PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Treatment of Necrotizing Pancreatitis

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This article has an accompanying continuing medical education activity on page e93. Learning Objectives—At the end of this activity, the successful learner will be able to describe the clinical features, diagnosis, and treatment options for patients with necrotizing pancreatitis.

See related article, Baron TH and Kozarek RA, on page 1202 in this issue of *CGH*.

Acute pancreatitis is a common and potentially lethal disease. It is associated with significant morbidity and consumes enormous health care resources. Over the last 2 decades, the treatment of acute pancreatitis has undergone fundamental changes based on new conceptual insights and evidence from clinical studies. The majority of patients with necrotizing pancreatitis have sterile necrosis, which can be successfully treated conservatively. Emphasis of conservative treatment is on supportive measures and prevention of infection of necrosis and other complications. Patients with infected necrosis generally need to undergo an intervention, which has shifted from primary open necrosectomy in an early disease stage to a step-up approach, starting with catheter drainage if needed, followed by minimally invasive surgical or endoscopic necrosectomy once peripancreatic collections have sufficiently demarcated. This review provides an overview of current standards for conservative and invasive treatment of necrotizing pancreatitis.

Keywords: Acute Pancreatitis; Necrotizing; Infection; Treatment; Conservative; Intervention.

Epidemiology and Diagnosis

Acute pancreatitis is an acute inflammation of the pancreas that in Western countries is mainly caused by gallstones (40%–50%) and alcohol abuse (10%–40%). Other causes (20%–30%) include medication, endoscopic retrograde cholangiopancreatography (ERCP), hypertriglyceridemia, hypercalcemia, and surgery. In around 10% the etiology remains unknown.[1,2]

The pathophysiology of acute pancreatitis is generally considered as a premature or inappropriate activation of digestive enzymes within pancreatic acinar cells, causing autodigestion of the pancreas and surrounding tissues with subsequent local and systemic inflammation.[3,4]

The incidence of acute pancreatitis is increasing. In the United States, acute pancreatitis accounts for more than 200,000 hospital admissions each year.[4–6] In Europe, the incidence ranges from approximately 4–45 per 100,000 patients a year.[2] Acute pancreatitis is associated with significant morbidity and enormous health care resources.[5,7] Overall mortality in acute pancreatitis is approximately 5%.[3]

Diagnosis of acute pancreatitis requires at least 2 of the following 3 features: (1) abdominal pain, typically epigastric; (2) serum amylase or lipase ≥3 times the upper limit of normal; and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT). In most cases, the clinical history and laboratory results accurately provide the diagnosis, and no diagnostic imaging is required. A CECT in the initial 3–4 days of acute pancreatitis might underestimate or miss the amount of necrosis.[8–10] In general, a CECT is advised if a patient does not improve after the first week of treatment to evaluate the extent of local complications.[8] In clinical practice, however, it is not uncommon for patients to undergo CT earlier than 1 week, especially in case of early complications.

Clinical Course

Acute pancreatitis has a mild clinical course in about 80% of patients, in whom the disease resolves spontaneously within about a week.[11] However, about 20% of patients develop severe acute pancreatitis, which is associated with mortality rates of 8% up to 39%.[3] The 1992 Atlanta classification defined severe acute pancreatitis as the presence of organ failure or local complications such as pancreatic necrosis. Pancreatic necrosis occurs in around 15%–20% of patients and is typically diagnosed as focal areas of

Abbreviations used in this paper: **ACS, abdominal compartment syndrome; CECT, contrast-enhanced computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; ETD, endoscopic transluminal drainage; ETN, endoscopic transluminal necrosectomy; FNA, fine-needle aspiration; IAH, intra-abdominal hypertension; PCD, percutaneous catheter drainage; RCT, randomized controlled trial; VARD, video-assisted retroperitoneal debridement.**

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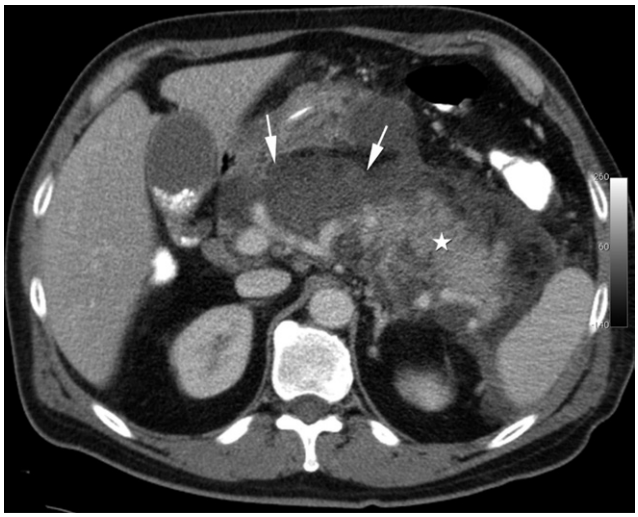

Figure 1. Acute necrotizing pancreatitis: a 47-year-old man with necrotizing pancreatitis of biliary origin. Perfusion defect is observed at the neck of the pancreas (*arrows*), with remaining viable pancreatic tissue at the body and tail (*asterisk*). Note the presence of gallstones.

nonenhancing pancreatic parenchyma on CECT (Figure 1).[3] The Atlanta classification is currently under revision.[12] In the revised classification the definition of necrotizing pancreatitis will not only include patients with pancreatic necrosis but also patients with extrapancreatic fat necrosis alone (ie, with normal enhancing pancreatic parenchyma on CECT). Some studies have suggested that patients with extrapancreatic necrosis alone may have a better outcome than patients with pancreatic necrosis. However, extrapancreatic necrosis alone is clinically a more severe entity than acute edematous pancreatitis.[13,14]

Several prognostic scoring systems are used to predict the severity of acute pancreatitis in the first days of admission; among them are Acute Physiology and Chronic Health Evaluation, (modified) Glasgow (Imrie) score, Ranson score, procalcitonin, C-reactive protein, and blood urea nitrogen.[15] These prognostic scoring systems are mainly used for severity stratification in clinical studies, and one can argue about their importance in daily clinical practice.

Theoretically, severe acute pancreatitis is divided in a biphasic clinical course. The first phase (ie, up to 1–2 weeks after onset of symptoms) is characterized by a proinflammatory immune response. A systemic inflammatory response syndrome often occurs, which is frequently accompanied by failure of 1 or more organ systems.[16–18] Organ failure develops in around 40% of patients with severe acute pancreatitis and is associated with a mortality rate of approximately 30%.[14,19] More than half of the cases of organ failure occur in the first week of admission.[14] Patients with persistent organ failure or multiorgan failure have a worse prognosis than patients with transient organ failure or single organ failure.[3,16,20] It has been suggested that approximately half of the deaths from necrotizing pancreatitis are caused by multiorgan failure in the early phase.[14,20,21]

In the second phase of the disease (ie, after 1–2 weeks from onset of symptoms) the proinflammatory immune response usually subsides. In this phase, the patient's immune system is probably suppressed, which renders patients more susceptible to infectious complications caused by bacterial translocation.[22–24]

The most severe infectious complication in necrotizing pancreatitis is infection of pancreatic or peripancreatic necrosis. The incidence of infected necrosis in patients with necrotizing pancreatitis has remained stable during the last decades (around 30%).[14,25] The peak incidence of infected necrosis is between 2 and 4 weeks after onset of disease.[26]

Infected necrosis is typically suspected when there is persistent sepsis, new-onset sepsis, or progressive clinical deterioration (ie, signs of sepsis) despite maximal support in the second phase of the disease, without another source of infection. A pathognomonic sign of infected necrosis is impacted peripancreatic or intrapancreatic gas bubbles in a collection on CECT (Figure 2), although this is present in only a minority of patients. In some patients, gas bubbles can also be explained by a fistulous communication between the collection and bowel, which, however, also means the collection is contaminated. A fine-needle aspiration (FNA) for microbiological culture can be performed to diagnose infected necrosis. However, FNA might not always be necessary in patients with necrotizing pancreatitis and suspected infected necrosis. In addition, FNA is associated with a risk of false-negative results.[27] Because suspected infected necrosis no longer represents an immediate indication for invasive treatment, an FNA culture result will not per se guide clinical decision-making. Intervention is generally postponed to 3–4 weeks after onset of disease, and the need for intervention is primarily dictated by clinical deterioration and encapsulation of the infected collection rather than a positive microbiological culture obtained by FNA. A recent Dutch multicenter randomized controlled trial (RCT) demonstrated that a strategy of intervention in patients with clinical suspicion of infected necrosis, without the routine use of FNA, yielded definitive proof of infected necrosis (ie, positive microbiological cultures from radiological drainage and operation) in more than 90% of patients.[28]

Even though much has changed in the management of necrotizing pancreatitis during the last 20 years, mortality of infected necrosis remains as high as 12%–39%.[14,28–32]

Treatment in the Early Phase

Initial treatment of acute pancreatitis is mainly conservative and focuses primarily on frequent monitoring of the

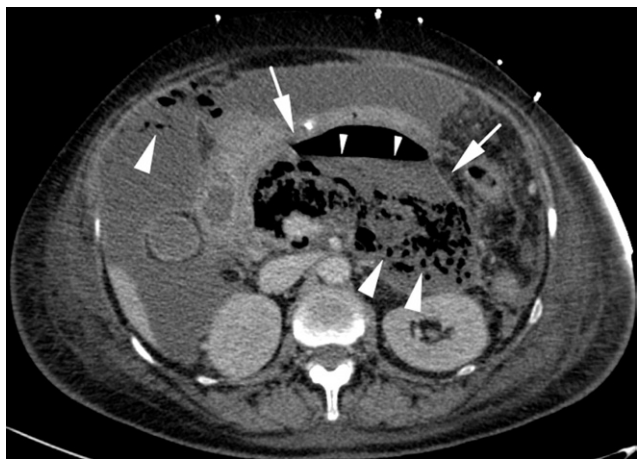

Figure 2. Infected necrosis: a 55-year-old woman with infected necrotizing pancreatitis. There is a large heterogeneous collection in the pancreatic and peripancreatic area (*arrows* point at the borders of the collection) with impacted gas bubbles (*big arrowheads*) and a gas-fluid level (*small arrowheads*), often a pathognomonic sign of infected necrosis.

clinical course, pain management, fluid resuscitation, and supportive measures for organ failure.

Supportive Measures

Patients admitted with acute pancreatitis should be closely monitored with adequate amounts of intravenous fluids and pain management. In case of hemodynamic, respiratory, or renal insufficiency with a diuresis of <0.5 mL/kg/h despite adequate fluid resuscitation, or metabolic disorders, patients need to be managed in an intensive care unit.

Aggressive fluid resuscitation is undertaken, especially in the setting of hemoconcentration, which reflects intravascular volume depletion. Prevention or reversal of hemoconcentration is the goal of volume resuscitation. Fluid balance should be maintained and closely monitored.[4] The need for large amounts of fluid administration during the initial 24 hours is associated with poor outcome, and therefore this group of patients should be watched carefully.[33–36] Two retrospective cohort studies suggested that aggressive early fluid resuscitation (at least one-third of the total 72-hour cumulative intravenous fluid volume given during the first 24 hours) is associated with decreased risk of systemic inflammatory response syndrome and organ failure, a lower rate of admission to the intensive care unit, a reduced length of hospital stay, and reduced mortality.[37,38] Most guidelines encourage targeting fluid resuscitation toward correcting hypotension, correcting hemoconcentration, and maintaining adequate urine output.[3,8,37] However, a recent RCT from China demonstrated that aggressive, uncontrolled administration of intravenous fluids in the first days of acute pancreatitis can also be detrimental because it was related to a 2-fold increase in mortality.[39]

The type of fluid administered has been investigated in 2 studies. A cohort study of 434 patients showed no difference in outcome on the basis of the type of fluid administered,[38] although a recent RCT suggests that lactated Ringer's solution reduces the systemic inflammation compared with fluid resuscitation with normal saline.[40]

Analgesia plays an important role in the treatment of acute pancreatitis. Parenteral analgesics are generally needed. There is no evidence to suggest an advantage of any particular type of medication. When abdominal pain is particularly severe, patient-controlled analgesia is usually preferred. It is important to obtain measurements of bedside oxygen saturation frequently whenever narcotic agents are administered to relieve pain.[3,8]

When organ dysfunction or organ failure is present, supportive treatment should be provided in an appropriate critical care facility.[41]

Several medical treatment options (eg, platelet-activating factor antagonist [lexipafant], activated protein C) to prevent organ failure in the early phase have been investigated, but none of them have been convincingly shown to be effective.[42,43]

Prevention of Infection of Necrosis

A recent prospective observational study of 731 patients with acute pancreatitis (28% with severe acute pancreatitis) showed that 25% of all patients developed 1 or more infections (ie, pneumonia, bacteremia, or infected necrosis). Mortality in patients with infection was 30%, whereas 80% of all deceased patients had an infection.[26] In severe acute pancreatitis, disturbed gastrointestinal motility may lead to bacterial overgrowth and failure of the structural mucosal barrier, which may lead to increased gut permeability.[44–47] These events may result in bacteria that cross the gastrointestinal mucosal barrier and invade the systemic compartment, so-called bacterial translocation.[44,48] Bacterial translocation is thought to be the mechanism causing most infections in acute pancreatitis. Strategies aimed at preventing bacterial translocation and subsequent infections have therefore been widely studied in recent years: antibiotics, probiotics, and enteral nutrition.

Antibiotics. Several meta-analyses, including 15 randomized trials, have been published on systemic antibiotics aimed at preventing infectious complications in acute pancreatitis.[49–51] Only 3 RCTs were double-blind placebo-controlled.[52–54] The design, methodological quality, and, most importantly, outcome of the included studies vary widely.[49] Most meta-analyses did not demonstrate a significant beneficial effect of antibiotic prophylaxis on infection of pancreatic necrosis and mortality.[49–51]

Although the discussion on antibiotic prophylaxis in acute pancreatitis continues, at the moment there is no convincing evidence in favor of routine antibiotic prophylaxis. If a beneficial effect actually exists, it will be difficult to perform a randomized study with sufficient statistical power to demonstrate this effect. Most international guidelines currently do not recommend routine antibiotic prophylaxis.[3,55]

Probiotics. Probiotics are nonpathogenic bacteria that, on delivery to the host's intestinal tract, are believed to prevent bacterial overgrowth, reinforce the mucosal barrier function, and regulate the systemic immune system that may reduce bacterial translocation and subsequent infections. Probiotics have been shown to prevent infections in elective major abdominal surgery.[48] Several studies on probiotics have also been performed in patients with acute pancreatitis. The first 2 double-blind, placebo-controlled, randomized trials from the same study group included 45 and 62 patients, respectively, with predicted severe acute pancreatitis. The first trial showed a significant reduction of infected pancreatic necrosis in patients receiving probiotics. The second trial showed a lower but not significant incidence of multiorgan failure, septic complications, and mortality in the probiotics group.[56,57] The third and largest double-blind, placebo-controlled trial included 298 patients with predicted severe acute pancreatitis. This study did not show an effect of an enterally administered multispecies probiotic mixture on the incidence of infections. However, patients receiving probiotics had an increased mortality as compared with patients receiving placebo (16% vs 6%; *P* value .01).[29] This negative effect was associated with an increase in nonocclusive mesenteric ischemia, which was predominantly seen in the patients with multiorgan failure, and has not yet been explained.[58] There is currently strong advice against the use of probiotics in patients with predicted severe acute pancreatitis.

Enteral nutrition. Nutritional support has a fundamental role in the management of severe acute pancreatitis. Besides maintaining adequate caloric intake, nutritional support is important in prevention of infectious complications.

Nutritional support can be achieved through parenteral and enteral feeding. Both strategies have been compared in several randomized trials and meta-analyses. Results show that enteral feeding significantly reduces mortality, multiorgan failure, systemic infections, and the need for operative intervention compared with parenteral feeding.[59]

Enteral nutrition can be administered through a nasogastric or nasojejunal tube. Two RCTs compared these 2 routes and did not show significant differences between recurrence or worsening of pain, hospital stay, complications, or mortality.[60,61] These studies, therefore, suggested that the simpler, cheaper, and more easily

used nasogastric feeding appears to be well tolerated and is as safe as nasojejunal feeding in patients with severe acute pancreatitis. A larger study to further test the safety of nasogastric feeding is currently underway in the United States (SNAP trial, http://Clinicaltrials.gov, NCT00580749).

Experimental and clinical research has shown that the phenomenon of bacterial translocation already takes place within a few hours after onset of symptoms.[22,62] This implies that there is only a very narrow therapeutic window for preventing bacterial translocation and subsequent infections.[26] Theoretically, enteral feeding should therefore be started as early as possible for a beneficial clinical effect. There is evidence in favor of this hypothesis in critically ill patients other than acute pancreatitis. In a meta-analysis of 15 randomized trials comparing early (within 36 hours) vs delayed (after 36 hours) start of enteral feeding on outcome of critically ill intensive care unit patients, early enteral nutrition significantly reduced the incidence of infections and length of hospital stay.[63] In acute pancreatitis, there is only indirect evidence for an early start of enteral feeding. A meta-analysis comparing the effect of enteral vs parenteral nutrition with subgroups based on the timing of start of nutrition showed that an early start of enteral feeding significantly reduced multiorgan failure, pancreatic infections, and mortality.[64] The first randomized trial specifically designed to compare early and selective delayed enteral feeding in predicted severe acute pancreatitis (PYTHON trial) is currently underway in the Netherlands (ISRCTN 18170985).[65]

Endoscopic Retrograde Cholangiopancreatography for Biliary Pancreatitis

Gallstones are the most common cause of acute pancreatitis in the Western world.[2,8] In patients with biliary pancreatitis, decompression of the common bile duct and removal of gallstones or sludge by early ERCP with subsequent sphincterotomy may mitigate the pancreatic inflammation and reduce complications. Several RCTs have investigated the clinical effect of early ERCP in acute biliary pancreatitis.[66–69] From the available evidence, 2 conclusions on the role of ERCP are generally drawn: (1) patients with biliary pancreatitis and concurrent cholangitis should undergo early ERCP and (2) in predicted nonsevere biliary pancreatitis, ERCP is not beneficial.[3,8] However, the role of early ERCP in patients with predicted severe biliary pancreatitis remains controversial. Although the 2005 United Kingdom guidelines on acute pancreatitis recommend emergency ERCP in these patients,[41] two more recent US guidelines state that the value of early ERCP in predicted severe biliary pancreatitis without cholangitis is yet undetermined.[3,8] This is due to the fact that the published RCTs included only a small number of patients with predicted severe acute pancreatitis and, hence, were statistically underpowered to detect clinical effects in the group of most severely ill patients.[66–69] A recent updated meta-analysis showed no effect of ERCP on complications or mortality in all patients with predicted severe biliary pancreatitis. However, the pooled sample size was still small (n = 126), and sphincterotomy was only performed in 53% of patients.[70]

A recent prospective observational study, including 153 patients with predicted severe biliary pancreatitis without cholangitis, showed no significant reduction of complications after ERCP in patients without radiological or biochemical signs of cholestasis. In the subgroup of patients with cholestasis, however, ERCP was significantly associated with fewer complications, including pancreatic necrosis.[71]

A future large and well-designed randomized trial should study the effect of ERCP in patients with predicted severe biliary pancreatitis without cholangitis, with a predefined subgroup analysis in patients with and without signs of cholestasis.

Early Complications Requiring Intervention

A rare but dramatic complication early in the course of severe acute pancreatitis is abdominal compartment syndrome (ACS).[17] ACS is preceded by intra-abdominal hypertension (IAH), which is defined as an intra-abdominal pressure at or above 12 mm Hg. ACS is diagnosed when the intra-abdominal pressure exceeds 20 mm Hg and there are signs of new organ failure (eg, respiratory, circulatory, renal).[72] IAH generally occurs early, and in some studies the incidence has been reported to be as high as 59%–78% in patients with severe acute pancreatitis.[73,74] The pathophysiology of IAH is directly related to the pancreatic inflammation, which may cause retroperitoneal edema, fluid collections, ascites, and a paralytic ileus. IAH may also be partly iatrogenic, resulting from aggressive fluid resuscitation. IAH can also manifest in the later phase of acute pancreatitis, associated with local pancreatic complications.[75] The incidence of ACS in severe acute pancreatitis has been reported up to 30% in some studies and is associated with extremely high mortality rates of 46%–75%.[73,74,76,77] ACS requires immediate measures such as sedation, analgesics, nasogastric decompression, fluid restriction, and diuretics to lower the abdominal pressure. If these measures do not result in a rapid clinical improvement, invasive intervention is required. Percutaneous catheter decompression seems to be effective in resolving ACS in patients with intraperitoneal fluid, abscess, or blood, thereby avoiding the need for surgical decompression.[78] This strategy may improve outcome and is currently evaluated in acute pancreatitis by a randomized trial (http://Clinicaltrials.gov NCT00793715). If percutaneous decompression does not immediately lower the intra-abdominal pressure, surgical decompression laparotomy should be performed.[73,77,78]

In rare cases where decompressive laparotomy is necessary in the early phase of necrotizing pancreatitis, it is advised not to open the retroperitoneum or to perform necrosectomy. At this stage, the necrosis is probably sterile, which means a formal necrosectomy is not indicated and, conversely, may cause severe complications such as bleeding, perforation, infection of necrosis, and death.[79]

Another uncommon but devastating complication requiring early intervention is bowel ischemia. The occurrence of nonocclusive mesenteric ischemia is well known in critically ill patients,[80] and several cases of nonocclusive mesenteric ischemia have been reported in acute pancreatitis.[81] Although data on the incidence and outcome of bowel ischemia in acute pancreatitis are limited, the incidence seems to be low (approximately 4%). However, if present, mortality rates are approaching 100%.[81]

Treatment in the Late Phase

Conservative Treatment

In about two-thirds of patients with necrotizing pancreatitis, the pancreatic or peripancreatic necrosis remains sterile. These patients can develop walled-off pancreatic necrosis late in the disease. Walled-off pancreatic necrosis is characterized by a thickened wall between the necrosis and the adjacent viable tissue (Figure 3). In accordance with international guidelines, patients with sterile necrosis can be successfully managed conservatively (ie, without any form of

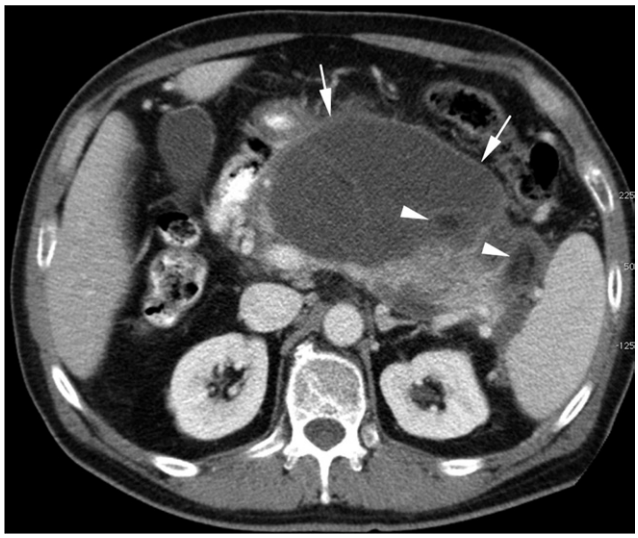

Figure 3. Walled-off necrosis: a 40-year-old man with necrotizing pancreatitis and walled-off necrosis. A completely encapsulated collection is observed in the pancreatic and peripancreatic area (*arrows*), with predominant fluid density interspersed with areas of fat density (*arrowheads*).

radiological, endoscopic, or surgical intervention).[3,17,55] An intervention for sterile peripancreatic collections with fluid and necrosis accommodates the risk of introducing infection of necrosis (55%–59%).[82,83] Iatrogenic infection of sterile necrosis requires additional interventions and considerably increases morbidity and mortality.[82,84,85] Probably the only exception are patients with persistent mechanical obstruction due to peripancreatic collections, in the absence of clinical signs of infection, causing ongoing nausea, vomiting, pain, anorexia, and inability to resume oral intake. In this case, the decision for intervention will be solely based on clinical symptoms, supported by CT findings, and should be delayed up to at least 4–6 weeks after onset of symptoms. This is due to the fact that most collections will resolve spontaneously.

In a recent prospective observational study of 639 patients with necrotizing pancreatitis, 62% of patients were treated conservatively. Mortality in these patients was 7%.[14]

Invasive Treatment

Although historically many patients with sterile necrosis also underwent necrosectomy, it is now accepted that the main indication for intervention is infected necrosis.[8,17,41,86]

The timing of intervention has also changed. Necrosectomy was once performed at a very early stage,[79] whereas it is now believed that intervention should be delayed to approximately 3–4 weeks after onset of disease.[27,87,88] To postpone intervention, patients with signs of infected necrosis are initially treated with broad-spectrum antibiotics and maximal support. This allows for encapsulation and demarcation of peripancreatic collections, which may improve conditions for intervention and thereby theoretically decrease the risk of complications such as bleeding and perforation. However, in some patients this is not feasible, and dramatic clinical deterioration will require earlier intervention.

A recent study of 242 patients undergoing intervention for necrotizing pancreatitis showed in a multivariable analysis adjusting for confounding factors that patients with longer time between admission and intervention had lower mortality: 0–14 days, 56%; 14–29 days, 26%; and >29 days, 15% ($P < .001$).[14]

It should be noted that there are several reports of patients with infected necrosis who were in such good clinical condition that they allowed treatment with intravenous antibiotics without invasive intervention.[14] However, the vast majority of patients with infected necrosis need to undergo radiological, endoscopic, or surgical intervention at some point.

Primary Open Necrosectomy

The traditional approach to infected necrosis used to be primary open necrosectomy to completely remove the infected necrosis.[25,89] This is an invasive approach associated with a high risk of complications (34%–95%) and mortality (11%–39%) and long-term pancreatic insufficiency.[31,32,86,90–95] As an alternative to primary open necrosectomy, minimally invasive radiological, surgical, and endoscopic techniques for intervention have gained wide popularity.

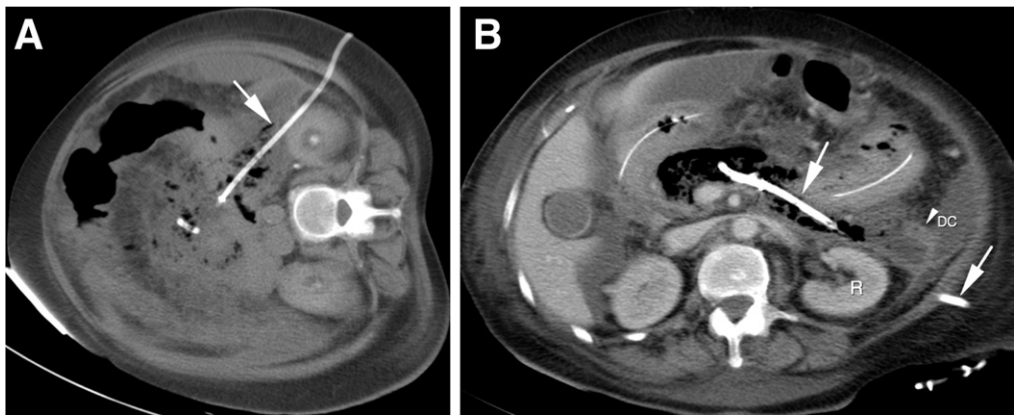

Figure 4. PCD: a 55-year-old woman with infected necrotizing pancreatitis (same patient as in Figure 2). Axial CT (*A*) performed in right decubitus position for optimal retroperitoneal positioning of a 12F percutaneous drain (*arrow*) via the left flank. Successive follow-up CT (*B*) reveals reduction in size of infected pancreatic collection, with PCD centrally positioned via the left retroperitoneal route (between the descending colon [DC] and the right kidney [R]).

Minimally Invasive Approaches

Minimally invasive interventions include percutaneous catheter drainage (PCD),[96] endoscopic transluminal drainage (ETD),[97–102] endoscopic (transluminal) necrosectomy (ETN),[98,99,103–112] and minimally invasive retroperitoneal surgical necrosectomy.[28,31,92,113–117] Minimally invasive techniques are thought to induce less physiological stress as compared with open surgical necrosectomy. Reduced surgical stress might decrease the risk of complications in these often already severely ill patients.

Percutaneous catheter drainage. Image-guided PCD (Figure 4) as primary treatment of infected necrosis was first described in 1998.[96] The rationale of PCD is to treat infected necrosis as an abscess and drain the infected fluid (ie, pus) under pressure, without removal of necrotic material. Successful drainage of the infected fluid will temporize sepsis and improve patient's clinical condition. This may lead to a situation where the patient is capable of resorbing the necrotic material without the need for formal necrosectomy. PCD is feasible in >95% of patients with infected necrotizing pancreatitis, often via a left-sided retroperitoneal approach.[28,118]

In a recent systematic review of 11 studies with a total of 384 patients receiving PCD for necrotizing pancreatitis, more than half of the patients were successfully treated with PCD alone and thus did not undergo additional necrosectomy.[119] This was confirmed by a recent prospective observational study. In 208 patients undergoing intervention for (suspected) infected necrosis, PCD was performed as the first intervention in 63% of patients, without the need for additional necrosectomy in 35% of patients.[14]

If necrosectomy is still needed after PCD, PCD may have allowed for further encapsulation of the necrotic collections and improvement of the patient's clinical condition. PCD thereby acts as a bridge to surgery. The preferred route for PCD is through the left retroperitoneum, so that the drain can be used as guidance for retroperitoneal surgical necrosectomy.

Minimally invasive retroperitoneal necrosectomy. Several less invasive surgical techniques to perform necrosectomy have been described in recent years. The most commonly used techniques are sinus tract endoscopy,[31,114,120] laparoscopic transabdominal necrosectomy,[121,122] and video-assisted retroperitoneal debridement (VARD).[115–117]

Sinus tract endoscopy involves serial dilatation of a percutaneous catheter drain tract by using fluoroscopic guidance in the operating room, with subsequent necrosectomy by jet irrigation and suction by using a nephroscope or flexible endoscope. Residual solid necrotic tissue is evacuated by using a variety of endoscopic instruments. Several retrospective studies reported a mean morbidity of 25%–88% and mortality of 0%–25%. A median of 3–4 sessions per patient (range, 1–9) were necessary to remove all infected necrosis.[92,114,120]

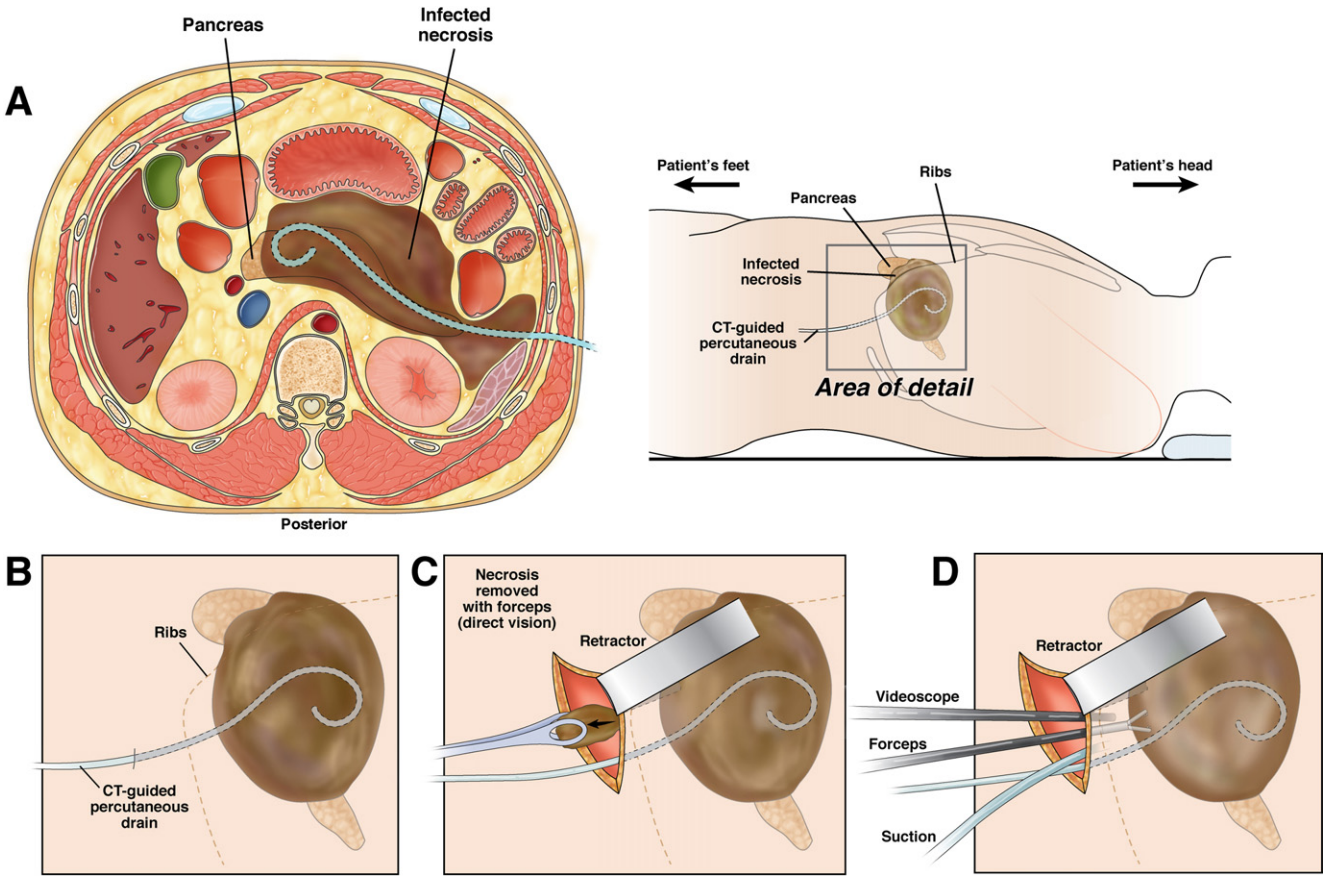

Figure 5. PCD and VARD. (*A*) Cross-sectional image and torso depicting a peripancreatic collection with fluid and necrosis. The preferred access route is through the left retroperitoneal space between the left kidney, dorsal spleen, and descending colon. A percutaneous drain is inserted in the collection to mitigate sepsis and postpone or even obviate necrosectomy. The area of detail is shown in (*panel B*). (*C*) A 5-cm subcostal incision is made, and the previously placed percutaneous drain is followed into the retroperitoneum to enter the necrotic collection. The first necrosis is removed under direct vision with a long grasping forceps. This is followed by further debridement under videoscopic assistance (*D*).

VARD (Figure 5) can be considered a hybrid between sinus tract endoscopy and an open lumbar approach.[123–125] By using a 5-cm subcostal incision, the previously placed percutaneous catheter drain is followed into the retroperitoneum to enter the necrotic collection. The first necrosis is removed under direct vision, followed by further debridement under videoscopic assistance.[116,117] VARD is associated with a morbidity and mortality of 24%–54% and 0%–8%, respectively.[115,116,126] VARD has several advantages; it uses regular surgical equipment, it is a straightforward, semiopen procedure, and it mostly requires only 1 session per patient.

Endoscopic transluminal drainage and necrosectomy. As an alternative to radiological and surgical techniques, ETD and ETN are gaining popularity. Endoscopic interventions are typically performed under conscious sedation without the need for general anesthesia. This potentially reduces the inflammatory response and may further reduce complications such as new-onset multiorgan failure. First, the collection with infected necrosis is visualized by endoscopic ultrasound to determine the extent of necrosis and the optimal site of drainage. Next, the collection is punctured through the gastric or duodenal wall, followed by balloon dilatation of the tract. Two double-pigtail stents and a

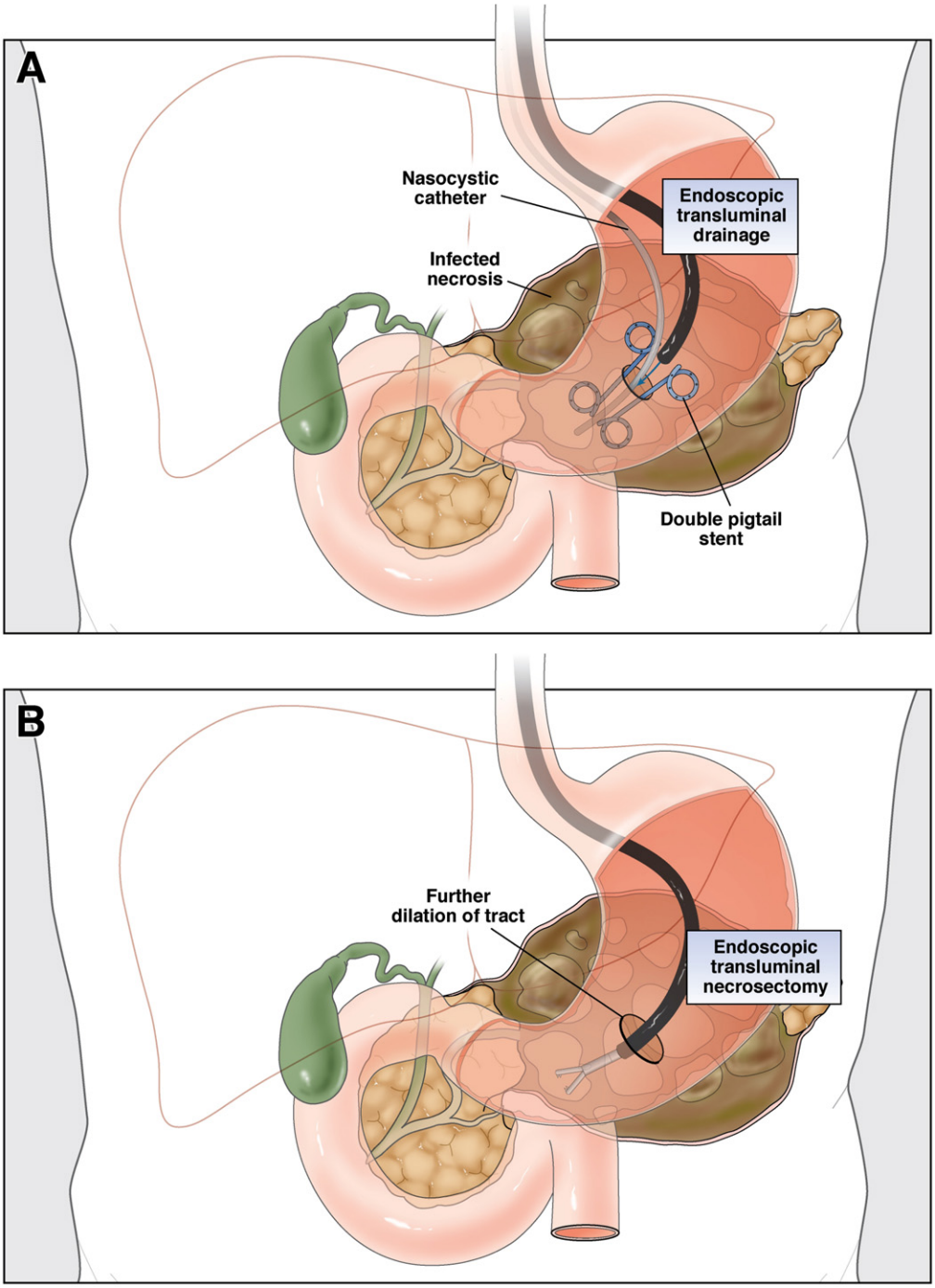

Figure 6. ETD and ETN. A large peripancreatic collection containing fluid and necrosis is shown. The preferred access route for endoscopic transluminal treatment is through the posterior wall of the stomach. The necrotic collection often bulges into the stomach, facilitating endoscopic transluminal treatment. (*A*) The collection is punctured through the gastric wall, followed by balloon dilatation of the tract. Two double-pigtail stents and a nasocystic catheter are placed for continuous postoperative irrigation. (*B*) The cystostomy tract is further dilated, the collection is entered by a forward viewing endoscope, and necrosectomy is performed.

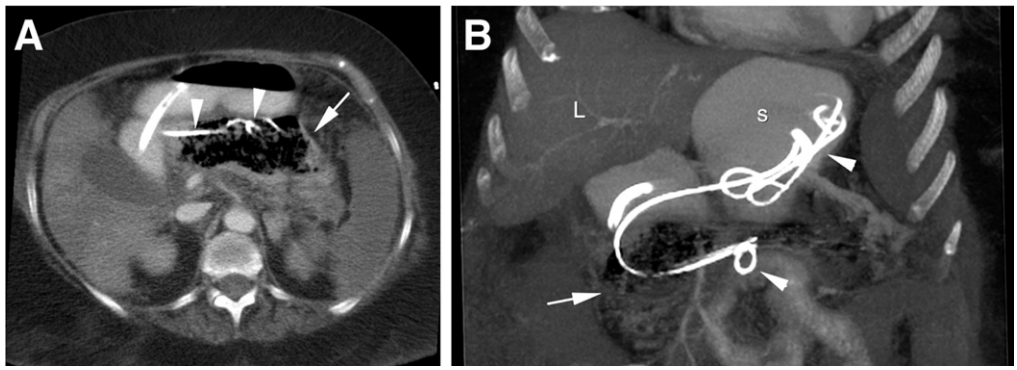

Figure 7. ETD: a 63-year-old woman with infected necrotizing pancreatitis. Axial CT (*A*) and coronal reconstructed mean intensity projection (*B*) show an infected pancreatic collection (*arrow*) with an endoscopic pigtail drain (*arrowheads*) positioned inside the collection (L, liver; S, stomach).

nasocystic catheter are placed for continuous postoperative irrigation (Figures 6*A* and 7). Several retrospective cohort studies show promising results of ETD, with complication rates of 2%–21% and mortality rates of 0%–6%.[97–102]

In case of no improvement or deterioration after ETD, ETN can be performed to remove infected necrosis. The cystostomy tract is further dilated, the collection is entered by a forward viewing endoscope, and necrosectomy is performed (Figure 6*B*). At the end of the procedure, 2 double-pigtail stents and a nasocystic catheter are placed. If necessary, ETN can be repeated until the majority of necrotic material is removed.[98,99,103–112] By avoiding any abdominal wall incision, typical complications related to surgical necrosectomy such as incisional hernias, pancreatic fistula, and wound infection will probably be reduced with ETN.

In a recent systematic review of 10 series on ETN in necrotizing pancreatitis, overall mortality after ETN was 5%, and the mean procedure-related morbidity was 27%. In 76% of patients, complete resolution of the necrotic collection was achieved by endoscopic interventions alone. On average, there were 4 endoscopic sessions (range, 1–35) needed to achieve complete resolution.[107] Although these results are promising, there is a risk of selection bias within these studies because the number of critically ill patients with infected necrosis included was relatively low.

A recent pilot RCT showed promising results. ETN significantly reduced the proinflammatory response (measured by serum interleukin-6 levels) as well as the composite clinical end point of major morbidity and mortality compared with surgical necrosectomy.[127]

The step-up approach. The minimally invasive techniques can be applied in a so-called step-up approach.[28,30,128] The first step is catheter drainage (ie, radiological, percutaneous, or endoscopic transluminal) of the collection with infected fluid and necrosis to mitigate sepsis and postpone or even obviate necrosectomy.[99,119] If drainage does not lead to clinical improvement, the next step is minimally invasive necrosectomy performed either surgically or endoscopically.[92,114,116,117] As compared with open necrosectomy, the step-up approach aims at control of the source of infection rather than complete removal of the infected necrotic tissue. The step-up approach can be performed both surgically and endoscopically.

The PANTER trial compared primary open necrosectomy with a surgical step-up approach in 88 patients with suspected or confirmed infected necrosis.[28] The step-up approach, which used PCD and was followed, if necessary, by VARD, reduced the combined primary end point of death and major complications (ie, new multiorgan failure, enterocutaneous fistula, perforation, or bleeding) from 69% to 40%. Furthermore, at 6-month follow-up, patients assigned to the step-up approach had a significantly lower rate of incisional hernias and new-onset diabetes. The step-up approach also reduced total costs by 12%. Finally, 35% of patients in the step-up approach group were treated with percutaneous drainage alone and did not need any form of surgery.[28]

These outcomes may further be improved by an endoscopic step-up approach that consists of ETD, followed, if necessary, by ETN. The Dutch Pancreatitis Study Group has recently started a nationwide randomized trial comparing the surgical step-up approach with the endoscopic step-up approach: TENSION (Trial registration: ISRCTN09186711).

Summary

Necrotizing pancreatitis remains a complex and challenging disease, even though several major improvements have occurred in the management of the disease during the last 2 decades.

In summary, the initial treatment of necrotizing pancreatitis should primarily focus on fluid resuscitation, pain management, and supportive measures for organ failure. With regard to prevention of infection of necrosis, routine antibiotic or probiotic prophylaxis is not recommended. Enteral nutrition, compared with parenteral nutrition, appears to be effective in preventing infected necrosis, but the optimal timing of start of enteral feeding requires further study. In patients with biliary pancreatitis and absence of cholangitis, there is no evidence that early ERCP with sphincterotomy is beneficial. However, in the subset of patients with predicted severe biliary pancreatitis and radiological or biochemical signs of cholestasis, early ERCP and sphincterotomy may prevent further complications. Conservative treatment is successful in about two-thirds of patients. Unnecessary intervention for sterile necrosis accommodates the risk of introducing infection and subsequent complications. However, 30% of patients spontaneously develop infection of necrosis and need to undergo invasive intervention. Whenever clinically feasible, intervention is postponed until there is sufficient encapsulation and demarcation of the infected peripancreatic collections, generally 3–4 weeks after onset of symptoms. Primary open necrosectomy has been replaced by a minimally invasive step-up approach that lowers the risk of major morbidity. The initial step is drainage of infected peripancreatic collections, which can be performed image-guided percutaneously or endoscopic ultrasound–guided endoscopic transluminally, depending on anatomic feasibility and local expertise. Catheter drainage is successful as definitive treatment in about 40% of patients. If catheter drainage does not lead to clinical improvement, the next step is minimally invasive drain-guided retroperitoneal necrosectomy or ETN. A treatment algorithm for severe acute pancreatitis is given in Figure 8. Future studies should

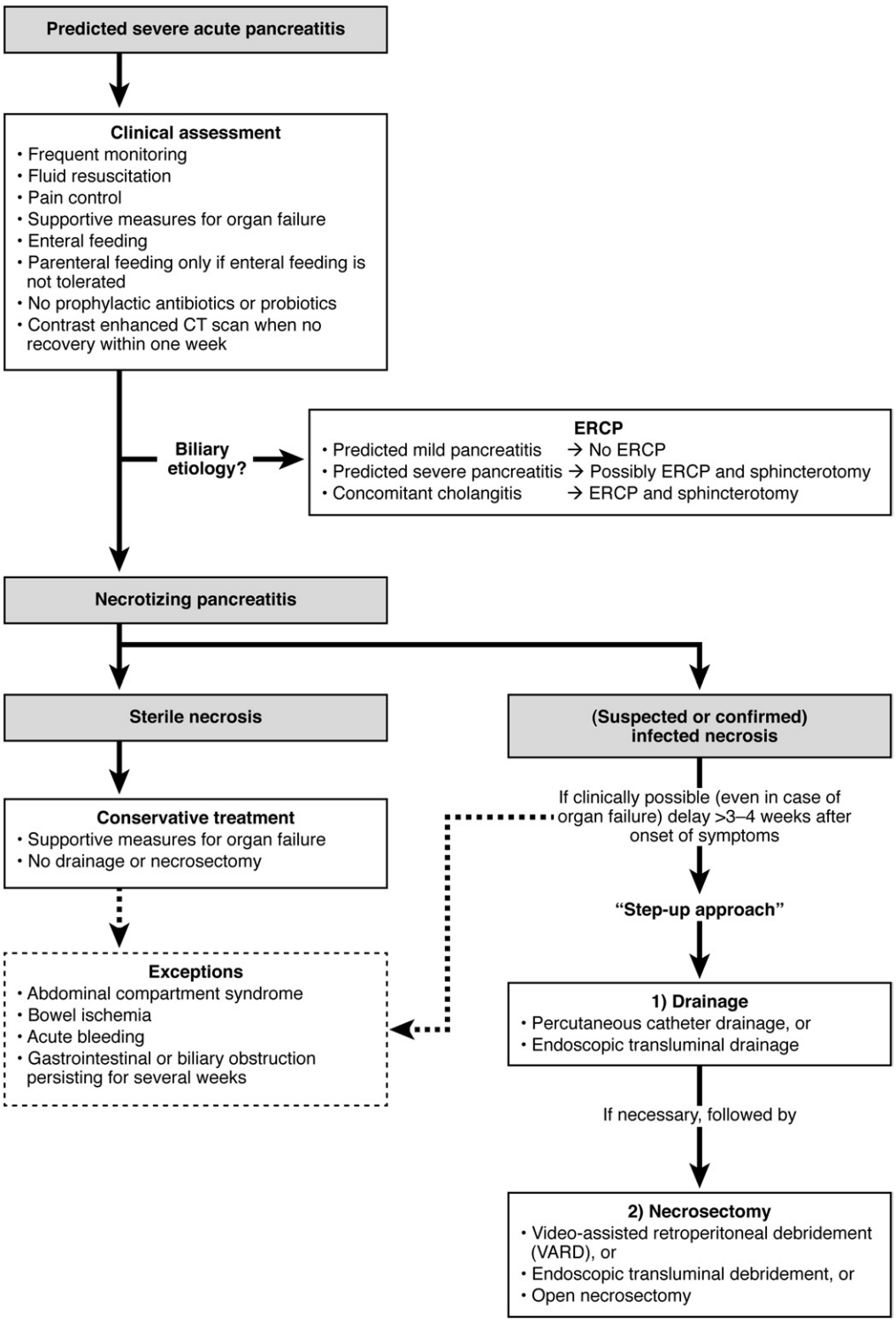

Figure 8. Treatment algorithm for severe acute pancreatitis.

further elucidate the role of both minimally invasive surgical and endoscopic interventions in patients with necrotizing pancreatitis.

References

1. Neoptolemos JP, Kemppainen EA, Mayer JM, et al. Early prediction of severity in acute pancreatitis by urinary trypsinogen activation peptide: a multicentre study. Lancet 2000;355:1955–1960.
2. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas 2006;33:323–330.
3. Banks PA, Freeman ML. Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006;101:2379–2400.
4. Whitcomb DC. Clinical practice: acute pancreatitis. N Engl J Med 2006;354:2142–2150.
5. Fagenholz PJ, Fernández-del Castillo C, Harris NS, et al. Direct

medical costs of acute pancreatitis hospitalizations in the United States. Pancreas 2007;35:302–307.
6. Swaroop VS, Chari ST, Clain JE. Severe acute pancreatitis. JAMA 2004;291:2865–2868.
7. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases. Am J Gastroenterol 2006; 101:2128–2138.
8. Forsmark CE, Baillie J, AGA Institute Clinical Practice and Economics Committee, et al. AGA Institute technical review on acute pancreatitis. Gastroenterology 2007;132:2022–2044.
9. Bollen TL, Singh VK, Maurer R, et al. A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis. Am J Gastroenterol 2012;107: 612–619.
10. Spanier BW, Nio Y, van der Hulst RW, et al. Practice and yield of early CT scan in acute pancreatitis: a Dutch observational multicenter study. Pancreatology 2010;10:222–228.
11. Beger HG, Rau B, Isenmann R. Natural history of necrotizing pancreatitis. Pancreatology 2003;3:93–101.
12. Revision of the ATLANTA classification of acute pancreatitis, 2008. Available at: http://pancreasclub.com/wp-content/uploads/2011/11/AtlantaClassification.pdf. Accessed April 9, 2008.
13. Sakorafas GH, Tsiotos GG, Sarr MG. Extrapancreatic necrotizing pancreatitis with viable pancreas: a previously under-appreciated entity. J Am Coll Surg 1999;188:643–648.
14. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 2011;141:1254–1263.
15. Wu BU, Bakker OJ, Papachristou GI, et al. Blood urea nitrogen in the early assessment of acute pancreatitis: an international validation study. Arch Intern Med 2011;171:669–676.
16. Mofidi R, Duff MD, Wigmore SJ, et al. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. Br J Surg 2006;93:738–744.
17. Nathens AB, Curtis JR, Beale RJ, et al. Management of the critically ill patient with severe acute pancreatitis. Crit Care Med 2004;32:2524–2536.
18. Werner J, Feuerbach S, Uhl W, et al. Management of acute pancreatitis: from surgery to interventional intensive care. Gut 2005;54:426–436.
19. Petrov MS, Shanbhag S, Chakraborty M, et al. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology 2010;139: 813–820.
20. Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. Gut 2004;53:1340–1344.
21. Blum T, Maisonneuve P, Lowenfels AB, et al. Fatal outcome in acute pancreatitis: its occurrence and early prediction. Pancreatology 2001;1:237–241.
22. Ammori BJ, Leeder PC, King RF, et al. Early increase in intestinal permeability in patients with severe acute pancreatitis: correlation with endotoxemia, organ failure, and mortality. J Gastrointest Surg 1999;3:252–262.
23. Deitch EA. The role of intestinal barrier failure and bacterial translocation in the development of systemic infection and multiple organ failure. Arch Surg 1990;125:403–404.
24. Van Leeuwen PA, Boermeester MA, Houdijk AP, et al. Clinical significance of translocation. Gut 1994;35:S28–S34.
25. Beger HG, Büchler M, Bittner R, et al. Necrosectomy and postoperative local lavage in patients with necrotizing pancreatitis: results of a prospective clinical trial. World J Surg 1988;12:255–262.
26. Besselink MG, van Santvoort HC, Boermeester MA, et al. Timing and impact of infections in acute pancreatitis. Br J Surg 2009; 96:267–273.
27. Besselink MG, Verwer TJ, Schoenmaeckers EJ, et al. Timing of surgical intervention in necrotizing pancreatitis. Arch Surg 2007;142:1194–1201.
28. van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362:1491–1502.
29. Besselink MG, van Santvoort HC, Buskens E, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet 2008; 371:651–659.
30. Besselink MG, van Santvoort HC, Nieuwenhuijs VB, et al. Minimally invasive "step-up approach" versus maximal necrosectomy in patients with acute necrotising pancreatitis (PANTER trial): design and rationale of a randomised controlled multicenter trial [ISRCTN13975868]. BMC Surg 2006;6:6.
31. Raraty MG, Halloran CM, Dodd S, et al. Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. Ann Surg 2010; 251:787–793.
32. Rodriguez JR, Razo AO, Targarona J, et al. Debridement and closed packing for sterile or infected necrotizing pancreatitis: insights into indications and outcomes in 167 patients. Ann Surg 2008;247:294–299.
33. de-Madaria E, Soler-Sala G, Sánchez-Payá J, et al. Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study. Am J Gastroenterol 2011;106:1843–1850.
34. Eckerwall G, Olin H, Andersson B, et al. Fluid resuscitation and nutritional support during severe acute pancreatitis in the past: what have we learned and how can we do better? Clin Nutr 2006;25:497–504.
35. Kuwabara K, Matsuda S, Fushimi K, et al. Early crystalloid fluid volume management in acute pancreatitis: association with mortality and organ failure. Pancreatology 2011;11:351–361.
36. Wu BU. Editorial: fluid resuscitation in acute pancreatitis: striking the right balance. Am J Gastroenterol 2011;106:1851–1852.
37. Gardner TB, Vege SS, Chari ST, et al. Faster rate of initial fluid resuscitation in severe acute pancreatitis diminishes in-hospital mortality. Pancreatology 2009;9:770–776.
38. Warndorf MG, Kurtzman JT, Bartel MJ, et al. Early fluid resuscitation reduces morbidity among patients with acute pancreatitis. Clin Gastroenterol Hepatol 2011;9:705–709.
39. Mao EQ, Fei J, Peng YB, et al. Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis. Chin Med J (Engl) 2010;123:1639–1644.
40. Wu BU, Hwang JQ, Gardner TH, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol 2011;9:710–717.
41. Working Party of the British Society of Gastroenterology, Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland, et al. UK guidelines for the management of acute pancreatitis. Gut 2005;54(Suppl 3):iii1–iii9.
42. Johnson CD, Kingsnorth AN, Imrie CW, et al. Double blind, randomised, placebo controlled study of a platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis. Gut 2001;48:62–69.
43. Pettilä V, Kyhälä L, Kylänpää ML, et al. APCAP—activated protein C in acute pancreatitis: a double-blind randomized human pilot trial. Crit Care 2010;14:R139.
44. Dervenis C, Smailis D, Hatzitheoklitos E. Bacterial translocation and its prevention in acute pancreatitis. J Hepatobiliary Pancreat Surg 2003;10:415–418.
45. Nieuwenhuijs VB, van Dijk JE, Gooszen HG, et al. Obstructive jaundice, bacterial translocation and interdigestive small-bowel motility in rats. Digestion 2000;62:255–261.
46. Nieuwenhuijs VB, Verheem A, van Duijvenbode-Beumer H, et al. The role of interdigestive small bowel motility in the regulation of gut microflora, bacterial overgrowth, and bacterial translocation in rats. Ann Surg 1998;228:188–193.

47. Van Felius ID, Akkermans LM, Bosscha K, et al. Interdigestive small bowel motility and duodenal bacterial overgrowth in experimental acute pancreatitis. Neurogastroenterol Motil 2003;15:267–276.
48. van Santvoort HC, Besselink MG, Timmerman HM, et al. Probiotics in surgery. Surgery 2008;143:1–7.
49. de Vries AC, Besselink MG, Buskens E, et al. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodological quality and outcome. Pancreatology 2007;7:531–538.
50. Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database Syst Rev 2010:CD002941.
51. Wittau M, Mayer B, Scheele J, et al. Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. Scand J Gastroenterol 2011;46:261–270.
52. Dellinger EP, Tellado JM, Soto NE, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg 2007;245:674–683.
53. García-Barrasa A, Borobia FG, Pallares R, et al. A double-blind, placebo-controlled trial of ciprofloxacin prophylaxis in patients with acute necrotizing pancreatitis. J Gastrointest Surg 2009;13:768–774.
54. Isenmann R, Rünzi M, Kron M, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology 2004;126:997–1004.
55. AGA Institute Governing Board. AGA Institute medical position statement on acute pancreatitis. Gastroenterology 2007;132: 2019–2021.
56. Oláh A, Belágyi T, Issekutz A, et al. Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. Br J Surg 2002;89:1103–1107.
57. Oláh A, Belágyi T, Pótó L, et al. Synbiotic control of inflammation and infection in severe acute pancreatitis: a prospective, randomized, double blind study. Hepatogastroenterology 2007;54:590–594.
58. Besselink MG, van Santvoort HC, Renooij W, et al. Intestinal barrier dysfunction in a randomized trial of a specific probiotic composition in acute pancreatitis. Ann Surg 2009;250:712–719.
59. Al-Omran M, Albalawi ZH, Tashkandi MF, et al. Enteral versus parenteral nutrition for acute pancreatitis. Cochrane Database Syst Rev 2010:CD002837.
60. Eatock FC, Chong P, Menezes N, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. Am J Gastroenterol 2005;100:432–439.
61. Kumar A, Singh N, Prakash S, et al. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. J Clin Gastroenterol 2006;40:431–434.
62. Rahman SH, Ammori BJ, Holmfield J, et al. Intestinal hypoperfusion contributes to gut barrier failure in severe acute pancreatitis. J Gastrointest Surg 2003;7:26–36.
63. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med 2001;29:2264–2270.
64. Petrov MS, Pylypchuk RD, Uchugina AF. A systematic review on the timing of artificial nutrition in acute pancreatitis. Br J Nutr 2009;101:787–793.
65. Bakker OJ, van Santvoort HC, van Brunschot S, et al. Pancreatitis, very early compared with normal start of enteral feeding (PYTHON trial): design and rationale of a randomised controlled multicenter trial. Trials 2011;12:73.
66. Fan ST, Lai EC, Mok FP, et al. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med 1993; 328:228–232.
67. Fölsch UR, Nitsche R, Lüdtke R, et al. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis: the German Study Group on Acute Biliary Pancreatitis. N Engl J Med 1997;336:237–242.
68. Neoptolemos JP, Carr-Locke DL, London NJ, et al. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet 1988;2:979–983.
69. Oría A, Cimmino D, Ocampo C, et al. Early endoscopic intervention versus early conservative management in patients with acute gallstone pancreatitis and biliopancreatic obstruction: a randomized clinical trial. Ann Surg 2007;245:10–17.
70. Petrov MS, van Santvoort HC, Besselink MG, et al. Early endoscopic retrograde cholangiopancreatography versus conservative management in acute biliary pancreatitis without cholangitis: a meta-analysis of randomized trials. Ann Surg 2008;247:250–257.
71. van Santvoort HC, Besselink MG, de Vries AC, et al. Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. Ann Surg 2009;250:68–75.
72. Malbrain ML, Cheatham ML, Kirkpatrick A, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. Intensive Care Med 2006;32:1722–1732.
73. Chen H, Li F, Sun JB, et al. Abdominal compartment syndrome in patients with severe acute pancreatitis in early stage. World J Gastroenterol 2008;14:3541–3548.
74. De Waele JJ, Hoste E, Blot SI, et al. Intra-abdominal hypertension in patients with severe acute pancreatitis. Crit Care 2005; 9:R452–R457.
75. De Waele JJ, Leppäniemi AK. Intra-abdominal hypertension in acute pancreatitis. World J Surg 2009;33:1128–1133.
76. Gecelter G, Fahoum B, Gardezi S, et al. Abdominal compartment syndrome in severe acute pancreatitis: an indication for a decompressing laparotomy? Dig Surg 2002;19:402–405.
77. Mentula P, Hienonen P, Kemppainen E, et al. Surgical decompression for abdominal compartment syndrome in severe acute pancreatitis. Arch Surg 2010;145:764–769.
78. Cheatham ML, Malbrain ML, Kirkpatrick A, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. II. Recommendations. Intensive Care Med 2007;33:951–962.
79. Mier J, León EL, Castillo A, et al. Early versus late necrosectomy in severe necrotizing pancreatitis. Am J Surg 1997;173:71–75.
80. Kolkman JJ, Mensink PB. Non-occlusive mesenteric ischaemia: a common disorder in gastroenterology and intensive care. Best Pract Res Clin Gastroenterol 2003;17:457–473.
81. Hirota M, Inoue K, Kimura Y, et al. Non-occlusive mesenteric ischemia and its associated intestinal gangrene in acute pancreatitis. Pancreatology 2003;3:316–322.
82. Walser EM, Nealon WH, Marroquin S, et al. Sterile fluid collections in acute pancreatitis: catheter drainage versus simple aspiration. Cardiovasc Intervent Radiol 2006;29:102–107.
83. Zerem E, Imamovic G, Omerović S, et al. Randomized controlled trial on sterile fluid collections management in acute pancreatitis: should they be removed? Surg Endosc 2009;23:2770–2777.
84. Besselink MG, van Santvoort HC, Bakker OJ, et al. Draining sterile fluid collections in acute pancreatitis? Primum non nocere! Surg Endosc 2011;25:331–332.
85. van Santvoort HC, Besselink MG, Bakker OJ, et al. Endoscopic necrosectomy in necrotising pancreatitis: indication is the key. Gut 2010;59:1587.
86. Büchler MW, Gloor B, Müller CA, et al. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann Surg 2000;232:619–626.
87. Fernández-del Castillo C, Rattner DW, Makary MA, et al. Debridement and closed packing for the treatment of necrotizing pancreatitis. Ann Surg 1998;228:676–684.
88. Uhl W, Warshaw A, Imrie C, et al. IAP guidelines for the surgical management of acute pancreatitis. Pancreatology 2002;2:565–573.
89. Traverso LW, Kozarek RA. Pancreatic necrosectomy: definitions and technique. J Gastrointest Surg 2005;9:436–439.
90. Ashley SW, Perez A, Pierce EA, et al. Necrotizing pancreatitis:

contemporary analysis of 99 consecutive cases. Ann Surg 2001;234:572–580.
91. Babu BI, Sheen AJ, Lee SH, et al. Open pancreatic necrosectomy in the multidisciplinary management of postinflammatory necrosis. Ann Surg 2010;251:783–786.
92. Connor S, Alexakis N, Raraty MG, et al. Early and late complications after pancreatic necrosectomy. Surgery 2005;137:499–505.
93. Howard TJ, Patel JB, Zyromski N, et al. Declining morbidity and mortality rates in the surgical management of pancreatic necrosis. J Gastrointest Surg 2007;11:43–49.
94. Rau B, Bothe A, Beger HG. Surgical treatment of necrotizing pancreatitis by necrosectomy and closed lavage: changing patient characteristics and outcome in a 19-year, single-center series. Surgery 2005;138:28–39.
95. Tsiotos GG, Luque-de León E, Sarr MG. Long-term outcome of necrotizing pancreatitis treated by necrosectomy. Br J Surg 1998;85:1650–1653.
96. Freeny PC, Hauptmann E, Althaus SJ, et al. Percutaneous CT-guided catheter drainage of infected acute necrotizing pancreatitis: techniques and results. AJR Am J Roentgenol 1998;170:969–975.
97. Baron TH, Thaggard WG, Morgan DE, et al. Endoscopic therapy for organized pancreatic necrosis. Gastroenterology 1996;111:755–764.
98. Gardner TB, Chahal P, Papachristou GI, et al. A comparison of direct endoscopic necrosectomy with transmural endoscopic drainage for the treatment of walled-off pancreatic necrosis. Gastrointest Endosc 2009;69:1085–1094.
99. Papachristou GI, Takahashi N, Chahal P, et al. Peroral endoscopic drainage/debridement of walled-off pancreatic necrosis. Ann Surg 2007;245:943–951.
100. Seewald S, Ang TL, Teng KC, et al. EUS-guided drainage of pancreatic pseudocysts, abscesses and infected necrosis. Dig Endosc 2009;21(Suppl 1):S61–S65.
101. Varadarajulu S, Phadnis MA, Christein JD, et al. Multiple transluminal gateway technique for EUS-guided drainage of symptomatic walled-off pancreatic necrosis. Gastrointest Endosc 2011;74:74–80.
102. Vitale GC, Davis BR, Vitale M, et al. Natural orifice translumenal endoscopic drainage for pancreatic abscesses. Surg Endosc 2009;23:140–146.
103. Charnley RM, Lochan R, Gray H, et al. Endoscopic necrosectomy as primary therapy in the management of infected pancreatic necrosis. Endoscopy 2006;38:925–928.
104. Coelho D, Ardengh JC, Eulálio JM, et al. Management of infected and sterile pancreatic necrosis by programmed endoscopic necrosectomy. Dig Dis 2008;26:364–369.
105. Escourrou J, Shehab H, Buscail L, et al. Peroral transgastric/transduodenal necrosectomy: success in the treatment of infected pancreatic necrosis. Ann Surg 2008;248:1074–1080.
106. Gardner TB, Coelho-Prabhu N, Gordon SR, et al. Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series. Gastrointest Endosc 2011;73:718–726.
107. Haghshenasskashani A, Laurence JM, Kwan V, et al. Endoscopic necrosectomy of pancreatic necrosis: a systematic review. Surg Endosc 2011;25:3724–3730.
108. Mathew A, Biswas A, Meitz KP. Endoscopic necrosectomy as primary treatment for infected peripancreatic fluid collections (with video). Gastrointest Endosc 2008;68:776–782.
109. Schrover IM, Weusten BL, Besselink MG, et al. EUS-guided endoscopic transgastric necrosectomy in patients with infected necrosis in acute pancreatitis. Pancreatology 2008;8:271–276.
110. Seewald S, Groth S, Omar S, et al. Aggressive endoscopic therapy for pancreatic necrosis and pancreatic abscess: a new safe and effective treatment algorithm (videos). Gastrointest Endosc 2005;62:92–100.
111. Seifert H, Biermer M, Schmitt W, et al. Transluminal endoscopic necrosectomy after acute pancreatitis: a multicentre study with long-term follow-up (the GEPARD study). Gut 2009;58:1260–1266.
112. Voermans RP, Veldkamp MC, Rauws EA, et al. Endoscopic transmural debridement of symptomatic organized pancreatic necrosis (with videos). Gastrointest Endosc 2007;66:909–916.
113. Baril NB, Ralls PW, Wren SM, et al. Does an infected peripancreatic fluid collection or abscess mandate operation? Ann Surg 2000;231:361–367.
114. Carter CR, McKay CJ, Imrie CW. Percutaneous necrosectomy and sinus tract endoscopy in the management of infected pancreatic necrosis: an initial experience. Ann Surg 2000;232:175–180.
115. Horvath K, Freeny P, Escallon J, et al. Safety and efficacy of video-assisted retroperitoneal debridement for infected pancreatic collections: a multicenter, prospective, single-arm phase 2 study. Arch Surg 2010;145:817–825.
116. Horvath KD, Kao LS, Wherry KL, et al. A technique for laparoscopic-assisted percutaneous drainage of infected pancreatic necrosis and pancreatic abscess. Surg Endosc 2001;15:1221–1225.
117. van Santvoort HC, Besselink MG, Horvath KD, et al. Videoscopic assisted retroperitoneal debridement in infected necrotizing pancreatitis. HPB (Oxford) 2007;9:156–159.
118. Besselink MG, de Bruijn MT, Rutten JP, et al. Surgical intervention in patients with necrotizing pancreatitis. Br J Surg 2006;93:593–599.
119. van Baal MC, van Santvoort HC, Bollen TL, et al. Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. Br J Surg 2011;98:18–27.
120. Connor S, Ghaneh P, Raraty M, et al. Minimally invasive retroperitoneal pancreatic necrosectomy. Dig Surg 2003;20:270–277.
121. Parekh D. Laparoscopic-assisted pancreatic necrosectomy: a new surgical option for treatment of severe necrotizing pancreatitis. Arch Surg 2006;141:895–903.
122. Zhu JF, Fan XH, Zhang XH. Laparoscopic treatment of severe acute pancreatitis. Surg Endosc 2001;15:146–148.
123. Castellanos G, Piñero A, Serrano A, et al. Infected pancreatic necrosis: translumbar approach and management with retroperitoneoscopy. Arch Surg 2002;137:1060–1063.
124. Fagniez PL, Rotman N, Kracht M. Direct retroperitoneal approach to necrosis in severe acute pancreatitis. Br J Surg 1989;76:264–267.
125. Nakasaki H, Tajima T, Fujii K, et al. A surgical treatment of infected pancreatic necrosis: retroperitoneal laparotomy. Dig Surg 1999;16:506–511.
126. van Santvoort HC, Besselink MG, Bollen TL, et al. Case-matched comparison of the retroperitoneal approach with laparotomy for necrotizing pancreatitis. World J Surg 2007;31:1635–1642.
127. Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA 2012;307:1053–1061.
128. Windsor JA. Minimally invasive pancreatic necrosectomy. Br J Surg 2007;94:132–133.

Reprint requests

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Conflicts of interest

The authors disclose no conflicts.