

# Diagnosis and Management of Acute Pancreatitis

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## ABSTRACT

**Objective:** To review the diagnosis and management of patients with acute pancreatitis.

**Data sources:** A review of articles reporting on the diagnosis and management of acute pancreatitis.

**Summary of review:** Acute pancreatitis is an acute inflammatory disorder of the pancreas caused by an intracellular activation of pancreatic digestive enzymes. The destruction of pancreatic parenchyma induces a systemic activation of coagulation, kinin, complement and fibrinolytic cascades with liberation of cytokines and reactive oxygen metabolites which, if severe and overwhelming, can lead to shock, acute renal failure and the acute respiratory distress syndrome. In approximately 45% of cases the disorder is associated with cholelithiasis, with ethanol abuse accounting for a further 35% of patients. In 10% of patients no cause may be found.

In 85 - 90% of patients, acute pancreatitis is self-limiting and subsides spontaneously within 4 - 7 days. Specific treatment for acute pancreatitis currently does not exist and management is still supportive, with therapy aimed at reducing pancreatic secretion, replacing fluid and electrolytes losses and analgesia. All patients with severe acute pancreatitis who have one (or more) organ failures (e.g. circulatory, pulmonary or renal) should be managed in an intensive care unit with mechanical ventilation, inotropic agents and renal replacement therapy being used to manage organ failure.

In selected circumstances, endoscopic retrograde cholangiopancreatography (ERCP), antibiotics and surgical drainage are used. For example, ERCP will reduce morbidity in patients with ampullary or common bile duct stones associated with acute pancreatitis, if obstructive jaundice or cholangitis are present. Prophylactic antibiotics (e.g. imipenem 500 mg i.v. 8-hourly for 7 - 10 days with fluconazole 400 mg i.v. daily) will reduce the incidence of pancreatic infection in patients with severe acute pancreatitis with pancreatic necrosis, and surgical intervention in severe acute pancreatitis, while rarely used, in patients who have a progressively increasing inflammatory mass and worsening multi-system organ failure, necrosectomy with open or closed drainage may be required.

**Conclusions:** Acute pancreatitis is a benign abdominal disorder in up to 85% of cases. In the remaining 10% - 15% of cases the disorder is life threatening with management of the disorder requiring admission to an intensive care unit with cardiovascular, respiratory, and renal monitoring and support. (Critical Care and Resuscitation 2004; 6: 17-27)

**Key words:** Acute pancreatitis, endoscopic retrograde cholangiopancreatography, necrosectomy

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Acute pancreatitis is defined as an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems.<sup>1</sup>

## PATHOPHYSIOLOGY

The exocrine pancreas secretes 1500 - 2000 mL of fluid daily and 150 - 200 mmol of HCO<sub>3</sub><sup>-</sup> daily in response to secretin stimulation, and secretes amylo-

tic, lipolytic and proteolytic digestive enzymes in response to cholecystokinin or muscarinic cholinergic stimulation. The proteolytic enzymes are secreted as inactive precursors that are activated by trypsin. The proteolytic enzyme precursor of trypsin (i.e. trypsinogen) is converted to trypsin by enterokinase secreted by the duodenal mucosa. Trypsin converts the precursor proteolytic enzymes (e.g. chymotrypsinogens, proelastase, procarboxypeptidases) and activates lipolytic enzymes (e.g. phospholipase A<sub>2</sub>) and amylolytic enzymes (e.g. amylase).

The formation of precursor enzymes, zymogen granules and antitrypsins (e.g. pancreatic secretory trypsin inhibitor,  $\alpha_1$ -antitrypsin,  $\alpha_2$ -macroglobulin) protects the pancreas from autodigestion. Acute pancreatitis occurs when defence mechanisms fail, allowing activation of precursor enzymes within the pancreas to cause gland damage.

The initial abnormality causing the activation of precursor enzymes may be a persistent increase in cytosolic calcium within the pancreatic acinar cell, inducing intracellular activation of the digestive enzymes.<sup>2,3</sup> The destruction of pancreatic parenchyma leads to the systemic activation of coagulation, kinin, complement and fibrinolytic cascades with liberation of cytokines (TNF- $\alpha$ , IL-1, IL-6, IL-8, platelet-activating factor) and reactive oxygen metabolites, all of which cause the systemic manifestations of pancreatitis (e.g. increased capillary permeability, vasodilation and reduced cardiac contractility) leading to shock, acute renal failure and the acute respiratory distress syndrome.

The reasons why the defence mechanisms fail are not completely clear although it is currently thought that it may be caused by one or all of the following mechanisms.

*Pancreatic duct 'hypertension'*. An increased pressure in the pancreatic duct, resulting from outflow obstruction created by a stone, oedema or sphincter spasm obstructing the ampulla of Vater, may rupture the small pancreatic ducts and cause extravasation of pancreatic juice into the gland.<sup>4</sup>

*Duodenopancreatic reflux*. Reflux of the duodenal contents through the papilla (perhaps made incompetent by inflammation caused by alcohol, passage of a stone, endoscopic cannulation, or recent surgical operation) allows enterokinase to activate trypsinogen, forming trypsin,<sup>5</sup> which in turn activates phospholipase A<sub>2</sub> in the pancreatic ducts. Phospholipase A<sub>2</sub> forms lysolecithin from lecithin (the latter is a normal constituent of bile) which damages pancreatic cell membranes causing oedema of the pancreatic ducts and progressive tissue damage.<sup>6</sup>

*Reduced apical exocytosis of pancreatic zymogens*. In acute pancreatitis there is a reduction in apical

pancreatic cell enzyme secretion while intracellular zymogen synthesis remains normal. It is proposed that with intracellular accumulation of zymogen granules eventually fusion of zymogen granules and lysosomal membranes occur. Within the lysosomes, cathepsin B activates trypsinogen, which activates other zymogens causing progressive tissue damage.<sup>7</sup>

*Hypersecretion*. In rare cases of acute pancreatitis the disease may be caused by an excess secretion of enzymes due to excess muscarinic stimulation associated with organophosphate poisoning or scorpion envenomation.<sup>8</sup>

## CAUSES

The causes of acute pancreatitis are listed in Table 1.<sup>8-11</sup> Cholelithiasis-associated pancreatitis accounts for approximately 45% of cases of acute pancreatitis and ethanol abuse accounts for 35; other causes account for 10%, and in up to 10% no cause may be found (i.e. idiopathic pancreatitis).<sup>8,12</sup> Alcoholic pancreatitis often occurs in patients less than 40 years of age and is predominantly a male disease. Acute pancreatitis associated with cholelithiasis usually occurs in patients aged from 50 - 60 years, and females predominate in a ratio of 3:1. While hypercalcaemia is commonly included in the list of causes of pancreatitis, the incidence of pancreatitis in patients with hyperparathyroidism or hypercalcaemia in one study approximated that of the general population.<sup>8</sup> On the other hand, calcium administration was closely associated with the occurrence of pancreatic injury in a study of risk factors for pancreatic injury after cardiopulmonary bypass.<sup>13</sup> It is now believed that corticosteroids and H<sub>2</sub>-blockers probably do not cause acute pancreatitis.<sup>8</sup>

## CLINICAL FEATURES

Epigastric abdominal pain, which may radiate through to the back, chest flanks or lower abdomen, is the predominant symptom of acute pancreatitis. It is usually gradual in onset, constant and boring in nature and may be mild or severe. The pain may be relieved if the patient sits forward or the legs are drawn up. Nausea and vomiting occur in 90% of cases.

The signs include tachycardia, tachypnoea, fever, hypotension and diaphoresis as well as the abdominal signs of tenderness, rigidity, guarding and distension. Respiratory signs of pleural effusions, basal collapse (characteristically on the left), wheezing, and basal crepitations are found in 10 - 20% of patients. A faint blue discolouration around the umbilicus (Cullen's sign) due to haemoperitoneum, and a blue red purple or brown discolouration of the flanks (Grey-Turner's sign), due to retroperitoneal haemorrhage, may be observed

after 48 hr. Occasionally, erythematous skin nodules due to subcutaneous fat necrosis are found.

**Table 1. Causes of acute pancreatitis**

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<i>Cholelithiasis</i>
<i>Ethanol abuse</i>
<i>Idiopathic</i>
<i>Infections</i>
mumps, coxsackie B, mycoplasma, ascariasis, viral hepatitis (A, B, C), HIV, cytomegalovirus, varicella, Epstein-Barr virus, echo virus, adenovirus legionella, leptospirosis, campylobacter jejuni, tuberculosis, mycobacterium avium
<i>Metabolic</i>
hypercalcaemia, hyperchylomicronaemia, diabetic ketoacidosis, uraemia, hypothermia, pregnancy (third trimester)
<i>Trauma</i>
postoperative trauma, blunt abdominal trauma, post renal or cardiac transplant, ERCP
<i>Ischaemia</i>
polyarteritis nodosa, systemic lupus erythematosus, thrombotic thrombocytopenic purpura, cardiopulmonary bypass
<i>Penetrating duodenal ulcer</i>
<i>Methyl alcohol</i>
<i>Organophosphate poisoning</i>
<i>Scorpion venom</i>
<i>Drugs</i>
Thiazides, frusemide, azathioprine, mercaptopurine, oestrogens (oral contraceptives), procainamide, sulphonamides, erythromycin, tetracycline, pentamidine, metronidazole, L-Asparaginase, phenformin, valproic acid, paracetamol, salicylates, ACE inhibitors, losartan, propofol, nucleoside-analogue reverse transcriptase inhibitors

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ERCP = endoscopic retrograde cholangiopancreatography

The differential diagnosis of acute pancreatitis includes a perforated, infarcted or ischaemic viscus, bowel obstruction, cholecystitis, renal or biliary colic, pneumonia, myocardial infarction, dissecting aneurysm and pulmonary embolism.

#### *Clinical severity*

Acute pancreatitis is classified as either mild ( 85% cases) or severe (15% cases).<sup>1,14</sup> The term haemorrhagic pancreatitis is not used, as variable amounts of pancreatic haemorrhage can be found in the absence of pancreatitis (e.g. severe cardiac failure).

Several prognostic scoring systems with clinical, biochemical and radiological criteria have been

proposed to classify the severity of the pancreatitis. The Ranson/Imrie scoring system uses a series of 11 prognostic signs (Table 2), where three or more criteria indicate the presence of severe acute pancreatitis.<sup>15,16</sup> Using the APACHE II criteria, a score of 10 or more during the first 48 hr following the onset of symptoms, indicates the presence of severe acute pancreatitis.<sup>17,18</sup> The Balthazar score predicts the severity of acute pancreatitis based on the abdominal CT appearances of the pancreas including presence or absence of pancreatic necrosis.<sup>19</sup> Numerous plasma biochemical markers (e.g. C-reactive protein, neutrophil elastase, pancreatitis-associated peptide, interleukins 1, 6, 8, 10 and soluble TNF receptors) and urinary trypsinogen activation peptide have also been used to assess the severity of acute pancreatitis.<sup>20</sup> One study concluded that a plasma C-reactive protein peak > 210 mg/L on day 2 - 4 or > 120 mg/L at day 7 was as predictive as any multiple scoring system.<sup>21</sup>

**Table 2. Ranson/Imrie prognostic criteria for acute pancreatitis**

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<i>On admission or diagnosis</i>
age > 55 years
White cell count > 15.0 x10 <sup>9</sup> /L
Hyperglycaemia > 10 mmol/L
Plasma LDH > 600 U/L
Plasma AST > 100 U/L
<i>During the initial 48 hr of hospitalisation</i>
Haematocrit fall > 10 percent
Hypocalcaemia < 2.0 mmol/L
BUN rise by > 1.8 mmol/L
Fluid sequestration > 4 litres
Hypoalbuminaemia < 32 g/L
Hypoxaemia < 60 mmHg (F <sub>I</sub> O <sub>2</sub> 0.21)

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Mild acute pancreatitis is a self-limiting disease associated with minimal organ dysfunction and characterised pathologically by scattered areas of fat necrosis, oedema and acute fluid collections (i.e. collections of fluid which lack a wall of granulation or fibrous tissue).

Severe acute pancreatitis is associated with organ failure (e.g. systolic blood pressure < 90 mmHg, tachycardia > 120 beats per minute, PaO<sub>2</sub> < 60 mmHg, urine output < 20 mL/hr for 2 consecutive hours, plasma calcium < 2.0 mmol/L, albumin < 30 g/L), local complications (e.g. necrosis, abscess, pseudocyst), and is often characterised by extensive peripancreatic and intrapancreatic fat necrosis, parenchymal necrosis and haemorrhage. It usually declares itself shortly after the onset of abdominal pain, and a delayed progression from

mild acute pancreatitis to severe acute pancreatitis is rare.<sup>1</sup> Failure to improve within 48 - 72 hr of supportive treatment should prompt the use of a dynamic contrast enhanced CT of the abdomen to determine the severity of the disease (e.g. presence or absence of pancreatic necrosis).

While scarring and pseudocyst formation may occur with an acute pancreatitis, once the acute episode has subsided functional and morphological restitution of the gland commonly occurs, and progression to chronic pancreatitis is unusual.<sup>8</sup>

## INVESTIGATIONS

The investigations performed in a patient suspected of having an episode of acute pancreatitis include blood, urine and imaging studies, although in cases where there is severe peritoneal irritation and no confirmatory biochemical or radiological results are found, an exploratory laparotomy may be the safest means of establishing a diagnosis and avoid missing a surgically correctable lesion.<sup>22</sup>

### Blood tests

*Plasma amylase.* The standard diagnostic test for acute pancreatitis is the plasma amylase level which, when elevated more than four times normal, will confirm the diagnosis in the majority of patients.<sup>23,24</sup> The remaining cases have another cause for hyperamylasaemia (Table 3).<sup>25,26</sup>

**Table 3. Causes of hyperamylasaemia**

#### *Spurious*

Acidaemia

#### *Pancreatic*

Acute pancreatitis

Pseudocyst

#### *Gastrointestinal*

Biliary colic

Small-intestine infarction or obstruction

Perforated peptic ulcer

#### *Non-abdominal*

Renal failure

Tumours of lung, ovary or pancreas

Pregnancy

Diabetic ketoacidosis

Multiple organ failure

#### *Salivary gland disease or trauma*

Mumps

Calculi

CPAP (using a facemask)

Isoenzyme determinations to distinguish pancreatic (P-type) from nonpancreatic (S-type) amylase have been used to help diagnose acute pancreatitis from non-pancreatic hyperamylasaemia.<sup>27</sup>

In patients who have acute pancreatitis, the amylase level rises within 2 - 3 hr, peaks at 12 - 24 hr and returns to normal after 3 - 5 days.<sup>28</sup> If the level is still elevated after 5 days then a pancreatic pseudocyst should be suspected. Plasma amylase levels do not correlate with the severity of the disease.

*Plasma lipase.* In acute pancreatitis, the plasma lipase levels increase within 4 - 8 hr, peak at 24 hr to > 2 x the upper limit of normal<sup>24</sup> and may remain elevated for 10 - 14 days. Because the pancreas is the only source of lipase, plasma lipase estimations are specific for pancreatic injury<sup>29</sup> and may be useful in instances where the diagnosis is delayed (i.e. > 24 hr from onset of pain) or to differentiate acute pancreatitis from other causes of hyperamylasaemia.

*C-reactive protein.* Plasma C-reactive protein level is the 'gold-standard' in predicting the severity of acute pancreatitis,<sup>30</sup> as a peak level of > 210 mg/L (on the second, third or fourth day), or a level > 120 mg/L at the end of the first week, discriminates between mild and severe acute pancreatitis. The C-reactive protein levels are also useful in monitoring the progression of the disease.<sup>20</sup>

*Procalcitonin.* In one study of patients with necrotising pancreatitis, the plasma procalcitonin level was the best predictor of a pancreatic infection when compared with C-reactive protein or IL-8 levels and had a predictive power almost equal to that of a fine needle biopsy.<sup>31</sup>

*Blood gases.* Blood gases may reveal hypoxia, hypocapnia and lactic acidosis in severe acute pancreatitis.

*Other blood tests.* Hypocalcaemia and hypomagnesaemia can be found in patients with acute pancreatitis and are caused by intraperitoneal saponification rather than parathyroid hormone resistance. Hyperglycaemia is due to an increase in secretion of glucagon, catecholamines, glucocorticoids, and a decrease in insulin secretion. Hyperbilirubinaemia, elevated plasma enzyme levels (e.g. LDH, AST, ALP), hyperlipidaemia, increased anion gap, and hypoalbuminaemia (plasma albumin levels < 30 g/L occur in 10%, and indicates a poor prognosis) are also features of an acute pancreatitis.

The complete blood picture with a leucocytosis above 15,000/mm<sup>3</sup> and a haematocrit of more than 50% (due to loss of plasma in the peritoneal and retroperitoneal space) are commonly found early in severe acute pancreatitis. With fluid resuscitation the haematocrit (and haemoglobin levels) decrease.

Methaemalbumin is a haem-albumin complex. An elevated plasma level of this compound is a nonspecific finding associated with severe acute pancreatitis which may also be found in patients who have abdominal trauma, fractures, and soft tissue trauma.

#### Urine tests

*Urinary amylase.* Approximately 25% of the plasma amylase is cleared by the kidney. If the patient presents 2 - 3 days after the onset of pancreatitis, the peak amylase level may be missed. A random urinary amylase of greater than 750 IU/L (normal 10 - 300 IU/L) may be a helpful indicator in this situation. While peritoneal fluid amylase levels are often more than 50,000 IU/L in the presence of acute pancreatitis, high amylase levels may also be detected in other acute abdominal conditions and aspiration of peritoneal fluid is not recommended as a routine procedure in patients with acute pancreatitis.<sup>23</sup>

*Urinary trypsinogen activation peptide (uTAP).* In one multicentre study, a high level of uTAP was found to precede all other systemic and clinical events in patients with acute pancreatitis allowing an earlier diagnosis of the disease.<sup>32</sup>

#### Diagnostic imaging

*Plain abdominal X-ray.* Nonspecific signs of a generalised or local ileus (sentinel loop) of the duodenum or jejunum, or a colon cut off and a renal halo sign may occur in acute pancreatitis. Pancreatic swelling or a pseudocyst may also displace the stomach anteriorly and widen the duodenal loop and retroperitoneal gas will indicate an infection. Pancreatic calcification only occurs with chronic pancreatitis. However, the main value of an abdominal X-rays is to exclude other diseases, especially a perforated viscus.

*Abdominal CT with contrast enhancement.* Contrast-enhanced CT is the 'gold standard' for diagnosing pancreatic necrosis and peripancreatic collections. It will also differentiate mild acute pancreatitis from severe acute pancreatitis, and is often performed between 3 and 10 days of the onset of symptoms to grade the severity of the disease (Table 4).<sup>1,33</sup> Mild acute pancreatitis has no significant pancreatic necrosis (mortality 6%) whereas severe acute pancreatitis is associated with significant pancreatic necrosis and has an associated mortality of 23%. The mortality increases to 40% if the pancreatic necrosis becomes infected.<sup>34</sup>

*Magnetic resonance cholangiopancreatography.* Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive method that does not require contrast for imaging the pancreaticobiliary tree and is performed when ERCP has failed or cannot be done.<sup>35,36</sup> It may also be as good as (if not better than) contrast enhanced

CT for assessing the severity and detecting pancreatic necrosis in patients with acute pancreatitis.<sup>37</sup>

*Abdominal ultrasound.* While the pancreas may be poorly visualised by abdominal ultrasound in up to 50% of cases of acute pancreatitis (due to overlying bowel gas), ultrasound is often used to detect free peritoneal fluid, cholelithiasis, dilatation of the common bile duct or pancreatic abscess or pseudocyst.

**Table 4 CT grading of the severity of acute pancreatitis**

Grade	Description
A	Normal
B	Focal or diffuse pancreatic oedema with small extra-pancreatic fluid collections
C	Any of the above, plus peripancreatic inflammation and < 30% pancreatic necrosis
D	Any of the above, plus single extra-pancreatic fluid collection and 30% to 50% pancreatic necrosis
E	Any of the above, plus extensive extra-pancreatic fluid collection and > 50% pancreatic necrosis

Endoultrasonography is a combination of endoscopy and ultrasonography and has a greater success rate in detecting cholelithiasis in cases of suspected biliary pancreatitis compared with transcutaneous ultrasonography. It is recommended when CT or MRI cannot be performed (e.g. when metallic implants are present), in pregnant patients, in the intensive care patient who is unable to be moved or when CT and MRI are unavailable.<sup>37</sup>

*Endoscopic retrograde cholangiopancreatography (ERCP).* This is the most reliable way of diagnosing and treating ductal stones,<sup>38</sup> although it is only indicated in patients with ampullary or common bile duct stones associated with acute pancreatitis, if obstructive jaundice or cholangitis are present.<sup>39</sup>

*Chest X-ray.* This is often performed to assess the pulmonary effects associated with acute pancreatitis (e.g. acute respiratory distress syndrome, pleural effusions, basal atelectasis).

#### TREATMENT

Specific treatment for acute pancreatitis currently does not exist and management is still supportive, reducing pancreatic secretion by reducing enteric stimulation, administering fluid and electrolytes, providing pain relief and preventing complications.<sup>23,40-42</sup> In 85 - 90% of patients, acute pancreatitis is self limiting and subsides spontaneously within 4 - 7 days.

All patients with severe acute pancreatitis who have one (or more) organ failures (e.g. circulatory, pulmonary or renal) should be managed in an intensive care unit.<sup>23</sup>

### Reducing enteric stimulation

Nasogastric suction is a time-honoured therapy for pancreatitis, although controlled studies have failed to demonstrate any therapeutic value of nasogastric suction in patients with mild pancreatitis.<sup>43</sup> In severe acute pancreatitis, nasogastric suction and intravenous fluid replacement is used to control gastric fluid losses due to the associated ileus. Nutrition is maintained using parenteral nutrition, although enteral nutrition (using a nasojejunal tube or percutaneous jejunostomy) has been found to be just as effective.<sup>20</sup> In some studies, enteral nutrition results in a greater beneficial effect on the systemic inflammatory response<sup>44</sup> and significantly fewer complications,<sup>45</sup> when compared with parenteral nutrition. Nevertheless, a recent large review of trials comparing enteral nutrition with parenteral nutrition in patients with acute pancreatitis concluded that while there was a trend towards reductions in the adverse outcomes of acute pancreatitis after administration of enteral nutrition, there were insufficient data to draw firm conclusions about the effectiveness and safety of enteral nutrition compared with parenteral nutrition.<sup>46</sup>

While parenteral nutrition may not offer advantages compared with enteral nutrition in mild pancreatitis, in patients with severe acute pancreatitis with paralytic ileus, parenteral nutrition may be the only method of supplying nutrient to the patient.

### Fluid and electrolyte management

In mild acute pancreatitis, oral fluids are usually initiated by the fifth day and a diet is taken after the seventh day. In severe acute pancreatitis, blood and plasma losses can be extensive, and a decrease in peripheral resistance, reduction in cardiac contractility (due to a circulating myocardial depressant factor) and reduction in intravascular volume (due to an increase in capillary permeability and intravascular haemolysis) can cause severe hypotension. Close haemodynamic monitoring (which will require management in an intensive care unit and may require right heart catheterisation) is needed to guide fluid therapy and the use of inotropic agents.

Intravenous calcium to correct hypocalcaemia is rarely, if ever, required and may even exacerbate pancreatitis.<sup>13</sup> In alcoholic patients, supplemental vitamins (e.g. thiamine, folic acid, vitamin C, pyridoxine) are often prescribed.

### Pain relief

Parenteral pethidine is commonly used to avoid the

traditional side effect of 'spasm' of the sphincter of Oddi with morphine in patients with pain associated with acute pancreatitis. However, all opiates increase the sphincter of Oddi's phasic wave frequency and therefore interfere with its peristalsis.<sup>47</sup> One reviewer found no evidence existed to indicate morphine was contra-indicated in acute pancreatitis and concluded that morphine may be of greater benefit than pethidine by providing longer pain relief with less risk of seizures.<sup>47</sup> In patients with acute pancreatitis who have severe and resistant pain, epidural narcotics or local analgesics may be used.

### Relief of common bile duct or pancreatic duct obstruction

Endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy within the first 1 - 3 days, in patients with ampullary or common bile duct stones and mild acute pancreatitis,<sup>48</sup> or severe acute pancreatitis,<sup>49</sup> does not appear to reduce morbidity or mortality, in the absence of obstructive jaundice (i.e. plasma total bilirubin < 90 µmol/L) or acute cholangitis. However, it can reduce morbidity in patients with ampullary or common bile duct stones associated with acute pancreatitis, if obstructive jaundice<sup>50,51</sup> or cholangitis are present.<sup>52,53</sup> One report of 13 patients with acute pancreatitis used endoscopic pancreatic duct cannulation with naso-pancreatic drainage for 7.3 (± 4 days) to treat pancreatitis within 72 hr of symptoms and reported a successful outcome in all cases.<sup>54</sup> Patients with mild gallstone pancreatitis should have definitive management of the gallstones, ideally within 14 days and no longer than 28 days.<sup>23</sup>

While clinically significant pancreatitis can occur in up to 10% of patients after an ERCP, this may be significantly reduced by a 12-hour infusion of gabexate mesilate.<sup>55</sup> Somatostatin and octreotide infusions, however, are ineffective<sup>56</sup> (octreotide may even increase the incidence of post-ERCP pancreatitis<sup>57</sup>) and one review concluded that somatostatin and octreotide should not be recommended for the prevention (or treatment) of acute pancreatitis.<sup>58</sup> In one prospective double-blind, randomised controlled trial, post-ERCP pancreatitis was reduced significantly by a single i.v. injection of IL-10 (4 - 20 µg/kg) 30 minutes before the procedure.<sup>59</sup>

### Antibiotics

The use of antibiotics in severe acute pancreatitis is contentious. Early clinical trials concluded that prophylactic antibiotics had no effect in reducing morbidity or mortality in patients with acute pancreatitis,<sup>60,61</sup> although recent clinical trials have disputed this in patients who have severe acute

pancreatitis (particularly as 30% of patients with severe acute pancreatitis develop local pancreatic infection).<sup>62,63</sup> However, after three randomised controlled studies<sup>20</sup> and two meta-analyses<sup>64,65</sup> reporting a reduction in mortality with prophylactic antibiotics compared with placebo in patients with severe acute pancreatitis, prophylactic antibiotics are now recommended in patients with necrotising disease to reduce the incidence of infection.

One study of 1100 patients with a secondary pancreatic infection reported a high incidence of enteric infections (*Escherichia coli* 35%, *Klebsiella pneumoniae* 24%, *Enterococcus* spp. 24% and 11% *Pseudomonas* spp), although they also reported a 14% incidence of *Staphylococcus* spp.<sup>66</sup> As other studies have reported a high incidence of fungal infections (which may be predisposed by the use of broad spectrum antibiotics),<sup>67,68</sup> the prophylactic antibiotic cover in patients with pancreatic necrosis should be broad and fine needle aspiration is required to confirm the organism responsible if a pancreatic abscess is suspected.

Currently prophylactic antibiotics (e.g. imipenem 500 mg i.v. 8-hourly for 7 – 10 days with fluconazole 400 mg i.v. daily) are now used, if there is severe acute pancreatitis (e.g. pancreatic necrosis on CT scan).<sup>37,69</sup> If there is no evidence of pancreatic necrosis prophylactic antibiotics are not used.

#### Other therapy

Pancreatectomy (partial or complete), glucagon,<sup>70,71</sup> somatostatin,<sup>72,73</sup> octreotide (which may increase the incidence of pancreatitis if given before an ERCP<sup>74</sup>), aprotinin,<sup>71</sup> fresh frozen plasma,<sup>75</sup> anticholinergics<sup>76</sup> and cimetidine,<sup>43</sup> have all been found to be of little value in the routine management of acute pancreatitis. Peritoneal lavage may improve the patients condition in the early phase of acute pancreatitis,<sup>77</sup> although it does not appear to lower the overall mortality rate.<sup>12,78</sup> While a randomised, double-blind study of the platelet-activating factor inhibitor, lexipafant (60 mg daily for three days) in patients with acute pancreatitis reported a reduction in the incidence of organ failure and improved recovery compared with placebo,<sup>79</sup> a recent double-blind, randomised, placebo controlled study reported an insignificant effect of lexipafant on the systemic inflammatory response and on mortality in patients with severe acute pancreatitis.<sup>80</sup>

In the experimental model, anti-TNF therapy,<sup>81</sup> IL-1 receptor antagonism<sup>82</sup> and endothelin-1 receptor antagonism<sup>83</sup> appear to have beneficial effects in pancreatitis, although clinical trials have yet to confirm these results.

#### TREATMENT OF COMPLICATIONS<sup>6,12,84,85</sup>

The complications that can be associated with severe acute pancreatitis are listed in Table 5.

#### Local complications

In severe acute pancreatitis, patients frequently develop a pancreatic inflammatory mass within the first 2 - 4 weeks. These may be extended areas of necrosis,

**Table 5. Complications associated with pancreatitis**

#### Local

*Pancreatic*  
necrosis, abscess, pseudocyst  
*Ascites*  
*Retroperitoneal*  
abscess, haemorrhage  
*Venous thrombosis*  
splenic, renal or portal vein

#### Systemic

*Pulmonary*  
effusions, chylothorax, ARDS, atelectasis,  
mediastinal abscess  
*Cardiovascular*  
hypotension, shock, pericardial effusion,  
ST and T changes simulating myocardial infarction  
*Disseminated intravascular coagulation*  
*Gastrointestinal*  
acute stress ulceration, peptic ulceration, ileus  
oesophageal variceal haemorrhage  
*Renal*  
acute renal failure, right hydronephrosis  
*Central nervous system*  
encephalopathy, seizures, psychosis  
sudden blindness (Purtscher's retinopathy)  
*Skin*  
subcutaneous nodules

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ARDS = acute respiratory distress syndrome

pseudocysts or abscesses, and are suspected if pain, fever and leucocytosis persist for greater than 5 days. They may cause fever, diaphoresis and a tender epigastric mass, and should be monitored by serial CT scans and plasma C-reactive protein levels. To differentiate between an infected area of necrosis, pseudocyst or an abscess, a CT guided needle aspiration is often required.

*Pancreatic necrosis.* Pancreatic necrosis is defined as diffuse or focal areas of non-viable pancreatic parenchyma, typically associated with peripancreatic fat necrosis.<sup>1</sup> These areas appear on contrast-enhanced CT

as focal or diffuse, well margined zones of non-enhanced pancreatic parenchyma that are larger than 3 cm or involve more than 30% of the area of the pancreas. The areas of devitalised pancreatic parenchyma and peripancreatic fat necrosis often appear as solid pancreatic inflammatory masses (previously called phlegmons) and may resolve in a few weeks with conservative therapy, although a 7 - 10 day course of antibiotics to reduce the incidence of pancreatic infection is often used.<sup>86</sup> Pancreatic infection occurs in 10% of patients with acute pancreatitis, which increases to 30 - 70% in patients with necrotising pancreatitis. It usually occurs 4 or more weeks after the onset of acute pancreatitis and if left untreated has a mortality approaching 100%.<sup>1</sup>

If the inflammatory mass continues to enlarge or becomes infected (diagnosed by CT or ultrasonographically guided aspiration) it requires laparotomy, surgical drainage (necrosectomy) and antibiotics.<sup>1,87</sup> While any of the three surgical techniques (e.g. necrosectomy combined with an open packing technique, planned staged re-laparotomies with repeated lavage, closed continuous lavage of the retroperitoneum) may be performed with a comparable outcome regarding mortality, only the last technique appears to be associated with a lower morbidity when compared with the first two techniques.<sup>88</sup>

*Pancreatic abscess.* A pancreatic abscess is a circumscribed intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis.<sup>1</sup> Treatment requires surgical drainage and antibiotics.

*Pancreatic pseudocyst.* This occurs after 4 or more weeks from the onset of the acute pancreatitis in 4% patients. It consists of a collection of fluid and debris, rich in pancreatic enzymes and enclosed by a wall of fibrous or granulation tissue. In approximately 70% of patients the pseudocyst resolves spontaneously (octreotide has been used to hasten the resolution of pancreatic pseudocysts<sup>89</sup>) in the remaining 30%, the pseudocyst becomes complicated (e.g. it enlarges, ruptures or haemorrhages) and requires endoscopic, percutaneous or surgical drainage.<sup>22</sup>

*Pancreatic ascites.* A nine day infusion of somatostatin has been used successfully to treat pancreatic ascites, reducing the leakage of pancreatic fluid into the peritoneal cavity.<sup>90</sup> Octreotide may also be of benefit in these cases.

### Systemic complications

*Respiratory failure.* Respiratory failure may be caused by one or all of the following: acute respiratory distress syndrome, a reduction in diaphragmatic

movement, atelectasis and pleural effusions. Oxygen and mechanical ventilation may be required.

*Acute renal failure.* Acute renal failure may be associated with a severe acute pancreatitis and is managed by conventional means.

*Hyperlipidaemia.* Plasmapheresis may be of benefit in patients with severe acute pancreatitis and persistent hyperchylomicronaemia.<sup>91-94</sup>

*Bleeding oesophageal varices.* Oesophageal varices may be caused by portal hypertension secondary to splenic vein thrombosis.

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