Clinical review

Acute pancreatitis

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Acute pancreatitis is a potentially lethal disease that is increasing in incidence. The high mortality associated with acute pancreatitis has improved as a result of a greater understanding of the natural history of acute pancreatitis and recent advances in critical care. Optimal management requires a greater willingness to consider the diagnosis of acute pancreatitis, stratification of severity, and adequate fluid resuscitation. Here, we review who gets acute pancreatitis and how to deal with those patients in whom the cause remains unclear. We also examine the current controversies in acute pancreatitis: how to deliver nutritional support, what role exists for antibiotic prophylaxis, when to do a computed tomography scan, and the role of early endoscopic retrograde cholangiopancreatography (ERCP).

Is acute pancreatitis becoming more common?

Incidence rates vary from 5.4 per 100 000 population per year to 79.8 per 100 000 per year. Variation is due to different diagnostic criteria, geographical factors, and changes over time. One constant, however, is an apparent increase in the incidence of acute pancreatitis in the past 40 years. For example, the incidence in Scotland has risen from 9.4 per 100 000 per year in 1968-80 to 41.9 per 100 000 per year in 1995.¹ This rise in incidence may be due to improved diagnostic capability during this period but may also reflect a true increase due to a greater prevalence of risk factors such as increased alcohol consumption.

How does acute pancreatitis present?

Abdominal pain, usually located in the epigastrium, is the cardinal symptom of acute pancreatitis. It typically increases in severity over a few hours before reaching a plateau that may last for several days. Continuance of the pain beyond this time is associated with the development of local complications, such as acute fluid collections, pseudocysts, and necrosis. Nausea and vomiting are associated symptoms. Abdominal signs may vary from mild tenderness to generalised peritonitis. Blue-grey discoloration of the flanks, due to exudation of fluid stained by pancreatic necrosis into the subcutaneous tissue, is known as Grey-Turner's sign. Similar discoloration in the periumbilical area is known as Cullen's sign.

Systemic inflammation may occur, producing respiratory failure and cardiovascular failure. The

Summary points

Early identification of the severity of an episode determines allocation of critical care beds, early endoscopic retrograde cholangiopancreatography, computed tomography scanning, and nutritional support

Early enteral nutrition is an important mode of acute treatment

The first double blind trial of antibiotic prophylaxis in acute pancreatitis did not show a benefit for development of infected pancreatic necrosis

Patients with acute severe biliary pancreatitis should have early endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy within 72 hours of symptom onset

Patients with gallstone pancreatitis should have cholecystectomy, ideally during the same admission

Diagnosis of infected necrosis is an indication for radiological or surgical intervention

resulting hypoxia and hypotension may lead to both a decreased level of consciousness and acute renal failure. Metabolic complications (hypocalcaemia, hypomagnesaemia, hyperglycaemia) and haematological complications (disseminated intravascular coagulopathy) may occur. Fever on presentation may represent cytokine mediated systemic inflammation, or acute cholangitis if biliary obstruction is present. Fever

Sources and selection criteria

- We searched Medline with the key word "acute pancreatitis"
- We searched personal archives of references and the reference lists of articles
- We also reviewed recent guidelines on the management of acute pancreatitis and several relevant Cochrane reviews

due to bacterial infection of pancreatic necrosis usually does not occur until the second or third week.

Painless acute pancreatitis is a recognised entity and occurs in cases of shock of unknown origin, during the postoperative period, in renal transplant and peritoneal dialysis patients, and in diabetic ketoacidosis.²

What is the initial management?

The main goal of initial management is adequate fluid resuscitation. Rapid transfusion of crystalloid fluid or colloid is needed to correct the plasma volume deficit. A urinary catheter ensures that output is accurately measured. Central venous monitoring may be needed in acute severe pancreatitis. Supplemental oxygen should be provided to maintain normal arterial oxygen saturation. All patients with severe acute pancreatitis should be managed in a high dependency unit or intensive therapy unit.

Adequate treatment of pain usually requires opiate analgesia. Despite the widespread belief that morphine exacerbates pancreatitis by stimulating the sphincter of Oddi, no definitive human study supports this view. A nasogastric tube is not useful routinely but may be helpful if protracted vomiting occurs in the presence of a radiologically demonstrated ileus.

How is it diagnosed?

Typical clinical features together with a high plasma concentration of pancreatic enzymes are the basis of diagnosis for most cases. Although serum amylase analysis is widely available, concentrations decline quickly over two to three days. Diagnosis should therefore rely not on arbitrary limits of values three or four times greater than normal but on values interpreted in light of the onset of abdominal pain.² Furthermore, because hyperamylasaemia is found in several non-pancreatic diseases (visceral perforation, small bowel obstruction and ischaemia, leaking aortic aneurysm, ectopic pregnancy), its specificity for acute pancreatitis is around 88%.³ Various tumours also secrete amylase.⁴ Lipase has a superior sensitivity and specificity for acute pancreatitis and, where available, is preferable to serum amylase for the diagnosis of acute pancreatitis.⁵

How can disease severity be predicted?

Early identification of the severity of an episode is important because it facilitates the appropriate allocation of critical care beds, ERCP, computed tomography scanning, and nutritional support. At initial assessment, clinical assessment, body mass index over 30, pleural effusion, and an APACHE II score greater than 8 all predict a severe attack. Other scoring systems, such as the Ranson and Glasgow scores, cannot be completed until 48 hours after the onset of symptoms. A cut-off value for C reactive protein of 150 mg/l at 48 hours predicts a severe attack.⁶ Activation peptides of pancreatic enzymes show promise in providing prognostic information,⁷ but clinically useful assays are not yet widely available.

What causes acute pancreatitis?

Gallstones continue to be the most common cause of acute pancreatitis in most series. Occult gallstones (microlithiasis or biliary sludge) cause acute pancreatitis too, so every effort should be made to diagnose these to reduce the incidence of recurrent pancreatitis. Alcohol is the second most common cause, but an episode requiring admission to hospital may represent an exacerbation of chronic pancreatitis rather than true recurrent acute pancreatitis. Other causes include hypertriglyceridaemia, hyperparathyroidism, pancreatic malignancy, ERCP, trauma, infectious agents (increasingly associated with HIV infection), drugs (box 1), autoimmunity, and heredity. Suspected but controversial causes include pancreas divisum (which arises from a failure of the dorsal and ventral ducts to fuse in embryo so that most of the pancreatic juice flows through the minor pancreatic duct and papilla) and sphincter of Oddi dysfunction.

How should idiopathic acute pancreatitis be investigated?

A thorough history and physical examination, liver function tests, and biliary ultrasonography will indicate the correct cause in most cases. Where this is not the case, follow-up investigations, during the recovery phase, should include fasting plasma lipids and calcium, viral antibody titres, and repeat biliary ultrasonography. Further investigations are appropriate for recurrent idiopathic acute pancreatitis. Exclusion of pancreatic cancer, microlithiasis, chronic pancreatitis, and pancreas divisum are facilitated by computed tomography, endoscopic ultrasonography, and magnetic resonance cholangiopancreatography, depending on local availability and expertise. ERCP may be needed to detect microlithiasis by bile

Box 1: Drugs that cause acute pancreatitis, for which at least one positive rechallange has been documented⁸

- α -methyl dopa
- 5-aminosalicylate
- Azathioprine
- Cimetidine
- Cytosine arabinoside
- Dexamethasone
- Ethinylestradiol
- Frusemide (furosemide)
- Isoniazid
- Mercaptopurine
- Metronidazole
- Norethindrone
- Pentamidine
- Procainamide
- Stilboglucuronate
- Sulfamethazole
- Sulfamethoxazole
- Sulindac
- Tetracycline
- Trimethoprim
- Valproic acid

sampling, and sphincter of Oddi manometry for the detection of sphincter of Oddi dysfunction.⁵ Sphincter of Oddi manometry is restricted to a few specialised centres because of the fivefold increase in post-ERCP pancreatitis in these patients compared with those who have endoscopic sphincterotomy for other indications.⁹

The only gene for which genetic testing is currently recommended is the cationic trypsinogen gene (PRSS1).¹⁰ Box 2 gives a summary of patients for whom genetic testing is recommended.

When is a computed tomography scan indicated?

Plain radiographs contribute little to the diagnosis of acute pancreatitis but may give clues to the cause (calci-fied gallstones and pancreatic calcification on abdominal radiograph), detect prognostic signs (pleural effusion on chest radiograph), or show complications (localised ileus on abdominal radiograph or adult respiratory distress syndrome on chest radiograph). The value of ultrasonography lies in its ability to show gallstones and dilated bile ducts, and it is recommended as the initial investigation in all patients with acute pancreatitis.

Computed tomography scanning is occasionally needed for diagnosis, when clinical and biochemical findings are equivocal and the possibility exists of an alternative abdominal emergency that would require a laparotomy. The main indication for computed tomography scanning is to detect and stage complications of acute severe pancreatitis, especially pancreatic necrosis. The full extent of pancreatic necrosis cannot be appreciated until at least three days after the onset of symptoms. Patients with persisting organ failure, signs of sepsis, or clinical deterioration occurring after an initial improvement should have computed tomography. This should be done according to a pancreas protocol, and all patients should receive oral and intravenous contrast. Follow-up scans are needed if the clinical status fails to improve or deteriorates.⁵

When and how should nutritional support be implemented?

For many years conventional teaching said that oral or enteral feeding might be harmful in acute pancreatitis; feeding was thought to stimulate exocrine pancreatic secretion and accelerate the autodigestive process. Today, early enteral nutrition is considered an

Box 3: Recommended nutrient requirements in acute severe pancreatitis¹¹

- Energy: 25-35 kcal/kg/day
- Protein: 1.2-1.5 g/kg/day
- Carbohydrates: 3-6 g/kg/day*
- Lipids: 2 g/kg/day**

*Account should be taken of the increasing understanding of the benefit of strict glycaemic control. Intensive insulin treatment to maintain blood glucose at or below 6.1 mmol/l reduces morbidity and mortality in critically ill patients¹⁴

**Administration of fat is safe, provided hypertriglyceridaemia (> 12 mmol/l) is avoided

important mode of acute treatment,¹¹ and it is supported by several trials. Most studies show that, compared with parenteral feeding, enteral feeding is cheaper, safer, and associated with fewer septic complications and improved clinical outcome.¹² Nutritional support is essential in patients with severe disease. The enteral route should be attempted in all patients, but when this is not tolerated additional or total parenteral nutrition may be needed. Box 3 outlines recommended nutrient requirements. Although the use of glutamine supplementation, "immunonutrition," and probiotics are conceptually sound, they are not supported by large scale studies.¹³

The nasojejunal route for enteral feeding is usually recommended, but this has been challenged by a recent randomised study of early nasogastric versus nasojejunal feeding in acute severe pancreatitis. This study of 50 consecutive patients found no significant differences between the groups for the endpoints of APACHE II score, C reactive protein, or pain pattern.¹⁵ As nasogastric feeding is simpler, cheaper, and easier to use than nasojejunal feeding, this study provides the basis for a very practical advance in the management of patients with acute pancreatitis.

Do antibiotics have a role?

The rationale for antibiotic prophylaxis in acute pancreatitis is based on the fact that mortality for infected pancreatic necrosis is higher than that for sterile necrosis. However, risks exist of encouraging antibacterial resistance and opportunistic fungal infections leading to even higher mortality rates.¹⁶ Randomised controlled trials have shown positive effects for the prevention of infected pancreatic necrosis and even a reduction in mortality, but these effects were not confirmed in all studies.¹⁷ A recent trial by Isenmann, however, was the first double blind trial of antibiotic prophylaxis in acute pancreatitis and is thus superior in methodological quality to previous trials.¹⁸ One hundred and fourteen patients with predicted acute severe pancreatitis received intravenous ciprofloxacin plus metronidazole or placebo, but no benefit was found for antibiotic prophylaxis with respect to developing infected pancreatic necrosis. The authors thus advocate a policy of antibiotic treatment "on demand" if any of the following occur: newly developed sepsis or sepsis inflammatory response syndrome, failure of two or more organ systems,

Box 2: Recommendations for genetic testing

PRSS1 genetic testing is recommended in symptomatic patients with any of the following features¹⁰ (www.guideline.gov):

- Recurrent attacks of acute pancreatitis for which no cause has been found
- Idiopathic chronic pancreatitis
- A family history of pancreatitis in a first or second degree relative
- Unexplained pancreatitis occurring in a child

Ongoing research questions

- Further evidence is needed to confirm that enteral feeding improves disease severity and clinical outcome, particularly in the context of strict glycaemic control; the consequences of gastric versus jejunal feeding should be further tested
- Further studies are needed before consensus is reached on the role of antibiotic prophylaxis against infection of pancreatic necrosis
- Studies comparing different strategies in the management of infected pancreatic necrosis are needed
- Clarification is needed of the role of genetic polymorphisms in conferring susceptibility to acute pancreatitis and of polymorphisms that modify the immunological response
- Further research into novel anti-inflammatory mediator therapies is warranted
- Ongoing research is taking place into reducing the risk, frequency, and severity of hereditary pancreatitis (www.liv.ac.uk/surgery/europac.html)

proved infection, or an increase in serum C reactive protein in combination with other evidence supporting the possibility of infection. Although no consensus has yet been reached, this study does take us closer to the goal of a more specific use of antibiotics in acute pancreatitis.

If antibiotic prophylaxis is used, patients with pancreatic necrosis proved by computed tomography should receive agents active against enteric organisms (cefuroxime, imipenem, or ofloxacin with metronidazole) for one to two weeks.⁵

How should gallstones be managed?

Widespread agreement exists that patients with acute pancreatitis and concomitant obstructive jaundice, cholangitis, or a dilated common bile duct should have early ERCP. The role of early ERCP in patients without evidence of biliary obstruction is more controversial. However, a Cochrane review of three randomised controlled trials showed a significant reduction in the complications of pancreatitis for patients with acute severe gallstone pancreatitis who had ERCP compared with those who had conservative management.¹⁹ ERCP and endoscopic sphincterotomy, within 72 hours of symptom onset, is now generally recommended for patients in this category.^{2 5 13}

Patients with mild gallstone pancreatitis should have cholecystectomy with intraoperative cholangiography, ideally during the same admission. Bile duct exploration or postoperative ERCP are both valid options for the further management of bile duct stones detected by intraoperative cholangiography. Failure to definitively clear gallstones results in unacceptable rates of readmission to hospital with recurrent pancreatitis.²⁰ For patients with severe gallstone pancreatitis, cholecystectomy may be delayed until systemic complications have resolved. For those unfit to undergo cholecystectomy, endoscopic sphincterotomy alone is considered sufficient treatment.⁵

Operative specimen after open pancreatic necrosectomy

How should pancreatic necrosis be managed?

Differentiation between sterile and infected necrosis is essential for patients with greater than 30% necrosis on computed tomography and persistent symptoms or those with any degree of necrosis and signs of sepsis. This is achieved by fine needle aspiration for bacteriology of pancreatic or peripancreatic necrosis or the presence of retroperitoneal gas on computed tomography.^{2 5} Patients with sterile necrosis should usually continue to be managed conservatively. The diagnosis of infected necrosis is an indication for radiological or surgical intervention.

Although good outcomes have been reported in patients with infected pancreatic necrosis managed by radiologically placed percutaneous drains, standard treatment remains surgical necrosectomy (figure).⁵ Techniques for necrosectomy include necrosectomy combined with open packing, planned staged relaparotomies with repeated lavage, closed continuous lavage of the lesser sac and retroperitoneum, and closed packing.²¹ Mortality rates are similar with all techniques, and the absence of randomised trials means that the choice can be based on local expertise.

Additional educational resources

- British Society of Gastroenterology. UK guidelines for the management of acute pancreatitis—www.bsg.org.uk/guidelines/index
- International Society of Pancreatology. IAP guidelines for the surgical management of acute pancreatitis—www.pancreasweb.com/Services/images/iap.pdf
- Pancreas Web—www.pancreasweb.com (resources include email alerts, consensus papers, and congress calendar)
- Journal of the Pancreas—www.joplink.net (the first electronic journal of pancreatology)

Information for patients

- University of Liverpool. Acute pancreatitis—www.liv.ac.uk/surgery/acute1.html (detailed information for patients, written by J P Neoptolemos)
- Pcreas.org—www.pancreas.org/patients/patients_ap.html (written by D C Whitcomb, this site provides information on acute and hereditary pancreatitis)

Novel minimal access approaches to necrosectomy have been described, and particularly encouraging results have been achieved by a retroperitoneoscopic approach combined with postoperative continuous irrigation.²² Whatever the approach, a successful technique is one that adheres to the principles of organ preservation, minimisation of intraoperative haemorrhage, and maximisation of postoperative removal of debris and exudates.²³

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A memorable patient

A salutary lesson

I had finished examining the little boy, and I thought the consultation was over when the patient's mother began to talk about the doctor whom she had consulted earlier about her abdominal pain. She complained that the doctor had not taken the time to examine her.

I didn't know what to say. According to the General Medical Council, when a patient complains about the care given by another healthcare professional, I have two (delicately balanced) duties: I must not undermine the patient's trust in those treating him or her by making unfounded criticisms of colleagues, but, at the same time, if I have serious concerns about a colleague's performance I must take steps to investigate and ensure that patients are protected.

A quick glance at the woman's records to ensure that nothing was missed and possibly a word with my colleague over coffee should be all that was needed, and normally that would have been my course of action. This case, however, was different: the woman had forgotten, or not realised, that I was the doctor she had seen earlier in the day about her abdominal pain.

In a large general practice it is easy to be lulled into a false sense of security. Even in today's increasingly litigious society, thanks from patients are far more common than complaints. Patients who like my consulting style come back to me, while those who don't will choose to see one of my colleagues. I am protected from the quiet grumble of complaint because it is heard by a colleague not by me. So this mother's complaint was a useful jolt to my complacency.

She was right; I had not examined her. She had been examined many times in the past and had undergone a full range of investigations. Nevertheless, she was right, I had not examined her at that earlier consultation. Examination may be as much a part of the ritual and mystique of the medical consultation as it is part of the diagnostic process. It shows patients that we are taking their complaint seriously and offers reassurance that nothing new is being missed.

So, did I examine her after she had complained? No, I reassured her that the doctor she saw that morning knew her case well and was correct in her judgment, using the traditional safety net of an offer of a further appointment if things changed. Nevertheless, I learnt a quiet lesson from the complaint that had not been intended for my ears.

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We welcome articles up to 600 words on topics such as *A memorable patient*, *A paper that changed my practice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. Please submit the article on <http://submit.bmj.com>. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.