Acute pancreatitis

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Abstract
Acute pancreatitis is an inflammatory condition with a variable clinical course. Diagnosis involves a combination of clinical assessment, laboratory tests, and imaging studies. Disease severity can be determined using clinical scoring systems or radiological evaluations like the CT Severity Index. While most cases of acute pancreatitis have a mild course, a subset of patients experience complications at both local and systemic levels. Conservative management is typically employed, but interventions are warranted in the presence of common bile duct stones or local complications such as walled-off necrosis or pseudocyst formation. This review provides recent insights into the pathophysiology, diagnostic approaches, and treatment strategies for acute pancreatitis, with a particular focus on the management of local complications.

Keywords
Acute pancreatitis
antibiotics
endoscopic necrosectomy
MRCP
nutrition
pseudocyst
severity

Key points
•In acute pancreatitis, care should focus on fluid resuscitation with correction of electrolyte disturbances, pain control 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 with an increasing incidence in both adult and paediatric populations. Most commonly secondary to gallstones and excessive alcohol consumption, AP is a leading cause of hospital admissions globally. Although the overall mortality in AP is around 1%, ~20% of cases are complicated by local and often life-threatening systemic complications where risk of mortality significantly increases. Over the last decade, the management of acute pancreatitis has shifted towards a personalised, multidisciplinary, and minimally invasive approach. Despite advancements in treatment and intensive care, severe acute pancreatitis continues to carry a significant risk of mortality. Less invasive, endoscopy-guided procedures are increasingly employed in the management of complicated AP, with improved outcomes and lower rates of procedure-related morbidity versus traditional surgical interventions.

Epidemiology
The incidence of AP is rising globally, reflecting the increasing prevalence of lifestyle related risk factors such as diet and obesity (gallstones), alcohol and smoking, diabetes and advancing age. (1) In the UK, the estimated incidence of AP is 15–42 cases per 100,000 per year. The aetiology of acute pancreatitis varies geographically, with gallstone disease and alcohol underlying majority of AP cases. Alcohol is 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. Additional risk factors include obesity, older age, smoking, and HIV-positive status. Other risk factors such as hypertriglyceridemia, hypercalcemia, familial pancreatitis, viral infections, and certain medications are less common causes. Anatomical obstructions of the pancreatic duct (i.e. by periampullary tumours, pancreatic masses, cystic lesions, pancreas divisum, or strictures) can lead to inappropriate enzyme activation within the pancreas. Instrumentation during procedures like ERCP and EUS carries a risk of pancreatitis (Table 1). AP most often follows a mild course yet roughly a fifth of cases are complicated by pancreatic (and/or peripancreatic) necrosis accompanied by a severe systemic inflammatory response and mortality rates as high as 40%.

Pathophysiology

Pancreatic duct obstruction (e.g. gallstones, obstructive lesions) 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, acinar cell death and a subsequent 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 (Revised Atlanta Classification 2012):

- a typical history of epigastric abdominal pain
- elevation of serum amylase and/or lipase of >3-fold the upper normal limit
- supportive findings on abdominal imaging (ultrasound, computed tomography (CT) and/or magnetic resonance imaging (MRI)

Following early resuscitation, efforts should be focused on establishing the aetiology, as the definitive treatment varies with different causative factors. Mild AP can progress to severe if not managed adequately and accurate prediction, as well as an appropriate response to severe disease are of paramount importance.

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. A thorough evaluation of patient history is therefore essential and history of gallstones, alcohol consumption, family history of pancreatic diseases or autoimmunity as well as complete drug history or trauma, could inform on the aetiology.

On examination, patients might 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 peri-umbilical 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 biliary tract obstruction due to migrating gallbladder stones as an underlying aetiology. Elevated serum IgG4 levels could suggest autoimmune pancreatitis. Abnormalities in renal function markers indicate renal injury that could be secondary to third space fluid sequestration and intravascular depletion.

Considering the risk of acid–base and oxygen disturbances in AP, arterial blood gasses in patients presenting with tachypnoea and/or low oxygen saturation levels should be monitored.

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. Early contrast-enhanced CT (CECT) is indicated in cases where the diagnosis of AP is in doubt. In most cases of acute pancreatitis, patients exhibit either diffuse or localized enlargement of the pancreas. When evaluating the pancreas using CECT, a common finding is the presence of homogeneous enhancement throughout the pancreas (Figure 1). Additionally, there may be mild stranding observed in the peripancreatic tissue surrounding the pancreas.

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 (Figure 1). 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.

Magnetic resonance imaging

Magnetic resonance cholangio-pancreatography (MRCP) is superior to CT in the diagnosis of biliary tract stones as most are CT-lucent; 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 (HAPS). The HAPS scoring system allows rapid initial stratification Past comparisons have shown a comparable predictive performance (with area under the receiver operating curve values of around 0.70) for these scoring systems. The Pancreatitis Activity Scoring System (PASS) which was introduced in 2018, incorporates factors such as organ failure (100 points/organ system), abdominal pain (5 points), solid diet intolerance (40 points), SIRS (25 points per SIRS criteria) and morphine equivalent dose (mg; 5 points). In a study of 439 patients presenting with AP, a PASS score >140 has been found to be associated with moderately severe and severe pancreatitis (OR= 3.5; 95% CI 2.0, 6.3), increased likelihood of ICU admission (OR 4.9; 95% CI 2.5, 9.4), development of SIRS (OR 2.9; 95% CI 1.8, 4.5), occurrence of local complications (OR 3.0; 95% CI 1.6, 5.7) and prolongation of hospitalization by 1.5 days (95% CI 1.3,1.7).The use of such scoring systems in clinical settings is, however, limited due to their complexity and moderate sensitivities.

The Revised Atlanta classification (RAC; 2012) is still applied universally in the classification of AP. Compared to the original system, RAC describes interstitial edematous (Type 1) and necrotizing (Type 2) types of AP. While the majority of cases are limited to type 1, up to 10% develop necrotizing AP affecting both the pancreas and the surrounding tissues while peri-pancreatic and solely parenchymal necrosis are less commonly observed.

Two phases of AP (early and late) are also described. The early phase typically lasts for the first week, where local inflammation or a systemic response are a feature. The associated cytokine storm, often manifests as a systemic inflammatory response syndrome (SIRS) or even multiorgan dysfunction syndrome (MODS) when unmitigated. The late phase can develop in patients with moderately severe or severe acute pancreatitis as systemic and/or local complications and may progress for weeks or even months following initial presentation. With respect to its severity, RAC divides 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 due to 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 may be suggestive of severe disease. CRP however, is not disease-specific, is not reliable for risk stratification at time of admission nor is a reliable prognosticator. In their new guidance from

2022, the French Society of Anesthesia and Intensive Care Medicine (SFAR) suggest a role for procalcitonin alongside CT scans in cases where the diagnoses of infected necrosis are unequivocal, with added benefit over CRP. Other novel markers such as cytokines (e.g. interleukin-6, 8 and 10) and the presence of activation peptides or pancreatic enzymes (Trypsinogen-2) in patient urine have been studied but are not routinely used in clinical practice in the UK due to lack of larger scale validation studies.

Markers of fluid status and hypovolaemia (BUN, creatinine, haematocrit) correlate with severity of AP, and a >5ml/dL increase in BUN concentration in the first 24 hours following admission predicted the risk of mortality in a study of 5,819 patients back in 2009. A smaller prospective study in 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, 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.

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. (2,3)

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 recent open label, international randomised controlled trial (RCT) (WATERFALL; the Early Weight-Based Aggressive vs. Nonaggressive Goal-Directed Fluid Resuscitation in the Early Phase of Acute Pancreatitis) randomised 249 AP patients who presented acutely (within 24 h of pain onset) with moderately severe or severe disease to receive aggressive or moderate rescuscitation. (4) In the aggressive-resuscitation group, patients were administered a bolus of lactated Ringer's solution at (20 ml/kg) over a 2-hour period. This was followed by a continuous infusion rate of 3 ml/Kg/hour. Conversely, in the moderate-resuscitation group, patients received lactated Ringer's solution at a rate of 1.5 ml/Kg/hour. In patients absent of hypovolemia a fluid bolus was not given, while in those with hypovolemia a bolus of 10 ml per kilogram over a 2-hour period was administered prior to the infusion. This study however was halted at the first interim analysis as the aggressive hydration resulted in fluid overload (20.5% of patients) with no significant differences in progression to severe disease across the two groups (22.1% vs. 17.3%; ARR, 1.30; 95% CI: 0.78–2.18; P=0.32). Moreover, aggressive fluid resuscitation was linked with worse outcomes in critically ill patients.

A smaller RCT in 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. (3)

Regarding 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. Lastly, evidence suggests that central venous pressure is not reliable when assessing volume responsiveness in acute pancreatitis (AP). This is primarily due to central venous pressure being significantly influenced by intra-abdominal pressure, which tends to be elevated in AP cases.

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.

The use of enteral (naso-intestinal) fluid resuscitation or Fluid Resuscitation Via Colon (FRVC) is increasingly reported as complimentary to IV fluid therapy in early stage severe AP (SAP). FRVC relies on the active colonic regulation of water absorption via intestinal aquaporins of pure water administered via retention enema. Enteral resuscitation aims to mitigate the capillary leak syndrome which occur in the early stage of SAP which results in third space fluid loss and subsequent haemodynamic and inflammatory sequelae (MODS, SIRS). A recent metanalysis reported the outcomes in a total of 580 patients receiving either FRVC (n=291) or intravenous fluid resuscitation (IVFR) (n=289). In comparison with the IVFR group, enteral resuscitation demonstrated significant reductions in the incidence of new organ failure (odds ratio [OR] = 0.23, 95% confidence interval [CI]: 0.12-0.43, P < 0.00001), persistent organ failure (OR = 0.38, 95% CI: 0.22-0.64, P = 0.0003), mechanical ventilation (OR = 0.15, 95% CI: 0.03-0.69, P = 0.01), ICU care (OR = 0.49, 95% CI: 0.27-0.88, P = 0.02), and pancreatic infection (OR = 0.38, 95% CI: 0.17-0.83, P = 0.02). There were no statistically significant differences however in mortality (OR = 0.77, 95% CI: 0.35-1.66, P = 0.50), surgical interventions (OR = 0.47, 95% CI: 0.19-1.18, P = 0.11) or in incidence of localized collections (OR = 0.65, 95% CI: 0.25-1.73, P = 0.39). Naturally, the role of enteral resuscitation in the management of SAP would require larger scale validations prior to its consideration in clinic.

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, 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 NICE guidelines, (2) 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: A ‘nil-by-mouth’ and/or parenteral nutrition support 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;

When managing patients who are not adequately hydrated, it is crucial to avoid aggressive enteral nutrition to prevent the risk of gut injury associated with non-occlusive mesenteric ischemia. in severe cases, feeding should be commenced once the patient has been fully resuscitated using either normal enteral or enteral tube feeding. (2) In cases where enteral intake alone is insufficient, a combination of enteral and parenteral nutrition may be considered. However, it is worth noting that current trials and meta-analyses have not yielded definitive evidence regarding the superiority of a combined approach. A 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. (3)

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, current guidelines limit its use to cases with accompanying cholangitis only. 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 with associated cholangitis. These recommendations were based on eight RCTs, albeit regarded as of low quality. (3) 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 the identification of biliary and pancreatic neoplasms <1.0 cm in size, outperforming cross-sectional CT imaging.

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 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. A recent RCT performed by the Dutch pancreatitis study group (2022) randomized 409 patients to receive rectal diclofenac either pre or post ERCP. The incidence of post-ERCP pancreatitis was found to be lower in the group that received pre-procedure rectal NSAID (8%) compared to the post-procedure group (18%) [overall RR= 2.32, 95% CI 1.21-4.46 (P = 0.02)]. Hospital stay was extended for patients who received post-procedure prophylaxis versus pre-procedure NSAIDs (median of 1 day; IQR 1-2 days vs. median of 1 day; IQR 1-4 days, P = 0.02). Moreover, post-procedure group patients had a higher likelihood of intensive care admissions (0.3% in the pre-procedure group vs. 6% in the post-procedure group; P = 0.002).

Cholecystectomy: Same-admission cholecystectomy may not be feasible in certain cases due to several factors, including patients not being medically optimized for surgery, limited hospital resources, and occasionally patient preference. In such situations, the optimal approach is to schedule cholecystectomy within 2 to 4 weeks after the patient's discharge, provided they are medically fit. This timeframe helps minimize the risk of recurrent acute pancreatitis associated with gallstones. Clinical outcomes from a meta-analysis of five RCTs (a total of 629 patients) in 318 and 311 patients undergoing early and late cholecystectomy (respectively) for mild biliary pancreatitis demonstrated a lower incidence of recurrent biliary events requiring readmission in the early intervention group compared to delayed surgery (OR 0.17; 95% CI 0.09 - 0.33). (5) No significant differences in intraoperative (OR 0.58; 95% CI 0.17 - 1.92) or postoperative complications rates (OR 0.78, 95% CI 0.38 - 1.62) were noted. A same-admission cholecystectomy is currently recommended by the 2018 AGA guidelines. (3) Similarly, the World Society for Emergency Surgery (WSES) 2019 position paper and the 2016 UK National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) report on AP recommend 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 (Figure 3). 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.

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 approach, initial conservative management is followed by 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 TENSION (Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis) trial 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.

In a recent trial conducted by the Dutch Pancreatitis Study Group, a comparison was made between 51 patients who underwent endoscopic step-up transluminal drainage of infected necrosis using double-pigtail plastic stents as part of the TENSION trial and 53 patients newly treated with LAMS. The study followed the same protocol as the TENSION trial. The results showed that the outcomes of using lumen-apposing metal stents (LAMS) and double pigtail plastic stents were comparable in terms of complications, including the occurrence of severe bleeding, as long as the LAMS was removed within 6 weeks.

NICE guidelines (2018) (2) 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 4). The performance of lumen-apposing metal stents (LAMSs) versus plastic stents in management of PFCs has been evaluated in a meta-analysis involving 2213 patients in 41 studies. LAMSs were superior to plastic stents, with reduced rates of complications 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.

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 (Figure 4).

Endoscopic guided debridement – endoscopic necrosectomy (Figure 5) 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 (cyst-gastrostomy) 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.

Aetiological factors for AP

Risk factors and causes of AP

•Cholelithiasis, choledocholithiasis, microlithiasis
•Alcohol
•Smoking
•Diabetes mellitus type 2
•Hypercalcaemia, hypertriglycerydaemia
•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

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
Glasgow Coma Scale (GCS) score	–	–	–	<15
Threshold score for severe acute pancreatitis	≥3	≥3	≥8	≥3

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

Table 2

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.

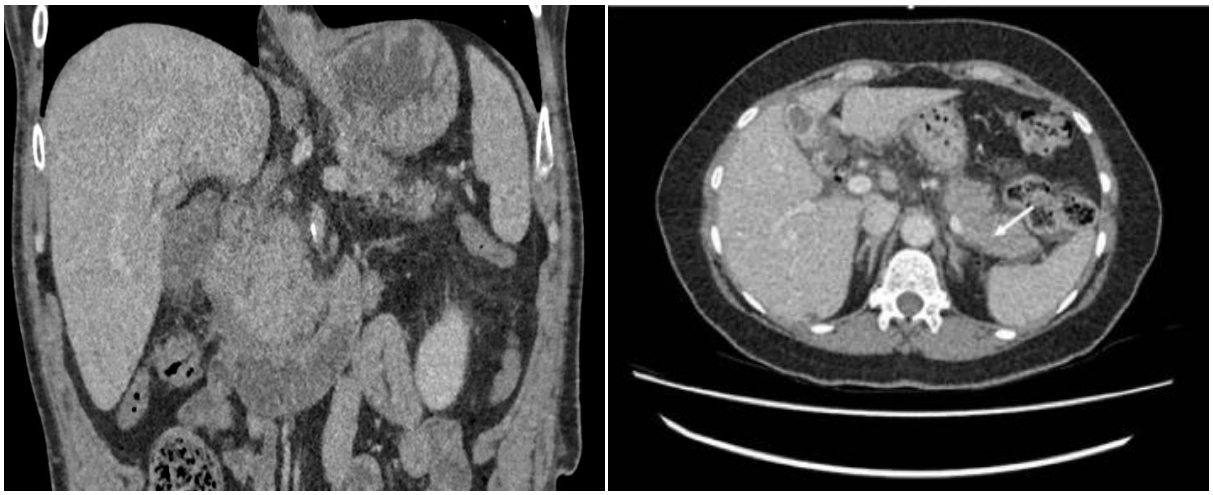

Figure 1. Abdominal (transverse section) CT image showing features of interstitial oedematous pancreatitis (left). There is oedema of the distal pancreatic region with peri-pancreatic fat stranding (arrow). On the right, CT with contrast: findings indicate the presence of pancreatitis with peripancreatic retroperitoneal fat stranding, specifically located around the head and uncinate process of the pancreas. There is also a noticeable focal enlargement and dilation of the bile duct.

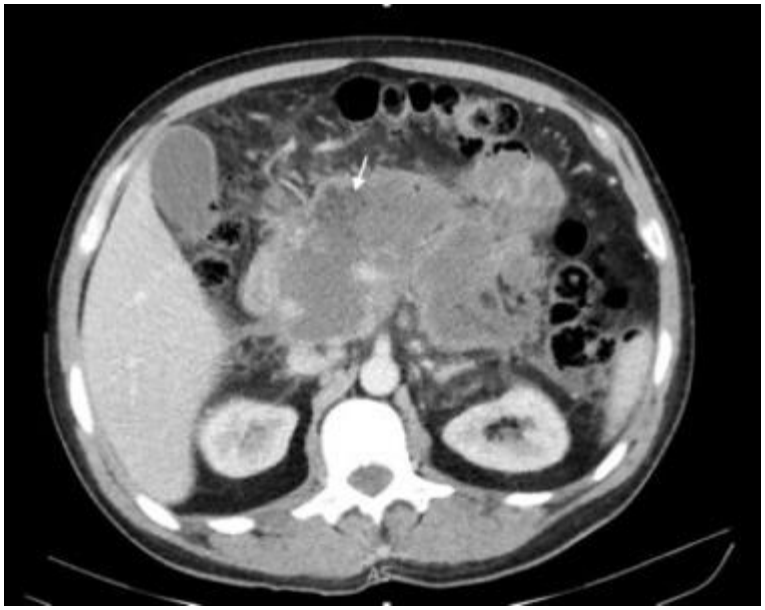

Figure 2. Abdominal (transverse section) CT image showing features of severe pancreatic necrosis. A walled-off collection is seen in the body/tail of the pancreas, with gas bubbles (arrow) that are suggestive of an infected component.

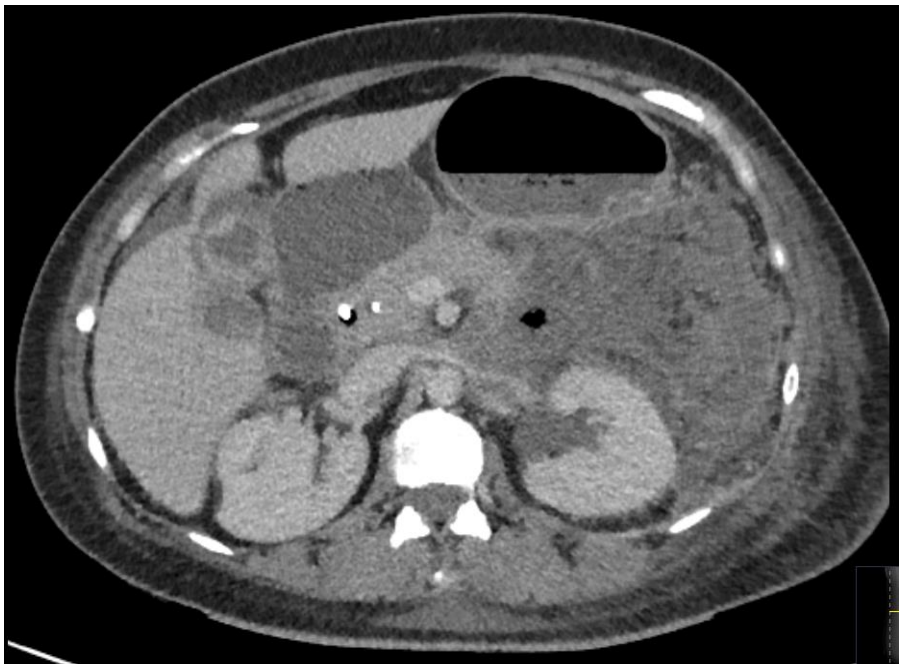

Figure 3: CT with contrast: Evolving necrotising pancreatitis with immature, heterogenous collections which are starting to form walls. In addition there is a focus of free gas adjacent to the pancreatic tail which is suggestive of possible infection.

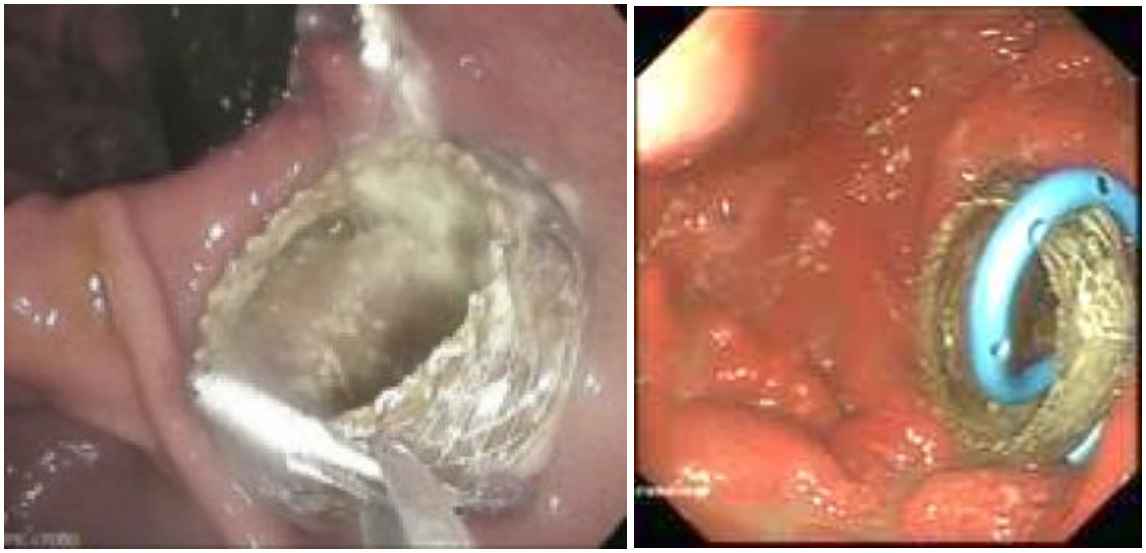

Figure 4. A lumen-apposing metal stent positioneed through the posterior gastric wall into the peri-pancreatic collection (left). 15mm LAMS into pancreatic necrosis with plastic pigtail stent through LAMS to prevent blockage by necrotic material 15mm LAMS into pancreatic necrosis with plastic pigtail stent through LAMS to prevent blockage by necrotic material (right).

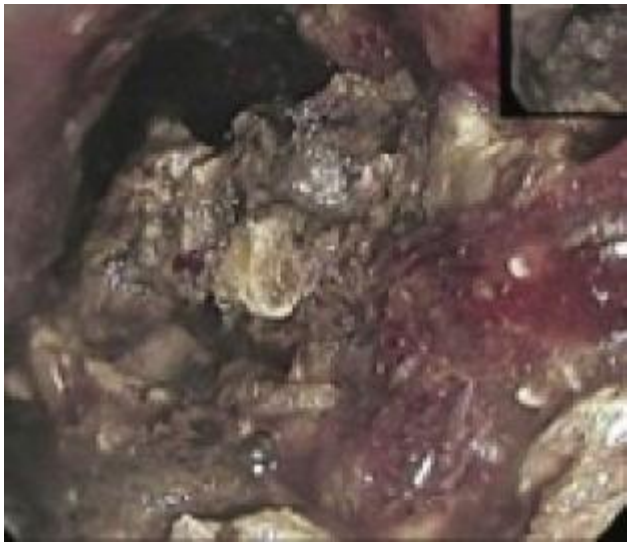

Figure 5. Necrotic debris seen during endoscopic necrosectomy.

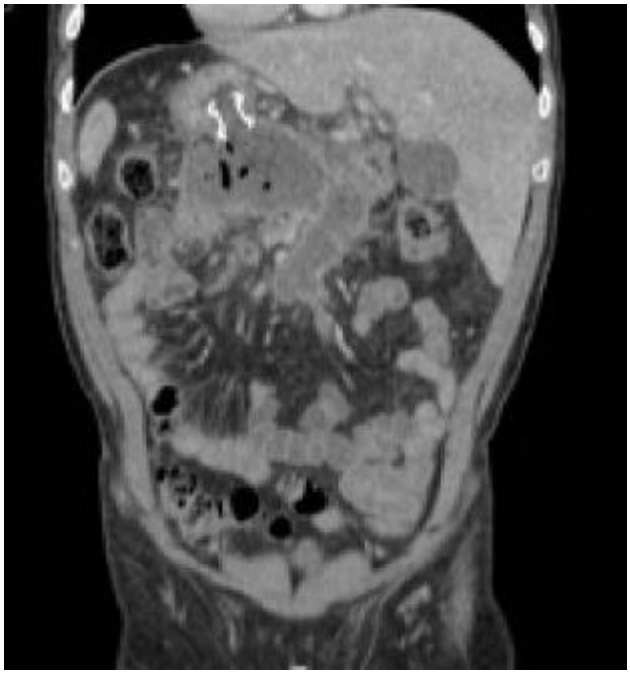

Figure 5. Abdominal (coronal) CT image showing a transgastrically placed LAMS positioned in WON.

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