Treatment of severe acute pancreatitis and its complications

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Abstract

Severe acute pancreatitis (SAP), which is the most serious type of this disorder, is associated with high morbidity and mortality. SAP runs a biphasic course. During the first 1-2 wk, a pro-inflammatory response results in systemic inflammatory response syndrome (SIRS). If the SIRS is severe, it can lead to early multisystem organ failure (MOF). After the first 1-2 wk, a transition from a pro-inflammatory response to an anti-inflammatory response occurs; during this transition, the patient is at risk for intestinal flora translocation and the development of secondary infection of the necrotic tissue, which can result in sepsis and late MOF. Many recommendations have been made regarding SAP management and its complications. However, despite the reduction in overall mortality in the last decade, SAP is still associated with high mortality. In the majority of cases, sterile necrosis should be managed conservatively, whereas in infected necrotizing pancreatitis, the infected non-vital solid tissue should be removed to control the sepsis. Intervention should be delayed for as long as possible to allow better demarcation and liquefaction of the necrosis. Currently, the step-up approach (delay, drain, and debride) may be considered as the reference standard intervention for this disorder.

INTRODUCTION

Severe acute pancreatitis (SAP) is associated with high morbidity and mortality due to the development of pancreatic and extra-pancreatic necrosis, their subsequent infection and multisystem organ failure (MOF)[1-3]. Despite overall reduced mortality in the last decade, SAP is a devastating disease that is associated with mortality ranging from less than 10% to as high as 85%, according to various studies[4-8]. The management of SAP is complicated because of the limited understanding of the pathogenesis and multi-causality of the disease, uncertainties in outcome prediction and few effective treatment modalities. Generally, sterile necrosis can be managed conservatively in the majority of cases with a low mortality...
rate (12%)\textsuperscript{[29]} However, infection of pancreatic necrosis can be observed in 25%-70% of patients with necrotizing disease; it is generally accepted that the infected non-vital tissue should be removed to control the sepsis\textsuperscript{[1,10,11]}. Laparotomy and immediate debridement of the infected necrotic tissue have been the gold standard treatment for decades\textsuperscript{[1,3,12]}. However, several reports have shown that early surgical intervention for pancreatic necrosis could result in a worse prognosis compared to cases where surgery is delayed or avoided\textsuperscript{[2,3,6,8,13-17]}.

Therefore, several groups worldwide have developed new, minimally invasive approaches for managing infected necrotizing pancreatitis\textsuperscript{[2,3,6,18-24]}. The applicability of these techniques depends on the availability of specialized expertise and a multidisciplinary team dedicated to the management of SAP and its complications\textsuperscript{[25]}.

** Naturial Clinical Course of SAP**

SAP develops in two phases (Figure 1). During the first 1-2 wk, a pro-inflammatory response occurs, which results in systemic inflammatory response syndrome (SIRS), a sterile response in which sepsis or infection rarely occurs. If the SIRS is severe, then proinflammatory mediators can cause early multiple (respiratory, cardiovascular, renal, and hepatic) organ failure. In parallel, pancreatic necrosis develops, usually within the first four days after the onset of symptoms. However, the extent of pancreatic necrosis is not fixed and may progress as the disease evolves during the first 2 wk\textsuperscript{[25]}. Although in the early phase of severe pancreatitis, SIRS can be found in the absence of significant pancreatic necrosis, the majority of patients with severe early organ dysfunction will have pancreatic necrosis that is evident on computed tomography scan\textsuperscript{[4,26]}. Peripancreatic fluid collections are common and are termed acute fluid collections if present for less than 4 wk, after which time they are referred to as pancreatic pseudocysts (PPCs).

After the first 1-2 wk, a transition from a pro-inflammatory to an anti-inflammatory response occurs. During this “second or late phase”, the patient is at risk for the translocation of intestinal flora due to intestinal barrier failure, which is followed by the development of secondary infection in the pancreatic or peripancreatic necrotic tissue and fluid collections. Mortality occurs in two peaks. Early mortality is the result of severe SIRS with MOF. Late mortality is the consequence of infection in the pancreatic necrosis and peripancreatic fluid collections resulting in sepsis\textsuperscript{[7,10,27,28]}.

** Diagnosis of SAP**

Diagnosis of SAP is based on clinical presentation, laboratory tests, and imaging results\textsuperscript{[29-34]}. Physical and radiologic scoring systems have been developed with the aim of predicting which patients will have a severe clinical course and which patients might recover without major physiologic insult\textsuperscript{[15,34]}. However, acute pancreatitis (AP) is a complex disease; despite the existence of several criteria, it is not easy to predict its subsequent course because often in patients with the same initial clinical and radiological scores, the clinical course of the disease may vary. It is difficult to assess the disease because of the lack of accurate and uniformly accepted definitions of disease severity and commonly encountered complications of AP\textsuperscript{[16,35,36]}. 

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*Figure 1  Natural clinical course of severe acute pancreatitis. SIRS: Systemic inflammatory response syndrome; MOF: Multisystem organ failure.*
The Atlanta Classification as the first reliable clinical classification system of AP, the accumulation of clinical data calls for a revision of the Atlanta criteria of severity[46].

### Imaging evaluation

Contrast-enhanced computed tomography (CECT) is currently the standard imaging modality in the setting of SAP. The most important roles for CECT are the diagnosis of pancreatic gland necrosis, the determination of the extent of necrosis, and the diagnosis of local complications[25,47]. Because the complete development of pancreatic necrosis may not occur for up to four days after the onset of SAP in the majority of patients, CECT cannot be used to reliably determine the presence or the full extent of necrosis before that time[59]. CECT cannot reliably detect underlying necrotic debris in an acute necrotic collection or walled-off necrosis (WON), especially fluid-predominant collections[25,47]. The Balthazar's CT severity index (CTSI) is commonly used to stratify the severity of the disease and to predict mortality (Table 1).

Ultrasound (US) has a limited role in the assessment of patients with AP; its primary disadvantage is the frequent association with the ileus, which tends to make the visualization of the pancreas difficult[49]. Another disadvantage of US is that it provides no information regarding the presence or the extent of pancreatic necrosis. However, compared to the majority of other modalities, the primary advantage of ultrasound is that it is a portable procedure that can be performed in any location, which is especially useful for patients who are in a critical care setting and who cannot be easily transported to the CT scan suite.

Endoscopic ultrasound (EUS) is a useful modality for evaluating patients with AP. Its role in the assessment of choledocholithiasis is to aid in triaging patients who require therapeutic endoscopic retrograde cholangiopancreatography (ERCP), thus eliminating potential complications that might be associated with diagnostic ERCP. The limitations of EUS are the inconsistent availability of skilled endosonographers with endoscopic and imaging skills, a potential for adverse events in critically ill patients, and a tendency to overestimate the necrotic debris content of pancreatic fluid collections[25,49].

Magnetic resonance imaging (MRI) is a useful alternative to CT for detecting parenchymal necrosis; magnetic resonance cholangiopancreatography (MRCP) may replace ERCP in the diagnostic evaluation of the pancreatic duct (PD)[57,58-61]. Due to its ability to characterize pancreatic and peripancreatic collections or abscesses as partial or full fluid in consistency, lack of radiation, ability of MRCP to detect bile duct stones, and ability to demonstrate the presence of disconnected PD, MRI has a fundamental impact on the course of additional management. Disadvantages of MRI/MRCP include longer acquisition times, difficult implementation in critically

#### Table 1  Computer tomography indeks of illness severity for acute pancreatitis[48]

| Computer tomography findings | Grade | Score |
|-----------------------------|-------|-------|
| Normal pancreas             | A     | 0     |
| Enlargement                 | B     | 1     |
| Inflammation of pancreas and fat | C | 2 |
| Single fluid collection     | D     | 3     |
| Two or more fluid collections | E | 4     |
| Necrosis                    |       |       |
| <30%                        |       | 2     |
| 30%-50%                     |       | 4     |
| 50%                         |       | 6     |
| Max = 10 points             |       |       |

During physical examination, the most common presenting symptoms of AP are epigastric pain, nausea, and vomiting with physical signs that can include rebound tenderness, distension and reduced bowel sounds. Systemic involvement and organ failure can be detected, including shock, pulmonary insufficiency, renal failure, gastrointestinal bleeding or any combination of these symptoms[37-39].

Laboratory findings in SAP usually reflect organ dysfunction and metabolic disturbances. Used for diagnosing AP, serum amylase and lipase levels greater than three times the upper normal limit is considered to be diagnostic of pancreatitis. In AP, these enzymes are elevated because of the pancreatic acinar cell leakage into the interstitial space and their subsequent absorption into the circulation[40].

There are various scoring systems (Ranson, APACHE II, SOFA, BISOP, etc.) that help stratify the severity of AP. The severity of AP which can be objectively assessed on the patient’s admission to the hospital by using Ranson’s score[38], or the APACHE II criteria for disease severity[33], which evaluate the disease severity based on laboratory and clinical parameters. During the course of AP, the disease is considered to be severe if 3 or more Ranson’s criteria are observed within 48 h of the onset of the attack, or if 9 or more APACHE II criteria are observed at any time during the course of the disease. The severity of organ failure, determined using SOFA score multi-step criteria, as introduced for septic patients, is considered to be clinically relevant and is being increasingly applied for scoring disease severity and for predicting outcome[42]. The bedside index for severity in AP (BISAP) is a simple clinical scoring system, which stratifies patients within the first 24 h of admission to the hospital according to their risk of in-hospital mortality and helps identify patients at increased risk for mortality before the onset of organ failure. A score of > 3 is associated with 5%-20% mortality[43,44].

However, as in other disease processes, physicians face numerous dilemmas in defining AP severity and its complications. To help physicians define AP, a multidisciplinary International Symposium was organized in Atlanta in September 1992 with the aim of achieving international consensus on the definition of AP and its complications. Despite the worldwide acceptance of The Atlanta Classification as the first reliable clinical classification system of AP, the accumulation of clinical data calls for a revision of the Atlanta criteria of severity[46].
ill patients, toxicity of gadolinium in patients with renal insufficiency, and contraindication of MRI in pacemakers and other metal objects. Image-guided, fine-needle aspiration of the necrotic area is a procedure used for obtaining culture and Gram stain and identifying the causative organism of infection. However, therapeutic trends have altered this approach to such a degree that the clinical relevance of this method has been substantially diminished.

**BASIS OF THERAPY IN SAP**

SAP should be managed in an intensive care unit that is equipped to apply intensive monitoring and systemic support, including supportive care, prompt fluid resuscitation to maintain circulation volume and prevent electrolyte imbalance, nutritional supplements, analgesics, oxygen supplementation, mechanical ventilation, as well as monitoring for respiratory, cardiovascular and renal insufficiency and their early correction. The principles of intensive monitoring and systemic support in SAP are summarized in Table 2.

There are two primary aims in the initial treatment of patients with SAP. The first aim is to provide supportive therapy and to treat specific complications that may occur. The second aim is to limit both the severity of pancreatic inflammation and necrosis and SIRS by specifically interfering with their pathogenesis. The clinical usefulness of protease inhibitors (somatostatin, octreotide, leupafant and gabexate mesilate) in the treatment of SAP has not been clearly confirmed despite the fact that several studies have shown a reduced incidence of complications and mortality after the administration of protease inhibitors.

**Nutritional support**

SAP is characterized by marked nutritional depletion, and nutritional support is required to achieve a positive nitrogen balance. Because these patients may often present with paralytic ileus and keeping the pancreas at rest is mandatory, the patients are parenterally fed. Parenteral nutrition should be started, and positive nitrogen balance should be obtained in the first 72 h after the onset of SAP. Enteral nutrition starting in the early phase of SAP is superior to total parenteral nutrition unless paralytic ileus is present. This positive effect is most likely achieved using enteral nutrition that supports maintenance of the intestinal barrier. Continuous tube feeding with peptide-based formulas is possible in the majority of patients, and the jejunal route is recommended if gastric feeding is not tolerated by the patient. If the volume of enteral nutrition tolerated by the patient is insufficient to achieve adequate caloric support, combined parenteral and enteral feeding should be instituted.

**Role of antibiotics**

The aim of antibiotic prophylaxis in SAP is to prevent superinfection in the necrotic tissues. Late deterioration of organ dysfunction, which occurs most commonly between the second and third week after the onset of SAP, most likely results from secondary infection in pancreatic and peripancreatic necrosis due to bacterial translocation from the gastrointestinal tract into the necrotic tissues. Because the development of necrosis is currently not preventable, the rationale for using prophylactic antibiotics in SAP is to prevent the infection in the pancreatic necrosis. However, antibiotic prophylaxis is controversial concerning the clinical management of AP. There are a large number of published studies with questionable study designs and contradictory results, which could be attributed to the inclusion of heterogeneous patients, different antibiotic regimes, and different study objectives. Several randomized controlled trials offer evidence for the effectiveness of prophylactic antibiotics in reducing septic complications and mortality of patients with necrotizing pancreatitis. However, other studies, of which several are meta-analyses, as well-designed studies, don't approve the routine use of prophylactic antibiotics because there are no significant differences related to surgery or mortality. Two randomized, double-blinded, prospective, controlled, multicenter trials proved antibiotic prophylaxis to be ineffective concerning the reduction of infection in necrosis and hospital mortality. A Cochrane meta-analysis concluded that antibiotic prophylaxis is not protective in SAP. The American Association of Gastroenterology recommends the administration of antibiotic prophylaxis in cases of extended necrosis involving more than 30% of the gland based on abdominal CT. Prophylaxis should be administered for no longer than 14 d because prolonged antibiotic therapy increases the prevalence of fungal infections. The role of prophylactic antifungal agents has not been fully defined.

**Treatment of biliary etiology**

Although there is no clear consensus on all of the indications for ERCP and endoscopic sphincterotomy (ES),

| Table 2  Principles of intensive monitoring and systemic support |
|---------------------------------------------------------------|
| **Parameters**                                                 |
| Intensive invasive monitoring of vital constants              |
| Analgesics (consider epidural analgesia if necessary)          |
| Fluid resuscitation with monitoring of central venous pressure |
| Electrolyte solutions                                          |
| Plasma expanders                                               |
| Humidified oxygen administration                               |
| Catecholamines (dopamine, dobutamine)                          |
| Early nutritional support                                       |
| Early treatment of systemic complications                      |
| Mechanical ventilation with positive end-expiratory pressure   |
| Catecholamines (epinephrine)                                   |
| Hemofiltration, dialysis                                       |
| Insulin and calcium substitution                               |

**Notes:**
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it is generally accepted that they are indicated for acute cholangitis and obstructive jaundice. Under these conditions, ERCP and ES ameliorate the symptoms and the progression of the disease when applied early, desirably within 72 h from the onset of the disease. The question remains whether patients classified as suffering from severe biliary pancreatitis but without associated biliary sepsis or obstructive jaundice would benefit from the endoscopic approach. Open cholecystectomy is an unacceptable emergency procedure in patients with severe gallstone-associated pancreatitis. Co-morbidity, which is a major predeterminant of cholecystectomy outcome, does not apply to the use of ERCP and ES. Generally, patients with AP of suspected biliary etiology and who are classified as suffering from severe disease should undergo ERCP. ES should be performed when there is biliary sludge or stones within the common bile duct.

**IMAGING-GUIDED AND ENDOSCOPIC PROCEDURE FOR TREATMENT OF NECROTIZING PANCREATITIS**

**Image-guided percutaneous treatment**

Image-guided percutaneous interventions, which seem technically feasible in a vast majority of patients with necrotizing pancreatitis, range from needle aspiration to the placement of multiple drainage catheters. The choice of image-guided intervention for percutaneous needle aspiration or percutaneous catheter drainage (PCD) depends on the size and the location of the collection and the patient’s habitus.

Image-guided PCD of collections in and around the pancreas in patients with acute necrotizing pancreatitis is an important therapeutic option either on its own or as an adjunct to surgery. The majority of pancreatic collections are located in the lesser sac, the anterior pararenal space, or other parts of the retroperitoneum and can be drained with a catheter inserted percutaneously. Moreover, the advantages of PCD include widespread availability, access by transperitoneal and retroperitoneal approaches to the left and right sides of the abdomen and pelvis, the ability to insert multiple catheters (Figure 2), and the ability to flush catheters between procedures without general anesthesia and with fewer traumas, simultaneously performing vigorous irrigation with similar effects as performed surgically.

Depending on the operator experience, tandem trocar technique or Seldinger technique can be used. If the Seldinger technique is used, then the catheter tract should be sequentially dilated over a guidewire. Access routes that avoid crossing the bowel and other intervening organs, or major mesenteric, peripancreatic, or retroperitoneal blood vessels are selected to minimize the risk of bacterial contamination and hemorrhage. Successful percutaneous treatment of necrotic collections of the pancreas depends on several important factors. Catheters often need to remain in place for several weeks and sometimes months; hence, close follow-up is required.

The value of drainage therapy for removing solid debris is equivocal. Generally, at the beginning of the disease, catheter drainage of the infected necrotic tissue is poor; several authors have considered that surgical resection of the necrotic tissue is mandatory. However, other authors have determined that solid tissue and necrotic debris could be removed with draining fluid and that the use of vigorous irrigation through large-bore catheters could effectively remove the tissue. The rationale for this strategy is that large-bore catheters may be more effective for mobilizing solid tissue and evacuating the necrotic tissue from the cavities. Other authors have reported no significant correlation between the drainage catheter size and the disease outcome.

Several percutaneous drainage procedures are performed to stabilize the seriously ill patient before surgical debridement, whereas other procedures are performed with the intent to cure. In 1998, Freeny et al. first described a consecutive series of patients who had infected pancreatic necrosis and who were treated primarily with imaging-guided PCD, as an alternative to primary surgical necrosectomy. They demonstrated that the majority of patients could be treated by drainage without the need for necrosectomy. A major limitation of PCD is the development of pancreaticocutaneous fistulae; several authors reported that several fistulas did not close after the procedure because of communication between the drain and an upstream disrupted PD. However, the disruption of PD is the initial pathologic event that triggers fistula formation in inflammatory disease and trauma of the pancreas. Therefore, the recovery of disrupted PD has been recognized as the primary prognostic factor for successful treatment of pancreatic fistula regardless of the treatment method (surgery or imaging intervention) used. Moreover, in several cases, the fistula can be successfully treated by image-guided PCD with irrigation by antiseptic and administration of proper antibiotics.

**Endoscopic treatment of SAP**

Endoscopic necrosectomy is a minimally invasive method...
for the drainage of symptomatic pancreatic collections and necroses whereby a nasocystic catheter is inserted through a transmural entry site alongside a 10-Fr stent to perform irrigation. Endoscopic necrosectomy was first described in 1996 by Baron et al., whereas peroral flexible endoscopic drainage of PPCs performed via transpapillary or transmural techniques had been reported more than 25 years ago. Using the direct endoscopic necrosectomy technique, a stoma is created endoscopically between the enteric lumen and the necrotic cavity to allow the insertion of an endoscope directly into the cavity, which allows mechanical debridement and lavage. Direct endoscopic necrosectomy can be performed only if the collection or necrosis is located within a few centimeters of the gastric or duodenal lumen. The site of transmural puncture for direct endoscopic intervention should be determined visually and fluoroscopically by an observed bulge that represents the extrinsic compression of the collection into the gut lumen. Approximately 50% to 80% of potentially drainable collections can be performed using this approach. However, a bulge is often absent with smaller collections, low serum albumin, and collections in or near the pancreatic tail.

Therefore, to minimize the risk of complications, such as puncturing adjacent structures, bleeding, and perforation, EUS is increasingly used to perform endoscopic drainage. The advantages of EUS-guided endoscopic drainage include the ability to visualize and determine the optimal access into the collection, to avoid intervening blood vessels, to assess the contents of the cavity, and to visualize bleeding into the collection and other complications during and immediately after the procedure. Randomized clinical trials of endoscopic transmural drainage with and without EUS guidance showed that EUS visualization had an advantage over conventional endoscopic techniques.

The advantages of the endoscopic approach compared to PCD include internal drainage and avoidance of external fistulae; however, limitations include the need for multiple repeated procedures under sedation or anesthesia. Additionally, in the case of superinfection or drainage problems, monitoring, catheter manipulation and analysis of cystic content are difficult using the endoscopic approach. Combining a percutaneous approach and endoscopic transmural drainage can prevent external fistulae and avoid repetitive endoscopic interventions to perform direct necrosectomy.

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**Table 3  Surgical treatment modalities in necrotizing pancreatitis**

| Surgical treatment modalities                                    |
|------------------------------------------------------------------|
| **Open necrosectomy with open packing** - after necrosectomy, the abdomen maybe left open and repeatedly debrided until there is no residual necrosis, and is allowed to close by secondary intention |
| **Open necrosectomy with closed packing** - after the removal of necrotic tissue, the abdomen is closed, packing with external drains left in place. The drains are removed singly every other day, starting 5-7 d postoperatively |
| **Open necrosectomy with continuous postoperative lavage** - the procedure is based on the insertion of 2 or more double lumen catheters. Repeated open necrosectomy is performed and the packing is removed when there is no residual necrosis. The smaller lumen of the drains is used for the inflow of the lavage, and the larger lumens is used for the outflow. The drains can be removed after 2-3 wk |
| **Programmed open necrosectomy** - necrosectomy of necrotic tissue is performed using multiple procedures. After necrosectomy, the pancreatic bed is packed with sponges and soft drains are placed on the top of the packs. The abdomen is closed using a zipper |

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**SURGICAL APPROACH TO NECROTIZING PANCREATITIS**

**Open surgical necrosectomy**

The indication for surgical intervention and the optimal timing of intervention in necrotizing pancreatitis are frequently subject to discussion. Traditionally, laparotomy and immediate surgical debridement have been the gold standard for the treatment of infected and symptomatic sterile necroses with the aim of complete removal of the necrotic tissue. Open necrosectomy, originally described by Beger et al., consists of a laparotomy through a bilateral subcostal incision. After blunt removal of all of the necrotic tissue, two large-bore drains for postoperative lavage are inserted, and the abdomen is closed.

Currently, there are various open surgical approaches for removing the pancreatic necroses. Table 3 outlines various strategies for open surgical necrosectomy.

Open necrosectomy is associated with a high morbidity (34%-95%) and mortality ranges from 6% to 25%. Randomized controlled trials have demonstrated that delayed surgical necrosectomy proves superior to early necrosectomy. Therefore, the current recommendation is to delay the surgery as late as possible after the onset of pancreatitis until the necrotic process has stopped expanding and when there is a clear demarcation between viable and nonviable tissues, so that the infected necrosis has become walled off or organized. Potential, immediate, postoperative, adverse events include organ failure, perforation of a hollow viscus, wound infection, and hemorrhage, any of which may require another surgery. Long-term adverse events include chronic pancreaticocutaneous and enterocutaneous fistulae, diabetes mellitus, exocrine pancreatic insufficiency, and abdominal wall hernias. Consensus supports the claim that postoperative continuous irrigation and “closed packing” are superior to open packing and planned relaparotomies. Relaparotomy increases the local intra-abdominal and systemic trauma and has negative systemic effects on hemodynamic and systemic inflammatory response.

**Minimally invasive surgical techniques**

The traditional limitations of open surgery (significant postoperative deterioration and organ dysfunction) have led to the development of minimally invasive necrosectomy techniques as less invasive treatment alternatives to open necrosectomy. They can be classified according to the type of scope used (laparoscope, nephroscope
and the route of access (transperitoneal, retroperitoneal) \cite{87,88,89} with the aim of minimizing the surgical stress and physiological insult in patients who are already critically ill \cite{1,90,91}. Carter \textit{et al} \cite{92} described their technique and good results from percutaneous retroperitoneal necrosectomy. The retroperitoneal approach may be selected in patients with left-sided, predominantly retroperitoneal necrosis with a semisolid collection. In 2001, Horvath \textit{et al} \cite{93} described the video-assisted retroperitoneal debridement (VARD) approach, using a 4-5 cm retroperitoneal incision and regular laparoscopic equipment for removing the infected necrosis. Critics of these techniques noted that they require several repeated procedures to perform complete necrosectomy with a likelihood of serious complications. Each access route has its own advantages and disadvantages, such as ease of access, ability to address multiple collections and risk of collateral injury. The actual status of endoscopic drainage seems to differ only slightly from that of the percutaneous techniques \cite{22}.

**MANAGEMENT OF COMPLICATIONS OF SAP**

Management of complications of AP varies depending on the severity and the type of complications. Considering the Atlanta classification system is an important step before determining the strategy for treating the complications of AP because different local complications should be treated in different ways, either conservatively, using interventional methods, or surgically \cite{45,46}. Treating the complications of SAP, including pancreatic fluid collections, necrosis, pseudocysts, abscesses, pancreatic fistulas, and hemorrhage, requires a multidisciplinary approach and the application of diagnostic, interventional and surgical methods.

**AP fluid collections and necroses**

Pancreatic necrosis develops early in the course of SAP and is usually well established by 96 hours after the onset of clinical symptoms. Acute necrotic collections, which occur simultaneously in approximately 40% of patients, as enzyme-rich pancreatic juice collections can be intrapancreatic or extrapancreatic. They are heterogeneous, can contain non-liquid material with varying amounts of fluid, and are without full encapsulation \cite{98,45,49,72}. Sterile acute necrotic collections rarely require intervention early in the course of disease, and the conservative approach and image-guided follow-up of acute sterile fluid collections and necroses are better than continuous drainage from the beginning, which is frequently associated with their bacterial colonization and catheter problems \cite{25}.

However, several patients with gross destruction of the pancreatic gland due to impairment of the microcirculation of the pancreas during SAP can develop massive sterile pancreatic necroses, which cause systemic release of numerous cytokines and inflammatory mediators, thus leading to activation of inflammatory cells, fever, and multiorgan failure (Figure 3).

Although sterile pancreatic necroses are not infected, they can lead to extravasations of amylase-rich and protein-rich intravascular fluid into the peripancreatic regions and can result in poor clinical course and initiate physiologic pathways, which progress to organ failure, cardiovascular collapse and formation of abscesses and sepsis \cite{40}. Therefore, in this clinical setting, the removal of toxic mediators and inflammatory substances from sterile collections may ameliorate the systemic consequences induced by SAP \cite{16,94}. Removing toxic mediators and inflammatory substances can be performed by percutaneous or endoscopic transmural drainage \cite{16,82,94,95}.

**Infected pancreatic necrosis**

More than 80% of deaths associated with AP are attributed to septic complications as a consequence of bacterial infection in pancreatic necrosis \cite{89}. Therefore, in

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Figure 3 Ultrasound appearance of pancreatic necroses and a large acute fluid collection before and after drainage. A: Large fluid collection and pancreatic necroses before drainage; B: Catheter in the peripancreatic fluid collection; C: Massive pancreatic necroses with secondary fluid collection.

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infected necrotizing pancreatitis, the infected non-vital tissue should be removed to control the sepsis. For patients with infected necrosis, there is convincing evidence that the early surgical intervention (before 3 wk) for pancreatic necrosis could result in a worse prognosis compared to patients where surgery is delayed. Surgical techniques are associated with total anesthesia and considerable trauma, which often causes escalation of multiorgan failure, uncontrolled bleeding and sepsis [2,3,6].

Recently, minimal invasive non-surgical management, using truly conservative or less invasive drainage techniques, was included in the treatment of infected necrotizing pancreatitis that allowed for the surgical debridement to be delayed or completely avoided [23,4,14,15]. In the beginning of the disease, catheter drainage of infected necrotic tissue is often ineffective because of catheter blockage by necrotic tissue fragments and viscous fluid. However, during the course of SAP, a transition from solid necrotic tissue to more liquid contents leads to a higher success rate of the evacuation of the necrotic tissue from the cavities, regardless of the catheter size (Figures 4 and 5A) [3,19].

Therefore, conservative treatment with proper intravenous hydration and the administration of proper antibiotics should be performed at the initial stages of the disease. Less invasive drainage techniques should be considered when truly conservative treatment fails to resolve the infected pancreatic necrosis. Surgical necrosectomy may represent overtreatment at the beginning of the disease onset in patients with usually poor general condition, with difficulties in discriminating between necrotic and normal tissue during the procedure. Additionally, surgical necrosectomy carries a high risk of bleeding from vessels in the necrotized tissue during or immediately after the intervention. With delayed intervention, demarcation between the necrotic and vital tissue occurs; therefore, if necrosectomy is performed later in the course, then resection of the vital tissue is minimized, leading to better long-term endocrine and exocrine function and a reduction in postoperative adverse events [3,19,69].

Pancreatic WON

According to the revision of the Atlanta classification, pancreatic IF’ON is defined as “a circumscribed collection of pus, containing little or no pancreatic necrosis, which arises as a consequence of AP or pancreatic trauma” [36,60]. IF’ON, which occurs only in the context of necrotizing pancreatitis, is heterogeneous, contains non-liquid material with varying amounts of fluid, and has an encapsulating wall (Figure 5B).

WON can be located intrapancreatically or extrapancreatically. This process develops due to liquefaction and subsequent superinfection of limited pancreatic and retroperitoneal necrosis as well as superinfection of acute fluid collections [97,99]. In general, pancreatic WON develops later in the course of the disease (usually after four or more weeks after the onset of SAP). Asymptomatic WON does not mandate intervention, regardless of the
Figure 5 Computed tomography. A: Computed tomography (CT) appearance of the infected pancreatic necrosis, which involves the entire pancreas (marked by an arrow); B: CT appearance of a large pancreatic walled-off necrosis in the tail of the pancreas (marked by arrows).

size and extension of the collection, and may resolve spontaneously over a period of time, even in rare cases of infected necrosis\[25\]. Symptomatic WON generally requires intervention later in the disease course if there is intractable pain, obstruction of the stomach or bile duct, or in the case of infection\[25,99,100\]. Due to their less aggressive behavior and circumscribed localization, minimally invasive treatment strategies, including percutaneous or endoscopic approach, can be easily performed with success in the majority of these cases\[99,100\].

**PPC**

A PPC is a collection of pancreatic content enclosed by a wall of fibrous or granulation tissue, which is not lined by the epithelium\[43\]. The majority of PPCs regress spontaneously and need no treatment, whereas some PPCs may persist and progress to produce complications. Factors that influence the decision regarding whether to treat PPC include pain, infection, pressure effects that can lead to gastric outlet, intestinal or biliary obstruction. Several conditions must be met to achieve the complete obliteration of the cyst cavity. PD anatomy is an important factor in the prognosis of the treatment\[6,8,102-104\].

Traditionally, surgery was the only treatment option for symptomatic PPC\[85,106\]. However, this surgical treatment involves considerable trauma and general anesthesia, with the risk of PPC recurrence not being entirely excluded. The recent trend in managing symptomatic PPC has been toward less invasive approaches, such as endoscopic and image-guided PCD\[80,102-104,106\]. The endoscopic approach is suitable because the majority of PPCs lie adjacent to the stomach, yet with both endoscopic and imaging skills being required here\[80\]. The major advantage of the endoscopic approach is that it creates a permanent pseudocyst-gastric tract with no spillage of pancreatic enzymes. However, with drainage problems, monitoring, catheter manipulation and the analysis of cystic content are difficult or impossible to perform endoscopically, unlike with PCD approach\[83\]. Drainage techniques have better results and lower recurrence rates in patients without communication between PPC and PD\[76\]. When PPC-PD communication is identified, the mean duration of drainage increases to between weeks and months, depending on the condition of the PD\[76,103,104\].

**Pancreatic fistula**

Disruption of the PD secondary to pancreatic necrosis leads to leakage of the pancreatic secretion and its accumulation inside the abdomen in the neighborhood of the pancreas and pseudocyst formation. However, the pancreatic juice can also flow to other locations, causing pancreatic ascites, pleural effusion, distant pseudocyst or pancreatocutaneous fistula. ERCP, MRCP and wirsunography by using CT may be utilized in the diagnostic evaluation of PD disruption\[1,47,56-52,54\]. ERCP, in the same endoscopic session, may be associated with the placement of a stent to bridge the leak site, which may contribute to the definitive resolution of PD disruption\[107\]. Traditionally, pancreatic fistulas have been managed primarily by conservative treatment with total parenteral nutrition and the administration of pancreatic secretory inhibitor octreotide. However, conservative treatment tends to fail in many patients whereby interventional therapies and even surgery become the next option. A subsequent surgery for fistula management is technically demanding and is associated with major morbidity and mortality\[7,116-118\].

**Hemorrhage**

Hemorrhage into the pancreatic bed or adjacent retroperitoneum is usually a consequence of gastrointestinal bleeding, which occurs due to gastroduodenitis, bleeding peptic ulcer and pancreatitis-induced enzymatic damage to the adjacent vasculature, such as the splenic, renal or gastroduodenal arteries and the development of an aneurysm in one of these arteries\[38,40\]. Rupture of an aneurysm in these arteries usually results in acute, severe, life-threatening hemorrhage. Diagnosis may be established by angiography or angio-CT. Occasionally, embolization can be performed using angiography, which may stop the bleeding. If this method fails, the definitive treatment must be surgery\[40,54,110\].
STEP-UP APPROACH

In recent years, the treatment of infected necrotizing pancreatitis has shifted from early surgical necrosectomy to postponed minimally invasive step-up strategy. This approach is based on the statement that surgical debridement may represent overtreatment at the beginning of the disease in patients with usually poor general condition, with difficulties in discriminating between necrotic and normal tissue during the procedure and a high risk of bleeding from vessels in the necrotized tissue during or immediately after the surgery. The initial step-up approach is percutaneous or endoscopic drainage of the infected collection to prevent sepsis. If this approach fails, minimal invasive surgery is employed, with open surgery being reserved for those patients who do not respond to less invasive techniques.[119,120,22,24,58,113]

If the patient's condition improves (in approximately 35% of cases)[20], after percutaneous or endoscopic approach, no surgical debridement is performed. Surgical intervention is postponed for as long as possible so that the infected collection may become encapsulated[22] and is performed when the patient's condition does not improve or if it deteriorates. Several recently published studies compared the outcomes of the step-up approach with open debridement as the primary treatment (step-down approach) and demonstrated that the step-up approach was superior because it reduced morbidity, mortality, and costs per patient[21,13,14,29]. Presently, the step-up approach may be considered the reference standard intervention for SAP. The individual components of the step-up approach may be subject to improvement. However, the concept of the step-up approach can be summarized as follows: delayed intervention with close monitoring and conservative treatment, catheter drainage and minimally invasive drain-guided debridement seem here to stay.[24]

CONCLUSION

The management of SAP varies depending on the severity and the type of complication that requires treatment. Classifying the complications of SAP according to the revised Atlanta classification system is important before deciding the appropriate treatment strategy because different complications of SAP are treated in different ways, either conservatively by interventional imaging techniques or by surgery. Although no universally accepted treatment algorithm exists, the step-up approach using close monitoring, percutaneous or endoscopic drainage, followed by minimally invasive video-assisted retroperitoneal debridement has been shown to produce superior outcomes to traditional open necrosectomy and may be considered as the reference standard intervention for this disorder. Several recently published studies showed that the step-up approach, compared with open debridement (step-down approach), reduced the rates of major complications and death by minimizing surgical trauma in already critically ill patients with necrotizing pancreatitis. The individual components of the step-up approach may be subject to improvement. Additional research, preferably randomized trials or prospective collaborative studies, are required to improve current minimally invasive interventional techniques (drainage, endoscopic and laparoscopic) and to define optimal duration and timing of each intervention as part of the step-up approach. The primary principle of intervention for necrotizing pancreatitis is that there is no unique treatment that is optimal for all patients. The best approach is a multidisciplinary one that is adaptable to the individual patient. Therefore, for the management of such complex disease entities, a multidisciplinary team approach is essential, and the final selection of the optimal treatment of SAP will depend on multiple factors, including the expertise available at a given center, specific patient characteristics and risk assessment findings.

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