Diagnosis and early management of acute pancreatitis

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Acute pancreatitis is a common emergency with the potential for significant complications. Despite advances in the understanding of the pathogenetic mechanisms of acute pancreatitis and the completion of a number of randomized trials studying specific therapies, the early management of patients remains supportive.

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Acute pancreatitis is an acute inflammatory process of the pancreas, with variable involvement of other regional or remote organ systems (Bradley, 1993). It is a common condition, with an incidence that appears to be increasing (McKay et al, 1999). Although most patients with acute pancreatitis have a mild illness with complete recovery, approximately one quarter of patients develop severe acute pancreatitis (*Table 1*) (Bradley, 1993). Those patients with severe disease have high morbidity and mortality rates with prolonged in-hospital stays, and as a consequence result in significant economic health-care implications.

In practical terms the management of acute pancreatitis can be divided into two stages.

1. Initial management includes diagnosis, severity stratification, resuscitation and the choice of appropriate disease-specific initial therapy
2. Following this, patients with severe disease may require intervention for intra-abdominal complications or intensive care for multiple organ dysfunction.

Guidelines (Banks, 1997; Glazer and Mann, 1998; Dervenis et al, 1999) suggest that patients with complications arising from severe acute pancreatitis are most appropriately managed in a specialist unit, and therefore this article focuses on the initial phase of management.

TABLE 1.
Definitions of mild and severe acute pancreatitis

Mild acute pancreatitis	Is associated with minimal organ dysfunction and an uneventful recovery
Severe acute pancreatitis	Is associated with organ failure and/or local complications such as necrosis, abscess or pseudocyst
Organ failure is defined as shock, respiratory dysfunction, renal failure, gastrointestinal bleeding, and systemic complications such as disseminated intravascular coagulation or severe metabolic disturbance	

AETIOLOGY

Acute pancreatitis may be caused by a wide variety of aetiological agents (*Table 2*). However, most cases result from either gall-stones or alcohol excess. Epidemiological studies (Jaakkola and Nordback, 1993) have demonstrated that alcohol excess is an increasingly frequent cause. The prevalence of idiopathic acute pancreatitis varies between reported series, and is probably a

TABLE 2.
Aetiological agents in acute pancreatitis

Common agents	Gall-stones	
	Alcohol	
Uncommon agents	Trauma	Endoscopic retrograde cholangiopancreatography
		Sphincterotomy
		Biliary manometry
	Pancreatic duct obstruction	
	Ampulla of Vater	
	Neoplasia	
	Drugs	Azathioprine
	Metabolic	Hypercalcaemia
		Hyperlipidaemia
	Infection	Mumps
		Coxsackie B
		Human immunodeficiency virus
	Vascular	Vasculitis
		Cardiopulmonary bypass
	Hereditary pancreatitis	

function of the degree to which investigations have been undertaken to identify a cause. Current UK guidelines state that no more than 25% of cases should be labelled as idiopathic acute pancreatitis (Glazer and Mann, 1998).

PATHOGENESIS

The mechanisms through which each aetiological agent causes pancreatic acinar cell injury are unclear, although it is believed that regardless of the aetiological factor the mechanisms of disease progression in acute pancreatitis following the initial pancreatic insult are similar.

Acinar cell injury induces local pancreatic inflammation. Although the inflammatory process may remain confined to the pancreas and peri-pancreatic tissues, a systemic inflammatory response may be triggered, which is characterized by the systemic activation of leucocytes and endothelial cells and the secretion of pro-inflammatory cytokines (Powell et al, 2000a).

The systemic inflammatory response is similar to that seen in other critical illness states, and is believed to be responsible for the development of the organ dysfunction that characterizes severe acute pancreatitis. It is not known why some patients develop severe acute pancreatitis while others with similar aetiological factors develop mild acute pancreatitis. However, there is evidence to implicate both excessive pro-inflammatory mediators and decreased anti-inflammatory mechanisms.

CLINICAL PRESENTATION

The presentation of acute pancreatitis may be varied. Typically, patients present with increasing epigastric and/or central abdominal pain radiating through to the back. However, the spectrum of illness ranges from patients complaining of mild abdominal pain to catastrophic cardiorespiratory collapse. Furthermore, post-mortem studies demonstrate that in a number of patients (Imrie and McKay, 1999) the diagnosis of acute pancreatitis is not made before death. Acute pancreatitis should therefore be considered in any patient with acute abdominal pain or major systemic upset.

Patients may have symptoms consistent with biliary colic before the presentation of gall-stone-induced acute pancreatitis, while those with alcohol-induced disease will have a long-standing history of alcohol ingestion and/or recent binge drinking.

Signs of cardiovascular and respiratory dysfunction may be present. Examination may reveal abdominal signs ranging from localized epigastric tenderness to generalized peritonitis. More specific signs of severe acute pancreatitis include peri-umbilical bruising (Cullen's sign) and flank bruising (Grey Turner's sign; *Figure 1*).

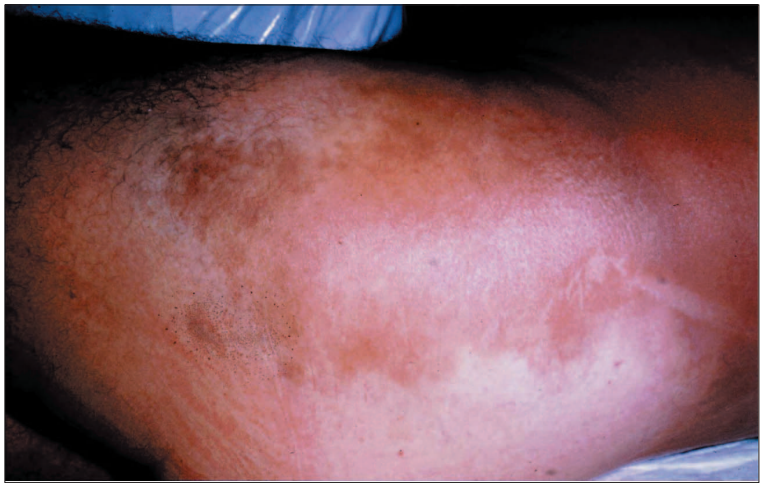

Figure 1. Flank bruising in a patient with severe acute pancreatitis (Grey Turner's sign).

DIAGNOSIS

The diagnosis of acute pancreatitis is usually based on the detection of a serum amylase concentration greater than three times the upper limit of normal. However, hyperamylasaemia may occur in several other conditions (*Table 3*), and a serum amylase concentration above the 'diagnostic threshold' does not definitely indicate acute pancreatitis.

Conversely, acute pancreatitis may exist with serum amylase concentrations below this threshold. Serum amylase concentrations may have normalized in patients with a prolonged history before admission to hospital. It should also be noted that serum amylase levels do not provide prognostic information, nor can they be followed as a marker of disease resolution in the early stages. However, high levels of serum amylase on admission are suggestive of a gall-stone aetiology.

Other markers have been used to diagnose acute pancreatitis. Serum lipase is the most common and is more sensitive and specific than serum amylase. Moreover, because of its longer half-life, serum lipase is more accurate if there has been a delay in presentation. However, as

TABLE 3
Main differential diagnoses of hyperamylasaemia

Acute pancreatitis
Pancreatic pseudocyst
Mesenteric infarction
Perforated viscus
Acute cholecystitis
Diabetic ketoacidosis

with serum amylase, serum lipase concentrations do not correlate with disease severity. Newer markers such as urinary trypsinogen activation peptide and serum carboxypeptide-B activation peptide provide both diagnostic and prognostic information but are not yet in routine use.

Contrast-enhanced computed tomography (CT) may be required in equivocal cases, and remains the 'gold' standard for the diagnosis of acute pancreatitis.

Finally, laparotomy may be required to confirm the diagnosis of acute pancreatitis while refuting other potential diagnoses such as acute mesenteric infarction. The decision to undertake a laparotomy is not made lightly as there is evidence that early operation has an adverse effect on outcome in acute pancreatitis. However, diagnostic delay may be deleterious in patients with other intra-abdominal conditions.

MANAGEMENT OF ACUTE PANCREATITIS

Guidelines for the initial management of acute pancreatitis have been published by the British Society of Gastroenterology (Glazer and Mann, 1998), the American College of Gastroenterology (Banks, 1997) and the Santorini Consensus Conference (Dervenis et al, 1999). Their recommendations are similar.

Initial resuscitation

Initial therapy is aimed at adequate resuscitation; provision of oxygen, intravenous fluid therapy and adequate analgesia constitute the mainstays of treatment. In addition, metabolic abnormalities such as hyperglycaemia or hypocalcaemia should be corrected with intravenous insulin or calcium. Consideration should be given to thromboprophylactic therapy.

Severity stratification

Following resuscitation, patients should be categorized into either prognostically mild or severe disease, enabling decisions to be taken regarding the degree of monitoring, supportive care and intervention that is appropriate for each patient. A validated prognostic scoring system is recommended for this purpose.

A number of systems exist and can be divided into: multiple-factor scoring systems, such as the Glasgow (Blamey et al, 1984), Ranson and APACHE II systems; biochemical markers, such as C-reactive protein; immunological markers (interleukin-6); and radiological markers (Balthazar; Balthazar et al, 1990; Helsinki; Schroder et al, 1985). Comparative studies (Glazer and Mann, 1998), however, suggest that no system is superior to the others. It is also important to recognize that scoring systems achieve approximately 80% accuracy in disease prognostication.

Radiological imaging

Transabdominal ultrasound should be undertaken in all patients with acute pancreatitis to determine the presence or absence of gall-stones. Intravenous contrast-enhanced CT should be performed in all patients with prognostically severe acute pancreatitis between 3–10 days after admission to determine the presence of pancreatic necrosis (*Figure 2*).

SPECIFIC THERAPIES FOR ACUTE PANCREATITIS

In general, patients with mild acute pancreatitis improve spontaneously and require little intervention other than therapy directed towards the aetiological agent. In contrast, patients with severe acute pancreatitis may develop significant complications and require aggressive support.

Unfortunately, despite intense research there remains few effective specific therapies for severe acute pancreatitis. Although there have been a number of randomized, controlled trials that have suggested benefit following endoscopic retrograde cholangiopancreatography (ERCP) or the administration of prophylactic antibiotics in patients with severe acute pancreatitis, controversy still persists regarding the value of these therapeutic options as a result of weaknesses within published trials.

Other interventions that have recently been assessed within the confines of randomized, controlled trials include early enteral nutrition and a specific anticytokine agent.

Early ERCP

Early ERCP with endoscopic sphincterotomy in gall-stone-induced acute pancreatitis aims to remove impacted ductal gall-stones, thereby eliminating the initiating stimulus and hopefully reducing pancreatic inflammation. Three randomized trials assessing early ERCP have been

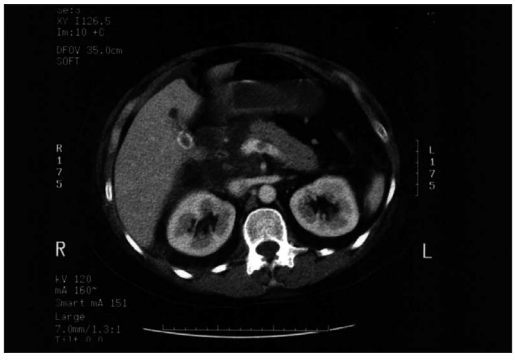

Figure 2. Contrast-enhanced computed tomography of a patient with gall-stone-induced severe acute pancreatitis. Although the body and tail of the pancreas enhances with contrast, the pancreatic head does not, which is consistent with necrosis of this area. A calcified gall-stone may be seen in the neck of the gall bladder.

published (Neoptolemos et al, 1988; Fan et al, 1993; Folsch et al, 1997). Although the initial two trials suggested that patients with gall-stone-induced severe acute pancreatitis benefited from early ERCP and sphincterotomy, the most recent trial suggested that ERCP and sphincterotomy were deleterious in patients with gall-stone-induced disease but without biliary obstruction.

Rationalization of the results of these three trials therefore suggests that early ERCP with endoscopic sphincterotomy is of benefit in patients with prognostically severe gall-stone-induced acute pancreatitis with biochemical evidence of obstructive liver function tests (serum bilirubin >90 μmol/litre) or cholangitis. However, further trials are required to determine the exact role of ERCP and sphincterotomy in gall-stone-induced severe acute pancreatitis.

Antibiotic therapy

The administration of prophylactic antibiotics in acute pancreatitis is based on the hypothesis that the prevention of infected pancreatic necrosis would improve outcome. Initial trials published in the 1970s failed to demonstrate benefit. However, because most patients within these trials had mild acute pancreatitis and would therefore have never developed infected pancreatic necrosis, these studies could not have detected any benefit from the administration of prophylactic antibiotics.

In contrast, more recent, randomized trials have only included patients with radiological evidence of pancreatic necrosis and have employed broad-spectrum antibiotics (Pederzoli et al, 1993; Sainio et al, 1995; Delcenserie et al, 1996; Nordback et al, 2001). These trials have suggested improved outcome in patients with severe acute pancreatitis following the administration of broad-spectrum prophylactic antibiotics.

It should, however, be appreciated that none of these individual studies in themselves have sufficient power to mandate antibiotic prophylaxis, and therefore further studies are required to confirm the early results as well as to determine the optimum antibiotic regimen. It also remains to be seen whether antibiotic prophylaxis results in increased rates of fungal infections and antibiotic-resistant organisms in cases of infected pancreatic necrosis.

Early enteral nutrition

Traditional beliefs held that organ dysfunction in acute pancreatitis arose as a consequence of circulating activated digestive enzymes causing systemic 'autodigestion'. Thus a nil-by-mouth regimen was required in order to 'rest the pancreas', thereby limiting the systemic effects.

In contrast, newer hypotheses (Powell et al, 2000a) hold that loss of enteral nutrition predisposes to intestinal dysfunction leading to bacterial translocation from the intestinal lumen, which in turn sustains organ dysfunction mediated by the systemic inflammatory response. It has therefore been postulated (Powell et al, 2000a) that the delivery of early enteral nutrition will ameliorate intestinal dysfunction, reduce the systemic inflammatory response and improve outcome.

On the basis of this hypothesis, a number of small, randomized trials have been carried out (Kalfarentzos et al, 1997; McClave et al, 1997; Windsor et al, 1998; Powell et al, 2000b). The results of these trials suggest that the delivery of enteral nutrition is possible in patients with severe acute pancreatitis. Furthermore, these trials have suggested improvement in a number of surrogate markers consistent with the hypothesis of intestinal dysfunction secondary to loss of enteral nutrition. Again, however, none of these trials is of sufficient power to mandate a change in current clinical practice, and therefore a definitive clinical trial is required to assess the impact of early enteral nutrition in patients with severe acute pancreatitis.

Anticytokine therapy

Anticytokine therapy aims to interrupt the cytokine cascade, thereby arresting the development of a systemic inflammatory response and preventing organ dysfunction. Lexipafant, a high-affinity, platelet-activating factor, receptor antagonist, acts as a general downregulator of the pro-inflammatory cytokine response and has been the focus of a number of clinical trials.

Initial trials appeared to demonstrate encouraging results, and on the strength of these an international, multicentre, placebo-controlled trial of lexipafant in predicted severe acute pancreatitis was carried out (Kingsnorth, 1997; McKay et al, 1997). This trial enrolled approximately 1500 patients and constituted the largest intervention trial in acute pancreatitis to date. Although definitive publication of the results is awaited, British Biotech, the manufacturers, have suspended further work on lexipafant in acute pancreatitis, suggesting that the promising results observed in earlier trials were not confirmed in this definitive trial.

TREATMENT OF GALL-STONES IN GALL-STONE-INDUCED ACUTE PANCREATITIS

Evidence relating to the timing of surgical intervention for gall-stones in patients with acute pancreatitis dates from the era of open cholecys-

tectomy. Based on these results, patients with gall-stone-induced mild acute pancreatitis should undergo cholecystectomy during the index admission. However, cholecystectomy should be delayed in those with severe disease until the inflammatory condition has resolved, or should be undertaken as an additional procedure during surgery for a complication of acute pancreatitis. Where possible, laparoscopic cholecystectomy is the procedure of choice.

In patients with severe, comorbid disease contraindicating cholecystectomy, definitive treatment may be provided by endoscopic sphincterotomy.

PROGNOSIS

Current UK guidelines provide targets for mortality rates in acute pancreatitis (Glazer and Mann, 1998). These guidelines state that overall mortality should be <10% of patients admitted with acute pancreatitis, with a mortality rate <30% in those with prognostically severe acute pancreatitis. Encouragingly, demographic data suggest that there has been a reduction in mortality rates over recent years (McKay et al, 1999).

CONCLUSION

Acute pancreatitis is a common illness with the potential for significant morbidity and mortality. At present there is a dearth of specific interventions for those patients with severe disease. However, it is hoped that as the pathogenetic mechanisms that underpin organ dysfunction are determined, effective interventions will become available. HM

Conflict of interest: The Royal Infirmary of Edinburgh was a participating site in the British Biotech multicentre lexipafant trial. One of the authors, JP, was involved in a randomized trial assessing enteral nutrition in acute pancreatitis.

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KEY POINTS

- Acute pancreatitis is a common emergency.
- Guidelines for the management of early acute pancreatitis exist.
- Early endoscopic retrograde cholangiopancreatography and sphincterotomy should be undertaken in patients with severe acute pancreatitis and either biliary obstruction or cholangitis.
- The role of antibiotic prophylaxis in severe acute pancreatitis is unclear.
- Contrary to previous beliefs, early enteral nutrition may improve outcome in patients with acute pancreatitis.