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Managing complicated pancreatitis with more knowledge and a bigger toolbox!

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SUMMARY

Acute pancreatitis (AP) is a heterogeneous inflammation of the pancreas, most frequently attributable to gallstones or alcohol. AP accounts for an estimated 300 000 patients admitted each year in the USA, and an estimated US$2.6 billion/year in hospitalization costs. Disease severity is classified as mild, moderate, or severe, dependent on the presence or degree of concomitant organ failure. Locally, pancreatitis may be complicated by fluid collections, necrosis, infection, and hemorrhage. Infection of necrotizing pancreatitis (NP) is associated with a doubling of mortality risk. The modern management of AP is evolving. Recent data suggest a shift from normal saline to lactated Ringer's solution, and from aggressive to more judicious volume resuscitation. Similarly, while historical wisdom advocated keeping patients nothing by mouth to 'rest the pancreas', recent data convincingly show fewer complications and reduced mortality with early enteral nutrition, when tolerated by the patient. The use of antibiotics in NP is controversial. Current recommendations suggest reserving antibiotics for cases with highly suspected or confirmed infected necrosis, as well as in patients with biliary pancreatitis complicated by acute cholecystitis or cholangitis. Regarding the management of local complications, control of acute hemorrhage can be attained either endovascularly or via laparotomy. Abdominal compartment syndrome is associated with a mortality risk of 50%–75%. Routine monitoring of intra-abdominal pressure is recommended in patients at high risk. Pancreatic pseudocysts require intervention in symptomatic patients or those with infection or other complications. Endoscopic transmural drainage may be considered as the first step when technically feasible. Necrotizing pancreatitis without suspicion of infection is often managed medically, while the delay, drain, debride approach remains the standard of care for the vast majority of infected pancreatic necrosis. Robotic surgery, in appropriately selected patients, allows for a one-step approach, and merits further study to explore its initially promising results.

INTRODUCTION/EPIDEMIOLOGY

Acute pancreatitis (AP) is a heterogeneous acute inflammation of the pancreas, which can often have an unpredictable course. AP is one of the most common diseases of the gastrointestinal tract requiring hospitalization, and the incidence is rising globally and in the USA. Recent data report the incidence ranging from 3.4 to 73.4 cases per 100 000 worldwide.[1] In the USA, AP accounts for an estimated 300 000 patients admitted each year, resulting in hospitalization costs, estimated to be US$2.6 billion/year. Progress in our knowledge of the disease and advancements in the management of AP have been associated with a reduction in the mortality rate. According to data from 2019, there are still approximately 115 000 AP deaths globally each year, with 5000–9000 deaths reported annually in the USA.[2] There are numerous established etiologies of AP, among which gallstones and alcohol are the most common (40%–70% and 25%–35%, respectively).[3] The remaining cases are primarily attributable to the following etiologic factors: hypertriglyceridemia, autoimmune, infection, hypercalcemia, malignancy, genetics, endoscopic retrograde cholangiopancreatography, and trauma. Despite accounting for approximately only 1%–2% of cases overall, drug-induced pancreatitis has become increasingly recognized as an underappreciated etiology that must be considered, especially with the recent exponential use of glucagon-like-peptide(GLP)-1 agonists for weight loss.[4]

CLASSIFICATION OF SEVERITY OF ACUTE PANCREATITIS

The Atlanta classification of AP was revised in 2012.[5] The working group identified two phases of the disease: early and late, and classified severity as mild, moderate, or severe. Mild AP, the most common form, is characterized by the absence of organ failure, local or systemic complications, and usually resolves within a week. Moderately severe AP is defined by the presence of transient organ failure (lasting <48 hours) or local complications. Severe AP (SAP) is defined by persistent organ failure lasting >48 hours. SAP is a systemic disease with two distinct phases. The first phase is sterile systemic inflammatory response syndrome (SIRS) that may lead to early primary multiple organ failure and even death within the first 72 hours. The second phase is late secondary organ failure, driven by infection of necrotic tissue or fluid collections.[6] Petrov *et al* reported that mortality rates for SAP can be as high as 43%.[7] The natural history of AP ranges from complete recovery after a single episode to prolonged hospitalization, requiring multiple invasive interventions, to rapidly progressing multiple organ failure and sepsis leading to death. In some cases, it can progress to a chronic, debilitating condition that persists for decades. The unpredictable clinical course of AP presents challenges, as 80% of patients with mild pancreatitis typically require only a short hospital stay without the need for advanced resources. The remaining 20% with moderately severe to severe pancreatitis require early aggressive treatment, admission to the

surgical intensive care unit, or referral to a tertiary center with a multidisciplinary team of specialists. This decision depends on the resources and capabilities of the hospital initially evaluating the patient, but it must also rely on the ability to accurately predict, at the time of admission, which patients with AP will progress.[8] Accurate early predictions are crucial for initiating effective management. Patients with severe AP require intensive care unit monitoring and support for circulatory, pulmonary, renal, and hepatobiliary function to reduce the risk of organ failure sequelae. Those trained in the 1980s recall using Ranson's criteria to prognosticate AP.[9 10] Since then, numerous prognostic models have been developed, incorporating patient-related risk factors, laboratory parameters, computed tomography (CT) imaging findings,[11] and complex scoring systems to predict mortality, severity of illness, and organ failure. As with many areas of medicine where multiple options are still being studied, no single approach has emerged as definitively superior to others in large-scale comparisons.[11–16] While there is no 'gold standard' prognostic score for predicting SAP, the Bedside Index of Severity of Acute Pancreatitis (BISAP) score is one of the more accurate. Due to its simplicity and the fact that it does not require data from 48 hours after admission, BISAP is particularly applicable in everyday clinical practice.[17] Zhu *et al* recently published a meta-analysis that comprehensively assessed and compared the performance of Ranson's criteria and BISAP in predicting the severity and prognosis of AP, and found that both were comparable.[18] Several biomarkers have also been studied in recent years. Measurement of serum cytokines such as interleukin (IL)-6, IL-8, angiopoietin-2, and resistin have been reported as an accurate method for predicting SAP.[19–21] Villasante *et al* recently published their work using machine learning and artificial intelligence to predict severe pancreatitis at a very early stage of the disease without laboratory data or imaging.[22]

LOCAL COMPLICATIONS OF ACUTE PANCREATITIS

The first 72 hours of initial management after diagnosis are pivotal and can influence the clinical course and outcome of the disease. Appropriate early interventions can prevent complications and improve outcomes. In the past, contrast-enhanced CT was used in the early diagnostic workup of AP to establish the diagnosis in uncertain cases. However, it is now ubiquitously used as part of the workup for abdominal pain in the emergency department. The value of contrast-enhanced CT imaging lies in its ability to detect potential local complications, such as fluid collections, necrosis, portal vein thrombosis, pseudoaneurysms, and bleeding. Magnetic resonance imaging (MRI) may be advantageous in some cases, particularly for detecting choledocholithiasis and identifying solid necrotic debris in fluid collections. Recently, the value of texture analysis/radiomics of medical images (such as contrast-enhanced CT and MRI), combined with machine learning, has shown promise in accurately predicting the severity of AP.[23–25] Routine follow-up CT (e.g., weekly or every 10 days) is advocated in several guidelines. However, some question whether there is sufficient evidence to justify this practice, as the vast majority of complications in patients with AP/SAP can often be suspected based on clinical or laboratory assessment.[26] Follow-up CT scans are needed if the patient's clinical status deteriorates or fails to show continued improvement. Local complications of AP, as defined in the revised Atlanta classification, can be categorized into four types of collections: (1) acute peripancreatic fluid collections, which are extrapancreatic and liquid; (2) pancreatic pseudocysts, typically extrapancreatic encapsulated fluid collections with no or minimal solid components, which usually develop after 4 weeks; (3) acute necrotic collections, which occur early before a discriminating wall develops; (4) walled-off necrosis (WON) (figure 1), an encapsulated necrotic collection with a distinct wall. Necrotizing pancreatitis (NP) occurs when the damage from AP causes necrosis of the pancreas and peripancreatic tissues. Necrosis is defined radiologically as the non-enhancing areas of pancreatic parenchyma on contrast-enhanced CT of the abdomen, and is observed in about 5%–15% of patients with AP,[5] but typically is not evident for 3–5 days after the onset. The amount of pancreatic necrosis is often graded as <30%, 30%–50%, and >50% (massive).[11] Pancreatic and peripancreatic necrosis can remain sterile or become infected, with no absolute correlation between the extent of necrosis and the risk of infection. Gas may be noted on imaging at any point in the course, and develops in 50% of the patients with infected NP. Traditional teaching held that encapsulation of necrosis did not occur until after 4 weeks, as noted in the revised Atlanta classification. However, several studies have shown that clinically relevant WON may develop within the first 3 weeks. A multicenter study found that 43% of demarcated collections had already formed within the first 3 weeks after the onset of NP.[27]

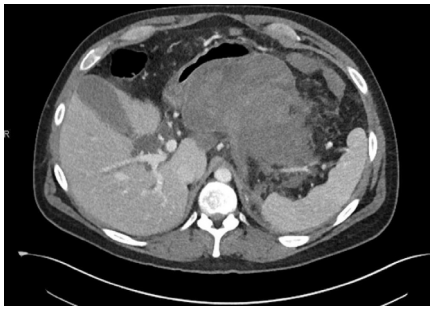

Figure 1 Axial CT of walled-off pancreatic necrosis.

Infection of pancreatic and peripancreatic necrosis occurs in about 20%–40% of patients with SAP. Although infection can occur early in the course of NP, it is most often observed later, typically after 10 days, with a peak incidence between the second and fourth week.[28 29] Both organ failure and infected necrosis increase mortality in NP. In a systematic review and meta-analysis by Werge *et al*, which included 6970 patients, the mortality rate for patients with infected necrosis and organ failure was 35.2%. In contrast, concomitant sterile necrosis and organ failure was associated with a mortality rate of 19.8%. The authors concluded that patients with NP are more than twice as likely to die if the necrosis becomes infected.[30]

UPDATED MANAGEMENT OF ACUTE PANCREATITIS

Driven by ongoing research over the past two decades, several key clinical updates have transformed the management of AP. Some of these updates are well accepted, others remain controversial, and some are still in need of further study. An example of the latter is the role of low molecular weight heparin (LMWH) in managing AP. Although LMWH has been routinely used for prophylaxis to prevent venous thrombotic events for years, it is believed to have a potential role in managing AP due to its anticoagulant, anti-inflammatory and antiprotease activities. Patil *et al* published a blinded single-center randomized controlled trial in which LMWH (1 mg/kg subcutaneously twice daily) was used in patients with moderately severe and severe pancreatitis. The study reported that LMWH significantly reduced the chances of disease progression, pancreatic necrosis, local complications,

and the need for invasive interventions, without increasing adverse effects or complications.[31] Obviously, a large multicenter trial is needed to confirm their findings before they can be incorporated into standard practice. The remainder of this review will focus on the substantial changes in the management of AP that have occurred in the following areas: fluid resuscitation, nutritional support, antibiotic usage, and the various invasive intervention options, along with their timing, to manage local complications, such as peripancreatic fluid collections, necrosis, and pseudocysts.

FLUID MANAGEMENT

Fluid resuscitation has widely been considered a quintessential part of the management of AP, but the optimal type and volume of fluid have only recently been addressed. Wu *et al* published a randomized controlled trial in 2011 in which 40 patients were randomized to one of four treatment arms: (1) goal-directed fluid resuscitation with lactated Ringer's solution (LR), (2) goal-directed fluid resuscitation with normal saline (NS), (3) standard resuscitation with LR, or (4) standard resuscitation with NS. They found a significant reduction in SIRS and C reactive protein (CRP) levels after 24 hours among patients resuscitated with LR compared with NS. The authors suggested that NS is detrimental for AP because of hyperchloremic acidosis.[32] A subsequent randomized controlled trial found similar results and suggested that NS, when compared with LR, is associated with a pro-inflammatory effect in patients with AP.[33] The WATERFALL[34] was a randomized trial to address the volume of fluid used in resuscitation of patients with AP. However, the trial was halted after preliminary analysis revealed that the early aggressive fluid resuscitation cohort had a higher incidence of fluid overload without any improvement in clinical outcomes. A meta-analysis[35] that included 11 studies found no significant difference in mortality between patients receiving aggressive intravenous fluid (IVF) resuscitation (n=1229) and those receiving non-aggressive IVF (n=1397). Patients receiving aggressive IVF therapy had a higher risk for acute kidney injury (AKI) and acute respiratory distress syndrome. Those receiving aggressive IVF therapy were more than two times more likely to develop AKI (relative risk (RR) 2.17; 95% CI 1.66 to 2.83). Renal vascular congestion, with a pathophysiology similar to that seen in cardiorenal syndrome, is believed to cause direct injury to the glomeruli. The authors found no significant difference in the overall incidence of SIRS, persistent organ failure, or pancreatic necrosis when comparing both study groups. These studies led to a strong recommendation for more judicious, goal-directed fluid resuscitation in AP—that is, until the FLIP (Fluid Resuscitation in Pancreatitis) study was published last year. The FLIP study[36] found that the effect of IVF volume on mortality differed significantly depending on the severity of pancreatitis. In patients with severe pancreatitis, increased IVF volume was associated with significant reductions in mortality (OR 0.655; 95% CI 0.459 to 0.936; p=0.020). The study concluded that more aggressive fluid resuscitation was associated with decreased mortality in severe pancreatitis but found the opposite result in cases with milder disease. For years, we have recognized that the incidence of abdominal compartment syndrome and respiratory failure increases with aggressive resuscitation regimens in other inflammatory disease processes. As a result, we are now more likely to use vasopressors for blood pressure support rather than excessive volumes of intravenous crystalloid fluids. Our current approach involves continued surveillance and strict attention to assessing intravascular volume using point-of-care ultrasound. This paradigm shift from aggressive hydration with NS to goal-directed hydration with a balanced salt solution such as LR or plasmalyte is an important change.

NUTRITION

Another past teaching was that patients with AP should remain nothing by mouth to 'rest the pancreas', based on the premise that feeding stimulates the release of cholecystokinin, leading to an increase in proteolytic enzyme secretion, auto-digestion, and further damage to the pancreas.[37] However, several studies have now shown that the early initiation of oral and enteral nutrition actually leads to reduced complications, reduced length of hospitalization, lower mortality, and improved prognosis. Enteral nutrition reduces the inflammatory response, improves intestinal barrier integrity, stimulates intestinal motility, prevents bacterial overgrowth, increases splanchnic blood flow, and prevents malnutrition, ultimately reducing the risk of bacterial translocation.[38] The evidence supporting the clinical benefits of early enteral feeding in patients with moderately severe and severe AP is now considered definitive and plays a vital role in managing AP. Despite this strong recommendation, debate has continued. Most patients with mild and moderate pancreatitis, after a short period of fasting, can generally begin with clear liquids, followed by a gradual progression to a low-fat solid diet, and therefore typically do not require nutritional support interventions.[39] The multicenter PADI (Immediate Oral Refeeding in Patients With Mild and Moderate Acute Pancreatitis) trial found that initiating a low-fat solid diet immediately after hospital admission, compared with the conventional oral refeeding approach (where the oral diet is progressively restarted once clinical and laboratory parameters improve), was safe and resulted in a significantly shorter length of stay without causing adverse effects or complications.[40] Of note from this study, the elevation of amylase or lipase levels should not curtail the advancement of these patient's diet. For those who are unable to be fed orally, and in the absence of contraindications (such as intestinal failure, bowel obstruction, prolonged paralytic ileus, high-output intestinal fistulae, mesenteric ischemia, abdominal compartment syndrome, or inability to access the gut), early enteral tube feeding (within 24–48 hours of admission) should be initiated.[41] The best route for enteral feeding in AP has been clarified. Historically, nasojejunal tube feeding was considered the best practice in patients with AP, based on the rationale that postpyloric feeding reduced the stimulus for pancreatic secretion and the risk of aspiration. However, numerous studies have shown that the early use of postpyloric feeding, as opposed to gastric feeding, does not correlate with any significant clinical advantages in critically ill patients, unless there is evidence of impaired gastric emptying. The best enteral formula for patients with AP has been thought to be elemental or semi-elemental formulas, based on their superior absorption profile, decreased pancreatic stimulation, and better tolerance. Numerous studies have been published in an attempt to answer the question. Petrov *et al*, published a meta-analysis of 20 randomized controlled trials comparing the use of polymeric versus semi-elemental formulas in AP. They found no significant difference in feeding intolerance (FI), infectious complications, or death, and also concluded that neither the supplementation of enteral nutrition with probiotics nor the use of immune-modulating formulas significantly improved clinical outcomes.[42] A large multicenter blinded randomized controlled trial is still needed. The recommendation to initiate early feeding is well-supported, but the reality is that not all patients with AP tolerate feeding. FI occurs in 13%–16% of patients fed orally

and in up to 26% of patients with moderate to severe AP when fed enterally. FI is clearly associated with more severe disease and poorer outcomes.[43–45] Total parenteral nutrition (TPN) should only be considered when oral or enteral feeds are not feasible or tolerated. In patients requiring TPN, adherence to goal-directed fluid resuscitation, provision of trophic doses of TPN to meet 20%–25% of protein and/or calorie requirements during the acute phases of illness, use of less-inflammatory intravenous lipid emulsions, and close monitoring of electrolytes, triglyceride levels, and vigilance for signs of refeeding syndrome all contribute to optimizing outcomes.

ANTIBIOTICS

The use of antibiotics in the initial management of AP remains a topic of significant controversy. Pancreatic or peripancreatic necrosis is initially aseptic but can progress to infected necrosis. Bacterial translocation, where bacteria migrate from the intestine to the pancreas, is known to contribute to the systemic inflammatory response in AP and is considered the primary source of infection in necrotic collections. Since infected pancreatic necrosis (IPN) results in more than twice the mortality when compared with sterile pancreatic necrosis, the question remains as to whether prophylactic antibiotics are beneficial. This question has been tough to answer due to the considerable heterogeneity in the cohorts and the numerous confounding variables that must be considered. Numerous studies looking at the effectiveness of prophylactic antibiotics in acute NP have been published, but with conflicting results. A meta-analysis by Bai *et al* (seven trials involving 467 patients) concluded that prophylactic administration of antibiotics was not statistically superior when compared with controls in the reduction of infected necrosis or mortality.[46] Another meta-analysis by Ukai *et al* (six randomized controlled trials totaling 397 patients) reported mortality rates were significantly different for those who received antibiotics (7.4%), compared with controls (14.4%) (OR 0.48; 95% CI 0.25 to 0.94). Additionally, these authors found that early prophylactic antibiotic use was associated with a reduced incidence of infected pancreatic necrosis, 16.3%, antibiotic group vs 25.1% in control (OR 0.55; 95% CI 0.33 to 0.92).[47] Guo *et al* in their 2022 meta-analysis looking at prophylactic carbapenem antibiotics in severe AP reported prophylactic carbapenem administration was associated with a statistically significant reduction in the incidence of infections (OR 0.27; p=0.03) and complications (OR 0.48; p=0.009). However, they did not find a statistically significant difference in the incidence of infected pancreatic or peripancreatic necrosis (OR 0.74; p=0.24), or mortality (OR 0.69; p=0.17). These authors concluded that current evidence of benefits is insufficient to support the use of routine prophylactic carbapenem antibiotic administration in severe AP.[48] Nearly all trials included in this meta-analysis had several limitations, including inaccurate definitions of disease severity, poor statistical testing and overlooked differences in the route of nutrition, the antibiotic used, its dosing, and other potentially important confounding variables. In the meantime, it is safe to say that the effectiveness of prophylactic antibiotics in NP remains debatable. The current recommendations, given the concerns for increasing bacterial resistance, are that antibiotics should be reserved for highly suspected or confirmed infected necrosis, and in patients with biliary pancreatitis with associated acute cholecystitis or cholangitis. The diagnosis of infection in peripancreatic or pancreatic fluid collections or necrosis no longer requires fine-needle aspiration for Gram stain and cultures. In most cases, clinical suspicion and CT findings (such as gas in the necrotic collection) are sufficient to make the diagnosis. Early diagnosis of infection is further improved by using biomarkers like CRP and procalcitonin. When infection of peripancreatic or pancreatic fluid collections or necrosis is suspected, early initiation of appropriate antibiotics is crucial to reducing mortality. Antibiotics with good penetration into pancreatic tissue, covering Gram-negative and Gram-positive bacteria, should be prioritized (e.g., carbapenems, quinolones, and metronidazole). Routine antifungal therapy is not recommended, but should be considered for patients who do not improve after several weeks of antibiotic treatment. The duration of antibiotic therapy should be minimized and tailored to the quality of source control, normalization of biomarkers, and the patient's clinical condition.[49 50]

MANAGEMENT OF LOCAL COMPLICATIONS

In deciding how to treat peripancreatic fluid collections, necrotic collections, and pseudocysts, two important questions must be addressed: what is the location of the collection(s) and what is the degree of encapsulation? Therefore, prior to any intervention, a present-day pre-procedure multiphase contrast-enhanced CT scan of the abdomen should be performed. Early imaging after contrast administration provides an arterial phase that is useful for defining the arterial anatomy and excluding the presence of a pseudaneurysm. The portal venous phase allows for the identification of portal venous anatomy and helps evaluate any associated mesenteric, splenic, or portal vein thrombosis. MRI is a reasonable alternative for patients with an iodine contrast allergy and has been reported to be more accurate than CT in detecting necrotic debris.[51] Strand *et al*. add that endoscopic ultrasound (EUS) should be considered in patients with AP when the etiology remains unexplained after initial evaluation and routine imaging.[52] Over the past 30 years, the surgeon's toolbox for managing local complications of AP has greatly expanded, from a single option of open laparotomy to now include percutaneous catheter-based, endoscopic, and surgical approaches.[53] Surgical options now include robotic and laparoscopic approaches in addition to traditional open operative procedures. In many cases, a combination of these procedures is required. The optimal management of complicated AP requires a surgeon-led multidisciplinary team, including gastroenterologists, interventional radiologists, and specialists in critical care medicine, infectious disease, and nutrition. If these resources are not available, consideration should be given to transferring patients with complicated pancreatitis to an appropriate tertiary-care center equipped and staffed to manage such cases. Local complications of AP are associated with a substantial increase in both morbidity and mortality. When infection occurs, as previously mentioned, mortality is doubled. When complicated by hemorrhage, the mortality rate more than triples.[54] The ongoing enzymatic destruction of pancreatic and peripancreatic tissues in NP may involve adjacent blood vessels, such as the splenic artery, gastroduodenal artery, or pancreaticoduodenal arcade, predisposing patients to pseudoaneurysm formation and subsequent hemorrhage. Bleeding complications occur in up to 6% of patients with NP.[54 55] All surgeons caring for patients with AP must maintain a heightened awareness of this potential complication. A sentinel bleed occurs in 75% of cases and requires immediate action. Prompt recognition, resuscitation with blood

products, and emergent angiographic embolization or laparotomy are essential for survival. The decision to proceed to the operating room for hemorrhage control versus angioembolization in the interventional radiology suite depends on the patient's condition, response to resuscitation, and the availability and timely response of the necessary resources. Another indication for emergent invasive intervention in AP is the development of acute abdominal compartment syndrome, which affects 20%–30% of patients with NP, and is associated with mortality rates as high as 50%–75%.[56] A high index of suspicion by the surgeon is critical to early identification and treatment. Avoiding excessive fluid resuscitation is key to reducing the incidence of this complication. Routine monitoring of intra-abdominal pressure in high-risk patients is recommended. Maximal medical management includes achieving a negative fluid balance, confirming adequate enteral decompression with a nasogastric tube, and considering pharmacological paralysis to improve abdominal wall compliance. If, despite these efforts, intravesicular pressure exceeds >25 cm H_2O and is accompanied by renal insufficiency or respiratory failure, intervention is required. An urgent bedside ultrasound should be performed to assess the volume of accumulating peritoneal fluid or ascites. If a significant volume is noted, ultrasound-guided percutaneous intraperitoneal catheter placement and drainage should follow. If this approach is ineffective in lowering intra-abdominal pressure, emergent decompressive laparotomy is indicated. The DECOMRESS (Decompressive Laparotomy With Temporary Abdominal Closure Versus Percutaneous Puncture With Placement of Abdominal Catheter in Patient With Abdominal Compartment Syndrome During Acute Pancreatitis) trial, proposed in 2010 to evaluate decompressive laparotomy versus intraperitoneal catheter drainage in AP, has yet to be published.[57]De In 2016, Wang *et al*. reported that reducing intra-abdominal pressure through percutaneous catheter drainage of early pelvic ascites in patients with severe pancreatitis led to a reduction in intra-abdominal infections, a decreased need for surgical intervention, and shorter hospitalizations.[58] Surgery was traditionally the mainstay of treatment for pancreatic pseudocysts until less invasive modalities emerged as viable alternatives. An important advancement has been the recognition that not all pancreatic pseudocysts require intervention, and most can be treated with supportive measures alone.[59 60] Intervention is indicated if the patient is symptomatic or if infection or complications are present. For most patients with symptomatic pancreatic pseudocyst abutting the stomach or duodenum, the preferred approach is EUS-guided transmural drainage rather than surgical drainage, as numerous studies have shown transmural drainage to be equally effective with lower associated morbidity.[61] Surgical cystgastrostomy is now being performed using the robotic platform, and it may represent a superior alternative.[62] Further studies comparing it with current endoscopic techniques are needed. The surgical management for sterile necrosis has been a point of contention among surgeons for decades. Historically, Senn, in 1886, was the first to propose the surgical removal of necrotic tissue as a treatment for NP.[63] Throughout the first nine decades of the 20th century, surgical treatment of pancreatic necrosis remained the standard, with several technical iterations evolving over time. In 1991, Bradley and Allen published their landmark paper, proclaiming that pancreatic necrosis alone, even when accompanied by organ failure, should not be considered an absolute indication for surgery. They proposed that a trial of medical treatment be considered for all patients with sterile pancreatic necrosis.[64] This led to the adoption of medical treatment as the accepted approach for patients with NP with sterile necrosis. Surgical intervention is now reserved for infected necrosis or necrosis associated with other complications. Current guidelines recommend that necrosectomy for sterile necrosis be considered only in specific situations: ongoing organ failure 4 weeks after the onset of disease; gastric, biliary, or intestinal obstruction due to WON; and cases of a disconnected pancreatic duct with ongoing symptoms or a growing pseudocyst.[65–67] The choice of intervention (endoscopic, robotic, laparoscopic, or open) should be individualised based on multiple factors, including the location and extent of the necrosis, the presence of communication with pancreatic duct, the maturity of the wall, presence of a pancreatic duct stricture or biliary obstruction, the patient's history of previous abdominal surgery, and their hemodynamic status and overall clinical condition. Drainage of infected necrosis/collection, with or without the presence of organ failure, remains the standard of care worldwide. In the 1980s, immediate surgical intervention was emphasized for managing infected necrosis. This frequently entailed multiple trips to the operating room for progressive debridement of the necrosum, daily open packing of the lesser sac, or placement of multiple drains, with both approaches often resulting in pancreatic fistulas. Several important technological advances have significantly contributed to changing our approach. In 1998, Freeny *et al* first described the use of percutaneous catheter drainage (PCD) in NP, reporting a 47% necrosectomy-free survival rate.[68] Today, the dictum has evolved to a delayed approach. The POINTER (Postponed or Immediate Drainage of Infected Necrotizing Pancreatitis) trial, published in 2021, was a multicenter randomized superiority trial in patients with infected NP comparing immediate drainage at the time of diagnosis of infection with delayed drainage, postponed until the stage of WON was reached.[69] These investigators reported no significant difference in mortality or complications between the two cohorts but found that patients in the delayed-drainage group required fewer invasive interventions. This finding is explained by the fact that the delayed-drainage group received antibiotics during the waiting period, and in 39% of cases, antibiotics and catheter drainage alone resolved the need for necrosectomy. Delaying necrosectomy for at least 3–4 weeks allows for liquefaction of the necrotic tissue and maturation of the encapsulation, seemingly making drainage more effective. While PCD has been shown to improve survival, it does not eliminate the risk of pancreatocutaneous fistula.[70–72] With the advancement of endoscopic techniques, endoscopic drainage is now reported by most authors to be the initial procedure of choice for drainage of walled-off infected collections and symptomatic pseudocysts that are adherent to the stomach or duodenum, as it helps avoid the risk of pancreatocutaneous fistula. Transmural drainage is performed by locating and accessing the collection via an endoscope using radiographic and/or EUS imaging. A tract is then created through the gastric or duodenal wall, followed by the placement of one or more stents (figure 2). If necrosectomy is necessary, the transmural tract allows for evacuation of the necrotic debris through direct endoscopic necrosectomy. Advances in stent technology have progressed from small plastic stents to expandable metal stents, and now to novel lumen-apposing metal stents, which have been shown to markedly reduce complications, including stent occlusion and migration.[73 74] PCD use is now reserved for cases where endoscopic drainage is either not technically feasible—such as when the necrotic collection is not in close proximity to the gastrointestinal tract—or when patients are too critically ill to tolerate the procedure. It is also used when endoscopic drainage fails to resolve the infected collection, which is often the case when the

collection extends into dependent regions like the paracolic gutters or pelvis. In these cases, placing an additional percutaneous drainage catheter into the dependent region should be strongly considered. Percutaneous and endoscopic drainage are the initial steps in the 'step-up approach'. The PANTER (Minimally Invasive Step Up Approach versus Maximal Necrosectomy in Patients with Acute Necrotising Pancreatitis) study confirmed that this minimally invasive approach leads to significantly better outcomes than open surgery, particularly in critically ill patients.[75] If drainage fails to resolve the infection, which occurs in 30%–75% of cases, debridement of the necrosum becomes necessary.[76] Failure to adequately control infected pancreatic necrosis results in an almost 100% mortality due to overwhelming organ failure.[77] A surgical approach is indicated for patients who are not candidates for endoscopic intervention or if endoscopic intervention fails. The surgical methods for performing necrosectomy have expanded significantly over the past decade. Minimally invasive operative approaches to debride the necrosum are preferred to open surgical necrosectomy when feasible, as they are associated with lower mortality and morbidity.[78 79] Multiple minimally invasive surgical techniques, including videoscopic-assisted retroperitoneal debridement, mini-access transperitoneal and retroperitoneal approaches, laparoscopic procedures, and robotic-assisted surgery, have proven to be both feasible and effective. Collections located at the root of the mesentery or to the right of the mesenteric vessels are challenging to access through percutaneous, endoscopic, or retroperitoneal approaches. In these cases, robotic or traditional open surgical approaches should be considered. For patients with a disconnected left pancreatic remnant following mid-body necrosis, a definitive surgical procedure, such as robotic transgastric drainage or distal pancreatectomy, should be performed. Insufficient evidence exists to support long-term stenting of the pancreatic duct for the management of a disconnected left pancreatic remnant.[80] The optimal approach for managing complicated NP must be individualized based on the patient's specific condition. This approach is strongly influenced by available resources and the experience and expertise of the multidisciplinary team involved in the patient's care. Today, the 'step-up' surgical strategy—also known by some as the 'delay, drain, debride approach'[81]—should be used for managing the majority of IPN cases. However, this approach may not be appropriate for patients lacking a safe puncture path (endoscopic or percutaneous). Additionally, indiscriminate implementation of the 'step-up' strategy may lead to an increased number of required operations. Robotic surgery, on the other hand, offers effective management with a single intervention. The robotic approach for drainage and debridement of IPN and symptomatic or infected pancreatic pseudocysts has been shown to be both safe and feasible.[82] The robotic platform is an important tool in providing a 'one-step' surgical management approach.[83 84] Robotic transenteric drainage and debridement techniques warrant further study, as they are likely to become the procedures of choice for appropriately selected patients in the future.

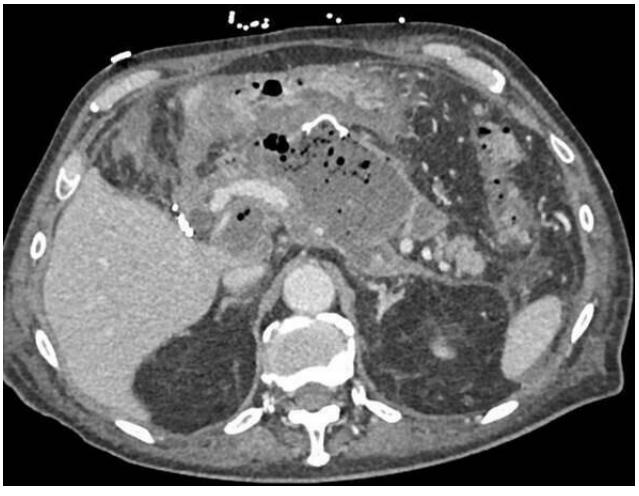

Figure 2 Axial CT of infected necrotizing pancreatitis status postendoscopic cystgastrostomy.

CONCLUSION

As our understanding of the pathophysiology of severe pancreatitis continues to grow, so too has our toolbox. What was once considered mandatory early operative management for infected necrotizing pancreatitis has evolved into a more delayed approach using less invasive methods. While the endoscopic 'step-up' procedure has recently been shown to be safer for patients, the robotic platform is now emerging as a potential replacement, offering a more efficient one-step approach.

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