Acute pancreatitis

Sarah C Thomasset

C Ross Carter

Abstract

Acute pancreatitis is a common diagnosis and its incidence may be rising. The most common aetiological agents remain gallstones and alcohol misuse. Eighty per cent 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 multiorgan failure may be as high as 50%. This article reviews the definition, aetiology, pathophysiology, therapeutic strategies and outcomes in light of recent evidence and guidelines.

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

General considerations

Epidemiology

The incidence of acute pancreatitis (AP) varies between populations (4.9–35 per 100,000 population), being reportedly higher in the USA and other European countries than in the UK.[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. 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 – defined as severe AP. 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.

Sarah C Thomasset *PhD PgDip FRCS is a Consultant Surgeon at the Royal Infirmary of Edinburgh, Edinburgh, UK. Conflicts of interest: none declared.*

C Ross Carter *MD FRCS is a Consultant Surgeon at the West of Scotland Pancreatico-biliary Unit, Glasgow Royal Infirmary, Glasgow, UK. Conflicts of interest: none declared.*

Aetiology

In the UK, approximately 50% of cases of AP are caused by **gallstones**, 25% by alcohol and 25% by other factors. 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. Population studies have suggested that 3–7% of patients with gallstones will develop AP. The mechanism by which gallstones induce AP is not certain but increased pressure in the pancreatic duct due to transient mechanical obstruction at the ampulla is thought to 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. Endoscopic ultrasound is more sensitive than transabdominal ultrasound at identifying biliary microlithiasis and should be considered in the diagnostic algorithm prior to labelling patients with idiopathic recurrent AP.

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 and several theories have been proposed. As in gallstone AP, despite a high prevalence of alcohol misuse, only 10% of chronic alcohol abusers eventually present with AP. The risk is highest in young males who drink in excess of 80 g of alcohol per day. Many patients with a significant alcohol history may also have gallstones and these should be excluded. Smoking has been considered a significant cofactor in the development of alcohol-related pancreatitis, but large population-based studies have established it as an independent risk factor for acute and chronic pancreatitis, with dose dependant and time dependent increases in hazard ratios observed.[4]

Endoscopic retrograde pancreatography (ERCP) is the most common cause of iatrogenic AP. In an era when CT 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. 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 requiring hospitalization after ERCP. Six out of 15 fatal ERCP lawsuits in the United States were due to pancreatitis and it is therefore advised that patients should be counselled appropriately prior to the procedure. 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, there should be a low threshold for investigating patients with urgent computerized tomography (CT). 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.

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A number of measures may serve to reduce the risk of developing AP following ERCP, a subject addressed in guidelines published by the European Society of Gastrointestinal Endoscopy (ESGE) in 2014.[5] Routine rectal administration of diclofenac or indomethacin immediately before or after ERCP is recommended in all patients without a contraindication to its use. In addition, placement of a small prophylactic pancreatic ductal stent should be considered in those patients at high risk of developing post-ERCP pancreatitis.

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 (EUS) have been undertaken. Repeat exposure resulting in a further episode of AP is the strongest evidence of a direct causal association. Specific viral infections associated with AP include mumps, Coxsackie B, viral hepatitis and increasingly HIV infection.[6]

Hypertriglyceridaemia in excess of 11 mmol/litre is known to precipitate AP and has been reported as the cause of AP 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.

Any **benign or malignant mass** that obstructs the main pancreatic duct can result in AP. It has been estimated that between 5% and 14% of patients with benign or malignant pancreaticobiliary tumours present with pancreatitis. The entity should be considered in any patient greater than 40 years of age presenting with no clear cause for AP. A dilated distal pancreatic duct may be the sole sign of malignancy on CT and should prompt further investigation, such as EUS.

Autoimmune pancreatitis (AIP) is a rare presentation and is considered as a manifestation of the IgG4-related disease spectrum which is associated with other autoimmune diseases (polyarteritis nodosa, SLE, other vasculitides) and inflammatory bowel disease. It usually presents with chronic symptoms of pain, weight loss and jaundice, but acute presentations are recognized. The distinguishing features are a sausage-shaped pancreas with ductal strictures, inflammatory infiltrates and high serum titres of immunoglobulin G(4).[7] A key feature in diagnosis is the response to steroid therapy. In some cases, focal autoimmune pancreatitis may be difficult to differentiate from malignancy.

Trauma related hyperamylasaemia usually results from a crush injury to the body of the pancreas against the vertebral column. Clinicians should have a high index of suspicion for associated injury to neighbouring organs. 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.

A **genetic predisposition** to AP has long been suspected and over recent years the influence of mutations in the PRSS1 (cationic trypsinogen) gene, CFTR (cystic fibrosis) gene and SPINK1, have been recognized.[8] The EUROPAC (European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer) study has observed multiple families and patients who 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.[8] They have a significantly increased lifetime risk of pancreatic cancer. 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.

Congenital or acquired anatomical abnormalities can occasionally present with AP. Examples including choledochal cysts, duodenal duplication and secondary fibrosis of the pancreatic duct causing ductal obstruction. The association between AP and pancreas diversum remains controversial and is probably overstated.

Guidelines

In 2018, guidelines on AP were published by the National Institute for Health and Care Excellence (NICE) and the American Gastroenterological Association (AGA).[9,10] Guidelines from the AGA focus on the initial management of AP. Those from NICE emphazise the importance of investigating the cause of AP and make recommendations concerning initial management, treating complications and when to refer to a specialist centre. Recommendations from these guidelines will be discussed further below.

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. 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 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

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circulatory interplay of pro-inflammatory cytokines (such as Il-1, Il-2, Il-6, 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 peripancreatic necrosis. Peripancreatic 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 states that leaning or sitting forwards alleviates the pain. The pain is frequently associated with nausea and vomiting. Patients may have a previous history of gallstone disease, alcohol indiscretion or similar attacks. Patients often appear pale, sweaty, tachycardic and may be hypotensive. The majority are normothermic although hypothermia can occur. 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 which tend to occur after day 2. 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 setting, confirmation of the clinical diagnosis is made by obtaining serum levels of amylase and/or lipase and excluding 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 an 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 as mentioned above. An erect chest film is useful to exclude a pneumoperitoneum (though free gas may be absent in up to a third of visceral perforations) or acute lung disease. Abdominal films may demonstrate features in keeping with bowel obstruction or rarely aneurysmal disease. Diagnostic uncertainty at this stage is unusual, but in this setting and especially in the unwell patient, CT should be undertaken. The presence of jaundice and pyrexia in association with hyperamylasaemia may indicate cholangitis and the need for urgent ERCP and biliary decompression.

An ultrasound scan (USS) in patients with AP is by convention performed early during an 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

- AP is common, with severe AP making up 20%
- Overall mortality is down but in complicated severe AP it still remains around 40%
- Diagnosis is usually straightforward but if in doubt a CT is useful
- Aetiology should not be assumed but actively confirmed by investigation

Severity scoring and classification of AP

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 in the order of 90%.

Organ failure assessment forms part of the severity grading of AP and can be performed using the Marshall scoring system. This is a simple 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 to the above-mentioned clinical scores, a radiological-based score is described by Balthazar.[11] 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

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deterioration in a patient with AP should involve thorough clinical, biochemical, microbiological and radiological assessment.

Classification of AP – the revised Atlanta Classification

The 2012 revised Atlanta Classification[12] divides AP into three categories: mild, moderate and severe, on the basis of organ dysfunction and local/systematic complications (Box 1). In addition to disease severity, mortality is strongly associated with age, comorbidity and the presence of infection. Two types of AP are recognized: interstitial oedematous pancreatitis (IOP) and necrotizing pancreatitis (NP). The majority of patients with AP have IOP, with diffuse enlargement of the pancreas due to inflammatory oedema. CT reveals relatively homogeneous enhancement of the pancreatic parenchyma and the clinical symptoms associated with IOP usually resolve within the first week. Approximately 5–10% of patients with AP develop necrosis, usually involving both the pancreatic parenchyma and peripancreatic tissue (NP). Early CT frequently underestimates the extent of pancreatic/peripancreatic necrosis which evolves over several days. After the first week of disease, a non-enhancing area of pancreatic parenchyma indicates the presence of necrosis.

Local complications are categorized on the basis of the type of pancreatitis and the time from presentation (<4 or >4 weeks) (Box 1). Within 4 weeks of IOP, acute peripancreatic fluid collections are described. These may either settle or mature into a pancreatic pseudocyst (a completely encapsulated fluid collection). Within 4 weeks of NP, acute necrotic collections may be evident which consist of variable quantities of both fluid and necrosis. Beyond 4 weeks, mature encapsulated collections may develop and are termed walled-off necrosis (WON). Although this temporal separation is somewhat arbitrary, as clinical management and any therapeutic approach is determined by multiple individual patient factors, it does serve to provide a timeline during which, if appropriate, intervention should be delayed.

Management phase I: early issues

Resuscitation

The approach to a patient with AP should be thorough and systematic. Whereas a 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. Previously, opiates were considered to lead to sphincter of Oddi spasm with concerns that this could be deleterious in AP, however, these concerns are not supported by available evidence.

Aggressive resuscitation is indicated. Hypoxaemia is often a reflection of disease severity and while 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 exceed 6 litres over a 24-hour period. AGA guidelines recommend goal-directed intravenous fluid administration, whereby fluids are titrated to specific cardiovascular parameters or biochemical measurements reflecting perfusion.[10] 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.

Grades of severity of AP (2012 Revised Atlanta Classification)[12]

Mild acute pancreatitis

- No organ failure
- No local or systematic complications

Moderately severe acute pancreatitis

- Transient organ failure (<48 hours)
- Local or systematic complications without persistent organ failure

Severe acute pancreatitis

- Persistent organ failure (>48 hours)
- Either single or multiple organ failure

Box 1

Nutrition

Maintenance of nutritional competence is of the utmost importance in AP. Severe AP contributes to a catabolic state and bowel rest through prolonged fasting has no place in the modern management of pancreatitic patients. Normal dietary intake, as tolerated, should be permitted in patients with mild AP. Nasogastric suction does not alter the disease course and it should only be used it in patients with gastroparesis. In patients with severe disease, early and close nutritional assessment and advice is recommended. A simple suggested algorithm is as follows:

1. Normal diet as tolerated.
2. Feeding by a fine-bore naso-gastric (NG) tube should be 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.
3. Feeding by a fine-bore naso-jejunal (NJ) tube should be used in preference when, through gastroparesis, naso-gastric feeding leads to high-volume aspirates implying impaired absorption.
4. Total parenteral nutrition (TPN) via a dedicated tunnelled line is indicated for the rare occasions when enteral nutrition is contraindicated (fistulation, short bowel, bowel obstruction or persistent ileus and inability to intubate the jejunum endoscopically).

Use of the NJ route has traditionally been preferred to avoid the gastric phase of stimulation. Randomized control trials (RCT) comparing NG and NJ routes in patients with AP have generally included small numbers of patients. A recent meta-analysis,

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which included data from three RCTs and a total of 157 patients, concluded that there was no significant difference in mortality, rates of tracheal aspiration or meeting nutritional requirements between NG and NJ routes in patients with predicted severe AP.[13]

TPN costs some three times more than EN. Enteral feeding has the potential for preserving gut barrier function by preventing atrophy and theoretically may reduce pancreatitis-related infective complications. Meta-analysis data suggest lower morbidity (infective complications and organ failure) and mortality in patients receiving EN when compared with TPN.[14]

Despite previous encouraging results with the addition of probiotics to nutritional regimes, a recent randomized trial suggested no benefit from this practice and the study reported an increased associated mortality.[15]

NICE and AGA guidelines recommend early oral feeding, as tolerated.[9,10] NICE recommends offering supplementary enteral nutrition to anyone with severe or moderately severe AP, to be started within 72 hours of presentation. If enteral nutrition fails in this situation, or is contraindicated, TPN is advised.

Antibiotics

The administration of antibiotics in AP has been the focus of many studies. 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 meta-analysis by Jafri and colleagues.[16] 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 concluded 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.[17] Indiscriminate use of antibiotics has been associated with up to 30% of patients developing superinfection of necrosis with *Candida* spp., which has been associated with a poor prognosis. Patients with severe AP often exhibit prolonged pyrexia related to the SIRS. Antibiotics have no proven benefit in this setting and both NICE and AGA guidelines recommend against prophylactic use.[9,10] The authors use short courses of antibiotics for bacteriologically proven 'septic episodes', guided by 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 a 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 that require urgent ERCP.

When pancreatitis exists in the absence of cholangitis, the role of early or urgent ERCP is debated. 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 who underwent ERCP compared with patients managed conservatively. However, the authors noted a trend towards higher APACHE scores and degree of necrosis in the conservatively managed sub-group. These effects were not observed in patients with no evidence of cholestasis. These results are supported by two meta-analyses. Petrov and colleagues included 6 trials in their meta-analysis and concluded that early ERCP conferred no benefit in mild or severe AP.[18] In addition, a trend towards excess mortality was observed after ERCP.

Key points

- Severe AP usually requires aggressive fluid resuscitation
- Severity scoring has limitations — treat the *patient* not the *score*
- Nutrition — route and composition do not alter outcome
- Antibiotics — do not give prophylactic antibiotics
- Urgent ERCP — probably only indicated in patients with features of cholangitis

Management phase II — definitive treatment and treatment of complications

Cholecystectomy

AGA guidelines address the timing of cholecystectomy in patients with AP.[10] In those with acute biliary pancreatitis, cholecystectomy during the index admission is recommended, 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 require bile duct imaging either by a staged approach of preoperative MRCP or by the single step of intra-operative cholangiography. Bile duct stones can be dealt with by ERCP or bile duct exploration depending on the available local expertise and of course, ductal anatomy. In the patient with poor operative risk, ERCP and definitive sphincterotomy is a suitable alternative to cholecystectomy. Of note, AGA guidelines do not address the severity of AP in decisions regarding the timing of cholecystectomy. Cholecystectomy should be delayed in patients with peripancreatic fluid collections until the collections either resolve, or if they persist, when operative intervention can be performed safely.

Specific local complications and their management (Table 1)

Acute peripancreatic fluid collection (APFC): These are common within the first few days and are formed of 'puddles' in the vicinity of the pancreas. These patients should be followed with serial imaging and as a rule do not require intervention.

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Local complications of AP (2012 Revised Atlanta classification)[12]

	Interstitial oedematous pancreatitis	Necrotizing pancreatitis
<4 weeks	**Acute peripancreatic fluid collection** • Homogenous • Confined by normal fascial planes • No definable wall • No intrapancreatic extension	**Acute necrotic collection** • Heterogeneous • No definable wall • May be intrapancreatic and/or extrapancreatic
>4 weeks	**Pancreatic pseudocyst** • Homogenous • Well defined wall • No solid component	**Walled-off necrosis** • Heterogeneous • Well defined wall • May be intrapancreatic and/or extrapancreatic

Table 1

These immature collections tend to resolve spontaneously in 50% of patients. By definition, APFC are associated with minimal necrosis and arise following IOP. 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.

Pseudocyst: Recommended management of the post-acute pseudocyst is to allow it to mature for at least 8 weeks. In symptomatic patients and those failing to thrive, the main options for intervention are endoscopic/laparoscopic cystgastrostomy. The choice between modalities is guided by patient fitness, the degree of debris within the cyst and local expertise. An advantage of the laparoscopic approach is that cholecystectomy can be undertaken concurrently, if required.

Acute necrotic collection (ANC) (Figure 1a): 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 1b). In patients with sterile necrosis, conservative management is advocated. Although intervention may be indicated in patients failing to thrive, this should not be undertaken before a minimum of 6–8 weeks and ideally delayed until 10–12 weeks. When possible, pancreatic necrosis should be allowed to mature and demarcate as this offers the least risk for intra-procedural haemorrhage.

Infection of pancreatic collections (Figure 1b): 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 peripancreatic) necrosis can be managed by a variety of approaches, including percutaneous, endoscopic and surgical approaches.

Current evidence supports a step wise approach to the management of infected pancreatic collections. This rationale is

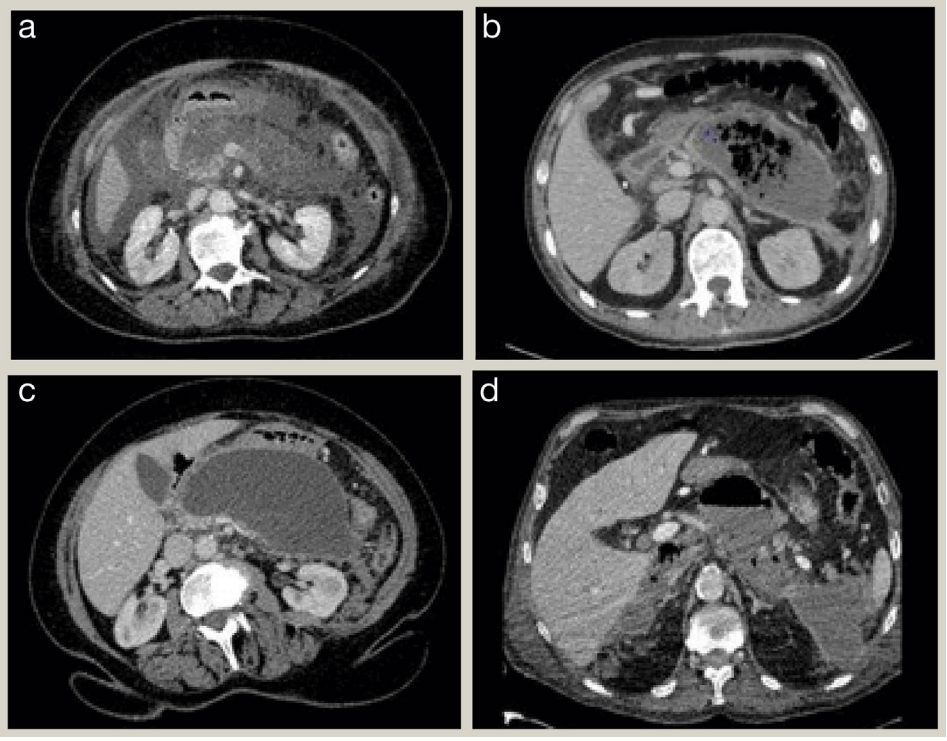

Figure 1 CT images from patients with severe necrotizing acute pancreatitis. (**a**) An acute necrotic collection. (**b**) Pockets of gas in an infected necrotic collection. (**c**) Walled-off necrosis. (**d**) An air-fluid level indicative of spontaneous fistulation.

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based on stabilization of organ function and sepsis, as a bridge to a more definitive procedure when required. The PANTER study, from the Dutch Pancreatitis Study Group, provided good quality randomized data regarding the management of infected pancreatic necrosis. Patients with infected pancreatic necrosis were randomized to either open necrosectomy or a 'step-up' approach based on endoscopic or percutaneous drainage as the initial intervention, progressing 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% of patients were successfully managed with percutaneous drainage alone and did not require progression to debridement.[19]

Secondary 'step-up' approaches include upsizing drains ± lavage, percutaneous necrosectomy, video-assisted retroperitoneal debridement (VARD) and endoscopic necrosectomy (Figure 2). In excess of 50% of patients will settle when percutaneous drains are upsized and lavage undertaken, without formal necrosectomy. However, disadvantages include the limited ability to remove any necrotic material, prolonged hospitalization and the need for multiple procedures. Percutaneous necrosectomy and VARD utilize a nephroscope and laparoscope, respectively, introduced via a pre-existing percutaneous tract which has been dilated. To minimize the risk of haemorrhage, only loosely adherent areas of necrosis are removed. In both techniques large drains are placed in the cavity at the end of the procedure to facilitate lavage. Endoscopic necrosectomy may be undertaken as a 'step-up' procedure following prior endoscopic cystgastrostomy. Where there is evidence of infection or systemic sepsis, a naso-cystic catheter may be utilized for continuous lavage of the cavity.

NICE guidelines recommend an endoscopic approach for managing infected or suspected infected pancreatic necrosis when anatomically possible, otherwise percutaneous methods will be required.[9] Endoscopic drainage is preferable in managing medially sited, retrogastric collections, whereas percutaneous drainage is better suited to lateral collections. A recent Dutch study randomized 98 patients with infected necrotizing pancreatitis to either endoscopic ultrasound (EUS) guided drainage, followed if necessary by endoscopic necrosectomy or percutaneous drainage, followed if necessary by VARD. There were no differences in mortality or major complications between the groups; however, the rate of pancreatic fistulae and length of hospital stay were lower in the endoscopic group.[20] A further advantage of EUS guided drainage is the ability to undertake the procedure on the intensive care unit rather than to transfer an unstable patient to the radiology department for CT guided drainage.

Walled-off necrosis (WON) (Figure 1c): This condition appears to arise from areas of necrosis and pancreatic juice leakage eliciting an inflammatory response which culminates in a walled-off solid-cystic collection. Indications for intervention in WON are: (i) infection; (ii) nutritional failure; and (iii) persistent symptoms. Spontaneous resolution of even large WON collections is not infrequent and, when possible, an expectant approach is preferred. The main options for intervention are endoscopic or laparoscopic cystgastrostomy. The degree of solid versus fluid content of these collections may influence the therapeutic strategy adopted. Fluid predominant collections may be more suitable for EUS, whereas solid predominant collections may be preferentially drained by laparoscopic cystgastrostomy.

Enteric fistulation (Figure 1d): Spontaneous discharge of a post acute collection into the gastrointestinal tract can decompress the collection and result in clinical improvement without intervention.[21] It can also present with haematemesis or melaena and should be managed as described below. Foregut fistulation into the stomach or duodenum will usually resolve without the need for intervention (other than drainage of a collection by percutaneous or endoscopic means) but colonic fistulation is often associated with clinical deterioration and on-going sepsis. In this situation, a defunctioning colostomy or resection may be required. CT will often demonstrate a gas/fluid level in the case of fistulation, compared to pockets of gas which are frequently seen in infected collections.

Haemorrhage (Figure 3): 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 may manifest in 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 after 10 weeks when it may complicate maturing pseudocysts. It is typically from

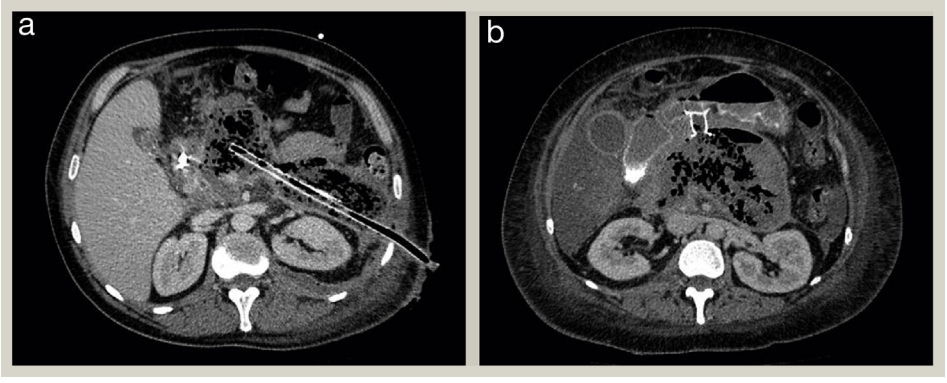

Figure 2 Pancreatic necrosis treated with (**a**) upsized percutaneous drainage and lavage; (**b**) endoscopic cystgastrostomy.

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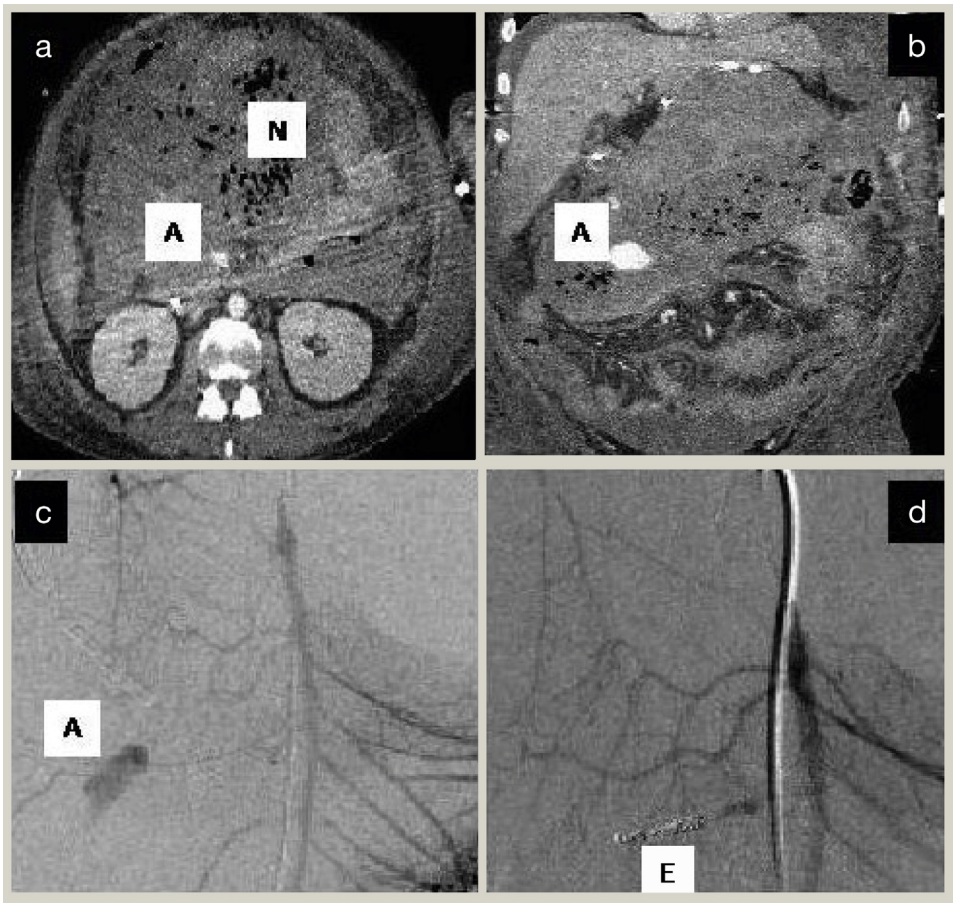

Figure 3 Haemorrhage from a pseudoaneurysm of a branch of the superior mesenteric artery in a patient with necrotizing pancreatitis. (**a**) and (**b**) are CT angiographic views (N, necrosis; A, pseudoaneurysm). (**c**) and (**d**) pre- and post-angiographic embolization views (A, pseudoaneurysm with 'blush'; E, embolization coils with successful sealing).

pseudoaneurysms of the left gastric, splenic, gastroduodenal or superior mesenteric artery. A high index of suspicion is essential in order to maximize proactive treatment. The patient should be rapidly stabilized with support of the circulation and an emergency CT angiogram 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.

Pancreatic fistulation: A persistent pancreatic fistula is a common sequela of percutaneous necrosectomy or VARDS. Although spontaneous resolution is the norm, persistent fistulae should initially be managed by insertion of a pancreatic ductal stent at ERCP. Persistent fistulae can be a challenging problem and are often associated with extensive parenchymal loss, or a disconnected pancreatic tail with loss of continuity of the main pancreatic duct. Prolonged percutaneous drainage leads to formation of a mature fistula tract and subsequent drain removal may result in spontaneous resolution or development of a fluid collection which could be drained into the stomach via EUS. A distal pancreatectomy may be appropriate in a selected patients with a disconnected pancreatic tail in whom endoscopic options are not feasible or unsuccessful.

Referral for specialist treatment: NICE guidelines suggest discussion with a specialist pancreatic centre within the referral network if a patient develops necrotic, haemorrhagic or systemic complications due to AP.[9] Most patients with AP can be managed

Key points

- Cholecystectomy and bile duct imaging in biliary AP should ideally be performed during the index admission in patients with 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 with a 'step-up' approach based on clinical status
- Intervention for necrosis is warranted after maturation and demarcation in the presence of sepsis
- Haemorrhage should be investigated with urgent angiography, interventional radiology is effective

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in their local hospital, but transfer may be required for specialist radiological, endoscopic or operative intervention.

Conclusion

While 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. ◆

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