Acute pancreatitis

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Abstract
Acute pancreatitis is an inflammatory condition with a variable clinical course. Diagnosis is based on clinical presentation, laboratory studies and imaging. Disease severity is assessed using clinical scoring systems or radiological assessments such as the CT Severity Index. In most cases, the disease follows a mild course; however, a minority of cases are complicated by local and systemic complications. Management is usually conservative, while interventions are indicated where common bile duct stones or local complications, such as walled-off necrosis or pseudocyst formation, coexist. This review summarizes recent insights into the pathophysiology, investigation and treatment of acute pancreatitis, as well as common approaches to the management of local complications.

Keywords Acute pancreatitis; antibiotics; endoscopic necrosectomy; MRCP; nutrition; pseudocyst; severity

Key points

- In acute pancreatitis, care should focus on pain control, fluid resuscitation with correction of electrolyte disturbances, and adequate caloric intake
- In severe or moderately severe acute pancreatitis, enteral nutrition should be commenced within 72 hours of presentation, aiming to meet nutritional requirements as soon as possible. Parenteral nutrition should be reserved for cases where enteral nutrition has failed or is contraindicated
- Endoscopy-guided drainage is the preferred first-line technique in the management of infected or suspected pancreatic necrosis. The timing of debridement should be balanced between clinical urgency and the advantages of delayed debridement

Introduction

Acute pancreatitis (AP) is an inflammatory process of the pancreas, most commonly secondary to gallstones and excessive alcohol consumption, and is a leading cause of hospital admissions globally. Although most cases follow a mild course, about 25% are complicated by local and often life-threatening systemic complications. Owing to recent advances in imaging and less invasive techniques for the management of such complications, endoscopy guided procedures have gained popularity over traditional surgical interventions, offering patients better outcomes and lower rates of procedure related complications. The incidence of AP however is increasing, and the associated mortality remains as high as 30% despite improvements in clinical care.

Epidemiology

Over the past few decades, there has been an increase in the incidence of AP globally, with gallstones and alcohol being the most common risk factors. In the UK, the estimated incidence of AP is 15–42 cases per 100,000 per year. A recent population-based study across 17 European countries reported geographical variability in both disease incidence and aetiology. Alcohol was the most common aetiology in eastern Europe, whereas gallstones were the leading cause in southern Europe. In western and northern parts of the region, a comparable incidence of these aetiological factors was observed. Although most cases follow a mild course, some are complicated by a severe systemic inflammatory response, resulting in mortality rates as high as 20%.

Pathophysiology

Several aetiological factors are associated with AP (Table 1). In gallstone pancreatitis, pancreatic duct obstruction prevents the flow of pancreatic secretions, leading to acinar cell injury and subsequent premature activation of pancreatic intracellular pro-enzymes. The pathological activation and conversion of trypsinogen into trypsin results in organ autodigestion. This, along with activation of other digestive enzymes, causes an inflammatory response characterized by the recruitment of neutrophils, macrophages and lymphocytes, with release of interleukins and tumour necrosis factor-α. Increased vascular permeability leads to fluid sequestration and oedema, but haemorrhage and necrosis are rarely observed. In severe cases, a systemic inflammatory response can lead to sepsis and multiorgan failure.

Several mechanisms by which alcohol induces AP have been suggested. Studies evaluating the effect of alcohol on the sphincter of Oddi have yielded conflicting results, showing that it can both increase and decrease sphincter tone. There is a direct toxic effect induced by alcohol and its toxic metabolites (acetaldehyde, reactive oxygen species) on acinar and pancreatic stellate cells. In addition, experimental studies have shown that alcohol increases the concentrations of digestive and lysosomal enzymes within acinar cells, and their close contact facilitates their pathological activation. Moreover, alcohol induces the precipitation of self-aggregating, non-digestive enzymes (lithostathine, glycoprotein 2); this induces the formation of duct-obstructing protein plugs that result in intrapancreatic duct obstruction, scarring and fibrosis.

Diagnosis

AP should be considered in the differential diagnosis of all patients presenting with abdominal pain. In order to confirm the diagnosis, two out of the following three criteria should be met:

- a typical history of epigastric abdominal pain
- elevation of serum amylase and/or lipase of >3-fold the upper normal limit

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Aetiological factors for AP

Risk factors and causes of AP

- Cholelithiasis, choledocholithiasis, microlithiasis
- Alcohol
- Smoking
- Diabetes mellitus type 2
- Hypercalcaemia, hypertriglyceridaemia
- Pancreatic anatomical abnormalities (e.g. pancreas divisum)
- Genetic — cystic fibrosis, hereditary pancreatitis
- After endoscopic retrograde cholangio-pancreatography
- Autoimmune
- Viral infections — mumps, coxsackievirus, HIV
- Venom — scorpion, spider
- Pancreatic duct-obstructing lesions — pancreatic tumours
- Peri-ampullary tumours, papillary fibrosis
- Idiopathic

Common medications

- Acetaminophen
- Azathioprine
- Corticosteroids
- Enalapril
- Erythromycin
- Furosemide
- Mercaptopurine
- Oestrogens
- Olanzapine
- Opiates
- Simvastatin
- Sulfonamides
- Tetracycline
- Valproate

Table 1

- supportive findings on abdominal imaging (ultrasound, computed tomography (CT) and/or magnetic resonance imaging (MRI)

In suspected AP, after early resuscitation, efforts should be focused on establishing the aetiology, as the definitive treatment varies with different causative factors.

Clinical presentation

Patients with AP typically present with upper abdominal pain described as 'belt-like' and 'stabbing' in nature, which often radiates to the back and may be alleviated by leaning forward. The pain, which is commonly accompanied by nausea and vomiting, is usually of sudden onset and can be triggered by a fatty meal or heavy alcohol consumption.

On examination, patients can show signs of hypovolaemia and diaphoresis, and are often tachycardic. Examination of the abdomen reveals epigastric tenderness and voluntary guarding. In severe cases, accompanying pyrexia can suggest pancreatic necrosis and systemic inflammation. Ecchymoses in the periumbilical area and flanks (Cullen's and Grey Turner's signs, respectively) are indicative of a haemorrhagic component, but are rarely observed.

Laboratory investigations

In addition to serum amylase and lipase concentrations, routine blood tests should include a full blood count and liver enzyme panel as well as calcium and triglyceride (triacylglycerol) concentrations. Electrolyte concentrations, renal function and blood urea nitrogen (BUN), blood glucose, total albumin and a coagulation profile should also be obtained.

Elevated serum amylase and lipase are evident a few hours after the onset of AP. Amylase concentrations typically return to normal after 2–4 days, whereas lipase returns to normal within 8–14 days. Amylase can be falsely elevated in the absence of AP in several other conditions (e.g. acute appendicitis, cholecystitis, peptic ulcer, salivary gland disease). In addition, it remains within the normal range in up to 19% of individuals with AP. Increased serum concentrations of liver enzymes at the time of presentation are highly suggestive of an aetiology attributed to biliary tract obstruction. Abnormalities in renal function markers indicate renal injury that could be secondary to third space fluid sequestration and intravascular depletion.

Owing to the risk of acid–base and oxygen disturbances in AP, patients presenting with tachypnoea and/or low oxygen saturation levels should undergo arterial blood gas analysis.

Imaging in acute pancreatitis

Chest and abdominal radiographs

Plain radiographs are non-diagnostic in AP. In severe AP, pleural effusions and parenchymal infiltrates can be observed on chest radiographs. On abdominal radiographs, a sentinel loop (an isolated loop of bowel usually located centrally) suggests intestinal ileus. Rarely, pancreatic calcifications are identified in chronic pancreatitis.

Trans-abdominal ultrasound

Ultrasonography is often the preferred technique when the suspected aetiology is gallstones. It is an inexpensive and readily available modality that allows visualization of the biliary tree and gallbladder. Despite being highly sensitive for identifying gallbladder stones (up to 90%), adequate visualization of the common bile duct in the setting of AP is often challenged by overlying bowel containing gas. Patient body habitus and operator skills can pose further challenges to its use.

Computed tomography

With a typical clinical picture supported by positive laboratory tests suggestive of AP, cross-sectional imaging is not indicated for establishing the diagnosis (Figure 1). Early contrast-enhanced CT is indicated in cases where the diagnosis of AP is in doubt. Complications such as peri-pancreatic collections, abscesses, vascular complications and pancreatic necrosis are not radiologically apparent during the first few days of AP; therefore CT is best performed >96 hours after the onset of pain to identify these complications. However, patients showing signs of clinical deterioration or who are failing to improve in the 2–4 days after initial presentation should have an urgent CT to exclude other causes of an acute abdomen. Disease severity is also more accurately assessed using delayed CT, as CT performed <96 hours from the onset of AP can underestimate disease severity.

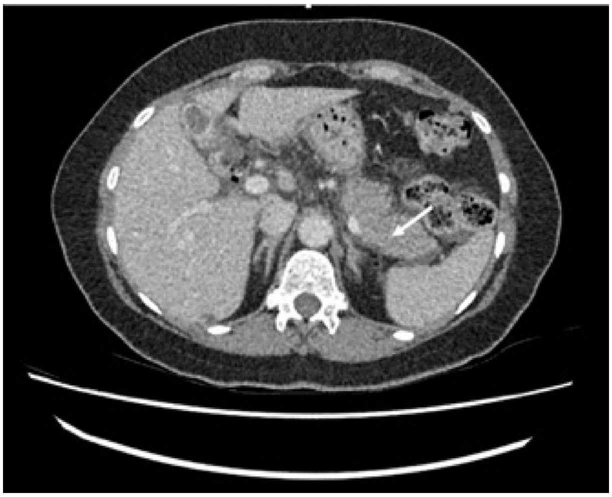

Figure 1 Abdominal (transverse section) CT image showing features of interstitial oedematous pancreatitis. There is oedema of the distal pancreatic region with peri-pancreatic fat stranding (arrow).

Magnetic resonance imaging

Magnetic resonance cholangio-pancreatography (MRCP) is superior to CT in the diagnosis of biliary tract stones smaller than 3 mm; it also offers better delineation of pancreatic and ductal anatomy. Moreover, MR imaging offers better depiction of fluid —solid phases in pancreatic collections, and therefore has a higher diagnostic yield in differentiating necrosis from purely liquid collections.

Endoscopic ultrasound (EUS)

In up to 20% of cases of AP, clinical evaluation including laboratory tests and simple imaging modalities fails to establish the cause, and the aetiology remains uncertain. EUS has gained popularity in recent years because of its high sensitivity in detecting biliary sludge or stones (sensitivity >95%, specificity 97%). In addition, features of chronic pancreatitis, pancreatic anatomical variants such as pancreas divisum, and ampullary and pancreatic neoplasms can be detected with high accuracy.

Management

Assessing disease severity

Early risk stratification within 48—72 hours after the onset of symptoms allows the prediction of potential complications, hence reducing associated morbidity and mortality. Numerous scoring systems exist, based on clinical, laboratory and radiological findings. These aim to help physicians triage patients onto appropriate levels of care as well as guiding appropriate management.

Clinical scoring systems: numerous clinical scoring systems have been developed since the introduction of the Ranson clinical scoring system in the 1970s. These scoring systems calculate the risk of developing severe AP using a combination of clinical, laboratory and radiological findings (Table 2). Examples include the Acute Physiology and Chronic Health Evaluation II (APACHE II), the Modified Glasgow—Imrie criteria, the newer Bedside Index for Severity in Acute Pancreatitis (BISAP) and the Harmless Acute Pancreatitis Score. Past comparisons have shown a comparable predictive performance (with area under the receiver operating curve values of around 0.70) for these scoring systems. Their use in clinical settings is, however, limited because of their complexity and moderate sensitivities.

The Revised Atlanta classification is a universally applicable classification system for AP. In 2012 the original classification was revised, and more accurate definitions of local and systemic complications provided new insights into prognostication and clinical management. This system classifies AP into mild (interstitial pancreatic changes in the absence of local or systemic complications), moderately severe (transient local or systemic complications and/or organ failure lasting <48 hours) and severe (persistent organ failure for >48 hours).

The American Pancreatic Association (APA)/International Association of Pancreatology (IAP) guidelines favour the use of the systemic inflammatory response syndrome (SIRS) criteria as a simple predictive tool for severe AP. SIRS is defined as two or more of the following:

- temperature <36°C or >38°C
- respiratory rate >20 breaths/minute or $PaCO_2$ <32 mmHg
- pulse >90 beats/minute
- white blood cell count <4.0 or >12.0 × 10^9/litre, or >10% immature bands.

Patients who have SIRS criteria on admission that persist for >48 hours have an increased risk of multiorgan failure and mortality.

Serum-based markers: although a number of biomarkers have been evaluated as candidate predictors of severity in AP, their utility in clinical practice has been limited because of their lack of specificity at an early disease stage, high cost and only moderate reliability.

The most widely used parameters are those suggesting an inflammatory process as well as hypovolaemia. A C-reactive protein (CRP) concentration of >150 mg/litre at 48 hours after AP onset is associated with severe disease. However, CRP is not disease-specific, is not reliable for risk stratification at the time of admission and does not reliably predict disease prognosis. Other novel markers including procalcitonin, cytokines (such as interleukin-6 and interleukin-8) and activation peptides of pancreatic enzymes have been investigated but are not routinely used in clinical practice in the UK.

Markers of fluid status and hypovolaemia (BUN, creatinine, haematocrit) correlate with severity of AP, and the trend in concentration from the time of admission to 24—48 hours later can predict the risk of mortality. A large prospective study of 1612 AP patients concluded that a haematocrit >44% on admission, associated with a rise in BUN at 24 hours, was highly predictive of persistent organ failure and pancreatic necrosis, with accuracy outperforming clinical scoring systems.

Cross-sectional imaging: the Computed Tomography Severity Index is a prognostic score that grades the severity of AP according to CT findings. Pancreatic and peri-pancreatic pathological changes indicative of disease severity, including features of pancreatic necrosis, can be identified using CT. However, the weakness of the Computed Tomography Severity Index is that it does not account for non-radiological aspects of AP.

AP severity scoring systems

Parameter	Glasgow–Imrie score (within 48 hours)	Ranson score (on admission and at 48 hours)	APACHE II (on admission, then daily)	BISAP
Clinical				
Age (years)	–	>55	✓	>60
Co-morbidity	–	–	✓	SIRS
Temperature	–	–	✓	–
Heart rate	–	–	✓	–
Respiration rate	–	–	✓	–
Mean arterial blood pressure (mmHg)	–	–	Shock/<90	–
Glasgow Coma Scale score	–	–	✓	<15
Fluid sequestration	–	>6 litre	–	–
Laboratory				
White cell count (× 10^9/litre)	>15	>16	✓	–
Packed cell volume (%)	–	>10↓	✓	–
Blood glucose (mmol/litre)	>10	>11.1	–	–
Serum sodium (mmol/litre)	–	–	✓	–
Serum potassium (mmol/litre)	–	–	✓	–
Serum calcium (mmol/litre)	<2	<2	–	–
Serum urea (mmol/litre), after hydration	>16	>1.8↑	Renal failure	BUN>8.9
Serum albumin (g/litre)	<32	–	–	–
Aspartate aminotransferase (U/litre)	>200	>250	–	–
Lactate dehydrogenase (U/litre)	>600	>350	–	–
PaO_2 (mmHg)	<60	<60	≤60	–
Base deficit (mEq/litre)	–	>4	pH arterial	–
Imaging				
	–	–	–	Pleural effusions
Threshold score for severe acute pancreatitis	≥3	≥3	≥8	≥3

↑/↓/increase/decrease by; SIRS, systemic inflammatory response syndrome.

Table 2

Treatment

Appropriate management in the first 48–72 hours after admission is essential for a favourable outcome for patients with AP. Care should focus on pain control, fluid resuscitation with correction of electrolyte disturbances, adequate caloric intake and, in cases of severe disease, interventions to address local and systemic complications. Mild disease usually resolves with supportive management (i.e: hydration and analgesia). In cases of alcohol-induced AP, both the National Institute for Health and Care Excellence (NICE) 2018 and the American Gastroenterological Association (AGA) 2018 guidelines recommend a brief alcohol intervention.[1,2]

Patients with severe disease accompanied by organ failure or poor prognostic signs (persistent SIRS, Glasgow–Imrie score >3, APACHE score >8 and Ranson score >3), should be assessed for whether high-dependency unit admission is needed.

Initial resuscitation: local and systemic inflammatory responses in AP result in third space fluid loss, which is often worsened by reduced fluid intake as well as increased sweating and respiration. Early fluid resuscitation aiming to avoid hypovolaemia and resultant organ failure is a cornerstone of management in the first 24 hours. Both the type of fluid and the rate of admission have been an area of debate, numerous studies comparing the clinical outcomes associated with different fluid resuscitation regimens. So far, however, no clear consensus exists with respect to the advantage of one strategy over another.

A randomized controlled trial (RCT) of 60 AP patients compared early aggressive resuscitation with Ringer's lactate (20 ml/kg bolus followed by 3 ml/kg per hour) against a standard regimen (10 ml/kg bolus followed by 1.5 ml/kg per hour). The aggressive intervention led to a faster clinical improvement with fewer complications and a lower incidence of persistent SIRS, as assessed at 36 hours after admission. Overly aggressive fluid resuscitation (>4.1 litres per 24 hours), on the other hand, was associated with a higher rate of respiratory and intra-abdominal complications, as well as mortality. It is therefore agreed that aggressive yet controlled hydration (3.0–4.0 litres per 24 hours) is optimal in the early phase of AP. An early goal-directed approach to resuscitation, using 5–10 ml/kg per hour of Ringer's lactate, aiming to promptly return clinical and biochemical parameters to normal (urine output >5 ml/kg/hour, heart rate <120 beats per minute, haematocrit 35–45%) is encouraged by the IAP/APA and AGA.[2]

With respect to the choice of fluid to be used, Ringer's lactate offers an advantage over normal sodium chloride, with reduced rates of SIRS secondary to its anti-inflammatory properties. The effect of the different types of fluid on specific clinical outcomes such as necrosis, organ failure and mortality has not been adequately assessed.

Abdominal pain associated with AP should be addressed promptly and adequately to avoid respiratory complications caused by decreased ventilation. Although some RCTs have focused on pain control in AP, no consensus has been reached regarding the best choice of drug and method of delivery; therefore clinicians should adhere to local perioperative pain management guidelines. Bedside monitoring of acid–base balance status, arterial blood oxygenation and blood glucose concentrations should be routinely measured.

Antibiotics in acute pancreatitis: patients with AP complicated by (peri-)pancreatic necrosis often develop secondary infections that result from intestinal bacterial translocation. In severe cases complicated by secondary infections, mortality rates as high as 40% have been observed. However, the use of antimicrobial prophylaxis in attempt to reduce infective complications remains an area of controversy in terms of their impact on incidence of infection, mortality or need for surgical intervention.

A recent meta-analysis that included 11 studies (nine RCTs, two cohort studies), involving 864 patients with AP, showed no evidence that the use of prophylactic antibiotics offered an improvement in mortality rates among the randomized cohorts. In addition, the incidence of infective necrosis and the need for surgery in these cases was not significantly reduced when antibiotics were used. In line with the recently published NICE guidelines,[1] prophylactic antibiotics should not be routinely offered to patients with AP.

In cases where infection is clinically suspected or confirmed, antibiotics should be used sensibly in order to avoid the development of antimicrobial resistance. The predictive value of fine needle aspiration for sampling and determination of bacterial sensitivities in the diagnosis of (peri-)pancreatic infection is comparable to that of clinical signs and imaging; therefore its routine use is controversial.

Nutrition: the historical approach whereby patients were put on 'nil-by-mouth' and parenteral nutrition support, advocating for reduced stimulation of pancreatic exocrine secretion, which was thought to worsen the associated inflammatory process, is no longer recommended. Early enteral feeding has a role in maintaining the integrity of the intestinal mucosal barrier, as well as preserving intestinal motility; these in turn reduce bacterial translocation and subsequent infective complications of pancreatic necrosis. With respect to the timing of feeding, early feeding supports the nutritional requirements and modulation of the oxidative stress response associated with a hypercatabolic state in the early stages of AP.

Early enteral feeding is recommended by the AGA since an analysis of 11 RCTs showed that delayed oral feeding is associated with an increased (2.5-fold) risk of surgical intervention, pancreatic necrosis and infective complications, multiorgan failure and total pancreatic necrosis. Early enteral feeding (within 24–72 hours into the admission) is also recommended in the IAP/APA and NICE guidelines for patients with mild pancreatitis; in severe cases, feeding should be commenced once the patient has been fully resuscitated using either normal enteral or enteral tube feeding.[1]

However, a first multicentre randomized study of 208 AP patients (the Pancreatitis, Very Early Compared with Selective Delayed Start of Enteral Feeding (PYTHON) study) assessed the benefits of early enteral tube feeding (<24 hours) versus an oral diet initiated 72 hours into admission. The trial results did not show any significant difference between the groups in terms of infective complications (30% versus 27%, respectively) and mortality (11% versus 7%, respectively).

In patients who do not tolerate normal enteral feeding, there is a choice between nasojejunal and nasogastric tube feeding. Previous evidence has supported the use of nasojejunal over nasogastric tube feeding to reduce pancreatic stimulation and subsequent worsening of inflammation, as well as to avoid complications such as tube migration and aspiration leading to pneumonia. However, recent evidence has suggested comparable complication rates and similar benefit from both. Nasogastric tubes are, however, logistically simpler to use, and nasojejunal tubes could be reserved for cases where patients are not able to tolerate the former, or when adequate energy balance cannot be achieved with nasogastric tube feeding. In patients who are severely ill or require intensive therapy unit care, supplementation of inadequate enteral nutrition using parenteral access is required in case caloric intake needs are not met with enteral feeding.[2]

With respect to the timing of parenteral nutrition in this cohort of patients, a meta-analysis was undertaken that included four RCTs and two observational studies comparing early (<48 hour into admission) and late (>7 days into admission) initiation of parenteral supplementation. This reported the delayed approach to be superior to early nutrition, with a significantly lower incidence of infections, enhanced recovery and shorter hospital stay. Further evidence is required to determine the ideal timing of initiation of supplemental parenteral nutrition.

Endoscopic retrograde cholangio-pancreatography (ERCP): despite past evidence supporting the early use of ERCP with or without sphincterotomy in cases of acute biliary pancreatitis, recent evidence has shown no benefit in cases where there is no accompanying cholangitis. However, ERCP within 24–72 hours into admission with acute biliary pancreatitis complicated by cholangitis improves associated morbidity and mortality rates. As most patients are likely to spontaneously pass biliary calculi within 24 hours after the onset of acute biliary pancreatitis, ERCP is held back until after the first 24 hours into admission. This approach is supported by the results of six meta-analyses and systematic reviews demonstrating that, in the absence of cholangitis and persistent biliary obstruction, early ERCP (24–72 hours into hospital admission) is not associated with a reduction in local or systemic complications and mortality.

The AGA (2018) does not recommend the use of early routine ERCP apart from in patients in whom associated cholangitis exists. These recommendations were based on eight RCTs, albeit regarded as low quality.[2] In the absence of sonographic and laboratory-based evidence for gallstones or biliary obstruction, and with no associated cholangitis, MRCP or EUS should be performed rather than a diagnostic ERCP. With a diagnostic yield of >80%, EUS is associated with significantly fewer complications than ERCP (10–15%) while allowing for an identification of biliary and pancreatic neoplasms <2.5 cm in size, outperforming cross-sectional CT imaging. In cases where EUS fails to establish the aetiology, secretin-stimulated MRCP can be of value when rare anatomical variations are linked to the aetiology.

Post-ERCP pancreatitis is a known complication of ERCP and is encountered in up to 30% of high-risk patients undergoing the procedure. The European Society for Gastrointestinal Endoscopy recommends the use of rectally administered non-steroidal anti-inflammatory drugs (NSAIDs; e.g. 100 mg indometacin) in low-risk patients, and consideration of placement of a prophylactic 5 French gauge pancreatic stent in addition to rectal NSAIDs in high-risk patients.

Cholecystectomy: recurrent gallstone-related complications can be reduced in mild cases of AP by performing a same-admission cholecystectomy; this approach is currently recommended by the 2018 AGA guidelines.[2] Clinical outcomes in patients undergoing index admission versus interval cholecystectomy were compared in a multicentre RCT that included 266 patients with mild gallstone pancreatitis. Patients were randomized into an early (same-admission) cholecystectomy and a delayed (25–30 days after discharge) cholecystectomy group. Significantly lower rates of gallstone-related complications (odds ratio (OR) 0.24, 95% (confidence interval) CI 0.09–0.61) were observed in the index admission cholecystectomy cohort compared with patients who underwent delayed removal of the gallbladder. In addition, a lower incidence of recurrent pancreatitis (OR 0.25 95% CI 0.07–0.90), as well as a lower risk of perioperative complications, was observed with this approach.

The 2016 National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) report on AP recommends early cholecystectomy (during the index admission or within 2 weeks of discharge) in mild AP, and a delayed intervention after resolution of pancreatitis in severe disease.

Local complications of acute pancreatitis: pancreatic and peri-pancreatic fluid collections (PFCs) are known complications of AP; they include pancreatic pseudocysts and walled-off necrosis (WON).

The Revised Atlanta Classification (2012) distinguishes four subtypes of peri-pancreatic collections (Table 3). Acute collections develop within 4 weeks of onset of the acute episode of pancreatitis and can be purely fluid or have a necrotic component (Figure 2). Most acute collections resolve spontaneously, but around 15% fail to resolve, often maturing and progressing to pseudocysts or WON. Pancreatic pseudocysts and WON represent a matured form of these collections that often develop over a course of 4–8 weeks, by which time they are encapsulated by a fibrous pseudocapsule that develops secondary to the surrounding inflammatory response. Pseudocysts are composed of a homogenous pancreatic fluid collection, whereas a WON is heterogenous in density and contains a mixture of fluid and necrotic debris.

Although sterile and asymptomatic collections often resolve over time and can be observed, intervention is clearly indicated by infected necrosis and subsequent clinical deterioration or the presence of a sterile collection that causes intestinal or biliary luminal obstruction. Pseudocysts most often resolve spontaneously, but if they become symptomatic, drainage is advised; this can be achieved percutaneously or endoscopically. Collections complicated by pancreatic necrosis are diagnosed based on clinical signs suggestive of sepsis, and confirmed by evidence of a gaseous component on cross-sectional imaging.

The ATLANTA 2012 classification of pancreatic fluid collections

Pancreatic collection	Morphological features	Maturation time (weeks)	Intervention
Non-necrotic collections (interstitial oedematous pancreatitis)			
Acute peri-pancreatic collection	• Homogenous fluid density without non-fluid components • Non-encapsulated • Peri-pancreatic	≤4	• Usually self-resolving
Pancreatic pseudocyst	• Homogenous fluid density without non-fluid components • Complete encapsulation • Peri-pancreatic	>4	• Usually self-resolving • If symptomatic, can be drained percutaneously or endoscopically
Necrotic collections (necrotizing pancreatitis)			
Acute necrotic collection	• Heterogenous density, often loculated • Non-encapsulated • Intra- or peri-pancreatic	≤4	• Symptomatic sterile or infected • Surgical/endoscopic drainage
Walled-off necrosis (WON)	• Heterogenous density • Complete encapsulation • Intra- or peri-pancreatic	>4	• Symptomatic sterile or infected • Surgical/endoscopic debridement

The ATLANTA 2012 classification distinguishes four types of pancreatic fluid collection. Non-necrotic acute peri-pancreatic collections and pancreatic pseudocysts are associated with interstitial oedematous pancreatitis, whereas acute-necrotic collections and WON are features of necrotizing pancreatitis.

Table 3

Figure 2 Abdominal (transverse section) CT image showing features of severe pancreatic necrosis. A walled-off collection is seen in the body/tail of the pancreas, with gas bubbles (arrow) that are suggestive of an infected component.

Management of persistent and necrotic peri-pancreatic collections: as pancreatic necrosis is associated with significant mortality (>30%), interventions for debridement and sepsis control should be prompt. Distinguishing pseudocysts from WON is crucial as they differ in management and prognosis. MRI and EUS are superior to CT as the latter often underestimates the anatomy and extent of solid necrotic debris. In one study, CT identified the presence of solid necrotic debris in PFCs in only 32% of patients; EUS, however, identified necrosis in 92% of patients ($p < 0.001$).

The traditional open surgical approach for the management of collections complicated by necrosis is associated with significant rates of complications, so minimally invasive approaches are gaining favour as a safer alternative.

Open surgical debridement – open surgical necrosectomy is performed using laparotomy and blunt debridement of necrotic tissue at least 4 weeks after disease onset to allow for maturation and localization of the necrotic collection. Open surgical drainage has, however, been associated with a high rate of complications (up to 95%) and mortality (39%) compared with less invasive approaches such as image-guided percutaneous drainage. A minimally invasive step-up approach (compared with open necrosectomy) is now favoured, as it has been shown to reduce the rate of major complications or death among patients with necrotizing pancreatitis and infected necrotic tissue, based on the results of the PANTER (Minimally invasive 'step-up approach' versus maximal necrosectomy in patients with acute necrotising pancreatitis) trial published in 2010.

Minimally invasive approaches – a 'step-up' approach can delay and often avoid the need for surgical interventions and to lower overall procedure-associated morbidity. In this, initial conservative management is followed by less invasive percutaneous or endoscopic drainage performed for sepsis control as well as management of pancreatic necrosis. Imaging (US or CT)-guided percutaneous drainage allows positioning of a large-bore drain (often more than one) within the necrotic area, preferably through a retroperitoneal approach to minimize the risk of potential contamination associated with a trans-peritoneal approach. As a next step, a less invasive approach such as video-assisted retroperitoneal debridement (in which a videoscope is inserted through a dilated percutaneous drain tract, allowing visualization of necrosis and debridement using laparoscopic forceps) can be performed; alternatively, laparoscopic or endoscopic (transluminal) drainage can be employed. Although percutaneous drainage is often used as a bridging step to further intervention (surgical or endoscopic), there is evidence to suggest that it allows definitive management in up to 50% of cases of necrotizing pancreatitis.

The recently published TENSION (Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis) trial[3] compared endoscopic (EUS-guided drainage with or without necrosectomy) and surgical step-up (percutaneous drainage with or without video-assisted retroperitoneal debridement) approaches in terms of complications (43% versus 45%, respectively) and mortality (18% versus 13%, respectively); the authors reported comparable rates with the two approaches. Lower rates of pancreatic fistula formation as well as shorter hospital admissions were observed with the endoscopic approach.

Recently published NICE guidelines (2018)[1] recommend an endoscopic approach and consideration of delaying drainage until the (peri-)pancreatic collection has reached the stage of WON, a process that usually takes 4–6 weeks, at which time drainage can be followed by necrosectomy when needed.

Laparoscopic surgical debridement – laparoscopic debridement allows visualization and complete removal of the necrotic tissue through a percutaneous port. It is, however, associated with up to a 36% risk of peritoneal spread of infection. In addition, induction of a pneumoperitoneum in critically ill patients increases the risk of cardiovascular and respiratory complications.

Endoscopic transluminal drainage – transluminal drainage using stent placement to keep the drainage tract patent is an increasingly popular technique (Figure 3). The performance of lumen-apposing metal stents (LAMSs) versus plastic stents in management of PFCs has recently been evaluated in a meta-analysis involving 2213 patients in 41 studies.[1] LAMSs were superior to plastic stents, with reduced rates of complications

Figure 3 A lumen-apposing metal stent positioneed through the posterior gastric wall into the peri-pancreatic collection.

Figure 4 Necrotic debris seen during endoscopic necrosectomy.

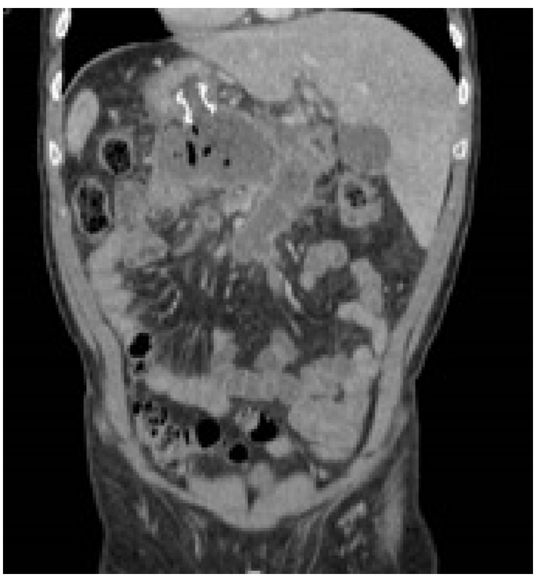

Figure 5 Abdominal (coronal) CT image showing a transgastrically placed LAMS positioned in WON.

such as bleeding (5.6% versus 12.6%, respectively; $p = 0.02$), perforation (2.8% versus 4.3%, respectively; $p = 0.2$) and occlusion (9.5% versus 17.4%, respectively; $p = 0.07$). The stent migration rate was similar (8.1% versus 5.1%; $p = 0.1$). Endoscopic drainage of PFCs using a LAMS is safe, technically feasible and efficient for the management of both pancreatic pseudocysts and WON, as was recently reported in a multicentre prospective case-series study from the UK and Ireland.[4]

For the drainage of pancreatic fluid collections, the use of a pigtail plastic stent that is positioned through the LAMS, can prevent occlusion of the LAMS by necrotic and food debris.[4,5]

Endoscopic guided debridement – endoscopic necrosectomy (Figure 4) can be performed as a next step after failure of percutaneous or endoscopic drainage procedures. Several endoscopic techniques can be used. The most common ones include direct endoscopic necrosectomy and transluminal drainage, involving the creation of a fistula between the stomach (cystgastrostomy) or duodenum (cyst-duodenostomy) using plastic or metal stents (e.g. LAMS), as well as the use of pigtail stents to maintain tract patency. In addition, EUS-guided drainage has become the gold standard in the USA, considering its safety and higher technical success rates compared with traditional endoscopic techniques.

Direct endoscopic necrosectomy involves the trans-oral insertion of a flexible endoscope that is positioned in either the stomach or duodenum depending on the anatomical location of the target collection. Mechanical removal of the necrotic debris is followed by irrigation and stent placement, and the contents are allowed to drain into the stomach or duodenum (Figure 5). Compared with surgical debridement, endoscopic necrosectomy offers a safer approach as it is associated with fewer complications, reduced morbidity, a shorter hospital stay and improved quality of life.[3] ◆

KEY REFERENCES

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 48-year-old man presented with a 10-hour history of severe epigastric abdominal pain. The pain was of sudden onset, radiating to the back, and associated with nausea and vomiting. He had attended a wedding the day before, where he had consumed 5 pints of lager. The patient reported having had a

cholecystectomy 2 years previously, and also mentioned regular heavy alcohol consumption.
On clinical examination, his temperature was 37.0°C, heart rate 88 beats/minute, and blood pressure 128/87 mmHg. There was epigastric tenderness.

Investigations

- Haemoglobin 140 g/litre (130–180)
- White cell count 13.5 × 10^9/litre (4.0–11.0)
- Platelets 160 × 10^9/litre (150–400)
- Serum bilirubin 16 micromol/litre (1–22)
- Serum alanine aminotransferase 30 U/litre (5–35)
- Serum aspartate aminotransferase 22 U/litre (1–31)
- Serum alkaline phosphatase 90 U/litre (45–105)
- Serum lipase 110 U/litre (0–60)
- Serum amylase 730 U/litre (60–180)

The most appropriate resuscitation measures include:

A. Early aggressive fluid resuscitation (30 ml/kg bolus of Ringer's lactate followed by 3 ml/kg per hour) with analgesia
B. Early fluid resuscitation (10 ml/kg bolus of 0.9% sodium chloride solution followed by 1.5 ml/kg per hour), analgesia and broad-spectrum antibiotics
C. Early goal-directed fluid resuscitation (5–10 ml/kg per hour of Ringer's lactate), analgesia and broad-spectrum antibiotics
D. Early goal-directed fluid resuscitation (5–10 ml/kg per hour of Ringer's lactate) and analgesia
E. Early aggressive fluid resuscitation (20 ml/kg bolus of Hartmann's solution followed by 3 ml/kg per hour), analgesia and broad-spectrum antibiotics

Question 2

A 36-year-old woman presented with a 2-hour history of sharp epigastric abdominal pain radiating to the back, and feeling generally unwell. She was awaiting elective cholecystectomy the following week.
On clinical examination, her temperature was 38.9°C, heart rate 110 beats/minute, and blood pressure 110/76 mmHg. Severe epigastric tenderness was observed.

Investigations

- Haemoglobin 140 g/litre (130–180)
- White cell count 22.1 × 10^9/litre (4.0–11.0)
- Platelets 290 × 10^9/litre (150–400)
- Serum bilirubin 41 micromol/litre (1–22)
- Serum aspartate aminotransferase 80 U/litre (1–31)
- Serum alkaline phosphatase 170 U/litre (45–105)
- Serum lipase 90 U/litre (0–60)
- Serum amylase 600 U/litre (60–180)
- CT scan of the abdomen with contrast showed features consistent with acute pancreatitis, thickening of the gallbladder wall, a small pericholecystic fluid collection and dilatation of the common bile duct with an 8 mm obstructing stone

After fluid resuscitation, analgesia and antibiotics, assessment of the biliary tree should follow using:

A. Magnetic resonance cholangio-pancreatography (MRCP) imaging
B. Endoscopic ultrasound of the biliary tree
C. Urgent cholecystectomy
D. Conservative management, as the stone is likely to pass spontaneously
E. Endoscopic retrograde cholangio-pancreatography (ERCP)

Question 3

A 51-year-old man presented with a 6-hour history of severe epigastric pain, nausea and vomiting. An episode of gallstone pancreatitis had been managed conservatively 3 weeks previously. Although he had a history of hypertension, he was not currently taking any medications. He did not drink alcohol.
On clinical examination, his temperature was 39.1°C, heart rate 115 beats/minute, blood pressure 87/50 mmHg and respiratory rate 24/minute. He was oliguric and required intensive monitoring.

Investigations

- Haemoglobin 140 g/litre (130–180)
- White cell count 18.0 × 10^9/litre (4.0–11.0)
- pH 7.31
- PO_2 14 kPa (11–13)
- PCO_2 3.7 kPa (4.7–6)
- Bicarbonate 18 mEq/litre (22–26)
- Serum lactate 3 mmol/litre (0.6–1.8)
- CT scan of the abdomen showed peri-pancreatic fluid, features of pancreatic body necrosis and massive fluid collections in the paracolic gutters

What is the best approach to nutritional support for this patient?

A. Nil-by-mouth with intravenous fluid administration
B. Early oral feeding
C. Delayed enteral feeding (>72 hours into admission)
D. Early enteral nutrition should be commenced
E. Nil-by-mouth and total parenteral nutrition