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 by radiological assessments such as the CT severity index. In the majority of 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 co-exist. This review summarises recent insights into the pathophysiology, investigation and treatment of acute pancreatitis, as well as common approaches for management of local complications.

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

Whats new?

- Evidence based updates to management guidelines:
  - National Institute for Health and Care Excellence – Pancreatitis (September 2018)
  - The American Gastronenterological association – Acute pancreatitis (February 2018)

- Minimally invasive approaches for the management of necrotic collections:
  - Results of the TENSION trial: Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial.
  - The use of lumen-apposing stent with coaxial plastic stent for endoscopic ultrasound-guided drainage of pancreatic fluid collections

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 for hospital admissions globally. Although the majority of cases follow a mild course, about 25% of cases are complicated by local and often life threatening systemic complications. As the incidence of AP is on the rise and the associated mortality rate remains as high as 30%, up to date evidence based knowledge of diagnostic and management strategies are essential to improve clinical outcome.

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 for the disease (1). In the UK, the estimated incidence of AP is 15-42 cases per 100,000 per year (2). 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 whilst gallstones were the leading cause in Southern Europe. In western and northern parts of the region, comparable incidence of these aetiological factors was observed (3). Although the majority of cases follow a mild course, some cases are complicated by a severe systemic inflammatory response resulting in mortality rates as high as 20% (4).

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 auto-digestion. This along with activation of other digestive enzymes causes an inflammatory response characterised by recruitments of neutrophils, macrophages and lymphocytes with release of interleukins and TNFα (5). Increased vascular permeability leads to fluid sequestration and oedema while haemorrhage and necrosis are rarely observed. In severe cases, a systemic inflammatory response can lead to sepsis and multi organ failure (5,6). Several mechanisms by which alcohol induces AP have been suggested. Early studies focusing on the stimulatory effect of alcohol on the Sphincter of Oddi have yielded conflicting results, showing both increased and decreased sphincter tone. In addition to a direct toxic effect induced by alcohol and its toxic metabolites (acetaldehyde; reactive oxygen species) on acinar and pancreatic stellate cells, experimental studies have proposed that alcohol increases the concentrations of digestive and lysosomal enzymes within acinar cells and their close contact facilitates their pathological activation. Moreover, alcohol induces precipitation of self-aggregating, non-digestive enzymes (i.e. lithostathine and glycoprotein 2) inducing formation of duct-obstructing protein plugs that result in intra-pancreatic duct obstruction, scarring and fibrosis(7).

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:

1. Typical history of epigastric abdominal pain
2. Elevation of serum amylase and/or lipase of more than 3 fold the upper normal limit
3. Supportive findings on abdominal imaging (Ultrasound, Computed Tomography and/or Magnetic Resonance Imaging)

In suspected acute pancreatitis, following early resuscitation, efforts should be focused on establishing the aetiology, as the definitive treatment will vary 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 may be triggered by a fatty meal or heavy alcohol consumption. On examination, patients may show signs of hypovolaemia, diaphoresis and are often tachycardic. Examination of the abdomen reveals epigastric tenderness and voluntary guarding. In severe cases, accompanying pyrexia may be suggestive of pancreatic necrosis and systemic inflammation. Ecchymoses in the peri-umbilical area and flanks (Cullen’s and Grey-Turner signs, respectively) are indicative of a haemorrhagic component, but are rarely observed (8).

Laboratory investigations

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

Elevated serum levels of amylase and lipase are evident a few hours after the onset of AP. Amylase levels normalise after 2-4 days, whereas lipase returns to normal within 8-14 days (9). Amylase can be falsely elevated in the absence of AP in several other conditions (e.g. acute appendicitis, cholecystitis, peptic ulcer, salivary gland disease) and can also remain within the normal range in up to 19% of cases of AP (10). Increased serum levels of liver enzymes at the time of presentation are highly suggestive of an aetiology attributed to biliary tract obstruction (11). Abnormalities in renal function markers indicate renal injury that could be secondary to third space fluid sequestration and intravascular depletion.

Due 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 (ABG) analysis.

Imaging in acute pancreatitis

Chest and abdominal radiographs

Plain radiographs are non-diagnostic in AP. In severe cases of AP, the presence of pleural effusions and parenchymal infiltrates may be observed on chest radiographs (12). On abdominal radiographs, a sentinel loop (an isolated loop of bowel usually located centrally) suggests intestinal ileus. Rarely, pancreatic calcifications in chronic pancreatitis may be identified.

Trans abdominal ultrasound (US)

US is often the preferred technique when the suspected aetiology is gallstones. It is an inexpensive and readily available modality that allows visualisation of the biliary tree and gallbladder. Despite being highly sensitive for identifying gallbladder stones (up to 90%), in the setting of AP, adequate visualisation of the common bile duct is often challenged by overlying bowel containing gas. Patient body habitus and operator skills may pose further challenges to its use (13).

Computed tomography (CT)

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, and 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 following initial presentation should have an expedited CT to exclude other causes of an acute abdomen. Disease severity is also more accurately assessed using a delayed CT, as CTs performed <96 hours from the onset of AP can underestimate disease severity (14,15).

Magnetic resonance imaging (MRI)

Magnetic Resonance Cholangiopancreatography (MRCP) is superior to CT in the diagnosis of biliary tract stones smaller than 3mm and offers better delineation of pancreatic and ductal anatomy (16). 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 fail to establish the cause, and the aetiology remains uncertain. EUS has gained popularity in recent years due to its high sensitivity in detecting biliary sludge or stones with a sensitivity of over 95% and specificity of 97% (17) (18). In addition, features of chronic pancreatitis, pancreatic anatomical variants such as pancreas divisum as well as ampullary and pancreatic neoplasms can be detected with high accuracy (19).

Management

Assessing disease severity

Early risk stratification within 48-72 hours following the onset of symptoms allows for the prediction of potential complications, hence reducing associated morbidity and mortality. Numerous clinical, laboratory and radiological findings-based scoring systems exist that aim to aid physicians in triaging 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 back in the 1970s. These scoring systems calculate the risk of developing severe acute pancreatitis using a combination of clinical, laboratory and radiology findings (Table 2). Examples include the Acute

Physiology and Chronic Health evaluation II (APACHE-II), the Modified Glasgow-Imrie and the newer Bedside Index for Severity in AP (BISAP) the Harmless Acute Pancreatitis Score (HAPS). Past comparisons have shown a comparable predictive performance (with area under the receiver-operating curve; AUC values of around 0.70) for these scoring systems. Their use in clinical settings however, is limited due to their complexity moderate sensitivities (20) (21).

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 (characterised by transient local or systemic complications and/or organ failure lasting less than 48 hours) and severe AP (characterised by persistent organ failure for >48 hours) (22).

The APA/IPA 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 ^{o}C or >38 ^{o}C
- Respiratory rate >20 breaths/minute or PaCO2 <32 mmHg
- Pulse >90 beats/minute
- White blood cells <4.0 or >12.0 X 109/litre or >10% immature bands.

Patients who have SIRS criteria present on admission that persist for more than 48 hours have an increased risk of multi-organ failure and mortality (23).

Serum based markers

Although numerous biomarkers have been evaluated as candidate predictors of severity in AP, limits to their use in clinical practice include a lack of specificity at an early disease stage, high cost, moderate reliability and complex technicality.

The most widely used parameters are those suggestive of an inflammatory process as well as hypovolaemia. A C-Reactive Protein (CRP) of >150 mg/L at 48 hours following 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 -8), and activation peptides of pancreatic enzymes have been investigated but are not routinely used in clinical practice in the UK (24).

Markers of fluid status and hypovolaemia (BUN, creatinine and haematocrit) correlate with severity of AP and the trend in their levels from the time of admission to 24-48 hours later can predict the risk of mortality (25) (26). A large prospective study of 1,612 AP patients concluded that a haematocrit level >44% on admission with a rise in BUN at 24 hours was highly predictive for persistent organ failure and pancreatic necrosis, with accuracy outperforming clinical scoring systems (26).

Cross sectional imaging

The Computed Tomography Severity Index (CTSI) is a prognostic score that grades the severity of AP according to CT findings (27). Pancreatic and peri-pancreatic pathological changes indicative of disease severity, including features of pancreatic necrosis, can be identified using CT. However, they fail to take into account systemic (non-radiological) manifestations of AP.

Treatment

Appropriate management in the first 48-72 hours following 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(28) (29).
Severe cases accompanied by organ failure or poor prognostic signs (persistent SIRS, Glasgow score >3, APACHE score >8, and Ranson score >3), should be assessed for need of high dependency unit admission (23).

Initial resuscitation

Local and systemic inflammatory responses in AP, result in third space fluid loss which is often exacerbated by reduced fluid intake as well as increased sweating and respiration. Early fluid resuscitation aiming to avoid hypovolemia and resultant organ failure is a cornerstone of management in the first 24 hours (30). Both the type of fluids and their rate of admission have been an area of debate with numerous studies comparing the clinical outcomes associated with different fluid resuscitation regimens. Yet, to this date, no clear consensus exists with respect to the advantage of one strategy over another. A randomised controlled trial (RCT) in 60 AP patients demonstrated that early aggressive resuscitation with Ringer's lactate (20 ml/kg bolus followed by 3 ml/Kg/h) compared to a standard (10 ml/Kg bolus followed by 1.5 ml/Kg/h) regimen showed faster rate of clinical improvement with less complications and lower incidence of persistent SIRS, as assessed at 36 hours post admission (31). Overly aggressive fluid resuscitation (>4.1 L/24 h) on the other hand, was associated with a higher rate of respiratory and intra-abdominal complications as well as mortality (32). It is therefore agreed that an aggressive yet controlled hydration (3.0-4.0 L/24 h) is optimal in the early phase of AP. An early goal-directed approach to resuscitation, using 5-10 ml/Kg/h of Ringer's lactate, aiming to promptly normalise clinical and biochemical parameters (i.e: Urine output >5 ml/Kg/h, Heart rate <120 bpm and haematocrit levels of 35-45%) are encouraged by both the International Association of Pancreatology (IAP)/American Pancreatic Association(APA) and American Gastroenterological Association (AGA) (23) (29). With respect to the choice of fluid to be used – Ringer's lactate offers an advantage over normal saline with reduced rates of SIRS secondary to its anti-inflammatory properties (33) (34). The effect of the different types of fluids on specific clinical outcomes such as necrosis, organ failure and mortality have not been adequately assessed.

Abdominal pain associated with AP should be addressed promptly and adequately in order to avoid respiratory complications due to decreased ventilation. Although some RCTs focused on pain control in AP, no consensus has been reached regarding the best choice of drug and method of delivery and therefore clinicians should adhere to local peri-operative pain management guidelines (35). Bedside monitoring of acid-base balance status, arterial blood oxygenation and blood glucose levels should be routinely performed as well.

Antibiotics in acute pancreatitis

AP cases complicated by (peri) pancreatic necrosis are often subject to secondary infections that result from intestinal bacterial translocation. In severe cases complicated by secondary infections, mortality rates as high as 40% have been observed (36). Yet, the use of anti-microbial prophylaxis in attempt to reduce infective complications remains an area of controversy in terms of their impact on incidence of infection, mortality or the need for surgical intervention. A recent meta-analysis that included 11 studies (9 randomised controlled trials and 2 cohort studies), involving 864 AP patients, showed no evidence that the use of prophylactic antibiotics offered improvement in mortality rates amongst the randomised cohorts. In addition, the incidence of infective necrosis and the need for surgery in these cases, was not significantly reduced when antibiotics were used (37). In line with the recently published NICE (2018) guidelines (28), prophylactic antibiotics should not be routinely offered to patients with AP. In cases where clinical suspicion for, or a confirmed infection exist, antibiotics should be used sensibly in order to avoid development of anti-microbial resistance. The predictive value of fine needle aspiration for sampling and determination of bacterial sensitivities in diagnosis of (peri) pancreatic infection compared to clinical signs and imaging is comparable and therefore its routine use is controversial (38).

Nutrition

The historical approach where patients were put on a 'nil by mouth' and parenteral nutrition support, advocating for reduction in stimulation of pancreatic exocrine secretion which was thought to worsen the associated inflammatory process, is no longer recommended. The induction of early enteral feeding has a role in maintaining the integrity of the intestinal-mucosal barrier as well as preserving intestinal motility which in turn reduce bacterial translocation and subsequent infective complications of pancreatic necrosis (39) . With

respect to timing of feeding, early feeding supports the nutritional requirements and modulation of the oxidative stress response associated with a hypercatabolic state in early stages of acute pancreatitis (40). Early enteral feeding is recommended by the AGA, following analysis of 11 RCT results that have shown an increased risk (2.5 fold) for surgical interventions, pancreatic necrosis and infective complications, multi-organ failure as well as total pancreatic necrosis, associated with delayed oral feeding (41). Early enteral feeding (within 24-72 h into admission) is also recommended in the IPA/APA and NICE guidelines in cases of mild pancreatitis and in severe cases, feeding should be commenced once the patient has been fully resuscitated using either normal enteral or enteral tube feeding((23) (28). However, a first multi-centre randomised study in 208 AP patients (the PYTHON study) assessed the benefits of early enteral tube feeding (<24 h) versus oral diet initiated 72 hours into admission. The results of this trial did not show any significant difference between the groups in terms of infective complications (30% vs. 27% respectively) and mortality (11% vs. 7% respectively) (42). In cases where normal enteral feeding is not tolerated, the choice between a nasojejunal versus nasogastric tube feeding exists. Despite previous evidence supporting the use of nasojejunal over nasogastric tube feeding in order to reduce pancreatic stimulation and subsequent worsening of inflammation as well as avoid complications such as tube migration and aspiration leading to pneumonia, recent evidence suggest comparable complication rates and similar benefit from using either (43). The use of nasogastric tubes are logistically simpler however, and the use of 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 a nasogastric feeding tube. In severe illness and patients requiring 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 (23,29) (43). With respect to timing of parenteral nutrition in this cohort of patients, a meta-analysis which included four RCTs and two observational studies comparing early (<48h into admission) and late (>7 days into admission) initiation of parenteral supplementation in this cohort of patients reported the delayed approach as superior to early nutrition with significantly lower incidence of infections, enhanced recovery and shorter hospital stay (44). Further evidence is required to determine the ideal timing of initiation of supplemental parenteral nutrition.

Endoscopic retrograde cholangiopancreatography (ERCP)

Despite past evidence supporting the early use of ERCP with or without sphincterotomy in cases of acute biliary pancreatitis (ABP), recent evidence showed no benefit in cases where accompanying cholangitis is absent (45). However, ERCP within 24-72 hours into admission with ABP complicated by cholangitis, improves associated morbidity and mortality rates (46). As most patients are likely to spontaneously pass biliary calculi within 24 hours following the onset of ABP, the timing of ERCP is held until after the first 24 hours into admission. This approach is supported by the results of 6 meta-analysis and systematic reviews which demonstrated that in the absence of cholangitis and persistent biliary obstruction, early ERCP (24-72 hours into hospital admission) is not associated with reduction in local or systemic complications and mortality (45).

The AGA (2018) does not recommend the use of early routine ERCP apart from cases in which associated cholangitis exists. These recommendations were based on 8 RCT studies, albeit regarded as low quality (29). In the absence of sonographic and laboratory based evidence for gallstones or biliary obstruction and no associated cholangitis, magnetic resonance cholangio-pancreatography (MRCP) or EUS should be performed rather than a diagnostic ERCP. With a diagnostic yield of over 80%, EUS is associated with significantly less complications compared to ERCP (10-15%) while allowing for identification of biliary and pancreatic neoplasms smaller than 2.5cm, outperforming cross-sectional CT imaging (47). In cases where EUS fails to establish the aetiology, a secretin stimulated MRCP can be of value when rare anatomical variations are linked to the aetiology (23).

Post ERCP pancreatitis (PEP) 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 (ESGE) recommends the use of rectally administered non-steroidal anti inflammatory (NSAIDS) agents (e.g. 100mg Indomethacin) (48) in low risk patients and consideration of a prophylactic 5-Fr pancreatic stent placement in addition to rectal NSAIDS in high risk patients (49).

Cholecystectomy

Recurrent gallstone related complications can be reduced in mild cases of AP by performing a same admission cholecystectomy and this approach is currently recommended by the 2018 AGA guidelines (29). Clinical outcomes in patients undergoing index admission versus interval cholecystectomy were compared in a multi-centre RCT that included 266 patients with mild gallstone pancreatitis. Patients were randomised into an early (same admission) cholecystectomy and a delayed (25-30 days following discharge) cholecystectomy groups. Significantly lower rates of gallstone related complications (OR 0.24, 95% CI 0.09–0.61) were observed in the index-admission cholecystectomy cohort compared to those who underwent a delayed removal of the gallbladder. A lower incidence of recurrent pancreatitis (OR, 0.25; 95% CI, 0.07−0.90) as well as lower risk for perioperative complications were observed with this approach in this recent study (50). The National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) report on acute pancreatitis (2016) recommends early cholecystectomy (during the index admission or within 2 weeks of discharge) in mild AP and a delayed intervention following resolution of pancreatitis in severe disease (51)

Local complications of acute pancreatitis

Pancreatic and peripancreatic fluid collections (PFC) are known complications of acute pancreatitis and include pancreatic pseudocysts and walled off-necrosis (WON). The Revised Atlanta Classification (2012) (22) distinguishes four subtypes of peripancreatic collections (Table 3). Acute collections develop within 4 weeks of onset of the acute episode of pancreatitis and can be composed of either purely fluid or have a necrotic component (Figure 2). The majority of acute collections resolve spontaneously, however, around 15% of these collections fail to resolve and often mature and progress to pseudocysts or WON(52). Pancreatic pseudocysts and WON represent a matured form of these collections which often develop over a course of 4-8 weeks by which time they are encapsulated by a fibrous pseudo-capsule which develops secondary to the surrounding inflammatory response. Pseudocysts are composed of a homogenous pancreatic fluid collection while WON is heterogenous in density and contains a mixture of fluid and necrotic debris(22). While sterile and asymptomatic collections often resolve over time and can be observed, infected necrosis and subsequent clinical deterioration or the presence of a sterile collection that causes intestinal or biliary luminal obstruction, are clear indications for intervention (23). Pseudocysts most often resolve spontaneously, however, if these become symptomatic, their drainage is advised which can be achieved percutaneously or endoscopically. Collections complicated by pancreatic necrosis are diagnosed based on clinical signs suggestive of sepsis and confirmed by the evidence of gaseous component on cross-sectional imaging.

Management of persistent and necrotic peripancreatic collections

As pancreatic necrosis is associated with significant mortality (>30%)(53), interventions for debridement and sepsis control should be prompt. Distinguishing pseudocysts from WON is crucial as they differ in management and prognosis. whether the patient has a pseudocyst or WON. The use of MRI or 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 compared to EUS which identified necrosis in 92% of patients (p<0.001) (54).

The traditional open surgical approach for management of collections complicated by necrosis is associated with significant rates of complications and therefore 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 localisation of the necrotic collection. Open surgical drainage however, has been associated with a high rate of complications (up to 95%) and mortality (39%) compared to less invasive approaches such as image guided percutaneous drainage. A minimally invasive step-up approach (as compared with open necrosectomy) is now favoured, as it has shown reduced the rate of major complications or death among patients with necrotizing pancreatitis and infected necrotic tissue, based on the results of the PANTER trial published in 2010 (55).

Minimally invasive approaches

A ‘step-up’ approach, in which initially conservative management, followed by less invasive percutaneous or endoscopic drainage is performed for sepsis control as well as management of pancreatic necrosis, can delay and often avoid the need for surgical interventions and lower overall procedure associated morbidity (55,56) .

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 minimise risk of potential contamination associated with a trans-peritoneal approach(53). As a next step, a less invasive approach such as Video Assisted Retroperitoneal Debridement (VARD) (where a videoscope is inserted through a dilated percutaneous drain tract, allowing visualisation of necrosis and debridement using laparoscopic forceps), laparoscopic or endoscopic (transluminal) drainage can be performed. 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 necrotising pancreatitis (57). With respect to the choice between endoscopic versus surgical step-up approach, the recently published TENSION trial (58) compared endoscopic (EUS-guided drainage +/- necrosectomy) and surgical step-up (percutaneous drainage +/- VARD) approaches in terms of complications (43% vs. 45% respectively) and mortality (18% vs. 13% respectively); the authors reported comparable rates with both approaches. Lower rates of pancreatic fistula formation as well as shorter hospital admissions were observed with the endoscopic approach. Recently published NICE guidelines (2018) (28) recommend an endoscopic approach and consideration of delaying drainage until the (peri)pancreatic collection has reached the stage of walled-off necrosis, a process that usually takes 4–6 weeks, at which time drainage may be followed by necrosectomy when needed.

Laparoscopic surgical debridement

Laparoscopic debridement allows visualisation 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 the infection. In addition, pneumoperitoneum induction in critically ill patients increases the risk for cardiovascular and respiratory complications(53).

Endoscopic transluminal drainage

Transluminal drainage using stent placement in order to keep the drainage tract patent is an increasingly popular technique (Figure 3). The performance of LAMS versus plastic stents in management of PFCs has been recently evaluated in a meta-analysis involving 2213 patients in 41 studies(28). The use of LAMS was superior to plastic stents with reduced rates of complications such as bleeding (5.6% vs 12.6% respectively; P = 0.02), perforation (2.8% vs 4.3%, P = 0.2) and occlusion (9.5% vs 17.4%, P = 0.07). Stent migration rate was also similar (8.1% vs 5.1%; P = 0.1). Endoscopic drainage of PFCs using LAMS is a safe, technically feasible and efficient in management of both pancreatic pseudocysts and WON as was recently reported in a multicentre prospective case series study from the UK and Ireland (59) .
In cases of pancreatic fluid collection drainage, the use of a pigtail plastic stent which is positioned through the LAMS, may prevent occlusion of the LAMS by necrotic and food debris(60) (59).

Endoscopic guided debridement

Endoscopic necrosectomy (Figure 4) can be performed as a next step following failure of percutaneous or endoscopic drainage procedures. Several endoscopic techniques can be used and most common ones include Direct Endoscopic Necrosectomy (DEN) and transluminal drainage which includes creation of a fistula between the stomach (cyst-gastrostomy) or duodenum (cyst-duodenostomy) using plastic or metal stents (e.g. LAMS – Lumen apposing metal stent) as well as the use of pigtail stents to maintain tract patency(61). In addition, the use of EUS guided drainage has become the gold standard in the united States considering its safety and higher technical success rates compared to traditional endoscopic techniques (62). DEN involves a trans-oral insertion of a flexible endoscope which is positioned either in the stomach or duodenum depending on anatomical location of the target collection. Mechanical removal of the necrotic debris followed by irrigation and stent placement are performed and the contents are allowed to drain into the stomach or duodenum (Figure 5) (62). Compared to surgical debridement, endoscopic necrosectomy offers a safer approach as it is associated with less complications, reduced morbidity, a shorter hospital stay as well as improved quality of life (56,58).

Summary

AP is a common and potentially life-threatening gastrointestinal (GI) condition with a globally increasing incidence and related hospital admissions. While most cases are mild and can be managed with adequate fluid resuscitation and analgesia, a substantial proportions of cases are subject to development of severe disease with local and systemic complications (i.e. fluid collections, pancreatic necrosis) requiring more invasive monitoring and interventions. In severe cases, prompt stratification of severity is crucial in order to ensure adequate support and timely therapeutic interventions. 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.

Tables and figures

Table 1: Aetiological factors for acute pancreatitis

Risk factors and causes of acute pancreatitis

- Cholelithiasis, choledocholithiasis, microlithiasis
- Alcohol
- Smoking
- Diabetes mellitus type 2
- Hypercalcaemia, Hypertriglyceridaemia
- Pancreatic anatomical abnormalities (e.g. pancreas divisum)
- Genetic: Cystic fibrosis, hereditary pancreatitis
- Post-Endoscopic retrograde cholangiopancreatography
- Autoimmune
- Viral infections: Mumps, Coxsackie virus, HIV
- Venom: scorpion, spider
- Pancreatic duct obstructing lesions: pancreatic tumours, peri-ampullary tumours, sphincter of Oddi dysfunction
- Idiopathic

Common Medications:

- Acetaminophen
- Azathioprine
- Enalapril
- Erythromycin
- Furosemide
- Mercaptopurine
- Oestrogens
- Olanzapine
- Opiates
- Simvastatin
- Steroids
- Sulphonamides
- Tetracycline
- Valproate

Table 2: Acute pancreatitis severity scoring systems

Parameter	Glasgow score (within 48h)	Ranson (on admission and at 48h)	APACHE II (on admission -then daily)	BISAP
Clinical				
Age	-	>55	✓	>60
Comorbidity	-	-	✓	SIRS
Temperature	-	-	✓	-
Heart rate	-	-	✓	-
Respiration rate	-	-	✓	-
Mean arterial blood pressure (mmHg)	-	-	Shock / <90	-
Glasgow coma scale	-	-	✓	<15
Fluid sequestration	-	>6 litre	-	-
Laboratory				-
WCC (X 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		-
Urea (serum; mmol/litre) following hydration	>16	>1.8 ⬆	Renal failure	BUN>8.9
Albumin (serum; g/litre)	<32	-		-
AST (U/litre)	>200	>250		-
LDH (U/litre)	>600	>350		-
PaO2 (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 in, decrease in; WCC – white cell count; BUN – blood urea nitrogen; AST - Aspartate transaminase;LDH- Lactate dehydrogenase

Table 3: The ATLANTA 2012 classification distinguishes four types of pancreatic fluid collections; The non-necrotic acute peripancreatic collection and pancreatic pseudocysts are associated with interstitial oedematous pancreatitis while acute-necrotic collections and walled off necrosis (WON) are features of necrotising pancreatitis.

Pancreatic collection	Morphological features	Maturation time (weeks)	Intervention
Non necrotic collections (Interstitial oedematous pancreatitis)			
Acute peripancreatic collection (APC)	• Homogenous fluid density without non-fluid components • Non encapsulated • Peripancreatic	≤4	• Usually self-resolving
Pancreatic Pseudocyst	• Homogenous fluid density without non-fluid components • complete encapsulation • peripancreatic	>4	• Usually self-resolving • If symptomatic can be drained percutaneously or endoscopically
Necrotic collections (Necrotising pancreatitis)			
Acute necrotic collection (ANC)	• Heterogenous density, often loculated • Non encapsulated • Intra or peripancreatic	≤4	• symptomatic sterile or infected • Surgical/endocopic drainage
Walled off necrosis (WON)	• Heterogenous density • Complete encapsulation • Intra or peripancreatic	>4	• Symptomatic sterile or infected • Surgical/endoscopic debridement

Figure 1. Abdominal (transverse section) Computed Tomography image showing features of interstitial oedematous pancreatitis. Oedema of the distal pancreatic region with peripancreatic fat stranding (arrow).

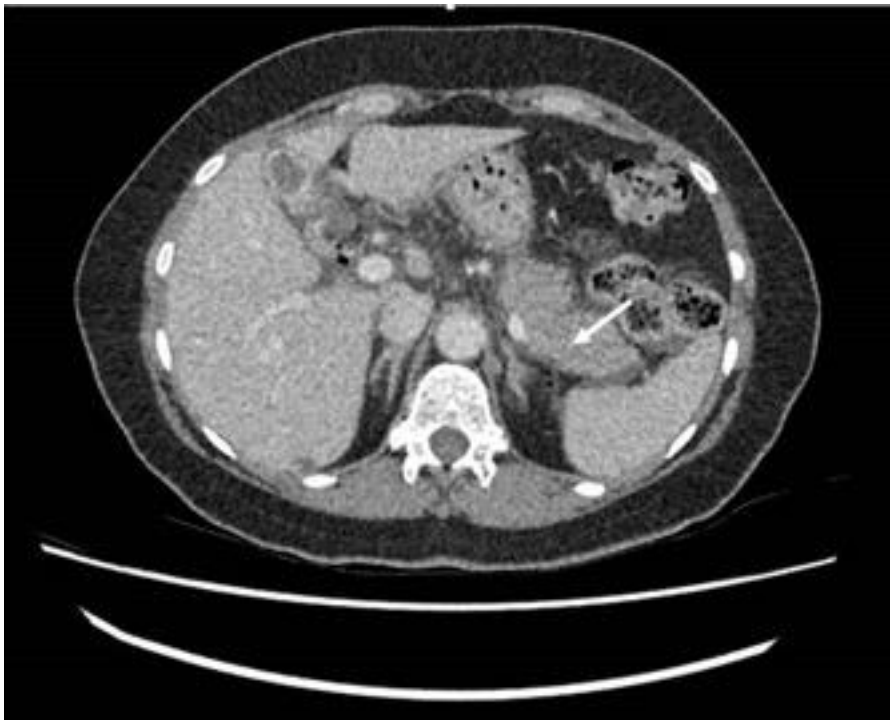


Figure 2. Abdominal (transverse section) Computed Tomography image showing features of severe pancreatic necrosis. A walled-off collection is seen in the body/tail of the pancreas with gas bubbles (arrow) suggestive of an infected component.

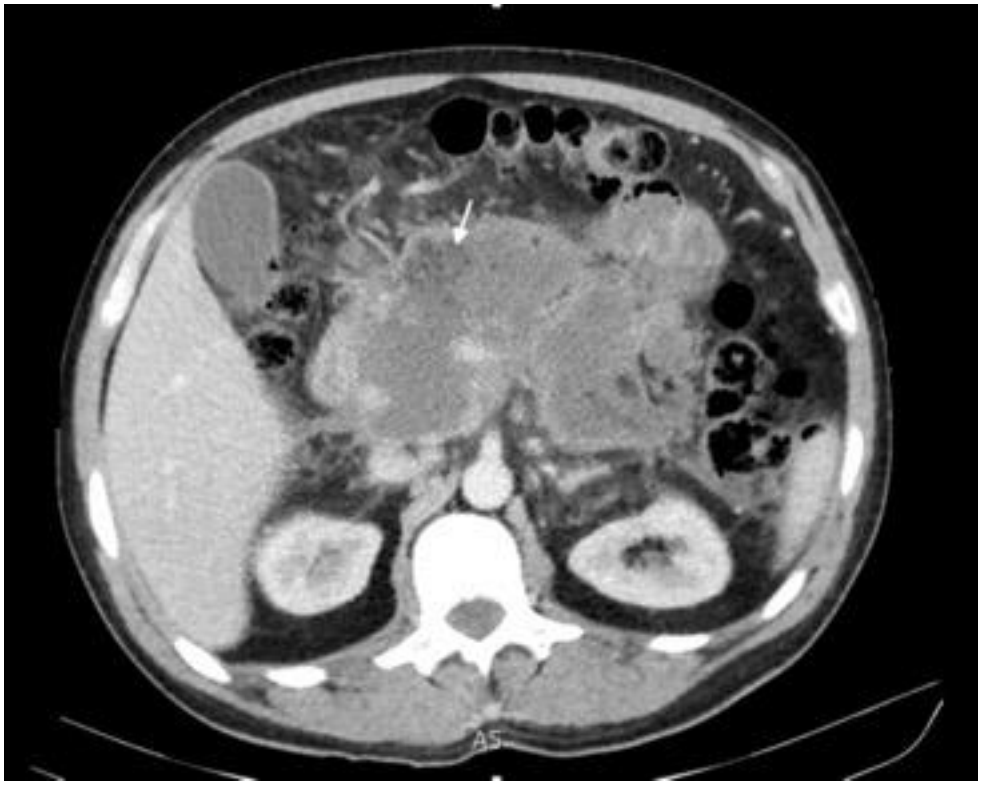


Figure 3. Lumen Apposing Metal Stent (LAMS) positioned through the posterior gastric wall into the peripancreatic collection.

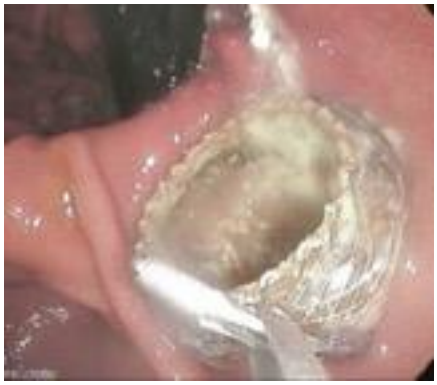


Figure 4. Necrotic debris as seen during endoscopic necrosectomy

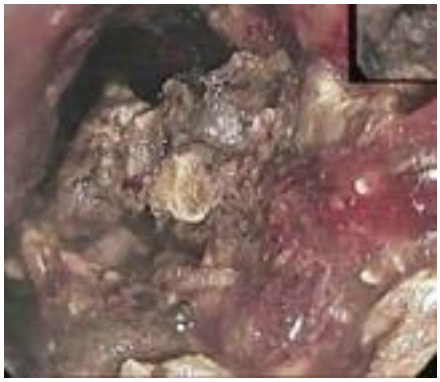
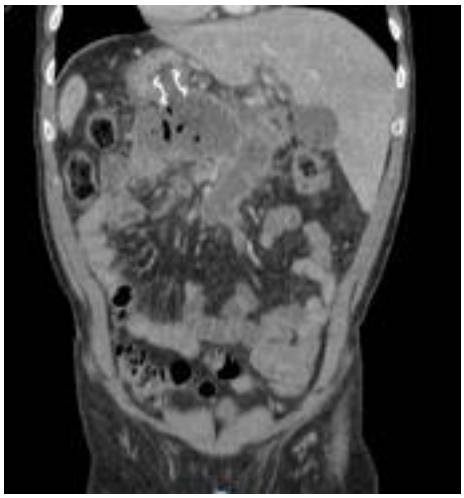


Figure 5. Abdominal (coronal) Computed Tomography image showing a trans-gastrically positioned Lumen apposing metal Stent positioned into walled off necrosis.



Self-assessment questions

Case 1

A 48-year-old caucasian male with a history of alcohol abuse presented with severe epigastric abdominal pain of a 10 h duration . The pain was described as sudden onset, radiating to the back, and was accompanied by nausea and vomiting. He reports attending a wedding the day before where he consumed 5 pints of lager. His relevant past medical history included a cholecystectomy 2 years ago. On physical examination, his vital signs were within normal limits with epigastric tenderness.

His laboratory tests on admission revealed a WBC of 13.5 × 10^3/µL, a haemoglobin level of 14 g/dL, and platelets 160 × 10^3/µL. His liver function tests including bilirubin levels were within normal reference ranges. Serum amylase and lipase levels were 730 IU/L and 110 IU/L, respectively. Acute pancreatitis secondary to alcohol was clinically diagnosed in the accident and emergency department.

What is the most appropriate next step in this patient's management?

A. Immediate risk stratification using the Glasgow- Imrie scoring system, followed by early aggressive fluid resuscitation (20 ml/kg bolus followed by 3 ml/Kg/h) and broad spectrum antibiotics. Alcohol intervention should be performed.

B. An immediate CT scan to rule out pancreatic necrosis, followed by early fluid resuscitation (10 ml/Kg bolus followed by 1.5 ml/Kg/h), analgesia and broad spectrum antibiotics. Patient should be kept nil by mouth.

C. Early goal directed fluid resuscitation (5-10 ml/Kg/h of Ringer's lactate) and analgesia. Clinical severity assessment at 48 hours post admission +/- abdominal computed tomography scan at 96h. Alcohol intervention should be performed.

D. Early goal directed fluid resuscitation (5-10 ml/Kg/h of Ringer's lactate) and analgesia. MRI scan should be arranged to rule out biliary stones as cause of AP. Clinical severity assessment at 48 hours post admission.

E. early aggressive fluid resuscitation (20 ml/kg bolus followed by 3 ml/Kg/h) and analgesia followed by Clinical severity assessment and admission to a high dependency unit.

Feedback: The correct answer is C. Typical history and pain supported by biochemical diagnosis of AP (elevated amylase and lipase levels) confirm a clinical diagnosis of AP. Clinical severity scoring is best done at 48-72 hours into admission. Early CT scan is not indicated in this case as the diagnosis is corroborated by clinical and laboratory findings, and should be reserved until 3-4 days into admission if patients fail to improve or show signs of complicated disease. An early goal-directed approach to resuscitation, using 5-10 ml/Kg/h of Ringer's lactate, aiming to promptly normalise clinical and biochemical parameters (i.e: Urine output >5 ml/Kg/h, Heart rate <120 bpm and haematocrit levels of 35-45%) are recommended by both the International Association of Pancreatology (IAP)/American Pancreatic Association(APA) and American Gastroenterological Association (AGA).

Case 2

A 36-year-old asian female presented with a two hour history of sharp epigastric abdominal pain radiating to the back and feeling generally unwell. She is awaiting cholecystectomy which is electively scheduled for the following week but no other significant medical history. On physical examination, she was febrile with a temperature of 38.9°C, heart rate of 110 beats/min, and a blood pressure of 110/76 mm Hg. Examination of the abdomen reveals severe epigastric tenderness. The remainder of her physical exam was normal.

A full blood count showed a WBC of 22.1 × 10^9/L with neutrophils 88%, a hemoglobin level of 14.0 g/dL, and platelets 290 × 10^3/µL. Her metabolic panel showed elevation in serum bilirubin 41umol/L (<20 µmol/L), Alkaline phosphatase (ALP) of 170 U/L (30-130 U/L) and Aspartate amino-transferase (AST) of 80 U/L (0-45U/L). Her serum amylase was 600 IU/L (20–160 U/L) and lipase was 90 IU/L (0-60 U/L).

As the patient was unwell and without a clear diagnosis an abdominal CT scan with intravenous contrast was performed at 12 hours into her admission. This showed features consistent with acute pancreatitis as well as thickening of her gallbladder wall with a small pericholecystic fluid collection and dilatation of her common bile duct with an 8 mm obstructing stone. Ascending cholangitis was clinically diagnosed. The patient was fluid resuscitated and commenced on antibiotics and analgesia and was admitted to a high dependency unit for observation.

The next step in assessment of this patient's biliary tree should be:

A. Magnetic resonance cholangiopancreatography (MRCP) imaging should be performed within 24-48 hours as an elevated ALP supports biliary stones as aetiology

B. Endoscopic ultrasound (EUS) of the biliary tree should be performed to look for microlithiasis or biliary sludge within 24 hours

C. Cholecystectomy should be performed immediately

D. This patient can be managed conservatively and requires no further imaging as she is likely to pass the biliary stone spontaneously

E. A diagnostic Endoscopic retrograde cholangio-pancreatography should be performed early (24-48 hours).

Feedback: answer E is correct. This patients shows features of biliary obstruction with ascending cholangitis. An early ERCP (within 24-48 hours) is recommended by the American Gastroenterological Association (AGA) 2018 guidelines. Cholecystectomy should be offered during the index admission or within 2 weeks of discharge in cases of mild AP.

Case 3

A 51 year old male bus driver presented to the emergency department with a 6 hour history of severe epigastric pain, nausea and vomiting. He reports a previous admission with gallstone pancreatitis managed conservatively three weeks prior to this admission. His medical history includes hypertension but he is currently not taking any medications for it. He denied alcohol consumption. On physical examination, the patient was found to be febrile (39.1^{o}C),oliguric, tachypnoeic and hypotensive and required intensive monitoring. A comprehensive blood panel showed elevation of his white blood cell count (18x10^{9}/L) and an arterial blood gas analysis revealed a metabolic acidosis with lactate levels of 3 mmol/L. A CT scan was requested which showed presence of peri-pancreatic fluid, features of pancreatic body necrosis and massive fluid collections in his para-colic gutters. He was resuscitated and commenced on intravenous anti-biotics.

With respect to management of this patient's nutritional support, the approach should be:

A. Nil by mouth with intravenous fluid administration until resolution of the disease

B. Early oral feeding should be commenced in order to support the nutritional requirements and modulation of the oxidative stress response associated with a hypercatabolic state in early stages of acute pancreatitis.

C. Early (within < 24 h) nasogastric tube feeding should be commenced as this is a logistically simple approach and is associated with less complications (i.e infection, tube migration) compared to nasojejunal tube feeding

D. Early enteral nutrition should be commenced. Parenteral nutrition should be considered only when nutritional demands are not met using enteral routes and should generally be started 7 days into admission.

E. This patient should be kept nil by mouth and should be started on total parenteral nutrition immediately to ensure adequate nutritional intake

Feedback: answer D is correct. This patient has a severe case of infected necrotic pancreatitis and requires intensive therapy unit admission. The IAP/APA and AGA support early enteral feeding with either nasogastric or a nasojejunal tube. In severe AP, enteral nutrition is recommended to prevent infectious complications. Parenteral nutrition should be avoided unless the enteral route is not available, not tolerated, or not meeting caloric requirements (strong recommendation, high quality of evidence).

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