Current Concepts in Severe Acute and Necrotizing Pancreatitis: An Evidence-Based Approach






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The incidence of acute pancreatitis continues to rise, inducing substantial medical and social burden, with annual costs exceeding $2 billion in the United States alone. Although most patients develop mild pancreatitis, 20% develop severe and/or necrotizing pancreatitis, requiring advanced medical and interventional care. Morbidity resulting from local and systemic complications as well as invasive interventions result in mortality rates historically as high as 30%. There has been substantial evolution of strategies for interventions in recent years, from open surgery to minimally invasive surgical and endoscopic step-up approaches. In contrast to the advances in invasive procedures for complications, early management still lacks curative options and consists of adequate fluid resuscitation, analgesics, and monitoring. Many challenges remain, including comprehensive management of the entire spectrum of the disease, which requires close involvement of multiple disciplines at specialized centers.

Keywords: Severe Acute Pancreatitis; Necrotizing Pancreatitis; Acute Pancreatitis.

Severe acute pancreatitis (AP) develops in 20% of patients with AP, with a historical mortality risk as high as 30%.[1,2] With annual costs up to $2.6 billion in the United States alone, AP poses an enormous financial burden.[3] Most patients with AP recover within a week, whereas patients with severe AP have a high risk of multiorgan failure, prolonged intensive care unit stay, and need for invasive interventions for local and systemic complications.[1]

In AP, release of inflammatory mediators initiates a systemic inflammatory response syndrome (SIRS) that may induce single or multiorgan failure, with or without concomitant necrosis, infection, and possibly death.[4] Initial management is based on supportive measures aimed to minimize the impact of SIRS. In contrast to the early phase, there are numerous specific treatment options for the later phase of AP. Management of complications such as collections associated with (peri)pancreatic necrosis, including infected necrosis, have been addressed in observational studies and randomized controlled trials. As a result, evidence-based guidelines have been developed to outline a multidisciplinary strategy for endoscopic, radiologic, and surgical interventions.[1,5–7] Evolution in optimal timing, route and techniques for treating (peri-)pancreatic collections and other complications imply the need for continuing reappraisal.

In 2013, an international, multisociety, multidisciplinary GRADE-based guideline for the management of AP was published.[1] Several reviews have subsequently built on this evidence.[2,8–12] The current article aims to provide an updated clinical approach specifically focusing on patients potentially needing an intervention, incorporating classification and prediction of severity, diagnosis of infection, indications, and strategies for invasive management.

Methods

As basis for this review, the previously mentioned international guidelines[1,5–7,12] and systematic reviews[8–11] were used and expanded with a literature search specific to the

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Abbreviations used in this paper: **AP, acute pancreatitis; CECT, contrast-enhanced computed tomography; CI, confidence interval; CRAI, continuous regional arterial infusion; DM, diabetes mellitus; DMD, dual-modality drainage; DPDS, disconnected pancreatic duct syndrome; DPS, double pigtail stent; EPI, exocrine pancreatic insufficiency; ETD, endoscopic transluminal drainage; ETN, endoscopic transluminal necrosectomy; EUS, endoscopic ultrasound; FNA, fine needle aspiration; LAMS, lumen-apposing metal stent; PCD, percutaneous catheter drainage; SIRS, systemic inflammatory response syndrome; SVT, splanchnic vein thrombosis; VARD, video-assisted retroperitoneal debridement; WON, walled-off necrosis.**

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topics of severity, early treatment, complications, and intervention strategies in patients with severe, necrotizing pancreatitis. A literature search was performed in 3 databases (PubMed, Embase, Cochrane Library of Clinical Trials) from the time of publication of the international guidelines until August 1, 2018.[1,5–7]

Severity Classification and Prediction

The variation in clinical course of patients with AP has led to the development of several severity classifications. The 2 most widely accepted classifications are the Revised Atlanta Classification and the Determinant-Based Classification (Supplementary Figure 1).[13,14] The Revised Atlanta Classification has 3 grades based on the presence of organ failure and local or systemic complications: mild, moderately severe, and severe AP.[13] The Determinant-Based Classification has 4 categories based on the presence of organ failure and status of (peri)pancreatic necrosis (eg, no necrosis, sterile, or infected): and mild, moderate, severe, or critical AP.[14] A recent nationwide retrospective multicenter cohort study compared these classification systems and concluded that both are able to distinguish worse outcomes by increasing severity categories.[15]

Several clinical scoring systems, (APACHE II, SIRS, Modified Glasgow Score, bedside index for severity of AP, Ranson criteria), imaging guided severity indexes (eg, Computed Tomography Severity Index, Balthazar score), and single laboratory parameters, including C-reactive protein, blood urea nitrogen, and procalcitonin have been proposed to predict severity in the early phase. The most reliable predictive scoring systems are complex and use multiple variables, decreasing their feasibility in daily practice. Recent systematic reviews have confirmed the APACHE II and simple bedside index for severity of AP scores as superior for severity prediction.[16,17] In daily clinical practice, however, these scoring systems are of little value. For instance, trials on early nutrition,[18] antibiotic prophylaxis,[19] or probiotic prophylaxis[20] all specifically performed in "predicted severe" AP found no beneficial impact on outcome. Moreover, most intensive care unit teams will not admit a patient preemptively because of a high risk of severe disease but rather base their decision on real-time measurements. A new method enabling evaluation of disease severity on real-time basis has recently been proposed.[21] In sum, current predictive scores are of little clinical use, although research should continue.

Early Treatment: Resuscitation and Pain Control

Key elements in the early treatment of severe AP are fluid resuscitation and pain control. Adequate assessment and treatment of fluid status requires 1 or 2 intravenous lines and a urinary catheter. Although patients may appear clinically well on admission, they can deteriorate rapidly in the following hours, with drastic consequences if the window of opportunity for resuscitation is missed. Rigorous instructions for both outreach and in-house treating teams, including early upscaling of care and adequate monitoring, especially after regular hours, are essential to deliver appropriate care.[22]

Pancreatic inflammation and tissue damage lead to fluid extravasation. Treatment of SIRS requires vigorous fluid infusion to maintain appropriate blood pressure and preserve organ (micro)perfusion. Unfortunately, high-quality evidence regarding the optimal amount, infusion rate, or type of fluid is lacking.[12] Infusion of lactated Ringers has been associated with reduced SIRS compared with normal saline, and is therefore often recommended for fluid resuscitation in AP.[23,24] Administration of several liters of fluid within the first 24 hours can be required, although excessive, uncontrolled fluid infusion may induce pulmonary edema, cardiac failure, and abdominal compartment syndrome.[25,26] Two randomized trials demonstrated the negative impact of uncontrolled massive fluid infusion. The first trial found that fluid infusion of 10 to 15 mL/kg per hour resulted in a higher rates of mechanical ventilation, abdominal compartment syndrome, sepsis, and mortality as compared with patients assigned to 5 to 10 mL/kg per hour infusion rates.[27] In a second trial from the same group, patients assigned to rapid hemodilution, aiming for a hematocrit $<35\%$ within 48 hours, had increased rates of sepsis within 28 days and in-hospital mortality as compared with patients titrated to a hematocrit $>35\%$ after 48 hours.[28] Efficacy of a goal-directed strategy was evaluated in another randomized controlled trial, but the study was terminated due to rarity of the primary endpoint.[24] In summary, goal-directed fluid strategies using clinical parameters (heart rate, mean arterial pressure, and urinary output) rather than a specific laboratory parameter are recommended.

Continuous regional arterial infusion (CRAI) has been used to infuse fluids, protease inhibitors, and/or antibiotics, theoretically resulting in increased drug and fluid concentrations in the pancreatic tissue. A meta-analysis considering 6 randomized controlled trials evaluating CRAI found decreased duration of abdominal pain, complications, length of hospital stay, and no mortality or catheter-related complications.[29] Although seemingly an effective strategy, based on older literature, current guidelines do not suggest or recommend the use of CRAI.[12] Randomized trials outside Asia are necessary to establish stronger evidence for the efficacy of CRAI.

Adequate analgesic therapy is essential in AP, as uncontrolled pain has been related to a negative effect on micro vascularization, and possibly on induction of necrosis.[30,31] Some randomized controlled trials in AP have suggested that epidural anesthesia, compared with intravenous analgesia, increases arterial perfusion of the pancreas and improves clinical outcomes.[32–34] The use of epidural anesthesia, however, should be weighed carefully, as evidence remains limited. Other analgesic interventions, such as acupuncture, have been suggested, however lack quality evidence. The use of the standard World Health Organization pain treatment ladder is advocated in future studies of pain in AP.

Nutrition

Nutritional support is important in the treatment of severe acute and necrotizing pancreatitis. Several randomized controlled trials and meta-analyses have demonstrated the superiority of enteral feeding over parenteral nutrition with respect to complications, need for surgery, and mortality.[35,36] Randomized trials have not demonstrated a significant difference between nasogastric and nasojejunal feeding.[37,38] In a randomized controlled multicenter trial, outcomes were similar if feeding was instituted within 24 hours as compared with on-demand after 72 hours; with only one-third of patients in the on-demand group requiring nasojejunal feeding.[18]

No specific recommendations regarding the composition of nutrition can be made in AP. Although trace elements, unsaturated fatty acids, vitamins, and other supplements have been evaluated, no beneficial effect has been confirmed thus far. The use of probiotics to stabilize the gut microbiome appeared to be effective in 2 small randomized trials, but led to increased mortality in a large trial in patients with predicted severe disease[20,39]

Feeding tubes may be placed by interventional radiology, per oral endoscopy, or electromagnetic guidance.[40] Other routes like percutaneous endoscopic or radiologically placed gastrostomy or gastrojejunostomy tubes, subsequent endoscopic transluminal therapy may lead to dehiscence or leakage at the gastrostomy site, unless the gastrostomy is secured to the abdominal wall by various minimally invasive gastropexy techniques.[41,42]

Diagnosis of (Peri)-Pancreatic Collections and Infected Necrosis

Local complications of AP have been defined in the revised Atlanta classification[13] (Figure 1). There are 4 types of collections associated with AP. The first 2 occur in the setting of interstitial edematous pancreatitis: (1) acute peripancreatic fluid collections, which are extrapancreatic and liquid; (2) pancreatic pseudocysts, which are rare after severe AP, are typically extrapancreatic, encapsulated, contain fluid with no or minimal solid components, and develop after 4 weeks; pseudocysts are rare after severe AP. The third and fourth types of collections occur in necrotizing pancreatitis: (3) acute necrotic collections, which occur early, before demarcation; and (4) walled-off necrosis (WON), which has encapsulating walls. Although the revised Atlanta classification indicates that WON typically develop 4 or more weeks after the onset of AP, a multicenter study found that 43% of demarcated collections had already developed within the first 3 weeks after onset of necrotizing pancreatitis.[43]

Pancreatic necrosis is defined as nonenhancement of pancreatic parenchyma on contrast-enhanced computed tomography (CECT), and is seen in 5% to 10% of patients with AP.[1,5–7,13] An important clarification in the Atlanta classification is that necrosis may involve the pancreas alone, extrapancreatic tissues alone, or most commonly, both. Although CECT scan is the current standard imaging for AP, it cannot exclude the presence of necrotizing pancreatitis on admission or within 48 to 72 hours. Therefore, presence or absence of necrosis is best assessed by CECT if performed at least 3 or more days after presentation. Although CECT can identify necrosis of the pancreas itself, it is inaccurate for detection of solid or necrotic content of collections within and outside the pancreas. Certain liquid collections in the pancreas itself represent central necrosis, whereas others may be the result of pooling of pancreatic juice due to disconnected pancreatic duct; both are often mislabeled as "pseudocysts." Accurate classification of collections is important because prognosis and management for necrotizing pancreatitis is substantially worse and more complex than for pseudocysts. Magnetic resonance imaging and endoscopic ultrasound (EUS) are superior to CECT for assessment of necrotic material within a fluid predominant collection.[44,45]

Pancreatic and peripancreatic collections are susceptible to infection with microorganisms, usually originating from the gut with an increasing frequency of fungal infections.[46] Infection of (peri-)pancreatic collections is associated with high morbidity and mortality, especially in necrotizing pancreatitis.[47] Infection of necrosis occurs typically after 3 to 4 weeks, although earlier presentation is possible.[43]

Infection of (peri-)pancreatic collections can be documented by presence of gas on CECT, or by positive culture from fine needle aspiration (FNA). Routine FNA is not recommended due to high rates of false negativity, although it has been suggested to help direct antibiotics; prospective studies confirming the benefit of such a strategy are lacking.[1,7,48,49] A positive Gram stain or culture alone does not mandate intervention, which is rather driven by combinations of other factors. In patients with (peri-)pancreatic collections, clinical deterioration or fever (>38.5°C or >100.3°F) in the absence of other explanations such as pulmonary, urinary tract, or line infections

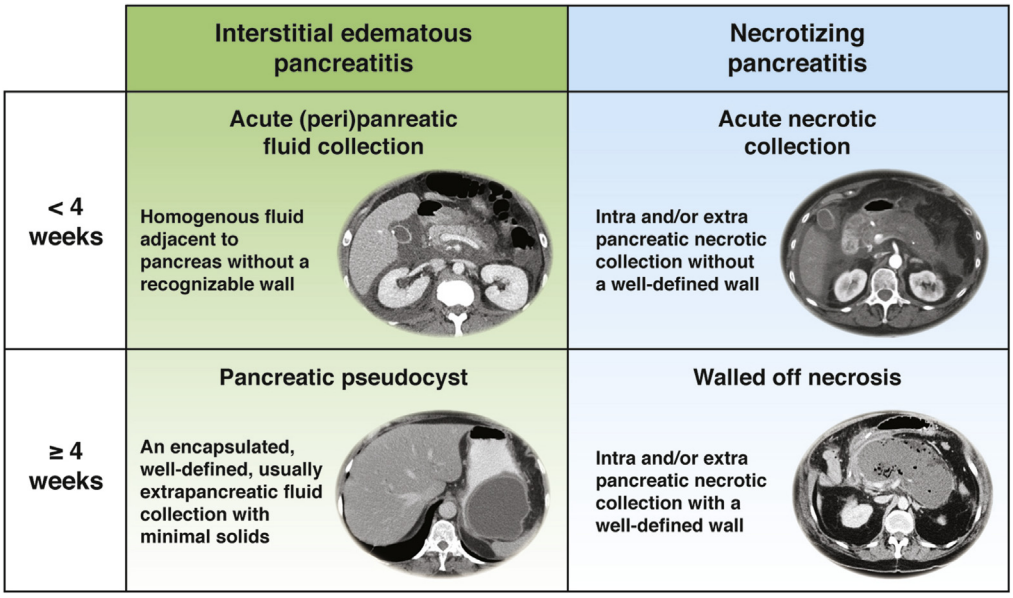

Figure 1. Collections associated with AP (revised Atlanta criteria).[13]

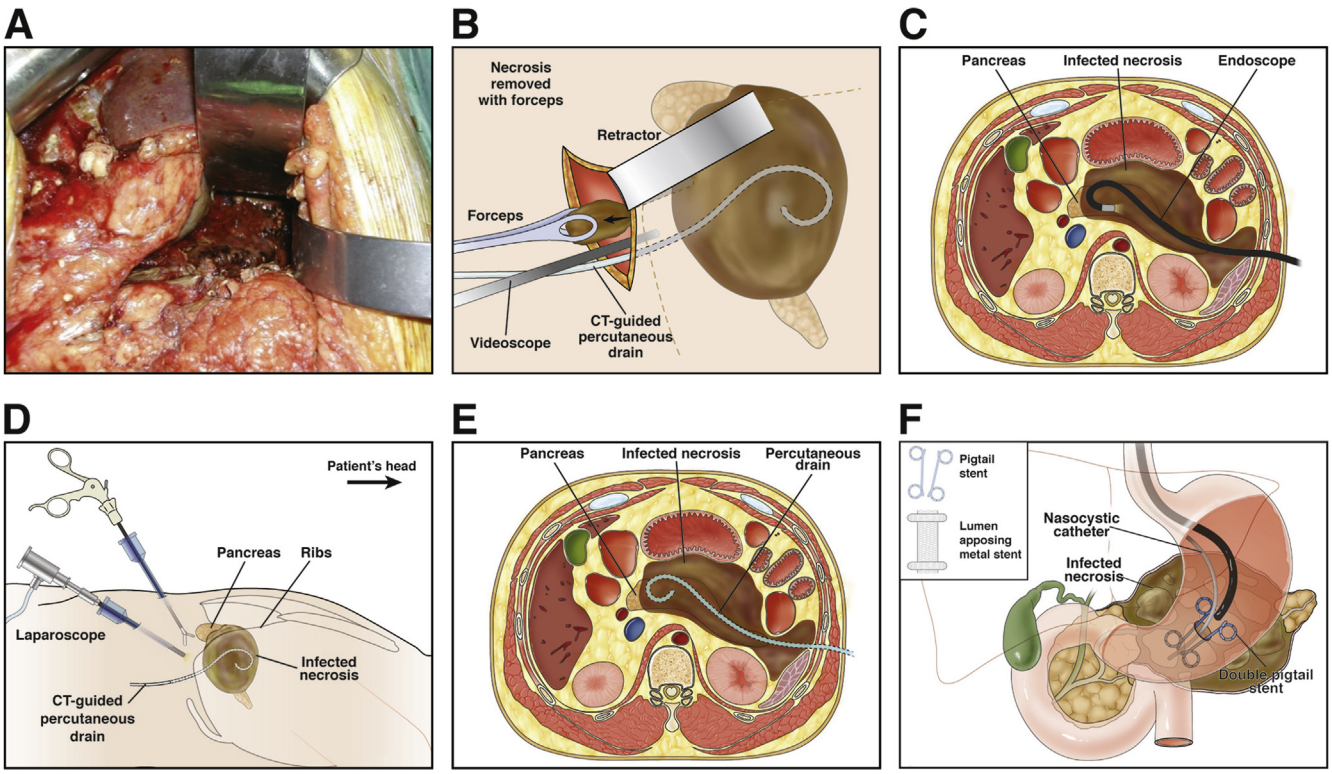

Figure 2. Interventions for necrotizing pancreatitis. Open surgical necrosectomy: (*A*) VARD; (*B*) sinus tract endoscopy (STE); (*C*) laparoscopic necrosectomy; (*D*) PCD; (*E*) endoscopic transluminal necrosectomy.

is adequate for a presumptive diagnosis of infected necrosis. In a recent survey and case vignette among international experts regarding diagnosis of infected necrosis, FNA was not routinely performed by most and never performed by 15%.[50] Presence of gas was considered as the strongest evidence of infected necrosis, although absent in approximately half of such patients.[43]

Indications and Timing of Interventions in Necrotizing Pancreatitis

The primary indications for intervention in necrotic collections, whether radiologic, endoscopic, or surgical, are listed in Table 1.[1,5–7,13] Indications include (1) infected necrosis; (2) in the absence of documented infected necrotizing pancreatitis, ongoing organ failure despite optimal medical management for several weeks after the onset of AP, preferably when the necrotic collection has become walled off; (3) in sterile necrosis, and only after delay with encapsulation: for ongoing symptomatic gastric, intestinal, or biliary obstruction; (4) "persistent unwellness," continued systemic illness, anorexia, and weight loss or intractable pain from mass effect of a large necrotic collection; and (5) disconnected pancreatic duct syndrome (ie, complete transection of the pancreatic duct in the presence of pancreatic necrosis) with ongoing symptoms. Rare indications for interventions include abdominal compartment syndrome, acute bleeding, and bowel ischemia.[1,7] Asymptomatic WON do not warrant any intervention regardless of the size and extension of the collection as they may spontaneously resolve over time.[1,7,11]

Current guidelines recommend delaying intervention ideally for at least 3 to 4 weeks after onset of pancreatitis, to allow liquefaction and encapsulation of necrotic collections.[1,5–7] The primary exception is in the setting of abdominal compartment syndrome, in which radiological or surgical decompression is potentially lifesaving if aggressive medical management fails.[1,7,51] Surgical decompression should involve primary fasciotomy without drainage or debridement of acute necrotic collections, and avoiding the lesser sac.[1,5,7,52] Other indications for emergency surgery include perforation of a hollow viscus, severe hemorrhage that is not amenable to angiographic or other coiling/embolization, and ischemic bowel infarction.[5,11]

Although infected necrosis is generally regarded as a late event in the course of AP, it may occur within the first 4 weeks in almost a quarter of patients.[43,53] Despite maximal medical management, clinical decompensation occurs in a subset of patients such that intervention becomes inevitable to stabilize sepsis and organ failure. International experts lack consensus regarding the optimal timing of intervention under such circumstances.[50] Guidelines that recommend delayed intervention stem primarily from studies in the era of open necrosectomy, wherein early debridement of unorganized collections causes physiologic stress, worsened organ failure, and poor clinical outcomes with high mortality.[1,54–56] In contrast, it has been hypothesized that minimally invasive drainage of infected (peri-)pancreatic collections lessens systemic sepsis and allows maturation of necrosis.[57] Several observational studies have also suggested that encapsulation of necrosis may not be as relevant for endoscopic or percutaneous catheter drainage as for open surgery.[58] A recent study has shown that early intervention before 4 weeks in ill patients with infected necrosis refractory to medical management, when centered

Table 1. Indications for Intervention in Necrotizing Pancreatitis (Radiological, Endoscopic, or Surgical)

1. Clinical suspicion of, or documented infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled-off, preferably (but not necessarily) after 4 weeks.
2. In the absence of documented infected necrotizing pancreatitis, ongoing organ failure for several weeks after the onset of AP, preferably when the necrosis has become walled-off (fine needle aspiration confirmation of infection not required).
3. Sterile necrotizing pancreatitis. Later in course after necrosis walled off:

(a) ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect, (b) persistent symptoms (eg, pain, "persistent unwellness"), (c) disconnected pancreatic duct (ie, full transection of the pancreatic duct) with ongoing symptoms.

Adapted from IAP/APA guidelines.[1]

around an endoscopic transluminal step-up approach, resulted in significant improvement in organ failure, acceptably low mortality, and no increase in complications such as perforation when compared with intervention at 4 or more weeks. Early intervention was effective in stabilizing deteriorating patients with infected collections that were poorly demarcated or walled-off.[59] A randomized controlled trial comparing immediate catheter drainage with delayed drainage, ideally at the stage of WON, is under way by the Dutch Pancreatitis Study Group (POINTER trial - ISRCTN33682933).[50,57] More data are needed regarding the ideal timing of endoscopic transluminal and percutaneous drainage. With the feasibility of early drainage, developing novel strategies becomes paramount to distinguish between SIRS from sterile necrosis, for which intervention is unlikely to be beneficial, and deterioration due to infected necrosis, where it is essential. For the time being, delaying drainage until >4 weeks is still advised when possible, but earlier intervention by endoscopic, percutaneous, or combined approaches may be appropriate in selected circumstances.

Strategies for Intervention: Evolution From Open, to Minimally Invasive, to Endoscopic

The traditional management of infected necrosis with open surgical debridement and peritoneal lavage has been almost completely replaced by minimally invasive surgical and endoscopic approaches (Figure 3). Less invasive strategies have been shown to minimize risk of perioperative stress, new-onset organ failure, and long-term complications such as external fistulas, exocrine and endocrine pancreatic insufficiency, and incisional hernias.[1,5–7,13,47,60] Minimally invasive necrosectomy can be classified according to a taxonomy proposed by Windsor and colleagues based on the method of visualization (open, radiologic, endoscopic, hybrid, or other), and route (per oral, transpapillary or transmural, percutaneous retroperitoneal, and percutaneous transperitoneal, with or without transmural puncture).[61] An intervention is said to be primary if it is the first intervention performed to access WON and secondary if preceded by another intervention.[7]

Selected patients with infected necrosis who are minimally symptomatic and clinically stable can be managed using antibiotics alone, with or without selective percutaneous drainage.[62–65] A meta-analysis involving 324 patients from 8 studies showed that primary nonoperative management of infected necrosis without necrosectomy was successful in 64% of patients and was associated with lower mortality, obviating the need for open necrosectomy.[63] However, there was considerable heterogeneity among the studies analyzed, and although percutaneous drainage was considered a conservative modality, endoscopic drainage was not addressed.[66] It remains unclear which patients with infected necrosis can be safely and effectively managed without any form of drainage or necrosectomy, but withholding intervention is likely suitable in only a small minority of patients.[11] Currently, either endoscopic transluminal drainage (ETD) or image-guided percutaneous catheter drainage, preferably via a retroperitoneal approach, are recommended as the first-line treatment for infected necrosis, followed by endoscopic or minimally invasive surgical necrosectomy as needed.[1,5,11] Although mortality has not been demonstrated to be significantly lower by these approaches in individual randomized trials, in a pooled, risk-adjusted analysis, risk of death appears to be significantly lower for endoscopic and minimally invasive interventions than open necrosectomy for necrotizing pancreatitis.[67] Given the complexity of patients with severe AP, multidisciplinary management using a well-defined algorithm in tertiary care centers is crucial to optimize outcomes.[7,8,68,69]

ETD and Endoscopic Transluminal Necrosectomy

ETD involves access to necrotic cavities using an EUS or, historically, by conventional transmural drainage using a standard endoscope.[7,11] Although large collections may create an endoscopically visible bulge into the surrounding stomach or duodenum, such a classic sign may be absent in collections that are smaller near the pancreatic tail, or in patients with lower serum albumin.[70,71] EUS is now considered standard for initial transluminal drainage, as it enables visualization and puncture of targeted collections independent of a visible bulge, and color Doppler allows avoidance of vessels,[11] with 2 randomized controlled trials[70,71] showing improved outcomes when compared with visual endoscopic drainage.[1,5–7] Following initial drainage, double pigtail (DPS) or metallic stents are placed across the lumen and extending into the necrotic cavity. Establishment of more than 1 access site is referred to as the multiple transluminal gateway technique.[72] Dual pathways theoretically allow increased egress of necrotic material, alternate sites for subsequent endoscopic transluminal necrosectomy (ETN), and reduced need for repeated interventions.[73] ETN, sometimes referred to as direct endoscopic necrosectomy, involves entering the necrotic cavity through the cystenterostomy with a flexible endoscope for debridement using a variety of accessories [7] Forward-viewing endoscopes are generally used to irrigate and debride necrotic material using balloons, baskets, snares, nets, and a variety of other standard endoscopic accessories.[7] Endoscopic necrosectomy can be performed at the index procedure,[74,75] but is most often performed at repeat procedures after decompression of purulent contents and evolution of the cavity.[11] ETN can be performed on a scheduled basis or on demand, with a typical endpoint of complete debridement of the necrotic cavity as documented by endoscopic inspection and radiographic imaging. Optimal timing, number, and

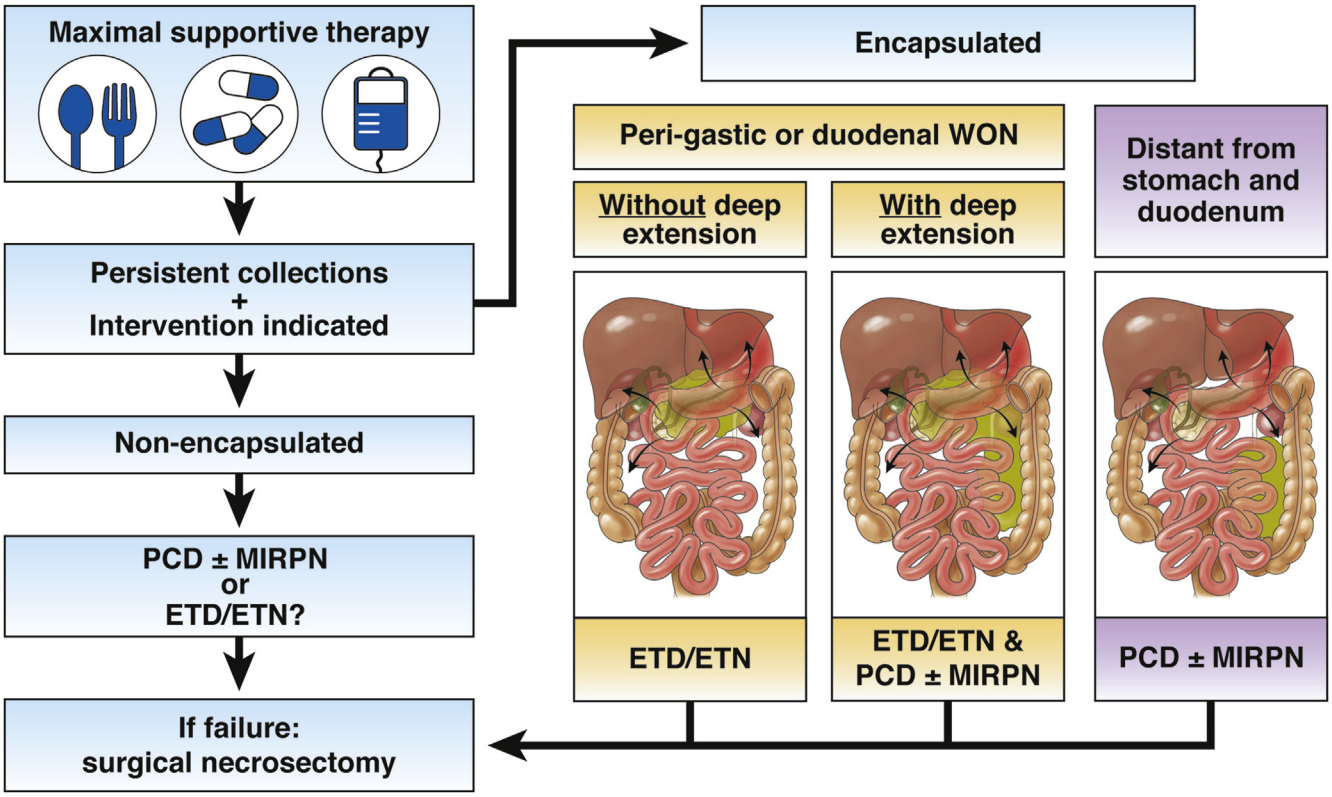

Figure 3. Strategy for interventions in necrotizing pancreatitis. MIRPN, minimally invasive retroperitoneal necrosectomy.

completeness of endoscopic debridements remains uncertain, with each procedure carrying a risk of complications including bleeding and perforation.[11]

Several retrospective studies have suggested a pooled success rate of 81% in resolution of WON but are hampered by case selection bias, and varying definitions of success.[76] The first prospective randomized trial (the PENGUIN trial) comparing endoscopic transluminal necrosectomy (n = 10) and a variety of techniques of surgical necrosectomy (n = 10) in infected necrosis demonstrated significantly reduced inflammatory response (as measured by a surrogate marker interleukin-6) and occurrence of new-onset multiorgan failure in patients in the endoscopic arm.[77] Superior outcomes were thought to be secondary to reduced physiological stress emanating from the less invasive transluminal orifice as access compared with surgical dissection.[77] A larger randomized trial (the TENSION trial) compared the endoscopic step-up approach (n = 51) and surgical step-up approach (n = 47) in patients with infected necrotizing pancreatitis. This study found no significant difference in the primary outcome of a composite endpoint including mortality and major morbidity between arms (endoscopic approach vs surgical step-up approach, 43% vs 45%, $P = .88$); however, the endoscopic approach resulted in shorter hospital stay (mean 53 vs 69 days, $P = 0.014$), lower indirect costs, and significantly less pancreatic fistulae (5% vs 32%, $P = 0.001$). A subsequent randomized trial (MISER) trial in the United States compared minimally invasive surgery (laparoscopic or video-assisted retroperitoneal debridement) with an endoscopic approach (transluminal drainage with or without necrosectomy).[78] Although there was no significant difference in mortality (endoscopy 8.8 vs surgery 6.3%; $P = .999$), patients assigned to the endoscopic approach did not develop enteral or pancreatic-cutaneous fistulae (0% vs 28.1%; $P = .001$). The composite adverse endpoints were significantly less frequent in the endoscopic as compared with minimally invasive surgical arms (12% vs 41%). Unlike the TENSION trial, the MISER trial considered enteral and pancreatic fistulae as major endpoints, explaining the primary difference in principal conclusions between the 2 studies. Total costs were also significantly lower for the endoscopic approach. A comparison of the 3 current randomized trials comparing endoscopic and surgical approaches for intervention in necrotizing pancreatitis is shown in Table 2. Although no individual trial has shown a significant difference in mortality, a large international risk-adjusted collaborative study involving 1980 patients with necrotizing pancreatitis from 51 hospitals across 8 countries demonstrated a significantly decreased mortality among high-risk patients undergoing a minimally invasive surgical or endoscopic management when compared with open surgical necrosectomy.[67]

The choice of cystenterostomy stents after ETD has evolved substantially, from double pigtailed plastic stents (DPS) (7-Fr to 10-Fr in diameter), to fully covered self-expanding metal stents or esophageal self-expanding metal stents,[79] and most recently to lumen-apposing metal stents (LAMSs; Axios stent, Boston Scientific, Natick, MA; Nagi stent or Spaxus stent, Taewoong, Seoul, South Korea).[7] The theoretical advantage of LAMS include ease of placement in a single step, a larger lumen, and apposition of the cavity lumen with the bowel wall. In a retrospective study involving 2213 patients, resolution of WON was more likely to occur when using metallic stents compared with DPS (91.5% vs 80.9%, odds ratio 2.5, 95% confidence

Table 2. Summary of Randomized Controlled Trials Comparing Endoscopic and Minimally Invasive Surgical Step-Up Approach

	PENGUIN trial[77]		TENSION trial[96]		MISER trial[78]	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Modality	Endoscopic	Surgical	Endoscopic	Surgical	Endoscopic	Surgical
No. of patients	10	10	51	47	34	32
Infected necrosis, n (%)	10 (100)	9 (90)	23 (45)	27 (57)	31 (91)	30 (94)
New-onset organ failure, n (%)						
Single	NR	NR	7 (14)	13 (28)	NR	NR
Multiple	0 (0)	5 (50)	2 (4)	6 (13)	2 (6)	3 (9)
Death, n (%)	1 (10)	4 (40)	9 (18)	6 (13)	3 (9)	2 (6)
Composite endpoint, n (%)	2 (20)	8 (80)	22 (43)	21 (45)	4 (12)	13 (41)
Complications, n (%)						
Bleeding	0 (0)	0 (0)	11 (22)	10 (21)	0	3 (9)
Perforation	0 (0)	2 (20)	4 (8)	8 (17)	0	0
Fistula (pancreatic)	1 (10)	7 (70)	2/42 (5)	13/41 (32)	0	9 (28)

interval [CI] 1.4–4.3, $P = .001$), with no difference in resolution of WON after initial drainage, and a trend toward less bleeding, occlusion, and perforation, but a higher rate of migration.[80] These conclusions were challenged by a recent prospective randomized trial[81,82] that compared LAMS (n = 31) with plastic stents (n = 29) and showed no significant difference in total number of procedures performed, adverse events, readmissions, length of stay, overall treatment success, or costs between arms.[81] In an interim analysis, delayed stent-related adverse events were actually more common with LAMS: 6 (50%) of 12 patients had complications, including bleeding from pseudoaneurysm requiring coil embolization, buried stent syndrome, and biliary stricture; it was thought that after collapse of WON, plastic stents gravitate toward the gut, whereas LAMS remain in place, causing friction against the back wall, sometimes precipitating bleeding.[82] These findings resulted in a change in protocol to removal of LAMS within 3 weeks, resulting in no significant difference in adverse events between the cohorts. LAMS have been suggested to be indicated in patients who might benefit from a shorter procedure duration, but avoided in patients with pseudoaneurysms in the vicinity of WON, in those with disconnected pancreatic duct, and in those who are unreliable to follow-up.[81]

Although ETN continues to remain a labor-intensive and time-consuming procedure, several innovations have been explored to simplify the debridement of necrotic tissue.[11,83] Irrigation of necrotic cavities with saline can be performed by placement of nasocystic tubes alongside DPS or through metallic LAMS. Irrigation through nasocystic tubes has been shown to decrease rates of stent occlusion for plastic DPS (13% vs 33%, $P = .03$).[84] but not through LAMS.[85] Irrigation with antibiotics based on microbiological findings has been proposed.[74,86] The low pH of gastric acid has been thought to facilitate liquefaction of necrosis and minimize bacterial overgrowth,[83] facilitate necrosectomy, and improve stent patency,[87,88] suggesting a possible role for discontinuation of acid-suppressing medications.[83] Novel auxiliary techniques such as high-flow water jet system,[89,90] hydrogen peroxide (0.1–3%),[91–93] and a vacuum-assisted closure system[94,95] have been described in small case series, but their efficacy remains uncertain.[7]

In a systematic review of 13 observational studies involving 455 patients, the overall complication rate of ETD and necrosectomy was estimated at 36%, with a procedure-related mortality of 6%.[76] Bleeding was the most common complication (18%), occurring during access to the collection, particularly if a vessel was punctured during dilation of the transmural tract, or during direct debridement of the necrotic cavity.[11,76] Subsequent studies have reported substantially lower rates of complications and all-cause mortality,[59,81,96] with very infrequent procedure-related mortality. Expertise at endoscopic techniques is evolving: use of color-flow Doppler in EUS-guided cystenterostomy enables identification and avoidance of vascular structures with a trend toward reduced risk of bleeding.[70,71] Stent-related occlusion and infection are common with a heavy solid necrotic burden and can be limited by scheduled ETN after ETD.[97] Fistulae have been reported in 5%, with enterocutaneous fistulae primarily in those having concomitant percutaneous catheter drainage.[76,97] The frequency of complications, and failure to resolve necrotic collections by endoscopic routes alone, should prompt therapeutic endoscopists to undertake therapy of necrotizing pancreatitis in appropriate multidisciplinary collaboration with interventional radiologists, surgeons, and intensivists.[11]

Percutaneous Catheter Drainage and Minimally Invasive Retroperitoneal Approaches

A purely endoscopic transluminal route for intervention in necrotizing pancreatitis is feasible in fewer than two-thirds of patients, even at centers with advanced expertise.[98] Although lesser sac and central collections are generally amenable to purely endoscopic management, flank or pelvic collections with deep retroperitoneal extension may warrant adjunctive percutaneous catheter drainage (PCD), followed by sinus tract endoscopy using flexible endoscopy, or video-assisted retroperitoneal debridement (VARD) if collections do not resolve.[11] PCD of pancreatic and peri-pancreatic collections involves placement of single or multiple catheters under real-time ultrasound or computed tomography guidance, that are serially upsized, irrigated, and repositioned.[7] The preferred route for PCD is via a flank approach through the retroperitoneum to

avoid enteric leaks and dissemination of infected necrotic material into the peritoneal cavity, and to provide access for further sinus tract endoscopy or VARD if needed.[58,99]

A systematic review of 10 retrospective series and 1 randomized controlled trial (n = 384) focusing on primary PCD for management of necrotizing pancreatitis showed that no additional surgical necrosectomy was needed in 56% of patients,[58] whereas 2 other prospective studies have suggested a success rate of only 33% to 35%.[55,99] PCD has been increasingly used to stabilize critical patients as a "bridge to minimally invasive intervention" rather than a sole primary therapy.[8] Once a percutaneous tract is established by a retroperitoneal route, minimally invasive necrosectomy can be performed by either sinus tract endoscopy or VARD. Sinus tract endoscopy involves intraoperative dilation of the percutaneous drain tract followed by irrigation, lavage, and suction using an operating nephroscope with a wide-bore operating channel.[100,101] After necrosectomy, a continuous lavage system is installed with a small inflow (eg, 10F) inflow drain and a large (eg, 28F) outflow drain. Recently, a variation using flexible endoscopy has also been described.[102] Although the angulation of the flexible endoscope may facilitate access to deep collections, the working channel of the endoscope restricts the extent and efficacy of debridement. More aggressive debridement can be performed using VARD, which involves a limited subcostal incision (ie, 5 cm) followed by videoscope-guided necrosectomy using simultaneous lavage and long surgical graspers allowing for sufficient necrosectomy in typically one procedure.[103] It is now well established that a minimally invasive retroperitoneal approach induces a smaller proinflammatory response and is associated with a lower rate of new-onset organ failure than open necrosectomy in patients with infected necrosis.[99,104] Regardless of technique used, a percutaneous catheter or retroperitoneal surgical approach is accompanied by a high risk (up to 35%) of external pancreatico-cutaneous or enterocutaneous fistulae.[100–104]

Dual-Modality Drainage

In most series reporting on ETN, whether retrospective or prospective randomized trials,[11,59,77,96] percutaneous catheter drainage is used in many cases as a preceding drainage technique, or as an adjunctive technique (Supplementary Figure 2). In 1 series including all consecutive patients with necrotizing pancreatitis requiring intervention of any kind, although purely endoscopic transluminal therapy was the preferred route, it was feasible as a sole approach in only 60% of patients, with more than one-third of patients requiring additional percutaneous catheter drainage and 4% requiring open surgery.[98] In a different center basing management primarily on PCD, the systematic addition of ETD dual-modality drainage (DMD) to PCD improved clinical outcomes.[105–107] DMD was associated with significantly decreased hospitalization (26 vs 55 days) and duration of external drainage (83.9 vs 189 days) when compared with PCD alone. Overall mortality and requirement for surgery were similar in both groups.[105,106] Although promising, DMD based primarily on percutaneous catheter drainage may not be optimal in necrotic collections directly behind the stomach or duodenum, and indwelling PCD catheters over extended intervals may impair quality of life.[11] Other approaches involve selective use of ETD/ETN combined with PCD for those patients with deep extrapancreatic collections, and using adjunctive sinus tract endoscopy or VARD for patients refractory to the combination of endoscopic and PCD. Staged, multidisciplinary algorithmic approaches based on the location of the WON and local expertise are likely to result in best outcomes.[59,68,69]

Role of Open Surgery in the Minimally Invasive Era

Despite major advances in minimally invasive endoscopic, percutaneous, and surgical interventions, open surgery is still required in a minority of cases for a number of indications. In the early course of interventions, these include refractory compartment syndrome, perforation of a viscus, ischemic bowel, and failure of step-up approach. Thresholds for open surgery due to failure of step-up approach may vary widely. In an unselected series of patients with necrotizing pancreatitis at a single center with a highly aggressive endoscopic and minimally invasive step-up approach, open surgery was nonetheless required in 1% of patients undergoing standard (>4 weeks) step-up intervention for all indications, and 7% of those undergoing early (<4 weeks) intervention for clinical deterioration mostly for infected necrosis.[59] Indications for open surgical intervention for later complications of necrotizing pancreatitis are discussed in the following sections, and include persistent enterocutaneous and cystenteric fistulae, pancreatico-cutaneous fistulae and chronic pancreatitis resulting from disconnected pancreatic duct syndrome, and bowel obstruction. The enduring role for surgery in management of necrotizing pancreatitis emphasizes the need for multidisciplinary management of these patients even as minimally invasive approaches continue to evolve.

Complications of Severe AP

Major complications of severe AP and interventions include perforation; splanchnic vein thrombosis (SVT); pseudoaneurysmal bleeding; pancreatic, enterocutaneous, and cystenteric fistulae; and disconnected pancreatic duct (Supplementary Figure 3).

Pancreatic fistulae. External pancreatic fistulae, defined as the output of any persistent measurable volume of fluid via a percutaneous drain, PCD tract, or from a surgical wound with an increased fluid amylase concentration ≥3 times the serum value[7] may close spontaneously. In one study, pancreatic fistulae closed after a median interval of 70 days.[108] When external pancreatic fistulae are associated with partial PD disruption and fluid collections are <5 cm, a transpapillary stent to bridge the site of leakage is effective in only 27% (9%–69%) of patients.[7] Transpapillary stents may reduce risk of recurrence of resolved collections. In a multicenter prospective study, 19 patients undergoing endoscopic transpapillary stenting for fistulae associated with necrotizing pancreatitis were compared with 16 patients undergoing conservative management, with similar rates of fistula closure (84% vs 75 %, $P = .18$) but a shorter median time to closure (71 vs 120 days, $P = .13$).[108] After ETN, some centers recommend imaging to assess the integrity of main pancreatic duct using CECT, secretin-stimulated magnetic resonance cholangiopancreatography, and/or endoscopic retrograde cholangiopancreatography before stent removal.[7] EUS at time of initial drainage can also demonstrate duct disruption with 100% correlation with computed tomography and pancreatography.[109]

Disconnected pancreatic duct syndrome. Disconnected pancreatic duct syndrome (DPDS) is an important, but often underrecognized complication of necrotizing pancreatitis, occurring in 30% to 50% of patients with necrotizing pancreatitis.[1,5,108,110,111] DPDS is characterized by complete transection of the main pancreatic duct by central necrosis, most often in the pancreatic neck, leading to discontinuity between viable secreting pancreatic tissue upstream and the gastrointestinal tract.[11] Patients with DPDS are more likely to require hybrid therapeutic interventions, reintervention, rescue surgery, and longer hospital stay.[112] In the earlier stages of severe AP, DPDS may result in persistent fluid collections, pancreatic ascites, or pancreatic-pleural and pancreatico-cutaneous fistulae. After ETD/ETN, and subsequent removal of stents, main pancreatic duct disruption may lead to recurrent collections, or to persistent pancreatic-cutaneous fistulae through percutaneous catheters.[7] Recurrent fluid collections after ETD/ETN have been reported in 7% to 15% after endoscopic necrosectomy and 7.8% after combined percutaneous and endoscopic management.[107,113]

The most widely used approach to attempt to prevent recurrent fluid collections after ETN is to leave cystenterostomy stents in place indefinitely to maintain patency of the internal fistula and divert pancreatic secretions back into the gastrointestinal lumen. Long-term indwelling DPSs have been demonstrated in a randomized trial to result in a substantially reduced rate of recurrence of collections (0 of 15 vs 5 of 13, $P < .05$),[114] an observation subsequently confirmed in a large retrospective study (1.7% vs 17.4%, $P < .001$),[112] with safety confirmed in long-term follow-up studies.[110,111,115] Another approach is to place transpapillary pancreatic stents proactively during the process of transluminal drainage and necrosectomy. Data regarding its efficacy are mixed, with one single-center retrospective study including specifics about extent and goal of stenting reporting improved outcomes,[116] whereas another retrospective multicenter study involving heterogeneous indications and measures reporting no advantage.[117]

Most reports have focused on recurrent fluid collections as the principal consequence of DPDS. However, another major and often underappreciated consequence of DPDS that typically occurs months or years after necrosis has resolved and the upstream duct has scarred over, is recurrent acute or chronic pancreatitis in the excluded gland.[5] The central end of the upstream duct may scar over and result in a closed-space obstruction with insidious consequences. Although leaving DPSs in cystenterostomy tracts has been shown to reduce risk of recurrent fluid collections, it is not clear whether they are effective at preventing scarring over of the central terminus of the upstream duct and its consequences.[112,114]

Treatment of chronic DPDS after necrosectomy has traditionally involved either surgical resection of the upstream gland, with or without islet cell autotransplantation to reduce risk of diabetes,[118] or if the upstream duct is of adequate size, Roux-en-Y pancreatojejunostomy.[5,119] In the absence of a fluid collection, an EUS-guided pancreaticogastrostomy technique has been described, involving placement of an indwelling transluminal stent into the upstream pancreatic duct to establish and maintain a duct-enteric fistula.[120] Another approach is to combine percutaneous tract puncture directly back into the stomach or duodenum to internalize the fistula, followed by endoscopic stenting.[121]

Large-scale studies of unselected cohorts of patients with necrotizing pancreatitis are needed to determine the exact incidence of DPDS and to determine optimal strategies for early diagnosis and to outline the most effective prevention and treatment strategies.

Exocrine and endocrine pancreatic insufficiency. Exocrine pancreatic insufficiency (EPI) is common after AP involving pancreatic necrosis. A recent meta-analysis of 32 studies involving 1495 patients estimated a pooled prevalence of EPI to be 27.1% (95% CI 20.3%–35.1%) at a mean of 36 months after index admission.[122] Pancreatic enzyme replacement therapy may have a positive impact during the early refeeding phase.[123] Diabetes is relatively common; meta-analysis of 24 prospective studies, involving 1102 patients with first episode of AP showed that pooled prevalence of prediabetes, diabetes mellitus (DM), and treatment with insulin after AP was 16% (95% CI 9%–24%), 23% (95% CI 16%–31%), and 15% (95% CI 9%–21%), respectively. [124] In contrast to EPI, the severity of AP appears to have little effect on either prediabetes or DM after AP,[124] suggesting that DM may develop due to mechanisms other than necrosis. Both exocrine and endocrine insufficiency are less common after minimally invasive step-up approach when compared with primary open necrosectomy.[99]

Splanchnic vein thrombosis. SVT may involve splenic (most common), portal, or superior mesenteric veins, and occurs in 16% to 18% of patients with necrotizing pancreatitis.[125–128] Necrotizing pancreatitis has been postulated to create a proinflammatory milieu that promotes development of SVT.[125] Although predominantly asymptomatic, especially when involving only the splenic vein, SVT rarely causes serious complications such as upper gastrointestinal variceal bleeding or ascites.[127] The role of anticoagulation is controversial, with no clear difference in the recanalization rates in patients treated with or without anticoagulation.[126] Risks of anticoagulation (hemorrhage into necrotic collections and other sources), should be weighed carefully before considering anticoagulation in patients with AP patients SVT, and is generally not recommended for patients with thrombosis of the splenic vein alone.[125]

Pseudoaneurysm. Necrosis may erode into walls of arteries and result in arterial pseudoaneurysms.[129] Percutaneous drains, cystenterostomy stents (especially LAMS), and necrosectomy can also cause direct trauma to vessels.[81,82,130] The most common site for pseudoaneurysms is the splenic artery (35%–50%) followed by gastroduodenal and pancreaticoduodenal arteries (20%–25%).[129] Ruptured pseudoaneurysms are associated with substantial morbidity and mortality, which has historically been reported as high as 34% to 52%.[129] Management involves angiographic trans-arterial embolization with or without stenting of pseudoaneurysms in the proximal and distal feeding vessel to isolate inflow and prevent back-filling via collaterals. Hemostasis may be augmented by placement of coils, or by injection of cyanoacrylate glue, ethiodized oil, gelfoam, thrombin, polyvinyl alcohol, or other particles. EUS has been used to perform transluminal coiling and cyanoacrylate glue for arterial pseudoaneurysms inaccessible to angiography.[131] Although such events have been perceived as relative contraindications, ETD has been performed safely after successful radiological obliteration of pseudoaneurysm.[132]

Conclusions

Interventions for necrotizing pancreatitis, and the evidence to support optimal approaches, have evolved substantially over recent years. Recommendations for a strategy for interventions in necrotic collections is summarized in Figure 3. A minimally invasive step-up approach is now preferred, involving endoscopic and or percutaneous catheter drainage as the first step, followed by endoscopic or minimally invasive surgical necrosectomy as required, is now preferred. Refinement of these processes is ongoing, as is supporting evidence. Regardless of the approach chosen at any given center, preferably one with a focused interest in necrotizing pancreatitis, a highly specialized multidisciplinary team at centers with defined protocols is necessary for best outcomes.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.01.269.

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Conflicts of interest
These authors disclose the following: Shawn Mallery, Boston Scientific; Martin Freeman: Consulting agreements, Boston Scientific, AbbVie; Marc Besselink: Consulting agreements, Ethicon, Medtronic. The remaining authors disclose no conflicts.

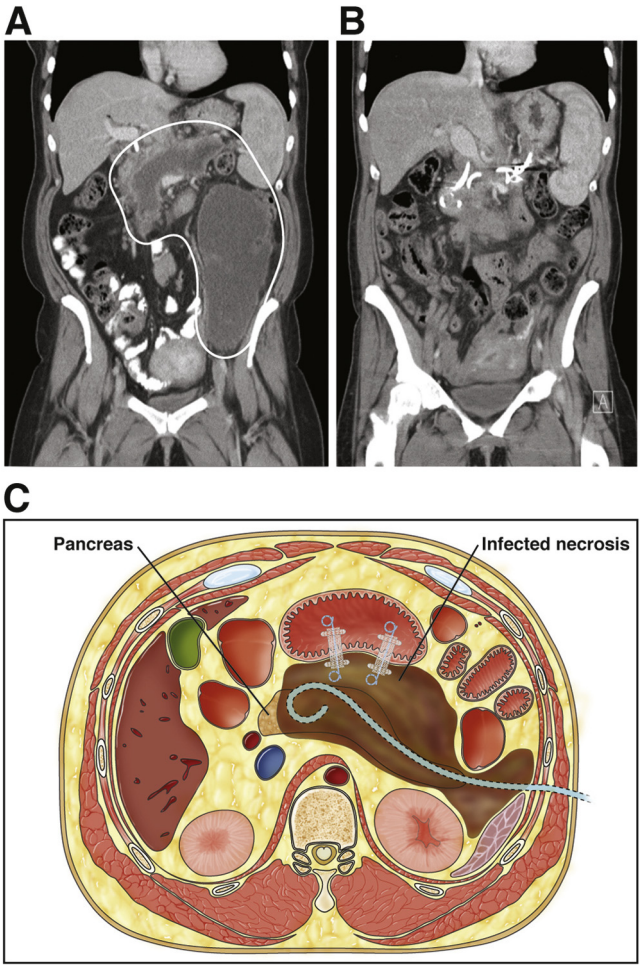
A

RAC	Mild	Moderately severe	Severe
Organ failure	No	Resolving < 48 hrs (transient OF)	Persistent > 48hrs
Local or systemic complications	No	Without persistent OF	Single or multiple OF
Mortality	0.1%	2.1%	52.2%

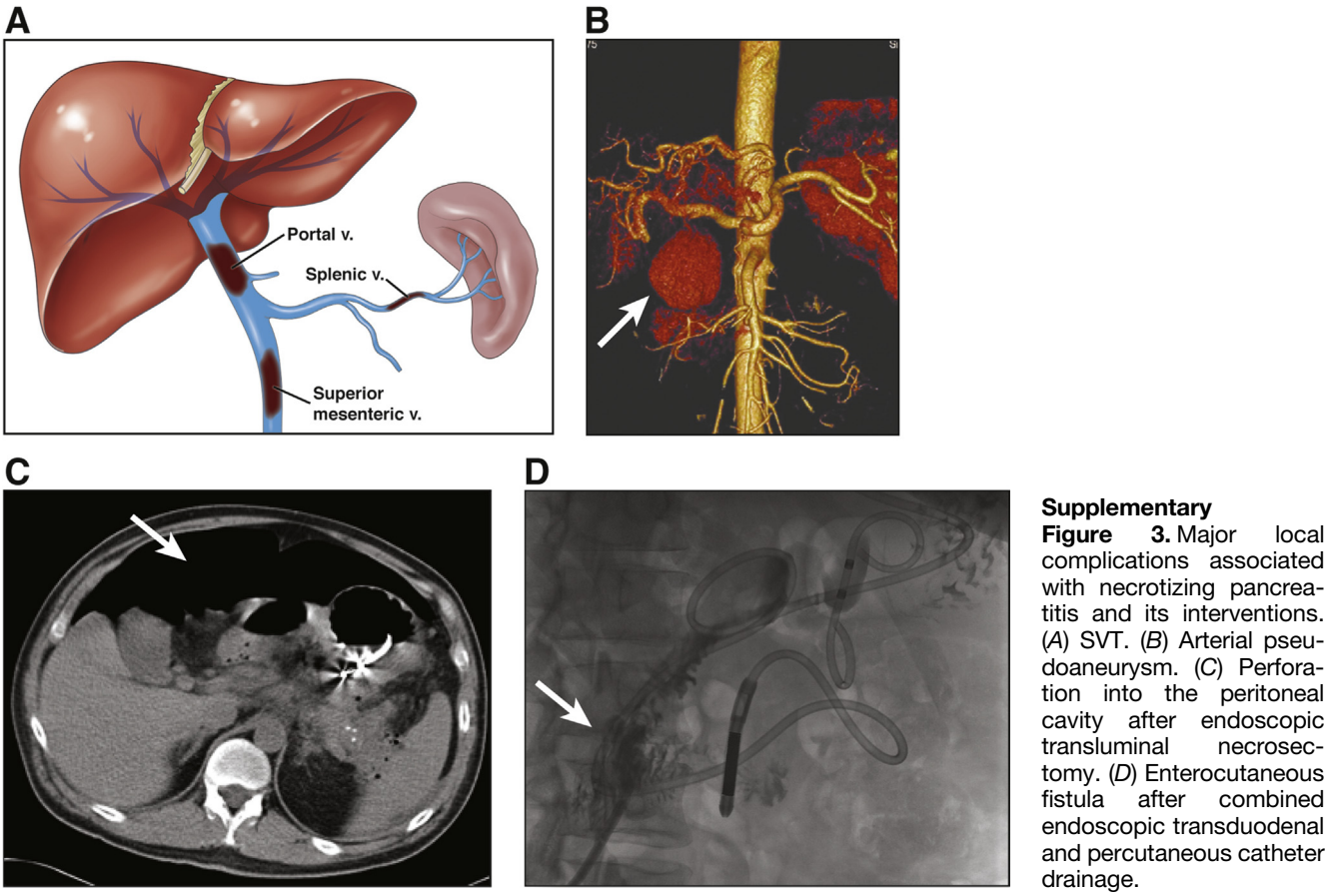
B

DBC	Mild	Moderate	Moderately severe	Severe
(Peri)pancreatic necrosis	No	Sterile	Infected	Infected
	And	And/or	Or	And
Organ failure	No	Transient	Persistent	Persistent
Mortality	0.1%	4%	39.2%	54.1%

Supplementary Figure 1. Revised Atlanta classification (RAC) and determinant-based classification (DBC) and mortality risk in different the severity categories. Modified with permission from Sternby et al.[15]



Supplementary Figure 2. Multimodality management of necrotic collection: multigate endoscopic transluminal drainage/necrosectomy combined with percutaneous catheter drainage. (*A*) Large WON involving most of the pancreas and deep left retroperitoneal extension into the pelvis. (*B*) Resolved WON as a result of combined multimodality apporach, including multigate ETD and necrosectomy, percutaneous catheter drainage, and sinus tract endoscopy. (*C*) Multigate ETD with lumen-apposing stents and DPSs, combined with retroperitoneal percutaneous catheter drainage.



Supplementary Figure 3. Major local complications associated with necrotizing pancreatitis and its interventions. (*A*) SVT. (*B*) Arterial pseudoaneurysm. (*C*) Perforation into the peritoneal cavity after endoscopic transluminal necrosectomy. (*D*) Enterocutaneous fistula after combined endoscopic transduodenal and percutaneous catheter drainage.