight loss due to exocrine pancreatic insufficiency respond to pancreatic enzyme supplementation. A number of commercial preparations are available, but, regardless of the preparation used, doses in excess of 30 000 IU of lipase and 10 000 IU of trypsin per meal are usually required. Concurrent use of acid-suppressing medications can reduce the degradation of the supplemental enzymes. Medium-chain triglycerides and fat-soluble vitamins may be supplemented in those who are severely malnourished or with specific vitamin deficiencies.

Insulin is the mainstay of therapy for diabetes in patients with chronic pancreatitis. Treatment is similar to that for patients with type 1 diabetes. Insulin therapy should be monitored closely because of an increased risk of hypoglycaemia due to the loss of counter-regulatory pancreatic hormones ("brittle" diabetes). Reliability of alcoholic patients is also a common issue.

The features of the disease (chronic and refractory pain, brittle diabetes and maldigestion) and the characteristics of the patient population it most commonly afflicts make chronic pancreatitis a difficult condition to manage. For these reasons, patients are best served by treatment within experienced multidisciplinary teams.

Competing interests

None identified.

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(Received 30 Jan 2008, accepted 4 Feb 2008) ❑