

# Severe acute pancreatitis

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Pancreatitis is an inflammatory disorder of the pancreas which occurs with an estimated incidence of 10–40 per 100 000 per year in the UK.<sup>1</sup> Mild acute (oedematous or interstitial) pancreatitis accounts for 80% of cases, is self-limiting, and usually resolves with simple supportive management in 3–5 days. Severe acute pancreatitis (SAP) accounts for the remainder of cases and was defined by the Atlanta Symposium as acute pancreatitis associated with organ dysfunction or local or regional complications (Table 1).<sup>2</sup> Most deaths from SAP result from sepsis and multiorgan failure. Mortality in patients with infected pancreatic necrosis is 25–30%, compared with 10–12% in those with sterile necrosis.<sup>3</sup>

## Anatomy and physiology

The pancreas is a secretory organ with both endocrine and exocrine functions. The main functional unit is the acinar cell, which comprises the parenchyma of the gland. Exocrine products from the acinar cells are secreted into a tubular system which coalesces to form the main pancreatic duct of Wirsung. This duct usually joins the common bile duct to form the ampulla of Vater. The ampulla opens into the duodenum, and is surrounded by the sphincter of Oddi. An accessory pancreatic duct, opening separately into the duodenum, is a variable finding. Approximately 1500 ml per day of pancreatic juice, an alkaline mixture of electrolytes (high in bicarbonate) and digestive proteolytic enzymes, is secreted. These proteases include proenzymes, such as trypsinogen, chymotrypsinogens, proelastase, procarboxypeptidases, and enzymes, such as lipase and pancreatic (cf. salivary) amylase. The endocrine cells form the Islets of Langerhans, consisting of B ( $\beta$ ) cells secreting insulin, A ( $\alpha$ ) cells secreting glucagon, D ( $\delta$ ) cells secreting somatostatin, and F cells secreting pancreatic polypeptide. These hormones are secreted into the portal circulation.

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## Aetiology and pathogenesis

There are many causes of pancreatitis, broadly classified as obstruction of the secretory tree or direct parenchymal cell damage (Table 2). Over 70% of cases of acute pancreatitis in the UK are caused by alcohol or gallstones. Women are more likely to suffer from gallstone pancreatitis, and men more likely to suffer from alcohol-related pancreatitis. Approximately 10–20% of cases are idiopathic.

The mechanism of local and systemic damage originates from inappropriate release and activation of proteases from acinar cells. These proteases not only cause direct damage to pancreatic tissue, but also induce an acute inflammatory response. Neutrophil polymorphs (NPM) and macrophages infiltrate the pancreas and release their own proteases, free radicals, and cytokines which compound the vicious cycle of tissue damage and inflammation. Additionally, pancreatic proteases released into the bloodstream can activate NPM and macrophages distant from the pancreas, releasing further inflammatory mediators causing the systemic inflammatory response syndrome (SIRS) and organ damage.

## Clinical features

The symptoms of pancreatitis usually include severe constant epigastric pain radiating to the back and flanks, and vomiting. Signs may include pyrexia, abdominal distension, and peritonism. The classical signs of discoloration of the flanks (Grey-Turner's sign), peri-umbilicus (Cullen's sign), and inguinal ligament (Fox's sign) are not always seen and are a result of retroperitoneal haemorrhage tracking along tissue planes. In addition, symptoms and signs of end-organ involvement may be evident, including respiratory distress, shock, oliguria, jaundice, and delirium. It is also possible for SAP to be painless.

The clinical course of SAP classically occurs in two phases. The first lasts 1–2 weeks and presents with features of SIRS and organ

## Key points

Severe acute pancreatitis (SAP) is associated with organ dysfunction and local or regional complications.

Enteral feeding is advocated via the gastric or jejunal routes. Parenteral nutrition should be considered if enteral feeding fails.

Approximately 25% of cases are associated with infected necrotic pancreatic tissue; without necrosectomy, mortality is nearly 100%.

Prophylactic antimicrobials are not indicated unless pancreatic necrosis is suspected or confirmed, or there is evidence of systemic sepsis or organ failure.

Necrosectomy should be delayed for 3–4 weeks after the onset of SAP if possible.

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**Table 1** Local or regional complications defining SAP

Local
Pancreatic parenchymal necrosis (sterile or infected)
Peripancreatic fat necrosis
Haemorrhagic pancreatitis
Pancreatic pseudocyst* (pancreatic fluid surrounded by a wall of fibrous or granulation tissue)
Abscess* (circumscribed collection of pus)
Regional
Fluid collections (intra-abdominal and pleural)
Portal venous thrombosis and portal hypertension
Systemic venous thrombosis
Pseudoaneurysm (aorta, splenic, or gastroduodenal arteries)
Massive haemorrhage (retroperitoneal, peritoneal, or GI tract)

\*Usually develops 4 or more weeks after clinical onset of pancreatitis.

dysfunction. Necrosis of the inflamed pancreas often occurs during this period. This phase may resolve or may progress to a second phase, consisting of sepsis and multiple organ failure 2–3 weeks later. This is usually associated with infection of necrotic pancreatic or peripancreatic tissue; without surgical intervention, it has a very high mortality.

## Investigations

Blood tests are performed for patients with acute pancreatitis in order to:

- (i) establish the diagnosis;
- (ii) determine the cause;
- (iii) assess target organ damage;
- (iv) monitor disease progress;
- (v) assist with prognosis.

Amylase, lipase, and trypsinogen are all enzymes derived from pancreatic acinar cells; they can be measured with relative ease. Serum amylase is most commonly used in clinical practice. A level of greater than three times the normal upper range (300 IU litre<sup>-1</sup>) supports the diagnosis of pancreatitis. Serum amylase tends to rise quickly in the first 12 h, returning to baseline within 3–5 days. Amylase is cleared by the kidneys and has a serum half-life of approximately 2 h; therefore, a single peak in amylase may be missed. Furthermore, amylase is non-specific and the degree of rise does not necessarily correlate with disease severity or prognosis. Hyperamylasaemia may be caused by bowel perforation, obstruction or ischaemia, fallopian tube pathology, diabetic ketoacidosis, and pneumonia or neoplasm, particularly when associated with renal failure.<sup>4</sup>

Serum lipase has been recommended as the assay of choice when available.<sup>5</sup> Lipase concentrations are increased for up to 14 days after onset of pancreatitis, and appear to be more sensitive and specific than amylase. A cut-off value of serum lipase of 600 IU litre<sup>-1</sup> is often used. Urinary trypsinogen-2 ‘dipstix’ are under investigation, both as a confirmation of diagnosis and as an indicator of severity.

Metabolic derangements (acidaemia, uraemia, increased creatinine, hypocalcaemia, hypomagnesaemia, and hyperglycaemia),

**Table 2** Aetiology of pancreatitis

Obstructive
Cholelithiasis: macrolithiasis (gall stones) or microlithiasis (‘biliary sludge’)
Neoplasm: head of pancreas, peri-ampullary, metastases (renal, gastric, breast, ovarian, and lung)
Chronic alcoholism (thick, proteinaceous pancreatic secretions)
Cystic fibrosis
Congenital anomalies: pancreas divisum, choledochocoele
Parenchymal
Local and regional
Trauma
Blunt (road traffic accidents, bicycle handlebars, sports, non-accidental injury)
Penetrating
Operative (laparotomy)
After ERCP, ES, or manometry
Ischaemia (cholesterol emboli, vasculitides)
Autoimmune disease (sclerosing cholangitis)
$\alpha_1$ -antitrypsin deficiency
Global
Hypoxaemia/ischaemia: SIRS, cardiac surgery
Toxins: alcohol, drugs (e.g. oestrogens, steroids, furosemide, sulphonamides, and azathioprine)
Hypothermia (particularly in the elderly)
Hyperalimentation (parenteral nutrition)
Hypercalcaemia / Hyperparathyroidism
Viruses (e.g. HIV, CMV, mumps, coxsackie B, and hepatitises)
Hyperlipoproteinaemia (types I and V)
Scorpion bites ( <i>Tityus trinitatis</i> and <i>Tityus serrulatus</i> ) and snake bites (adder)
Idiopathic

liver enzyme derangement (transaminitis and hyperbilirubinaemia), and haematological disturbance (anaemia, neutrophilia, and disseminated intravascular coagulopathy) may all occur. Many of these derangements form the basis of the older acute pancreatitis scoring systems, for example, Ranson or Glasgow (Imrie) scores. Obesity and old age are associated with a worse outcome.<sup>6</sup> There are also CT-based scoring systems (e.g. Balthazar CT severity index) which correlate well with disease severity and likelihood of local or systemic complications.<sup>7</sup>

Several imaging modalities may be useful (Table 3). Biliary tract ultrasound is recommended in the initial assessment of all cases of acute pancreatitis. Demonstration of a pleural effusion indicates severe disease. CT is indicated if the diagnosis is equivocal, to rule out alternative intra-abdominal catastrophes, and to detect and stage regional complications such as pancreatic necrosis.<sup>8</sup> If the diagnosis is clear, it may be appropriate to delay CT imaging for at least 48–72 h after onset of symptoms because the full extent of pancreatic necrosis cannot be determined until this time. Patients with SAP often require multiple contrast-enhanced CT scans to assess progress and screen for complications. The risk of contrast nephropathy should be considered in patients who have already had septic, hypoxaemic, and ischaemic insults to the kidneys.

## Management

Many studies have examined the role of specific medical therapies in SAP and post-ERCP pancreatitis. These have included drugs

**Table 3** Imaging in acute pancreatitis

Modality	Pertinent findings
Abdominal X-ray	Ileus, loss of psoas shadow, sentinel loop, pancreatic calcification, and calcified gallstones
Chest X-ray	Pleural effusions (usually on left) and pulmonary infiltrates
Chest US	Visualization of pleural effusion; guided drainage for diagnosis or treatment of respiratory failure
Abdominal US	Superior to CT at detecting stones in the gallbladder or biliary duct; may be difficult to visualize pancreas, especially in the presence of ileus; free peritoneal fluid
Endoultrasonography	Combination of endoscopy and high-frequency US; useful if abdominal US/CT fail to detect CBD stones; useful when CT/MRI are not available/feasible
Renal tract US	If oliguric, to rule out obstruction/pyelonephrosis
Contrast-enhanced CT	Contrast deficit indicating necrosis, local pathology, e.g. abscess, acute fluid collections (pseudocysts/abscesses usually form after approximately 4 weeks), haemorrhage, thrombosis, pseudoaneurysm; can guide interventional procedures (FNAB and drain placement)
MRI/MRCP	May be of use in the stable patient in whom CT contrast is contraindicated; can delineate necrotic areas; excellent at assessing biliary tree
Angiography	Haemorrhage localization and guided endovascular management

targeting the inflammatory response (lefixant), antioxidants (*N*-acetyl cysteine), antiproteases (aprotonin and gabexate), or anti-secretory drugs (somatostatin, octreotide, and lanreotide). However, to date, the results of these trials have been disappointing and the mainstays of management remain resuscitation and supportive care, with appropriate surgical and radiological intervention.

### Critical care management

Approximately 50% of patients with SAP will have organ failure. The goals of supportive therapy should be similar to other patients with SIRS/sepsis within the framework of the *Surviving Sepsis Campaign* guidelines. In addition, recent guidelines for the management of critically ill patients with SAP have been produced.<sup>8</sup> Strong indicators for admission to a critical care unit in those fulfilling the diagnosis of SAP include:

- (i) an ongoing need for fluid resuscitation;
- (ii) age >70 yr;
- (iii) body mass index >30 kg m<sup>-2</sup>;
- (iv) presence of indicators of more severe disease:
  - (a) necrosis of over 30% of the pancreas,
  - (b) pleural effusions,
  - (c) ≥ 3 of Ranson's criteria present,
  - (d) CRP >150 mg dl<sup>-1</sup> at 48 h.

Diaphragmatic splinting (peritonism, pain, peritoneal fluid collection, and intra-abdominal tissue oedema), pleural effusions, and acute lung injury all contribute to hypoxaemia and ventilatory failure in SAP. Patients with severe respiratory failure and abdominal compartment syndrome may benefit from decompressive

laparotomy, but this should be considered carefully between critical care and surgical teams.

Patients with SAP are hypovolaemic because of reduced fluid intake (nausea), increased losses (vomiting and fever), and ongoing extravasation as a result of capillary leak and hypo-albuminaemia. Intravascular fluid depletion may be severe and fluid requirements in the initial resuscitation phase may be several litres per day. Drugs are often required to maintain adequate arterial perfusion pressure; in our unit, the vasopressor of choice is norepinephrine, with dobutamine being used in addition, as required. Patients requiring ICU admission for SAP will require central venous access and cardiovascular management should be guided by CVP, direct systemic arterial pressure, and additional appropriate monitoring. This may include central or mixed venous oxygen saturation, assessment of cardiac output by pulse contour CO estimation or oesophageal Doppler. Acute renal failure (ARF) is common in SAP. Optimizing fluid management and perfusion pressure early in the disease process, avoidance of nephrotoxins, and maintenance of good glycaemic control are the most effective ways of preventing progression to renal replacement therapy-dependent ARF.

The historical approach to management in SAP included complete rest of the pancreas and gastrointestinal (GI) tract with the institution of early parenteral feeding. It is now well established that enteral feeding is cheaper, safer, and associated with fewer infective complications and a better overall outcome.<sup>9</sup> Gastric feeding should be tried in the first instance, but often fails as a result of duodenal ileus or obstruction from the inflammatory mass. Jejunal feeding is advocated if gastric feeding fails.<sup>10</sup> However, paralytic ileus is common in SAP and parenteral nutrition (PN) is recommended if enteral feeding has failed after 5–7 days; glutamine-enriched PN should be considered.<sup>8</sup> All patients should receive stress ulcer prophylaxis.

Some (but not all) studies have suggested that the administration of prophylactic antibiotics reduces the risk of pancreatic necrosis becoming infected.<sup>11</sup> However, routine blind antibiotic prophylaxis may increase the incidence of infection with resistant bacteria or fungi and is therefore not recommended.<sup>12</sup> A more rational approach is to commence antibiotics if infected pancreatic necrosis is suspected or confirmed, or if there is evidence of systemic sepsis or organ failure, while recognizing that many of the signs of the inflammatory response (tachycardia, tachypnoea, fever, and leucocytosis) also suggest sepsis. At the same time, vigorous attempts to detect causative organisms should be made, including radiologically guided aspiration of pancreatic or peripancreatic tissue, if appropriate. To differentiate between sterile necrotic and infected necrotic pancreatitis, investigations include abdominal CT scanning (to look for retroperitoneal gas) or image-guided fine needle aspiration for bacteriology (FNAB). FNAB is indicated in patients with pancreatic necrosis on CT and clinical signs of sepsis. Most infections in SAP are caused by Gram-negative organisms translocated from the GI tract; approximately 25% are polymicrobial infections. The carbipenems

(imipenem and meropenem) have a good broad-spectrum coverage of the likely pathogenic organisms and excellent pancreatic penetrance.<sup>8</sup> Other agents with reasonable pancreatic penetrance are ofloxacin and third-generation cephalosporins. Aminoglycosides have poor penetrance to the pancreas and are therefore of little use. Antifungal therapy may also be considered.

The use of systemic protease inhibitors (e.g. aprotinin) in SAP has largely been abandoned, after randomized controlled trials showing no improvement in morbidity or mortality. The selective infusion of protease inhibitors into the coeliac arterial trunk is under investigation.

### Surgical management

The role of surgery in management includes:

- (i) relieving biliary obstruction;
- (ii) minimizing regional and distal organ damage;
- (iii) removing infected intra- and extra-pancreatic necrosis.

In the presence of obstructive jaundice or acute cholangitis, endoscopic retrograde cholangiopancreatography (ERCP), with or without endoscopic sphincterotomy (ES), is indicated within 72 h of symptom onset. Consideration of ERCP/ES should also be given in the presence of persistently abnormal liver function tests (serum ALT >150 IU litre<sup>-1</sup>), or a dilated common bile duct on imaging. Only 50% of patients with gallstone pancreatitis will present with an elevated ALT. In mild gallstone pancreatitis, laparoscopic cholecystectomy with intraoperative cholangiography is advised during the same hospital admission. On its own, cholecystectomy is not advisable in the early stage of severe pancreatitis as mortality is very high.

Early (weeks 1–2) surgical intervention is associated with a very high mortality. Necrosis develops in approximately 50% of cases of SAP. In approximately 50% of these cases, a necrotic pancreas will become infected by the third or fourth week. Without debridement, death from infected necrotic pancreatitis is almost inevitable. The mortality from infected necrotic SAP with multiple organ failure has, in some centres, been reduced to <20% with surgical intervention. Thus, necrosectomy should be delayed to week 3 or 4 to ensure optimal surgical conditions, that is, allowing for a single procedure with good demarcation of necrotic tissue and allowing for optimal pancreatic preservation. After necrosectomy, measures to allow continual removal of retroperitoneal debris are required by: planned repeated laparotomies and lavage; closed continuous irrigation of the lesser sac and retroperitoneum; formation of a laparostomy; or by closed packing.<sup>3, 8</sup> Patients with SAP undergoing intra-abdominal surgery should be considered for cholecystectomy at the same time, even if gallstones have not obviously been the aetiological agent. In contrast, sterile necrosis has a much lower mortality and the consensus is that it should be managed conservatively and not routinely drained.

Massive haemorrhage occurs in 1–3% of cases of SAP. Late haemorrhage is often due to rupture of a pseudoaneurysm, commonly of the splenic artery. Where expertise is available, these cases should be initially managed radiologically by catheter-directed balloon tamponade, coil embolization, or both. These techniques can provide definitive haemostasis or stabilization for surgical intervention in most cases.<sup>8</sup>

### The convalescent phase

Serum calcium may be spuriously normal or low during the acute phase of pancreatitis; it must be rechecked during convalescence to rule out surgically amenable hyperparathyroidism. Fasting triglycerides >11.3 mmol litre<sup>-1</sup> in convalescence suggest hyperlipoproteinaemia as an aetiological factor. If no other cause of pancreatitis is found, early and convalescent antibody assays for mumps, coxsackievirus, CMV, VZV, HSV, HIV, and HBV should be considered.<sup>8</sup> Exocrine and endocrine dysfunction can persist after recovery from acute pancreatitis and repeated bouts of pancreatitis can occur.

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Please see multiple choice questions 7–10