Acute pancreatitis

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Acute pancreatitis is a common disease. As knowledge of its pathophysiology improves, evidence is found to confirm and refute present management and also to suggest new approaches. This article addresses some of these areas in the context of the management of acute pancreatitis.

Acute pancreatitis (AP) is a common disease, seen in both surgical and non-surgical practice, accounting for around 3% of admissions with acute abdominal pain. It carries a relatively high mortality of 5–10% and, at present, there is no specific non-operative therapy. Mortality seems to have plateaued in the last decade. In the previous two decades a decrease in mortality has resulted from a number of factors: increased diagnosis of mild cases, improved diagnosis, understanding of natural history, imaging and selective operative intervention. Unsurprisingly, mortality varies with the severity of cases: the mortality for severe cases is ≈20%, for cases of infected necrosis is ≈25%, and for cases of sterile necrosis is ≈10%.

Death tends to occur in the first week from multiple organ failure or thereafter from sepsis, either local to the pancreas or systemic. Patients who survive, even severe episodes, generally have low long-term morbidity and good quality of life.

DEFINITIONS

Attempts to categorize AP have been made in recent years in light of improved knowledge of the pathology and natural history of the disease. From Marseilles and Cambridge to Atlanta (Bradley, 1993) these have given a basis from which to compare the outcomes of different management techniques and enabled discussions to be carried out using agreed and standardized terminology.

Many aspects of management have developed and are developing. Although many of these are still contentious a number of consensus documents have been produced giving guidelines on the management of AP (Banks, 1997; Glazer and Mann, 1998; Dervenis et al, 1999). This article discusses some recent developments and contentious areas, within a framework of the management of AP.

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ASSESSMENT

Aetiology

The two common causes of AP remain gallstones, accounting for around 40–50% of cases in Britain, and ethanol, accounting for around 20–30% of cases. The mechanisms by which the various causes lead to AP are not fully understood. If these causes are not identified other potential causes should be sought which include:

- Hyperlipidaemia
- Tumours (especially periampullary tumours)
- Infective causes, including viral, e.g. mumps and coxsackie, and parasitic, e.g. ascaria and clonorchis.

'Idiopathic' (or unidentified aetiology) remains a common diagnosis in reported series and appears to diminish with repeated investigation. The UK guidelines (Glazer and Mann, 1998) suggest that this group should constitute no more than 20–25% of diagnoses of AP.

Diagnosis

Common presenting features are abdominal pain, especially epigastric, with or without radiation to the back, associated with vomiting. There may be signs of abdominal tenderness (ranging from mild through rebound to rigidity) and, less commonly, Cullen's and Grey-Turner's signs, which contribute to a more specific diagnosis. However, presentation can be varied and missed diagnosis remains a factor in the high mortality (Kingsnorth, 1998).

From 12–42% of cases of fatal AP go undiagnosed before death. In one analysis of patients diagnosed post-mortem, Wilson and Imrie (1988) suggest that a timely diagnosis may have altered management, potentially allowing survival, in 45% of cases. In addition to a variable clinical presentation, the lack of a highly specific diagnostic test leads to difficulties.

Diagnostic tests

At present the mainstay of diagnosis, beyond clinical assessment, is the biochemical tests of amylase (blood or urine) and lipase. These pancreatic enzymes are typically elevated (amylase >3–5x normal, lipase >2x normal) during an attack of AP. However, they must be sought to give a result. Levels may not be elevated even in a severe attack (lack of sensitivity) and can be non-specifically elevated in clinically similar conditions (lack of specificity). In addition, amylase is short lived in the blood (leading some commentators to recommend urine levels to be tested). Amylase has other isoenzymes which may, rarely, be the source of an abnormally high result. Lipase is marginally superior to amylase (*Table 1*). Combination of the two investigations improves sensitivity and specificity.

Assays which show promise include:

- Trypsin 2-alpha 1 antitrypsin complex, which also correlates with severity
- Alpha 2 macroglobulin-trypsin complex
- Trypsinogen 2. This is probably closest to a practical, accurate form and a simple urine test is available (Kylanpaa-Back et al, 2000) (*Table 1*). Serum levels also correlate with severity.

Prognostic tests, indicators, systems and imaging

As AP has such a range of clinical courses it is useful to be able to predict which patients are likely to have a severe (complicated) course. This allows intensive observation of those at greatest risk, implementation of investigation and appropriate and opportune management. It also provides for standardized comparisons in studies.

Attempts at predicting severity in AP have been made for over two decades, initially consisting of multi-factor scoring systems, such as Ranson's (Ranson et al, 1974) and Glasgow criteria (Blamey et al, 1984). Other simple indicators are now also known and a large number of potential serum markers are being evaluated. The details of all the potential predictors are extensive and a number of reviews exist. A combination of recognized predictors of severe outcome is, at present, the best approach:

- Simple tests:
  a. Clinical assessment — not regularly reliable, still a vital component
  b. Obesity — body mass index ≥30 kg/m^2
  c. Chest X-ray — pleural effusions (especially left sided and bilateral)
  d. C-reactive protein level >150 mg/litre.
- Multi-factor scoring systems: e.g. APACHE-II score ≥8 (values between ≥6 and ≥9 recommended by various authors), which is equal or superior to other systems
- Computed tomography (CT) imaging: (dynamic) contrast-enhanced CT of the pancreas. Necrosis and fluid collections correlate with outcome. Systems such as that of Balthazar et al (1990) are useful measures.

TREATMENT

The mainstay for the patient with a predicted severe or severe episode of AP is supportive care and appropriate fluid resuscitation in a high dependency or intensive care setting. There are also medical and interventional options available.

Antibiotic prophylaxis

As discussed above, mortality in AP is primarily the result of septic complications beyond the first week, this accounting for the majority of deaths. In addition infected pancreatic necrosis is associated with a much higher mortality than sterile necrosis. A debate regarding antibiotic prophylaxis has been ongoing for many years, with the weight of evidence most often said, in the past, to fall against prophylaxis. However, much of the data covered ampicillin which we now know has limited pancreatic penetration, and studies included mild cases which may have masked a significant effect in severe cases.

With more recent trials and increasing evidence on which antibiotics attain appropriate tissue levels this debate continues (Barie, 1996), but on balance probably favours antibiotic prophylaxis in patients with predicted severe disease (Golub et al, 1998; Powell et al, 1998). This corresponds to current practice in the UK (Powell et al, 1999). Comparisons of penetration in different degrees of inflammation, into pancreatic juice and even into peripancreatic fat (Barie, 1996) may be of significance in the clinical setting.

However, even recent studies have not consistently shown a survival benefit or reduced pancreatic infections with antibiotic prophylaxis. The question of 'which antibiotic?' leads to even less widespread evidence; with clinical trials, animal studies and penetration studies not consistently testing the same antibiotics and variation also seen within antibiotic 'families'. Although further studies are required, it would be reasonable to recommend one of:

TABLE 1.
Sensitivity and specificity of some tests for acute pancreatitis

	Sensitivity (%)	Specificity (%)
Amylase	52–95	86–98
Lipase	74–100	34–100
Trypsinogen-2 (serum or urine)	91–8	89–95

Data from Kemppainen et al (1998)

- Cefuroxime, which has been shown to decrease total infectious complications, need for operative intervention and death, but not pancreatic infection, in a trial of 60 patients (Sainio et al, 1998)
- Ceftazidime, which (with amikacin, which is poorly penetrant, and metronidazole) reduced all infections but not mortality in a small trial (Delcenserie et al, 1996)
- Ofloxacin, which (with metronidazole) in a small trial was shown to decrease physiological disturbance (Schwarz et al, 1997) and has good penetration and spectrum characteristics
- Imipenem, which has been shown to decrease pancreatic and extrapancreatic infection (Pederzoli et al, 1993) and be superior to perfloxacin without metronidazole (Bassi et al, 1998), but not to show survival benefit. It has good pancreatic penetration and is the most consistently tested; however, its cost may exclude it as first-line prophylaxis, especially in light of its lack of comparison with some of the viable alternatives.

Any of the above (except imipenem) should probably be combined with metronidazole.

Other issues in antibiotic prophylaxis awaiting resolution include the role of gut decontamination in an attempt to prevent bacterial translocation, either alone or with systemic prophylaxis, the duration of administration, and whether to commence antibiotics on purely prognostic grounds or only after necrosis is seen (as in most of the trials).

Pancreatic rest and suppression

A mainstay of AP management has been to maintain the patient nil by mouth. This can avoid worsening pain and nausea and rests the pancreas from stimulation by food, with the aim of decreasing pancreatic secretion and thus autodigestion, although basal secretion may already be suppressed in AP. Other avenues to rest the pancreas seem to lack any significant benefit:

- Nasogastric aspiration has not been shown to benefit outcome; however, it has a role in selected cases to rest an ileus and prevent vomiting and aspiration
- Cimetidine has not consistently been shown to benefit patients
- Evidence for ranitidine in patients is limited although it probably plays a worthwhile role in gastritis and ulcer prophylaxis
- Somatostatin and its analogue octreotide are known to decrease pancreatic secretion but have failed to consistently show benefits in patients with AP (Uhl et al, 1999a). Although a meta-analysis suggested a benefit (Andriulli et al, 1998) this was before the largest study (Uhl et al, 1999b), a randomized, double-blind trial which failed to show any significant benefit.

Suppression of the inflammatory response

Blockade or suppression of the inflammatory pathways involved in AP is an appealing therapeutic avenue. As our rapidly developing understanding of this area is in its early days, there are many potential but not yet fully evaluated therapies.

The most studied to date is the platelet-activating factor antagonist lexipafant. After two phase II trials and a multicentre UK phase III trial there appeared to be a significant improvement in organ failure incidence and severity, and reduction in pseudocyst formation and mortality in selected patients (Kingsnorth, 1997). However, a second larger, international phase III trial failed to show any benefit for lexipafant (unpublished data, British Biotech, Oxford, 1999).

Nutrition

Patients unable to eat for a prolonged period, in the catabolic state of AP, require nutritional supplementation. This is most commonly achieved with total parenteral nutrition (TPN). With the apparent paradox of feeding enterally a patient whose gut and pancreas is being rested, recent evidence (in the form of three small, randomized trials) would suggest that enteral nutrition (jejunal feeding, distal to the cholecystokinin cells) is safe and possibly superior to TPN (Dervenis et al, 1999).

The potential benefits are improved nutritional status, protection of the gut's mucosal barrier against bacterial translocation and fewer septic complications of the means of administration.

Analgesia

Many AP patients suffer from severe abdominal pain. Prescription of pethidine, rather than morphine, in acute biliary pain (including pancreatitis) is often advised because of the potential for morphine to cause the sphincter of Oddi to spasm, thus increasing intraductal pressure. However, concern over the addictive potential of pethidine and possible inferiority to morphine confounds the issue. Anecdotal evidence abounds on both sides of this debate, but objective clinical data are lacking.

Morphine causes increased rate and amplitude of sphincter of Oddi contractions and increased basal pressure (Helm et al, 1988) while pethidine can decrease the frequency of contractions (Thune et al, 1990). However, findings are inconsistent and the clinical significance is untested. Patient-controlled analgesia with pethidine can be useful for systemic analgesia in AP. Alternatives include epidural analgesia, transcutaneous electrical nerve stimulation and coeliac plexus block.

Interventions

CT-guided aspiration of pancreatic necrosis is a useful technique for distinguishing between infected and sterile pancreatic necrosis (Banks, 1997; Dervenis et al, 1999), which are often clinically indistinguishable.

Endoscopic retrograde cholangiopancreatography (ERCP) definitely has a role to play in management of AP. However, the exact circumstances in which it should be used have not been fully evaluated. A number of trials have shown a benefit of early ERCP in biliary pancreatitis, although those showing survival benefit did not exclude patients with cholangitis or biliary obstruction (Banks, 1997; Dervenis et al, 1999). A study which did so failed to show survival benefit (Folsch et al, 1997). It can be said that ERCP should be used in biliary pancreatitis with evidence of cholangitis or biliary obstruction and may benefit patients with severe AP caused by gallstones. These groups of patients may be indistinguishable, so ERCP is reasonable in all patients with prognostically severe AP and gallstones.

Surgical intervention is indicated in patients with infected pancreatic necrosis, but its role in sterile necrosis is uncertain and should probably only be employed in patients who are deteriorating or failing to settle after attempts at conservative management have been exhausted (Banks, 1997; Dervenis et al, 1999). A further indication, which is not uncommon, is the patient in whom imaging is unavailable or unable to exclude an intra-abdominal catastrophe for which an operation would be necessary, e.g. mesenteric infarction.

CONCLUSIONS

Many aspects of our knowledge of AP and its management have been and are being advanced. In many areas further evaluation is required. The end-point of such work will hopefully be improved outcome for our patients. Debate and study to this end can be facilitated by use of standardized terminology and assessment against accepted guidelines and practices. HM

Conflict of interest: none.

More details and comments on the references and some points raised are available at: www.cartmellsreferences.freeserve.co.uk

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KEY POINTS

- Acute pancreatitis is a common disease with relatively high mortality.
- Standardized terminology is now available and should be employed to aid debate and comparison.
- Diagnosis is still hampered by lack of a highly sensitive and specific test; however, many potential tests are being developed.
- On balance, antibiotic prophylaxis is advisable in severe acute pancreatitis.
- Suppression of inflammation may, in the future, be a therapeutic option.
- Enteral nutrition is probably as, or more, safe than total parenteral nutrition.
- Infected necrosis is an absolute indication for operation.