Acute pancreatitis

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Abstract

Acute pancreatitis is a common diagnosis and its incidence may be rising. The commonest aetiological agents remain gallstones and alcohol misuse. Eighty percent of patients will have a mild attack which resolves within a few days without specific treatment. Severe disease is characterized by a significant systemic inflammatory response which may be associated with varying degrees of organ dysfunction. The mortality in patients with multi-organ failure may be as high as 50%.

This article reviews the definition, aetiology, pathophysiology, outcome and complications of acute pancreatitis. Therapeutic strategies are discussed in light of recent advances.

Keywords Acute pancreatitis; multi-organ failure; necrosectomy; pancreatic necrosis; severity scoring

General considerations

Epidemiology

The incidence of acute pancreatitis (AP) varies between populations ranging from 150 to 420 cases per million population in the UK to 330–430 cases per million in the USA.[1] Overall incidence is rising with a 100% increase in the hospitalization rate in the USA over the last 20 years, a 75% increase in admissions in the Netherlands and a 3.1% yearly rise in incidence in the UK.[2] The mean age at presentation is 53 years with a roughly equal gender distribution, although the largest increase in incidence has been among women under 35 years, and socioeconomic deprivation confers a twofold increase in incidence. The overall mean hospital stay is around 7 days suggesting that most cases are mild and settle spontaneously. One in five cases, however, will develop organ failure with or without local complications – a setting which defines severe acute pancreatitis. In the first week after admission organ failure persisting for more than 2 days of supportive care has profound prognostic implications.[3] Half of the deaths attributable to AP occur within the first 7 days of admission, with the majority in the first 3 days. Patients with severe AP who survive this first phase of illness are at risk of developing secondary infection of pancreatic necrosis. Mortality in patients with infected necrosis and organ failure may reach 30–40% and an increased mortality is seen with increasing age.

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Aetiology

Some 40% of cases of AP are linked to **gallstones**. Gallstones are common in the general population and European studies estimate prevalence rates in excess of 20% in females and 11–15% in males over the age of 60 years. The population studies of Olmsted County, USA, suggest that 3–7% of patients with gallstones will develop AP. The mechanism by which gallstones induce acute pancreatitis is not certain, but increased pressure in the pancreatic duct due to a transient mechanical obstruction of the ampulla is thought be the likely initiating event. This is believed to lead to the activation of pancreatic enzymes and development of a local inflammatory response. Smaller stones pass through the cystic duct more easily and are at increased risk of precipitating AP. Stones smaller than 5 mm pose a higher risk for AP when compared to larger ones. Endoscopic ultrasound is more sensitive than transabdominal ultrasound at identifying biliary microlithiasis and should be considered in the diagnostic algorithm prior to the label of idiopathic recurrent acute pancreatitis.

Alcohol is the other major cause of AP, depending on the level of consumption and misuse prevailing in the population being considered. It appears that the incidence in Northern Europe is rising. The exact mechanism whereby alcohol causes AP is still unclear. As in gallstone AP, despite a high prevalence of alcohol misuse, only 10% of chronic alcohol abusers eventually present with acute pancreatitis. The risk is highest in young males who drink in excess of 80 g of alcohol per day. Both acute alcohol intake and chronic alcohol exposure result in a highly-charged monocyte response to inflammatory signals and may contribute to increased inflammation in pancreatitis. Many patients with a significant alcohol history may also have gallstones and this should be excluded. **Smoking** has been considered a significant cofactor in the development of alcohol pancreatitis but large population-based studies have established it as an independent risk factor for acute and chronic pancreatitis, with dose-dependent and time-dependent increases in hazard ratios observed.[4]

Endoscopic retrograde pancreatography (ERCP) is the commonest cause of iatrogenic AP. Post-ERCP hyperamylasaemia is not uncommon and should not be equated with pancreatitis. Post-ERCP pancreatitis refers to a condition where the patient develops abdominal pain associated with hyperamylasaemia and requiring hospitalization after ERCP. Six out of 15 fatal ERCP lawsuits in the USA were due to pancreatitis and it is therefore advised that patients should be counselled appropriately pre-procedurally. Conversely, the clinician should always be aware that pain and hyperamylasaemia following ERCP may be caused by duodenal perforation, especially when a sphincterotomy has been performed. In this setting we have a low threshold for investigating patients with urgent computed tomography (CT) scanning. The incidence of post-ERCP AP ranges from 0 to 10%. Risk factors are a normal pancreas, therapeutic procedures (including balloon sphincteroplasty), low operator case-load, female gender, young age, sphincter of Oddi dysfunction (30% of such patients may develop AP), pancreatic duct injection (especially high pressure) and previous post-ERCP AP. Several drugs have been tested for their prophylactic potential. In a randomized trial conducted in our unit, rectal diclofenac was

found to be protective. A meta-analysis of four such trials published in 2008 confirms this observation but the authors recommend further multi-centre studies.[5] In an era when CT scanning and magnetic resonance imaging (MRI) are readily available there is no place for early diagnostic ERCP in the non-septic jaundiced patient. More often than not the risks outweigh the benefits in this setting.

Other iatrogenic causes of AP include **pharmaceutical agents** (amongst them: furosemide, corticosteroids, thiazides, sulindac, azathioprine, various antibiotics and pentamidine) as well as biliary, pancreatic and gastric surgery. However attributing AP to a specific drug should be avoided unless viral titres and adequate biliary investigations (endoscopic ultrasonography, EUS) have been undertaken. Repeat exposure resulting in a further episode of AP is the strongest evidence of a direct causal association.

Viral infection can cause AP, particularly mumps, Coxsackie B and viral hepatitis and increasingly HIV infection.[6]

Hypertriglyceridaemia in excess of 11 mmol/litre are known to precipitate acute pancreatitis and have been reported as the cause of acute pancreatitis in up to 4% of patients. However no correlation between triglyceride levels and severity has been observed. Hypercholesterolaemia is not associated with pancreatitis.

Hypercalcaemia (of any cause) may cause pancreatitis, possibly by calcium crystal deposition in the pancreatic ducts or by calcium mediated activation of pancreatic enzymes. It should be noted, however, that in a large population of patients with hyperparathyroidism only 1.5% developed acute pancreatitis.

The UK guidelines for the management of acute pancreatitis issued by the British Society of Gastroenterology (BSG) in 2005 are now largely out of date. The guidelines stipulate that not more than 20–25% of cases of acute pancreatitis should be termed **idiopathic**. Idiopathic AP requires a thorough investigative strategy. The exclusion of a **neoplastic** cause (pancreatic or ampullary cancer) can be carried out with CT scanning or EUS. Recurrent idiopathic attacks, especially if also experienced by relatives should alert the clinician to seek genetic advice. The development of AP is a complex interplay of environmental and, as yet incompletely characterized genetic factors. A **genetic predisposition** has long been suspected and over recent years the influence of mutations in the *PRSS1* (cationic trypsinogen gene) gene, *CFTR* (cystic fibrosis) gene and *SPINK1*, have been recognized.[7] The EUROPAC study has observed multiple families and patients usually have a long history of recurrent abdominal pain from childhood or adolescence and changes of chronic pancreatitis are often present by the age of 20–40 years.[7] They have a significantly increased lifetime risk of pancreatic cancer. It should be noted that hyperamylasaemia with no evidence of pancreatitis is not uncommon and patients with other pathology may be misdiagnosed as suffering from AP.

Autoimmune pancreatitis (AIP) is a rare presentation and is considered as a manifestation of the immunoglobulin G4 (IgG4)-related disease spectrum which is associated with other autoimmune diseases (polyarteritis nodosa, systemic lupus erythematosus, other vasculitides) and inflammatory bowel disease. It usually presents with chronic symptoms of pain, weight loss and jaundice but acute presentations are recognized. The HISORt criteria (Table 2) are integral to the diagnosis and management of AIP. The distinguishing features are a sausage-shaped pancreas with ductal strictures and inflammatory infiltrates (and high serum titres) of IgG4.[8] A key feature in diagnosis is the response to steroid therapy. However focal autoimmune pancreatitis may be difficult to differentiate from carcinoma.

Trauma-related hyperamylasaemia usually results from a crush injury to the body of the pancreas against the vertebral column. A high index of suspicion for associated injury to neighbouring organs should be employed. The majority of cases can be managed by simple drainage, but transection of the pancreatic duct may necessitate endoscopic (transpapillary stenting) or operative (distal pancreatectomy) interventions.

Pancreas divisum is an embryological aberration whose association with pancreatitis remains controversial.

Pathophysiology

The mechanisms giving rise to AP and its complications are complex and still incompletely understood. Whatever the aetiology, AP commences as a sterile inflammatory process.

Approaches to pancreatic necrosectomy

Technique	Authors	Outcome
Open necrosectomy/lavage	Buechler et al	Mortality 6.2–15.8%
Laparotomy and closed lavage	Fernandez del-Castillo et al	(in high-volume centres)
Laparotomy and closed packing +	Bradley et al	
Penrose-type drains	Chang et al	
Laparostomy and re-exploration		
Lumbotomy		
Laparoscopic necrosectomy	Adamson and Cushieri	Mortality 15%
Percutaneous retro-peritoneoscopic	Carter et al	Mortality 14.3%–25%
	Connor et al	
Endoscopic	Seifert et al (GEPARD study)	Mortality 7.5%
	Gardner et al	

Table 1

HISORt criteria for diagnosis of autoimmune pancreatitis

Diagnostic criteria

Histology: At least one of the following:
- Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis
- Lymphoplasmacytic infiltrate with storiform fibrosis with abundant immunoglobulin G4 (IgG4) cells (>10 IgG4 cells/high-power field)

Imaging:
- Typical: diffusely enlarged gland with delayed 'rim' enhancement, diffusely irregular, attenuated main pancreatic duct
- Other: focal pancreatic mass/enlargement, focal pancreatic ductal stricture, pancreatic atrophy, calcification, pancreatitis

Serology:
- Elevated serum IgG4 level (normal 8—140 mg/dl)

Other organ involvement:
- Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis

Response to steroid therapy:
- Resolution or marked improvement of pancreatic/extrapancreatic manifestation with corticosteroid therapy

Table 2

Premature activation of zymogens appears to be crucial in the initiation of pancreatic injury. The trigger is still elusive but circumstantial evidence implicates cathepsin B which is a lysosomal serine protease. Zymogen activation results in the release of active enzymes such as trypsin (from trypsinogen) which in turn activates other proteases leading to acinar cell injury by unchecked autodigestion. Alcohol may generate aldehydes and esters which are directly toxic to the pancreatic acinar cells. Moreover it may sensitize acinar cells to the effect of cholecystokinin, potentiating the latter's effect on zymogen synthesis and activation. Both acute alcohol intake and chronic alcohol exposure result in a highly-charged monocyte response to inflammatory signals and may contribute to increased inflammation in pancreatitis.

The **first phase** of AP is a stage characterized by calcium mediated enzymatic activation and cellular injury giving rise to abdominal pain and other early symptoms.

The systemic inflammatory response (SIRS) emerges as the **second phase** in AP. This variable systemic process depends on the circulatory interplay of pro-inflammatory cytokines (such as interleukin-1 (Il-1), Il-2, Il-6, tumour necrosis factor (TNF)-α and nitric oxide) and anti-inflammatory mediators. SIRS as well as organ dysfunction may therefore, develop early on in the absence of established necrosis and infection. Necrosis is itself a potent monocyte activator which results in TNF-α production. The extent of pancreatic necrosis correlates with the development of organ failure and subsequently with superinfection. It should be noted, however, that the relationship between necrosis and systemic dysfunction is not necessarily linear.

The **third phase** in AP refers to the development of complications which supervene during the dynamic process of resolution. Translocation of gut bacteria may result in secondary infection of pancreatic and peri-pancreatic necrosis. Peri-pancreatic collections may organize to form walled-off lesions which may or may not become infected.

Diagnosis

AP classically presents with constant upper abdominal pain radiating to the back. The patient often maintains that leaning or sitting forwards alleviates the pain. The pain is frequently associated with nausea and vomiting. The patient may have a previous history of gallstone disease, alcohol indiscretion or similar attacks. Patients often appear pale and sweaty, tachycardic and may be hypotensive. The majority are normothermic although hypothermia is not uncommon. Fever is rarely a feature of AP in the first day after onset and if present, it should alert the clinician to the possibility of cholangitis. The abdomen may be distended and is usually tender with varying degrees of guarding. The eponymous descriptions of Grey-Turner (flank bruising) and Cullen (periumbilical bruising) are in keeping with retroperitoneal haemorrhage; they are rare and non-specific signs and tend to occur after the second day from onset. The differential diagnosis includes common surgical conditions such as biliary colic and cholecystitis, peptic ulcer disease (and perforation), bowel obstruction, bowel ischaemia and/or infarction and ruptured aortic aneurysm, as well as other non-surgical diagnoses including myocardial infarction, lower lobe pneumonia and diabetic emergencies.

In the emergency room confirmation of the clinical diagnosis is made by obtaining serum levels of amylase and/or lipase and exclusion of other pathology. The cornerstone of diagnosis is a serum pancreatic enzyme level equal to or exceeding three times the upper limit of normal. Within 24 hours of the onset of symptoms this has accuracy in excess of 90%, with lipase elevations tending to persist longer than amylase. Very high amylase levels (in excess of 4000 IU) as well as female gender and a deranged liver function test profile have a significantly positive predictive value (PPV) (90% or more) for gallstone aetiology. Hyperamylasaemia may not occur in patients with a background of hypertriglyceridaemia or chronic pancreatitis. Conversely, it is important to note that pancreatic enzymes may be elevated in other conditions mentioned above. An erect chest film is useful to exclude a pneumoperitoneum (though free gas may be absent in up to one-third of visceral perforations) or acute lung disease. Abdominal films may demonstrate features in keeping with bowel obstruction, bowel ischaemia or rarely aneurysmal disease. Diagnostic uncertainty at this stage is unusual but in this setting, and especially in the unwell patient, we consider CT scanning as the safest option. The presence of jaundice and pyrexia in association with hyperamylasaemia may indicate cholangitis and the need for urgent ERCP and biliary decompression.

Ultrasonography scan (USS) examination in patients with AP is by convention (or through guidelines) performed early during admission in order to identify gallstones (accuracy in excess of 90%). USS may be hampered by intestinal ileus and a negative result needs to be confirmed (or refuted) once the ileus has resolved.

Key points

- Acute pancreatitis (AP) is common with severe AP making up 20%
- Overall mortality is down, but in complicated severe AP is still around 40%
- Diagnosis is usually straightforward, but if in doubt CT is useful
- Aetiology should not be assumed but actively confirmed by investigation, especially in alcohol abusers

Management phase I — early assessment and treatment

Severity scoring

Few diseases have had so much written about prediction of severity. The severity scoring systems in use at present will be briefly summarized here.

The Ranson, Glasgow (or Imrie) and APACHE II scores are widely employed clinical scores and have a predictive accuracy in the region of 70%. The former two are similar in that a score of 3 or more in the first 48 hours is associated with severe disease. The latter is used in the intensive care setting and a score higher than 8 is associated with a worse outcome. Even simpler are single measurements of serum C-reactive protein (CRP) and urinary trypsinogen activation peptide (TAP) or procalcitonin (>3.8 ng/ml). The former is in common use and a level of less than 150 mg/dl has a negative predictive value for necrosis of the order of 90%.

Organ failure assessment rather than the identification of severe disease can be performed using the Marshall scoring system. This is a simpler organ failure scoring system with respiratory (p_aO_2/F_iO_2), renal (serum creatinine) and cardiovascular (systolic pressure) domains. However the dynamic assessment of organ failure carries greater prognostic significance with a mortality of 38.2% in those with persistent organ failure versus 1—2.7% in those with transient or no organ failure.[3]

In contrast with the above-mentioned clinical scores, a radiologically based score is described by Balthazar.[9] It (and its modifications) is based on the degree of pancreatic necrosis and other local complications and correlates well with morbidity and mortality.

Severity scores are mainly useful in audit and research. In clinical practice the key concept is to recognize organ dysfunction early in order to maximize organ support at the earliest opportunity; in brief: treat the *patient* not the *score*. Sequential physiological scoring systems (e.g. SEWS) can assist the identification of clinical deterioration and efforts to identify the cause of a clinical deterioration in a patient with acute pancreatitis should involve thorough clinical, biochemical, microbiological and radiological assessment.

Classification of severity

The Atlanta definitions of acute pancreatitis were traditionally considered the standard definitions in disease severity but were criticized as the definitions were based on descriptions of clinical occurrences that were associated with severity but could not accurately discriminate between patient subgroups with differing outcomes. The PANCREA consultation recently described a classification of severity that is based on local and systemic determinants of severity.[10] The definitions of pancreatic necrosis and organ failure are described in Table 3.

Definitions of local and systemic features of acute pancreatitis

Local

Pancreatic necrosis is non-viable tissue in the pancreas or peri-pancreatic tissues

Sterile pancreatic necrosis is the absence of proven infection in necrosis

Infected pancreatic necrosis is defined when at least one of the following is present — gas bubbles within peri-pancreatic necrosis on CT, positive culture of pancreatic necrosis obtained on first drainage and/or necrosectomy or positive culture obtained by image-guided fine-needle aspiration

Systemic

Organ failure is defined for three organs (cardiovascular, renal and respiratory) on the basis of the worst measurement over a 24-hour period.

- Cardiovascular: need for inotropic agent
- Renal: creatinine > 171 μmol/litre (>2.0 mg/dl)
- Respiratory: PaO_2/FiO_2 <300 mmHg (40 kPa)

Persistent organ failure is the evidence of organ failure in the same organ system organ system for 48 hours or more

Transient organ failure is the evidence of organ failure in the same organ system for less than 48 hours

Table 3

Mild acute pancreatitis is characterized by the absence of both (peri) pancreatic necrosis *and* organ failure. Mild AP is associated with a low mortality and rarely requires prolonged hospitalization. In those with gallstones, cholecystectomy should be performed during the index admission or within 2—4 weeks to prevent a recurrent attack. In those with significant comorbidity ERCP with sphincterotomy is definitive management.

Moderate acute pancreatitis is characterized by the presence of sterile (peri) pancreatic necrosis *and/or* transient organ failure. Mortality in this group is also low with management determined by the local complication not acute inflammation.

Severe acute pancreatitis is characterized by the presence of either infected (peri) pancreatic necrosis *or* persistent organ failure.

Critical acute pancreatitis is characterized by the presence of infected (peri) pancreatic necrosis *and* persistent organ failure.

Severe and critical acute pancreatitis is managed by adhering to the general principles of optimizing oxygen delivery, maintaining tissue perfusion through restoration of circulating volume and appropriate organ support in a critical care setting. Early restoration of circulating blood volume is associated with improved outcome.[11] This is combined with concurrent management of infected necrosis (discussed below).

Early management issues

Resuscitation

The approach to the patient with AP should be thorough and systematic. Whereas, the patient with mild AP usually requires

little in the way of monitoring and supportive care, the unwell patient requires serial and regular measurement of respiratory rate, arterial oxygen saturation, pulse rate, blood pressure and urine output. The administration of high flow oxygen and good intravenous access are essential. The critically unwell patient requires central venous access, invasive blood pressure monitoring and catheterization. Early analgesia is safe and crucial in relieving patient distress and allowing proper assessment and nursing. Opiates were considered to lead to sphincter of Oddi spasm and there were concerns that this could be deleterious in AP. These concerns are not supported by available evidence.

Aggressive resuscitation is indicated. Hypoxaemia is often a reflection of disease severity and whilst supplemental oxygen for most cases will be sufficient, positive pressure ventilation may be required. AP renders patients hypovolaemic secondary to vomiting and poor oral intake, ileus and fluid sequestration in third spaces. Cardiovascular parameters (heart rate, blood pressure, urine output, central venous pressure) and biochemical measurements (serum urea and creatinine, blood pH, base excess, lactate level and mixed venous oxygen saturation) all contribute towards determining fluid status and requirements, which in the patient with AP may run into more than 6 litres over a 24-hour period. Admission to the high-dependency unit is warranted in patients with anything other than mild transient organ dysfunction despite the administration of oxygen and adequate fluid resuscitation and early discussion with the intensive care team is recommended.

Nutrition

Maintenance of nutritional competence is of the utmost importance in AP. SAP contributes to a catabolic state and bowel rest through prolonged fasting has no place in the modern management of pancreatitic patients. In our unit we encourage a normal dietary intake, as tolerated, in patients with mild AP. Nasogastric suction does not alter the disease course and we only use it in patients with gastroparesis. In patients with severe disease we recommend early and close nutritional assessment and advice. Our algorithm is simple:

- normal diet as tolerated
- feeding by a fine-bore naso-gastric (NG) tube is started as soon as it is clear that a normal diet is not being tolerated and in cases where a negative nitrogen balance persists despite adequate oral intake
- feeding by a fine-bore naso-jejunal (NJ) tube is used in preference when, through gastroparesis, NG feeding leads to high-volume aspirates implying impaired absorption
- total parenteral nutrition (TPN) via a dedicated tunnelled line for the rare occasions when enteral nutrition (EN) is contraindicated (fistulation, short bowel, bowel obstruction or persistent ileus and inability to intubate the jejunum endoscopically).

In a pilot study from our unit, 85% of patients with severe AP tolerated NG feeding with no adverse outcome. A small trial from the same unit subsequently proved that NG feeding was not inferior to NJ feeding. These results were confirmed by a recent systematic review. The Dutch EARL study performed and observational study of current management of nutritional support in AP, EN was employed in 20% of mild AP patients whilst 80% of severe AP patients required supplemental feeding (50% EN and 25% TPN).

TPN costs some three times more than EN. Enteral feeding has the potential for preserving gut barrier functioning by preventing atrophy and theoretically may reduce pancreatitis-related infective complications. Recent meta-analyses suggest lower morbidity (infective complications and organ failure) and mortality in patients receiving EN when compared with TPN.[12]

Despite previous encouraging results with the addition of probiotics to nutritional regimes, a recent randomized trial suggests no benefit from this practice and the study suggested an increased associated mortality.[13]

Antibiotics

The administration of antibiotics in acute pancreatitis has received much attention. On the one hand broad-spectrum antibiotic prophylaxis may be perceived as desirable in order to prevent secondary infection of pancreatic necrosis. However, this rationale has to be tempered with the problematic realities of antibiotic resistance as well as the emergence of fungal sepsis. Antibiotic prophylaxis has been addressed in a recent meta-analysis by Jafri's group.[14] Using data from eight studies, the authors analysed the outcome of patients with severe AP who were randomized to receive antibiotics or placebo. The authors conclude that while prophylaxis reduced the rates of non-pancreatic infections, it did not reduce the risk of infected necrosis or death and the need for intervention. It should be noted that antibiotic regimes in these studies vary and are not standardized. The methodological quality also varied and analysis of the studies of highest quality demonstrated least effect.[15] Indiscriminate use of antibiotics has been associated with up to 30% of patients developing necrosis superinfection with *Candida* spp., which has been associated with a poor prognosis. The patient with severe AP often exhibits prolonged pyrexia related to the SIRS. Antibiotics have no proven benefit in this setting. We prefer to use short courses of antibiotics for bacteriologically proven 'septic episodes', guided by subsequent microbiological sensitivities.

ERCP

While a gallstone may initiate an episode of pancreatitis, stone impaction is not thought to be responsible for disease progression and after a few days some two-thirds of patients with biliary AP will have no evidence of choledocholithiasis. An important differential diagnosis of AP is cholangitis. Patients with cholangitis classically present with the triad of fever (and/or rigors), jaundice and abdominal pain. In these patients hyperamylasaemia may be observed but organ failure is usually driven by gram negative sepsis secondary to cholestasis, rather than a true pancreatitic SIRS response. This is the only patient group in whom we currently perform urgent ERCP.

In pancreatitis and in the absence of cholangitis, the role of early or urgent ERCP is debated. In the latest reported observational (and non-randomized) study to date the Dutch Acute Pancreatitis Group report a subset analysis of predicted-severe AP patients entered in a probiotic study (PROPATRIA). In the presence of cholestasis, early ERCP (within 72 hours of symptom onset) may be of benefit — significantly less complications and a

tendency to reduced mortality were observed in patients receiving ERCP when compared with patients managed conservatively. It has to be said, however, that the authors noted a trend towards higher APACHE scores and degree of necrosis in the conservative subgroup. These effects were not observed in patients with no evidence of cholestasis and this result is supported by two meta-analyses published in the past 2 years. Petrov's group included six trials in their meta-analysis and concluded that early ERCP conferred no benefit in mild or severe AP.[16] In addition a trend towards excess mortality was observed after ERCP.

Key points

- Severe acute pancreatitis usually requires aggressive fluid resuscitation
- Severity scoring has limitations — treat the *patient* not the *score*
- Nutrition — route and composition do not alter outcome
- Antibiotics 1 — contentious issue especially with emergence of resistance and fungal infections
- Antibiotics 2 — avoid treating persistent systemic inflammatory response rather than microbiological sepsis; in our unit we use short courses as indicated by microbiology
- Urgent ERCP — probably only indicated in the patient with features of cholangitis

Management phase II — definitive treatment and treatment of complications

Cholecystectomy

The International Association of Pancreatology formulated guidelines with respect to the timing of cholecystectomy in AP. In mild disease cholecystectomy should ideally be performed during the index admission, thus obviating the risk of further attacks. This can be performed without a significant impact on conversion to open surgery or other complications. All patients with AP

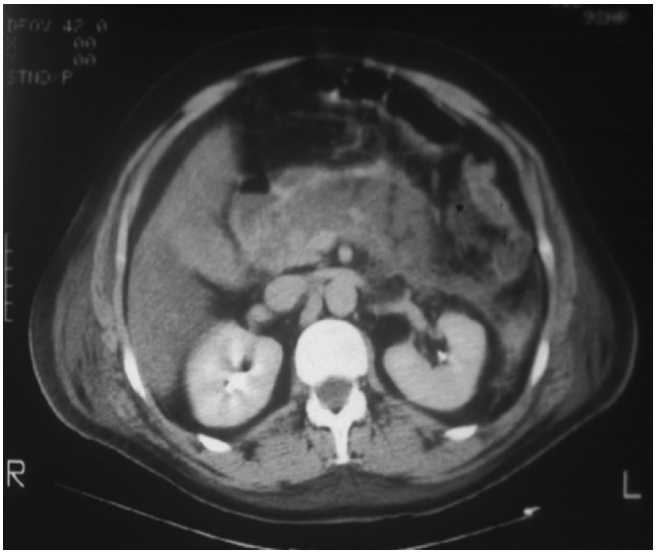

Figure 1 Acute necrotic collection (ANC) and a non-enhancing pancreas 2 weeks after the onset of severe acute alcohol-related pancreatitis.

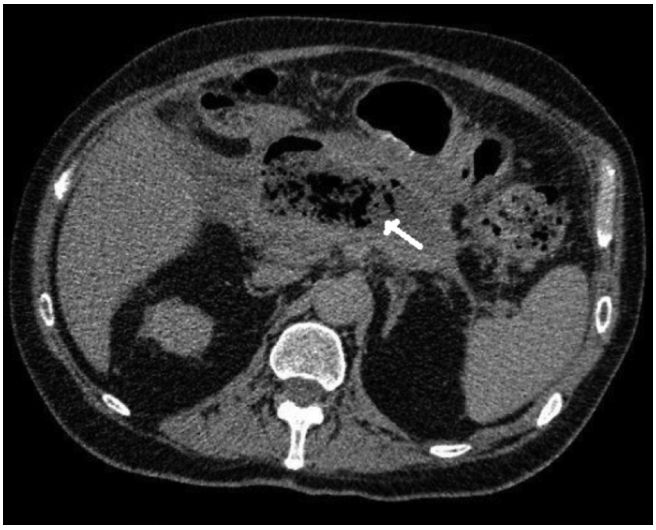

Figure 2 Infected acute necrotic collection in a 55-year-old with alcohol-related acute pancreatitis. White arrow marks gas formation.

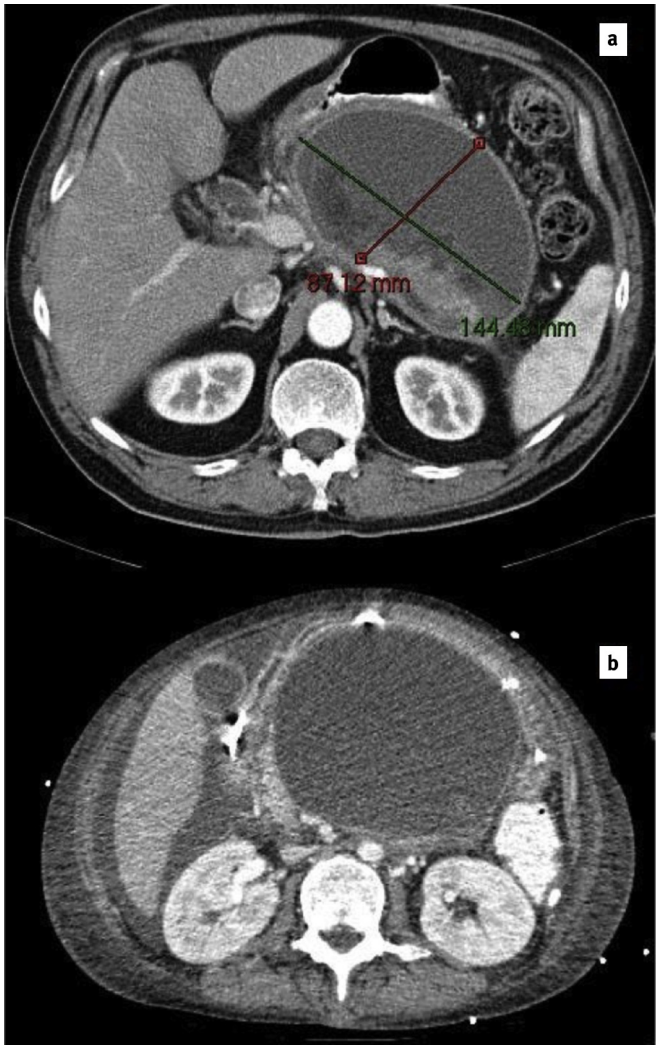

Figure 3 Differentiating between walled-off pancreatic necrosis which is rich in necrotic solid elements (**a**) and the fluid-predominant chronic pseudocyst (**b**).

require bile duct imaging either by a staged approach of preoperative magnetic resonance cholangiopancreatography or by the single step of intraoperative cholangiography. Bile duct stones can be dealt with by ERCP or bile duct exploration depending on the available local expertize and of course, ductal anatomy. In the patient with poor operative risk, ERCP and sphincterotomy by itself is a suitable alternative to cholecystectomy.

In patients with severe AP, cholecystectomy should be deferred until after clinical recovery. In this setting the patient will generally require monitoring and management of local complications (described in the next section) as they arise.

Specific local complications and their management

Acute peri-pancreatic fluid collection (APFC): these are common within the first few days and are formed of 'puddles' in the vicinity of the pancreas (Figure 1). We follow patients with this finding with serial imaging but do not as a rule intervene. These immature collections tend to resolve spontaneously in 50% of patients. By definition APFC are associated with minimal necrosis. Complete resolution probably depends on the absence of parenchymal necrosis and duct disruption. An acute fluid collection that persists beyond 4 weeks is then termed a 'pseudocyst' and is differentiated from organized necrosis (see below) by the absence of solid content.

Acute necrotic collection (ANC): surgical intervention for necrosis in the first 2 weeks carries a high risk of morbidity and mortality and is therefore, to be avoided. Intervention is currently limited to patients with infected necrosis which on imaging often exhibits gas pockets (Figure 2). In patients with sterile necrosis full conservative management is advocated though in patients failing to thrive we do not tend to intervene before a minimum 6–8 and ideally 10–12 weeks. Ideally, pancreatic necrosis should be allowed to mature and demarcate as this offers the least risk for intra-procedural haemorrhage.

Infection of pancreatic collections: both acute fluid collections and acute necrotic collections may be sterile or infected, but it is unusual for a significant acute fluid collection to not contain at least a small amount of necrosis. Superinfection of poorly demarcated pancreatic (and peri-pancreatic) necrosis can be managed by a variety of approaches as shown in Table 1. Our preferred technique is percutaneous necrosectomy – a radiologically placed drain is used as a guide for sinus tract endoscopy after dilatation. We use an operating nephroscope for debridement under direct vision and establish continuous drainage/irrigation thereafter using the same tract. There is evidence that minimal access techniques may pose less of a challenge to the patient's systemic inflammatory response and we have observed this in that our patients have reduced requirements for intensive

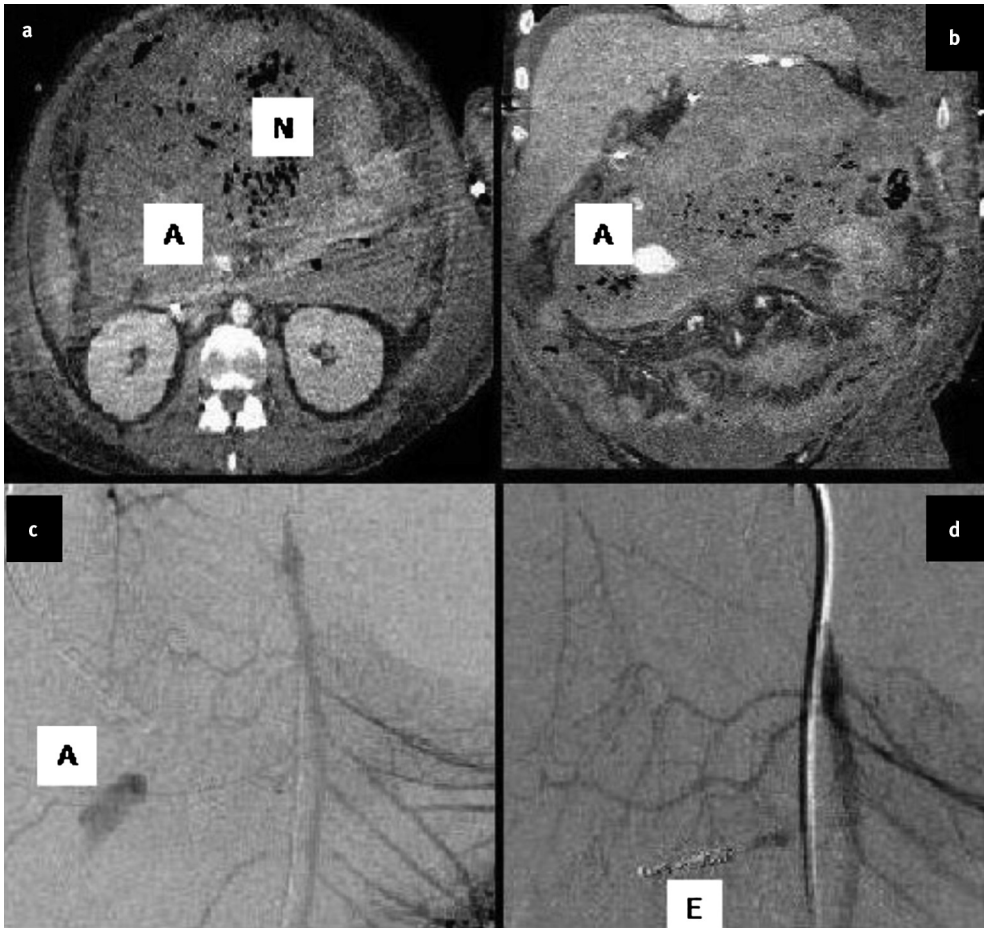

Figure 4 Haemorrhage from a pseudoaneurysm of a branch of the superior mesenteric artery in 44-year-old male with severe acute pancreatitis secondary to alcohol. (**a, b**) Computed tomography angiographic views (N, necrosis; A, pseudoaneurysm). (**c, d**) Pre- and post-angiographic embolization views (A, pseudoaneurysm with 'blush'; E, embolization coils with successful sealing).

care unit support.[17] Connor and colleagues reported half as many deaths in patients treated with a minimal access approach when compared with those having laparotomy (the result tended to but was not statistically significant).

The PANTER study provided good quality randomized data regarding the management of infected pancreatic necrosis. Patients with IPN were randomized to either open necrosectomy or a 'step-up' approach based on endoscopic or percutaneous drainage as the initial intervention, with progression to retroperitoneal debridement with lavage if no improvement was observed. The composite endpoint of death or major complication demonstrated a significant benefit with the step up approach. Indeed 35% were successfully managed with percutaneous drainage alone and did not require progression to debridement.[18]

If a persistent pancreatic fistula occurs or the development of an organized pseudocyst secondary to pancreatic disruption our procedure of choice is endotherapy with pancreatic duct stent placement when the patient is well with no evidence of ongoing sepsis. Failure of endotherapy indicates that operative management (usually distal pancreatectomy) is necessary.

Walled-off pancreatic necrosis (WOPN)

These conditions appear to arise from areas of necrosis and pancreatic juice leakage eliciting an inflammatory response which culminates into a walled-off solid-cystic 'pseudocyst' (a term which should be avoided in this setting). Although all contain some solid component, clinically may be differentiated into two sub-types — solid predominant walled-off pancreatic necrosis (WOPN) and fluid predominant post-acute collection. These lesions differ from the fluid-predominant pseudocyst which complicates duct disruption in chronic pancreatitis (Figure 3). Whereas, the latter type lends itself well to endoscopic drainage, we believe that the former is best treated laparoscopically. A retrospective series suggests that whereas, laparoscopic and conventional open cyst-gastrostomy are largely equivalent in terms of primary success rates, endoscopic cyst-gastrostomy appears to lag behind. Although direct endoscopic necrosectomy has been compared favourably to endoscopic drainage alone with 88% v 45% resolution of WOPN without further operative or endoscopic intervention, these data were neither prospective nor randomized.[19]

Our management of the post-acute pseudocyst is to allow it to mature for at least 8 weeks. In progression, symptomatic patients and those failing to thrive we perform laparoscopic cyst-gastrostomy. This minimal access technique allows excellent debridement and internal drainage and unpublished results from our unit are very encouraging and compare well with currently published reports. Cholecystectomy may be undertaken at the same time in patients with gallstones who are clinically stable.

Enteric fistulation

Spontaneous discharge of a post-acute collection into the gastrointestinal tract is also recognized and can decompress the collection and result in a clinical improvement without intervention.[20] It can also present with haematemesis or malaena and should be managed as described below. Whilst spontaneous resolution is possible, fistulation into the colon can result in ongoing sepsis and poorly drained collections in this situation defunctioning colostomy or resection may be necessary.

Haemorrhage

In severe AP bleeding may be gradual or intermittent or sudden and massive. The patient may develop haematemesis and/or rectal bleeding, may bleed internally, or into abdominal or retroperitoneal drains. Probably the most frequent scenario, however, is brisk haemorrhage complicating early or over-enthusiastic necrosectomy. Overall, the mortality exceeds 30%. Arterial haemorrhage tends to occur either early on in necrotizing disease or else after 10 weeks when it may complicate maturing pseudocysts. It is typically from pseudoaneurysms of the left gastric, splenic, gastroduodenal or superior mesenteric artery (or branches thereof, Figure 4). A high index of suspicion is essential in order to maximize proactive treatment. In our unit the patient is rapidly stabilized with support of the circulation and an emergency CT angiogram is obtained. Upper gastrointestinal endoscopy in this setting is usually non-diagnostic and often delays definitive management. Formal angiography and embolization offers the chance of survival. Venous bleeding is uncommon and should be suspected in patients with a non-diagnostic angiogram. In this setting control by packing or emergency distal pancreatectomy may have to be considered.

Key points

- Cholecystectomy and bile duct imaging in biliary AP should ideally be performed during index admission in mild AP but should be deferred until after resolution in severe AP
- Early peri-pancreatic fluid collections should not be treated
- In the presence of local complications the key is sepsis control and a 'step-up' on the basis of clinical status is advocated
- Intervention for necrosis is warranted after maturation and demarcation in the presence of sepsis
- Post-acute collections differ from chronic pseudocysts and our management of the two is different
- Haemorrhage should be investigated with urgent angiography; interventional radiology is effective.

Conclusion

Whilst mild AP tends to resolve spontaneously with minimal supportive care, severe AP has a complicated course with considerable morbidity and mortality. In this condition outcome largely depends on aggressive supportive care. Careful monitoring with serial imaging is warranted and intervention is indicated for infected necrosis. It appears that minimal access debridement and lavage for this complication is associated with a reduced systemic inflammatory response. ◆

REFERENCES

1 Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas* 2006; **33:** 323–30.

2 Lowenfels AB, Maisonneuve P, Sullivan T. The changing character of acute pancreatitis: epidemiology, etiology and prognosis. *Curr Gastroenterol Rep* 2009; **11:** 97—103.

3 Buter A, Imrie CW, Carter CR, et al. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. *Br J Surg* 2002; **89:** 298—302.

4 Tolstrup JS, Kristiansen L, Becker U, et al. Smoking and risk of acute and chronic pancreatitis among women and men: a population-based cohort study. *Arch Intern Med* 2009; **169:** 603—9.

5 Elmunzer BJ, Waljee AK, Elta GH, et al. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. *Gut* 2008; **57:** 1262—7.

6 Fessel J, Hurley LB. Incidence of pancreatitis in HIV-infected patients: comment on findings in EuroSIDA cohort. *AIDS* 2008; **28:** 145—7.

7 Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol* 2004; **2:** 252—61.

8 Pickartz T, Mayerle J, Lerch MM. Autoimmune pancreatitis. *Nat Clin Pract Gastroenterol Hepatol* 2007; **4:** 314—23.

9 Balthazar EJ, Robinson DL, Megibow AJ, et al. Acute pancreatitis: value of CT in establishing prognosis. *Radiol* 1990; **174:** 331—6.

10 Dellinger DP, Forsmark CE, Layer P, et al. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. *Ann Surg* 2012; **256:** 875—80.

11 Gardner TB, Vege SS, Chari ST, et al. Faster rate of initial fluid resuscitation in sever acute pancreatitis diminishes in hospital mortality. *Pancreatol* 2009; **9:** 770—6.

12 Petrov MS, van Santvoort HC, Besselink MG, et al. Enteral nutrition and the risk of mortality and infectious complications in patients with severe acute pancreatitis: a meta-analysis of randomized trials. *Arch Surg* 2008; **143:** 1111—7.

13 Besselink MG. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008 23; **371:** 651—9.

14 Jafri NS, Mahid SS, Idstein SR, et al. Antibiotic prophylaxis is not protective in severe acute pancreatitis: a systematic review and meta-analysis. *Am J Surg* 2009; **197:** 806—13.

15 deVries AC, Besselink MG, Buskens E, et al. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodological quality and outcome. *Pancreatol* 2007; **197:** 531—8.

16 Petrov MS, van Santvoort HC, Besselink MG, et al. Early endoscopic retrograde cholangiopancreatography versus conservative management in acute biliary pancreatitis without cholangitis: a meta-analysis of randomized trials. *Ann Surg* 2008; **247:** 250—7.

17 Elgammal S, McKay CJ, Imrie CW, Carter CR. Does surgical approach affect outcome in patients with infected pancreatic necrosis requiring necrosectomy. *Br J Surg* 2003; **90:** 93.

18 Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrose tommy for necrotising pancreatitis. *New Engl J Med* 2010; **362:** 1491—502.

19 Gardner TB, Chahal P, Papachristou GI. A comparison of direct endoscopic necrosectomy with transmural endoscopic drainage for the treatment of walled-off pancreatic necrosis. *Gastro Endosc* 2009; **69:** 1085—94.

20 Kochhar R, Jain K, Gupta V, et al. Fistulization in the GI tract in acute pancreatitis. *Gastrointest Endosc* 2012; **75:** 436—40.

