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AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEW

American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis

Todd H. Baron,[1] Christopher J. DiMaio,[2] Andrew Y. Wang,[3] and Katherine A. Morgan[4]

[1]Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, North Carolina; [2]Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; [3]Division of Gastroenterology and Hepatology, University of Virginia, Charlottesville, Virginia; and [4]Division of Gastrointestinal and Laparoscopic Surgery, Medical University of South Carolina, Charleston, South Carolina

DESCRIPTION: The purpose of this American Gastroenterological Association (AGA) Institute Clinical Practice Update is to review the available evidence and expert recommendations regarding the clinical care of patients with pancreatic necrosis and to offer concise best practice advice for the optimal management of patients with this highly morbid condition. **METHODS:** This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*. This review is framed around the 15 best practice advice points agreed upon by the authors, which reflect landmark and recent published articles in this field. This expert review also reflects the experiences of the authors, who are advanced endoscopists or hepatopancreatobiliary surgeons with extensive experience in managing and teaching others to care for patients with pancreatic necrosis. **BEST PRACTICE ADVICE 1:** Pancreatic necrosis is associated with substantial morbidity and mortality and optimal management requires a multidisciplinary approach, including gastroenterologists, surgeons, interventional radiologists, and specialists in critical care medicine, infectious disease, and nutrition. In situations where clinical expertise may be limited, consideration should be given to transferring patients with significant pancreatic necrosis to an appropriate tertiary-care center. **BEST PRACTICE ADVICE 2:** Antimicrobial therapy is best indicated for culture-proven infection in pancreatic necrosis or when infection is strongly suspected (ie, gas in the collection, bacteremia, sepsis, or clinical deterioration). Routine use of prophylactic antibiotics to prevent infection of sterile necrosis is not recommended. **BEST PRACTICE ADVICE 3:** When infected necrosis is suspected, broad-spectrum intravenous antibiotics with ability to penetrate pancreatic necrosis should be favored (eg, carbapenems, quinolones, and metronidazole). Routine use of antifungal agents is not recommended. Computed tomography–guided fine-needle aspiration for Gram stain and cultures is unnecessary in the majority of cases. **BEST PRACTICE ADVICE 4:** In patients with pancreatic necrosis, enteral feeding should be initiated early to decrease the risk of infected necrosis. A trial of oral nutrition is recommended immediately in patients in whom there is absence of nausea and vomiting and no signs of severe ileus or gastrointestinal luminal obstruction. When oral nutrition is not feasible, enteral nutrition by either nasogastric/duodenal or nasojejunal tube should be initiated as soon as possible. Total parenteral nutrition should be considered only in cases where oral or enteral feeds are not feasible or tolerated. **BEST PRACTICE ADVICE 5:** Drainage and/or debridement of pancreatic necrosis is indicated in patients with infected necrosis. Drainage and/or debridement may be required in patients with sterile pancreatic necrosis and persistent unwellness marked by abdominal pain, nausea, vomiting, and nutritional failure or with associated complications, including gastrointestinal luminal obstruction; biliary obstruction; recurrent acute pancreatitis; fistulas; or persistent systemic inflammatory response syndrome. **BEST PRACTICE ADVICE 6:** Pancreatic debridement should be avoided in the early, acute period (first 2 weeks), as it has been associated with increased morbidity and mortality. Debridement should be optimally delayed for 4 weeks and performed earlier only when there is an organized collection and a strong indication. **BEST PRACTICE ADVICE 7:** Percutaneous drainage and transmural endoscopic drainage are both appropriate first-line, nonsurgical approaches in managing patients with walled-off pancreatic necrosis (WON). Endoscopic therapy through transmural drainage of WON may be preferred, as it avoids the risk of forming a pancreatocutaneous fistula. **BEST PRACTICE ADVICE 8:** Percutaneous drainage of pancreatic necrosis should be considered in patients with infected or symptomatic necrotic collections in the early, acute period (<2 weeks), and in those with WON who are too ill to undergo endoscopic or surgical intervention. Percutaneous drainage should be strongly considered as an adjunct to endoscopic drainage for WON with deep extension into the paracolic gutters and pelvis or for salvage therapy after endoscopic or surgical debridement with residual necrosis burden. **BEST PRACTICE ADVICE 9:** Self-expanding metal stents in the form of lumen-apposing metal stents appear to be superior to plastic stents for endoscopic transmural drainage of necrosis. **BEST PRACTICE ADVICE 10:** The use of direct endoscopic necrosectomy should be reserved for those patients with limited necrosis who do not adequately respond to endoscopic transmural drainage using large-bore, self-expanding metal stents/lumen-apposing metal stents alone or plastic stents combined with irrigation. Direct endoscopic necrosectomy is a therapeutic option in patients with large amounts of infected necrosis, but should be performed at referral centers with the necessary endoscopic expertise and interventional radiology and surgical backup. **BEST PRACTICE ADVICE 11:** Minimally invasive operative approaches to the debridement of acute necrotizing pancreatitis are preferred to open surgical necrosectomy when possible, given lower morbidity. **BEST PRACTICE ADVICE 12:** Multiple minimally invasive surgical techniques are feasible and effective, including videoscopic-assisted retroperitoneal

debridement, laparoscopic transgastric debridement, and open transgastric debridement. Selection of approach is best determined by pattern of disease, physiology of the patient, experience and expertise of the multidisciplinary team, and available resources. **BEST PRACTICE ADVICE 13:** Open operative debridement maintains a role in the modern management of acute necrotizing pancreatitis in cases not amenable to less invasive endoscopic and/or surgical procedures. **BEST PRACTICE ADVICE 14:** For patients with disconnected left pancreatic remnant after acute necrotizing mid-body necrosis, definitive surgical management with distal pancreatectomy should be undertaken in patients with reasonable operative candidacy. Insufficient evidence exists to support the management of the disconnected left pancreatic remnant with long-term transenteric endoscopic stenting. **BEST PRACTICE ADVICE 15:** A step-up approach consisting of percutaneous drainage or endoscopic transmural drainage using either plastic stents and irrigation or self-expanding metal stents/lumen-apposing metal stents alone, followed by direct endoscopic necrosectomy, and then surgical debridement is reasonable, although approaches may vary based on the available clinical expertise.

Keywords: Pancreatitis; Necrosis; Nutrition; Antibiotics; Percutaneous; Endoscopic; Necrosectomy; Step-Up; Surgery.

Acute pancreatitis is one of the most common gastrointestinal illnesses encountered in clinical practice. The majority of cases are mild, self-limited, and follow an uncomplicated course. However, 10%–20% of cases can be associated with necrosis of the pancreatic gland, peripancreatic tissue, or both. This subset of patients may face a complex, prolonged clinical course, with associated mortality of up to 20%–30% if infection develops in the necrotic collection.[1] Successful management of these patients requires expert multidisciplinary care by gastroenterologists, surgeons, interventional radiologists, and specialists in critical care medicine, infectious disease, and nutrition.

Over the past decade, there has been progress and improvement in understanding disease presentation and natural history. An expert consensus panel reclassified how pancreatic fluid collections are defined, noting the importance of not only the length of time a pancreatic fluid collection has been present, but also its contents (Supplementary Figure 1).[2] Similarly, approaches to managing necrotizing pancreatitis have evolved. Whereby major surgical intervention and debridement were once the mainstay of therapy for patients with symptomatic necrotic collections, a minimally invasive approach focusing on percutaneous drainage and/or endoscopic drainage or debridement is now favored.

There is general agreement that drainage and/or debridement of pancreatic necrosis is indicated in patients with infected necrosis, as this group carries the highest risk of death. Drainage and/or debridement may be required in patients with sterile pancreatic necrosis and persistent unwellness marked by abdominal pain, nausea, vomiting, and nutritional failure, or with associated complications, including gastrointestinal luminal obstruction; biliary obstruction; recurrent acute pancreatitis; fistulas; or persistent systemic inflammatory response syndrome.

However, management of patients with pancreatic necrosis depends on other critical issues, such as appropriate use of imaging, intravenous fluids, antibiotics, and nutritional support, in addition to the type and timing of endoscopic, radiologic, and/or surgical interventions. Evidence-based guidelines on the management of acute pancreatitis reported that Grade 1A evidence exists to support an initial minimally invasive drainage approach to infected walled-off pancreatic necrosis (WON), but only Grade 1C evidence in terms of appropriate indications and timing of interventions and Grade 2C evidence for intervention in sterile necrosis.[3] Moderate-strength evidence exists pertaining to various aspects of antibiotics, nutrition, and intravenous fluids, and as such, variability exists among practitioners and institutions regarding the preferred management approach.

We refer the reader to the American Gastroenterological Association Technical Review[4] and Guideline[5] on the "Initial Medical Treatment of Acute Pancreatitis" for management at the onset and in the earliest phase of this disease, and to a recent systematic review published in this journal that comprehensively discusses the recent data and technical aspects of caring for patients with severe acute and necrotizing pancreatitis.[1] The purpose of this American Gastroenterological Association Clinical Practice Update was to review the available evidence and expert recommendations regarding the management of pancreatic necrosis and to offer concise best practice advice for the optimal management of patients with this highly morbid condition.

Antimicrobial Therapy

Infection of pancreatic necrosis is associated with mortality rates as high as 30%. Therefore, in the management of pancreatic necrosis much attention is given to prevention of infection, as well as treatment of suspected or confirmed infection. Infected necrosis should be suspected when cross-sectional imaging demonstrates gas in a pancreatic or peripancreatic collection. Other factors that may be indicative of infected necrosis include the presence of fevers, bacteremia, worsening leukocytosis, persistent unwellness, or clinical deterioration. Many of these factors can be seen in the setting of systemic inflammatory response syndrome, ongoing pancreatitis, or cholangitis, and thus distinguishing infected necrosis from these other conditions can be difficult based on clinical parameters alone.

When infected necrosis is suspected, initiation of broad-spectrum intravenous antibiotics with good penetration into

Abbreviations used in this paper: **DEN, direct endoscopic necrosectomy; DPDS, disconnected pancreatic duct syndrome; EUS, endoscopic ultrasound; LAMS, lumen-apposing metal stent; SEMS, self-expandable metal stent; TEN, total enteral nutrition; TPN, total parenteral nutrition; VARD, video-assisted retroperitoneal debridement; WON, walled-off pancreatic necrosis.**

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the pancreas is recommended. These include carbapenems, quinolones, metronidazole, and third- or higher-generation cephalosporins. Computed tomography–guided percutaneous biopsies of necrotic collections with samples sent for Gram stain and cultures can be performed to confirm the presence of infection. However, this is unnecessary in the vast majority of cases. In addition, false-negative results are possible, and there is a theoretical risk of contaminating a sterile collection. One scenario where computed tomography–guided biopsy/aspiration may help is for guidance in antibiotic selection, for example, in a patient with suspected infected necrosis but continued deterioration despite antibiotic administration.

Much debate exists as to the role of antibiotics in the prevention of infected necrosis. However, multiple prospective, randomized, placebo-controlled trials have demonstrated that in patients with severe acute necrotizing pancreatitis, the administration of prophylactic broad-spectrum antibiotics has no impact on rates of developing infected necrosis, systemic complications, mortality, or need for surgical intervention.[6–8] Furthermore, there is a lack of evidence to support prophylactic use of antifungal therapy in patients with pancreatic necrosis, and thus routine administration is not recommended.

Nutrition

The role of nutrition has generated intense debate over the past few decades. It was generally believed that patients with acute pancreatitis would be at risk for a worsening clinical course if the pancreas was stimulated by oral or enteral nutrition, and would benefit from "pancreatic rest" by receiving total parenteral nutrition (TPN) and remaining nil per os. However, these theories have been largely disproven.

Most patients with severe and/or necrotizing pancreatitis are acutely ill, in a hypercatabolic state, and subject to a multitude of metabolic and systemic derangements. The gastrointestinal tract is subject to decreased mucosal integrity with subsequent increase in gut permeability, as well as decreased gut motility and increased risk of bacterial overgrowth. This combination of factors can result in increased bacterial translocation and a higher risk of infected pancreatic necrosis. Administration of enteral feeds can mitigate these effects.

For patients without nausea, vomiting, or evidence of intestinal obstruction or ileus, a trial of oral nutrition should be commenced immediately. For patients unable to tolerate oral intake, early nutritional support should be prioritized within the first 24–72 hours (Figure 1). Numerous studies have demonstrated that early initiation of enteral nutrition in patients with severe pancreatitis is associated with significantly improved outcomes. In a prospective randomized study, Petrov et al[9] demonstrated that patients receiving total enteral nutrition (TEN) had significantly lower rates of pancreatic infectious complications (20% vs 47%), multiorgan failure (20% vs 50%), and death (6% vs 35%) compared to patients receiving TPN. Similarly, Wu et al[10] demonstrated that TEN was associated with significantly lower rates of organ failure (21% vs 80%), multiorgan failure (15% vs 65%), need for surgery (22% vs 80%), septic pancreatic necrosis (23% vs 72%), and mortality (11% vs 43%) compared to TPN.

While it is clear that TEN is the preferred type of nutritional support for patients with severe pancreatitis, debate remains about the preferred route of administration. A number of small, prospective, randomized studies demonstrated that nasogastric feeding was not inferior to nasojejunal feeding in terms of infectious complications, pain, inflammatory markers, or analgesia requirements.[11,12] Therefore, either route is acceptable, although nasogastric (or nasoduodenal) tubes are easier to place and maintain.

For those patients in whom nasoenteric feeding is not tolerated (eg, due to nasal irritation) and/or in whom long-term TEN is anticipated (>30 days), endoscopic placement of a feeding tube should be considered. Patients who are able to tolerate nasogastric tube feeds are candidates for a percutaneous endoscopic gastrostomy tube. For those patients who are unable to tolerate gastric feeds and/or who are at high risk for aspiration, a direct percutaneous endoscopic jejunostomy tube is a reasonable option. For those patients with gastric outlet obstruction, delayed gastric emptying, and/or prolonged ileus, placement of a percutaneous endoscopic gastrostomy tube with jejunal extension enables on-demand gastric decompression in addition to providing downstream enteral nutrition.

Despite the advantages of TEN, there remains a role for TPN in patients with severe pancreatitis. Patients who are unable to tolerate TEN due to luminal obstruction or severe dysmotility, who cannot tolerate a nasal tube and have a problem (eg, leak or infection) at a percutaneous feeding tube site, or who are unable to reach their goal caloric needs via the enteral route, should be considered for TPN.

Percutaneous Drainage

Percutaneous drainage, alone or in combination with other minimally invasive approaches, remains an important treatment modality for patients with symptomatic WON. Percutaneous drainage can provide a rapid and effective means for source control in patients with infected pancreatic necrosis who are too ill to undergo endoscopic transmural drainage. Percutaneous drainage monotherapy may provide definitive therapy for a subset of patients.

A large prospective, multicenter, observational, cohort study demonstrated that, in the subgroup of patients managed by primary percutaneous catheter drainage, 35% did not require further intervention.[13] Two prospective randomized trials comparing various approaches to the management of symptomatic WON demonstrated that percutaneous drainage alone was successful in 35% and 51% of patients, respectively.[14,15]

Percutaneous drainage should be employed when endoscopic drainage is unavailable, unsuccessful, or not technically feasible. In cases where necrosis extends into one or both paracolic gutters and/or into the pelvis, the dependent portions of the collection will not be able to drain

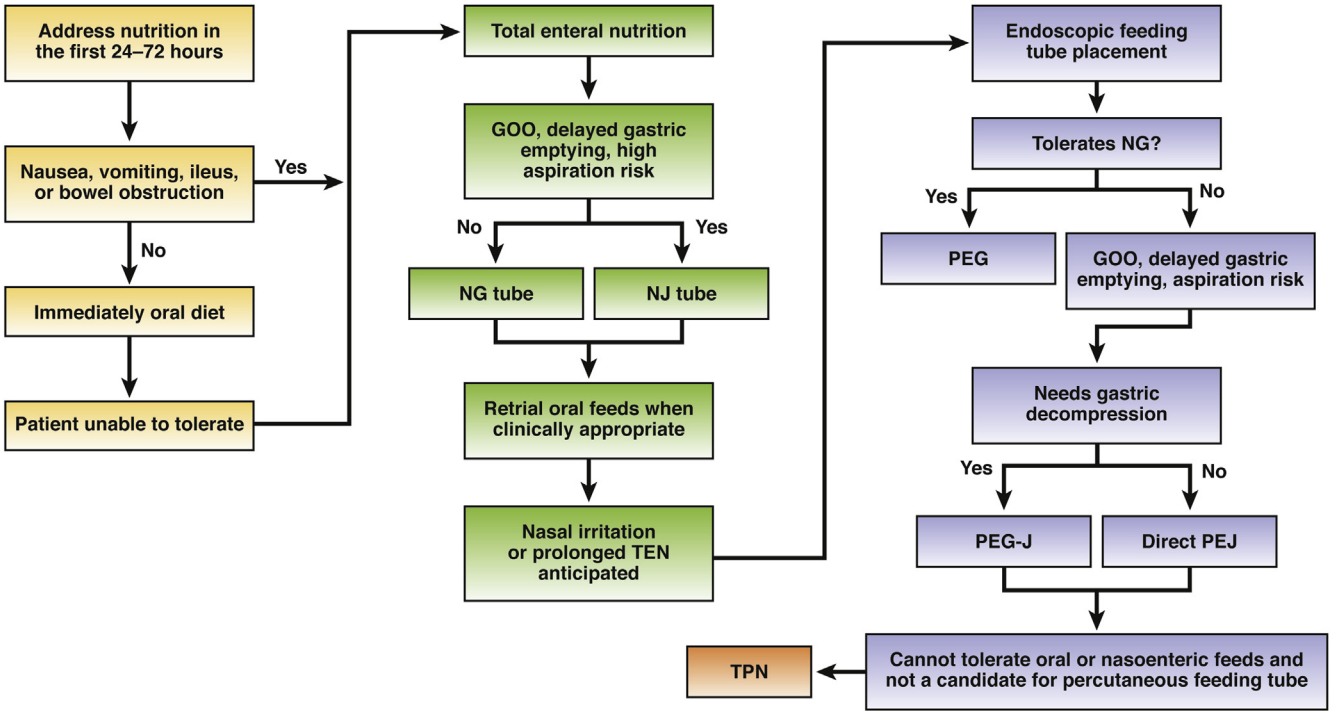

Figure 1. Flow diagram on the suggested nutritional management of patients with severe acute pancreatitis and necrosis. GOO, gastric outlet obstruction; NG, nasogastric; NJ, nasojejunal; PEG, percutaneous endoscopic gastrostomy; PEG-J percutaneous endoscopic gastrostomy with jejunal extension; PEJ, percutaneous endoscopic jejunostomy.

effectively through superiorly located transmural endoscopic stents. Percutaneous catheter placement into the retroperitoneum and/or pelvis will not only facilitate drainage of these dependent areas, but also allows for bedside irrigation and clearance of necrotic material. Multiple large series have demonstrated that the adjunctive use of percutaneous drainage catheters (ranging in size from 8F to 24F) in patients undergoing endoscopic drainage and debridement can result in improved outcomes.[16–18]

Another major advantage to the use of percutaneous drainage catheters is that the catheter tract can act as an entry portal for other minimally invasive debridement methods, such as video-assisted retroperitoneal debridement or endoscopic sinus tract debridement. A 24F or larger percutaneous drain reduces the need for dissection at the time of video-assisted retroperitoneal debridement (VARD). Lastly, for patients in the early phase of acute necrotizing pancreatitis (<2–4 weeks) who have suspected or confirmed infected necrosis—without the presence of a walled-off collection—and are failing conservative medical management, percutaneous drainage can provide safe and effective drainage and source control.

The one major potential downside to using percutaneous drainage is the risk of pancreatocutaneous fistula formation. One large prospective study comparing endoscopic drainage approaches to a combined percutaneous/VARD approach showed the rate of pancreatic fistula formation was significantly higher in the percutaneous/VARD group (32% vs 5%; $P < .01$).[15] However, the risk of fistula formation can be eliminated by combining percutaneous drainage with simultaneous endoscopic drainage using 2 double-pigtail stents.[18]

Endoscopic Necrosectomy

Endoscopic transmural therapy for pancreatic necrosis was first described in 1996 and has evolved (Figure 2).[19,20] Pancreatic necrosis can affect the head, body, or tail and is endoscopically approachable transgastrically or transduodenally, depending on the largest component and relationship to the gastric or duodenal walls. Collections in the area of the pancreatic head are drained transduodenally, while the others are drained transgastrically. There does not appear to be an advantage of one approach over the other in terms of success and safety, though the transgastric approach is used most often, and if endoscopic necrosectomy is performed, this allows the most direct endoscopic access to the collection.

While large randomized trials of endoscopic ultrasound (EUS) and non-EUS transmural drainage are lacking, most experts agree that EUS-guided transmural entry is safer, particularly with regard to avoidance of bleeding. Plastic stents and self-expandable metal stents (SEMS) have been used for transmural drainage. Because plastic stents were used before SEMS, much of earlier literature related to their use. Large-diameter SEMS (≥15 mm diameter) appear to provide better egress of necrotic material than plastic stents,[21] while also allowing for endoscopic access to perform necrosectomy. The newer lumen-apposing metal stents (LAMS), a type of SEMS, are being used increasingly,

as their short length (1 cm) is more suitable than commercially available covered esophageal SEMS (usually no shorter than 6–7 cm). Additionally, when available, cautery-enhanced delivery systems decrease technical difficulty, avoid the need for tract dilation for stent insertion, shorten procedural time, and may obviate adjunctive debridement techniques.[22] However, a recent randomized trial did not show superiority to plastic stents.[23] Some endoscopists place one or more double-pigtail plastic stents through LAMS to reduce the risks of early occlusion by necrotic tissue and LAMS migration.

Debridement of necrotic tissue can be in the form of irrigation through endoscopically placed nasocystic tubes or percutaneously placed drains, or by way of passing an endoscope into the cavity with mechanical removal, which is referred to as direct endoscopic necrosectomy (DEN). The need for debridement, especially when large-diameter SEMS are placed, is likely dependent on the degree of solid material present within the walled-off necrotic cavity. Whether to perform DEN or irrigation is also unclear, although patients are less tolerant of nasal irrigation. Similarly, whether the approach to DEN should be up front (at the time of LAMS placement) or delayed, and whether to perform scheduled vs "on-demand" DEN are unknown. DEN has been shown to improve the outcome of endoscopic therapy compared to irrigation when plastic stents are used in patients with WON.[24] However, DEN carries risks for severe adverse events that include air embolism, intracavitary bleeding, and perforation.

The decision as to when DEN should or can be performed for patients with WON is in evolution. Traditionally, waiting 4 weeks for necrotic collections to wall-off and mature has been advocated, which was largely an extrapolation from the surgical literature. While data have emerged that endoscopic step-up therapy and DEN starting at <4 weeks are clinically possible when indicated, patients who could clinically wait ≥ 4 weeks before endoscopic intervention had decreased mortality.[25]

The duration of stent placement is variable. Plastic stents can remain in place until the collection resolves, as evidenced by cross-sectional imaging studies, and potentially indefinitely for prevention of disconnected duct syndrome when the main pancreatic duct has been disrupted. There are concerns for leaving LAMS in place beyond several weeks due to reports of delayed bleeding, and SEMS of any type should not remain in place long-term.

Adjunctive chemical therapies that have been used to prevent infection and to promote debridement include antibiotic lavage and hydrogen peroxide irrigation. Comparative trials to placebo are not available and thus cannot be routinely recommended. Tools used for DEN include grasping forceps, polypectomy snares, and retrieval nets. Recently, a through-the-scope device to facilitate mechanical debridement has become commercially available and preliminary data are promising.[26] Endoscopists with experience in managing WON have recommended avoidance of acid suppressive medications after transmural drainage, given the potential for auto-debridement from secreted gastric acid. However, data are lacking to support this practice.

Surgical Approach to Pancreatic Necrosis

In patients with infected pancreatic necrosis or those with sterile pancreatic necrosis who have persistent organ dysfunction or failure to thrive, operative debridement should be considered (Figure 3). Timing of intervention is paramount, as debridement during the early phase of acute pancreatitis, when the systemic inflammatory response is the driver of clinical morbidity (within 2–4 weeks of onset), carries a significantly higher mortality rate than supporting the patient through to the subacute period. The goals of operative debridement are to control the source of infection and decrease the burden of necrosis, while minimizing the pro-inflammatory insult of the intervention itself on the debilitated patient. In the modern era, there are multiple approaches to operative debridement, including VARD ("step-up"), laparoscopic and open transgastric debridement, and open operative debridement. Each approach has distinct advantages and disadvantages that should be considered in individual case planning. The selection of approach is best determined by pattern of disease, physiology of the patient, experience and expertise of the multidisciplinary team, and the resources of the center.

The VARD approach first entails image-guided placement of a percutaneous catheter into the retroperitoneal peripancreatic collection via the left flank. Notably, a significant number of patients (23%–47%) will resolve their necrosis with this percutaneous drainage alone.[14,27,28] In those with persistent disease, a step up to operative intervention is undertaken. The tract formed from the previously placed drain is utilized to access the retroperitoneal space for an intracavitary videoscopic necrosectomy, employing traditional laparoscopic instrumentation under direct visualization with the laparoscope. Drains are left in the cavity for postoperative lavage and fistula control, if needed. The Dutch Pancreatitis Study Group compared the step-up approach to open necrosectomy in a prospective randomized multicenter trial (PANTER) and found equivalent mortality between the groups, but a higher rate of new-onset multiple-organ failure in the open necrosectomy group (40% vs 12%), as well as a higher rate of new-onset diabetes (38% vs 16%) and hernias (24% vs 7%).[14] The VARD procedure is best suited to patients with a central distribution of necrosis that extends down into the left paracolic gutter and can be ineffective in reaching necrosis to the right of the mesenteric vessels.

Surgical transgastric debridement is similar to endoscopic transgastric debridement in concept and draws on the experience of cystgastrostomy. It can be accomplished laparoscopically or open, and involves an anterior gastrotomy to access the posterior wall of the stomach for transmural access to the necrosis cavity. The variety of available surgical instrumentation allows for an easy, short, single debridement procedure, in contrast to the endoscopic

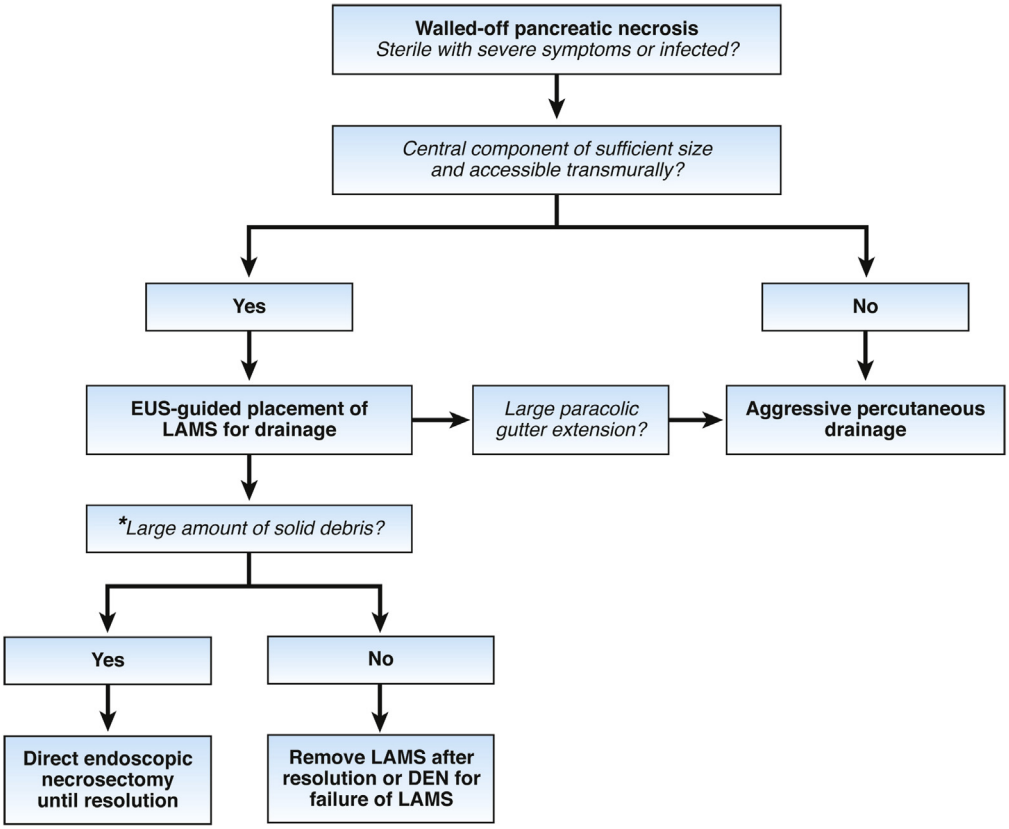

Figure 2. Flow diagram outlining the suggested approach to endoscopic management of walled-off pancreatic necrosis in a patient with a strong indication for drainage and/or debridement. *As per Best Practice Advice 10, DEN of large necrotic collections should be performed at referral centers with the necessary endoscopic expertise and interventional radiology and surgical backup.

approach. A nasogastric tube is placed across the posterior gastrotomy into the necrosis cavity for postoperative lavage. Simultaneous cholecystectomy can be performed in patients with biliary pancreatitis. Several small single-institution series demonstrated efficacy with an attendant low morbidity for the transgastric approach.[29–31] The relatively large size of the cystgastrostomy has the potential benefit of a durable avenue for enteric drainage of a pancreatic fistula in the case of disconnected pancreatic duct syndrome. The transgastric approaches are best suited to the patient with centrally located necrosis, and extension of the necrosis burden into either paracolic gutter can lead to incomplete debridement.

Open surgical debridement maintains an important role in the management of pancreatic necrosis, even in the modern era. Open debridement entails a laparotomy with entry into the lesser sac and gentle blunt debridement of necrotic tissue. Concurrent cholecystectomy can be performed in cases of biliary pancreatitis. Large-bore drains are left for postoperative lavage and fistula control, if needed. Multiple single-institution series have demonstrated acceptable rates of efficacy and morbidity for open necrosectomy,[32–34] although a randomized trial found increased morbidity with open necrosectomy compared to a step-up approach.[14] Comparative studies with the exception of randomized trials should be interpreted with caution, given the often-higher severity of disease in patients undergoing open debridement in the current era. Open debridement may be best undertaken in patients with a large burden of necrosis that is distributed diffusely throughout the abdomen.

Disconnected Pancreatic Duct Syndrome

In a subset of patients with severe acute pancreatitis, necrosis and disruption of the main pancreatic duct can result in a lack of continuity between the duct in the left-sided pancreas (body/tail) and the luminal gastrointestinal tract. This disconnected pancreatic duct syndrome (DPDS)[35] can produce a persistent pancreatic fistula, most often presenting as a peripancreatic fluid collection. Recognition of this condition is important for therapeutic decision-making (Supplementary Figure 2). Standard treatment for DPDS is operative resection of the disconnected pancreas. Distal pancreatectomy can be undertaken in the subacute setting (in the first 30–60 days of illness) concurrent with debridement. This intervention entails relatively high periprocedural morbidity (that might include perioperative transfusion, postoperative pancreatic fistula, increased length of stay, and need for readmission), but offers a single procedure and a concise overall disease course. Alternatively, pancreatic necrosis can be managed initially with percutaneous, endoscopic, or minimally invasive surgical techniques with planned elective distal pancreatectomy in several months when the patient's physiology has recovered. Because of the significant inflammation and fibrosis with obliteration of normal tissue planes, including potential splenic vein

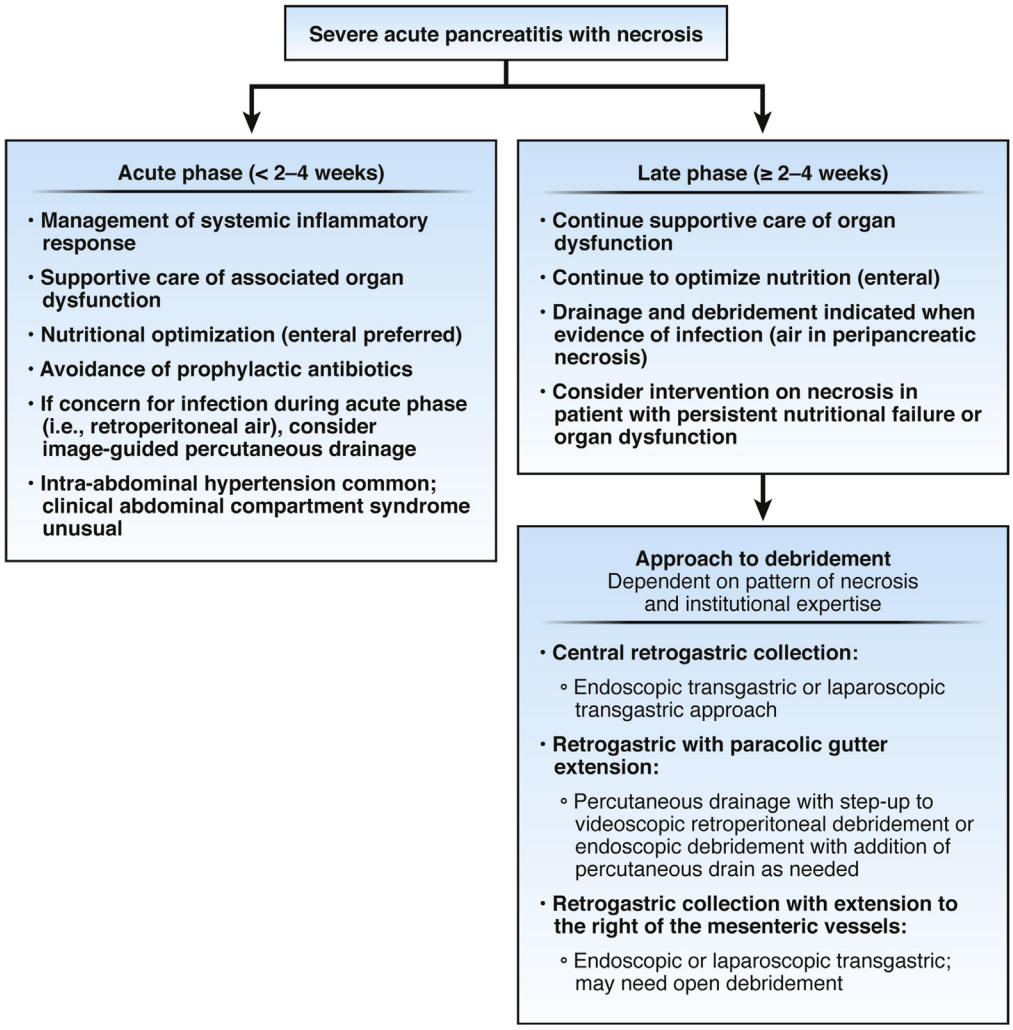

Figure 3. Decision tree outlining the acute- and late-phase management of patients with severe acute pancreatitis and necrosis, including a multidisciplinary approach to drainage and/or debridement when required.

thrombosis with sinestral hypertension, these resections are most often performed via laparotomy, even in the elective setting, and include a concomitant splenectomy.[36–38] When the resected pancreatic remnant is of substantive size, consideration can be given to concurrent islet autotransplantation in order to preserve endocrine function, as new diabetes is reported in a significant percentage of patients after DPDS even without pancreatic resection.

Less-invasive approaches to DPDS, namely endoscopic and minimally invasive surgical techniques, are an evolving field of exploration. EUS-guided transmural stenting is an effective means of temporizing DPDS. The safety and efficacy of long-term (permanent) indwelling transmural stents is an important field of study. True rates of stent migration, stent occlusion, or stent fracture with resultant infection or cyst recurrence are not yet known, but appear reasonable in intermediate experiences. Clearly, endoscopic transmural stenting is the preferred option for poor surgical candidates with DPDS to avoid operative morbidity.[39–41] An additional option for consideration is management of the initial necrosis in the setting of DPDS with laparoscopic or open transgastric debridement. Ideally, the large cystgastrostomy created during the debridement may persist as an avenue for internal drainage of the disconnected left pancreatic remnant, obviating the need for additional intervention.

Endoscopic Step-Up Therapy—An Emerging Paradigm

The step-up approach was initially applied as a less-invasive alternative to surgical open necrosectomy for infected pancreatic necrosis. It consisted of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy. Open necrosectomy was performed when the step-up approach failed. This less-invasive approach led to a reduction in morbidity and mortality,[14] with the superiority of the step-up approach demonstrated recently at long-term follow-up (mean duration of 86 months).[42]

More recently, a multicenter, randomized, superiority trial of patients with infected necrosis was performed in the Netherlands.[15] Patients were randomly assigned to undergo either the endoscopic or the previously mentioned step-up approach, although open necrosectomy was not undertaken. Both groups could receive endoscopic or percutaneous therapy, as needed. The endoscopic approach consisted of EUS-guided transluminal drainage followed, if necessary, by

DEN. Initial transmural drainage consisted of EUS-guided placement of two 7F stents and a nasocystic irrigation catheter. Although the endoscopic step-up approach was not superior to the surgical step-up approach in reducing major complications or death, the rate of pancreatic fistulae and length of hospital stay were lower in the endoscopy group. It is likely that large-diameter SEMS would have been superior to the use of small-caliber stents in this study.[15] A single-center trial conducted in the United States enrolled 66 patients with confirmed or suspected infected WON and randomized patients to minimally invasive surgery or an endoscopic step-up approach (transluminal drainage with or without necrosectomy) starting with two 7F stents or later use of a 15-mm LAMS, when it became commercially available.[43] The primary end point, which was a composite of major complications or death during 6 months of follow-up, was reached in 11.8% of patients who received the endoscopic procedure and in 40.6% of patients who received minimally invasive surgery (risk ratio, 0.29; 95% confidence interval, 0.11–0.80; $P = .007$). Although there was no significant difference in mortality, none of the patients assigned to the endoscopic approach developed enteral or pancreatocutaneous fistulae compared to 28.1% of the patients who underwent surgery ($P = .001$).[43] Taken together, these trials[15,43] lend credence to an endoscopic step-up paradigm as the evolving first-line approach to treating patients with infected pancreatic necrosis.

Necessity of a Multidisciplinary Interventional Approach

Management of patients with pancreatic necrosis is most effective at a specialized referral center with nutritionists, medical intensivists, procedural radiologists, advanced endoscopists, and pancreatic surgeons who have expertise in caring for this complex patient population in a multidisciplinary manner. While there will always be variations in local expertise and approaches between expert centers, for patients with infection or severe symptoms attributed to pancreatic necrosis, percutaneous drainage remains an important adjunctive or definitive therapy in the early stage of the disease. Similarly, EUS-guided drainage and DEN when required for WON, particularly in the era of LAMS, and a step-up approach that utilizes minimally invasive and open surgical approaches for debridement are important and effective interventions in the management of patients with this complex and highly morbid disease.

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.2019.07.064.

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Author names in bold designate shared co-first authorship.

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Reprint requests
Address requests for reprints to: Andrew Y. Wang, MD, AGAF, FACG, FASGE, Division of Gastroenterology and Hepatology, University of Virginia, Box 800708, Charlottesville, Virginia 22908. e-mail: ayw7d@virginia.edu; fax: 434-244-7590.

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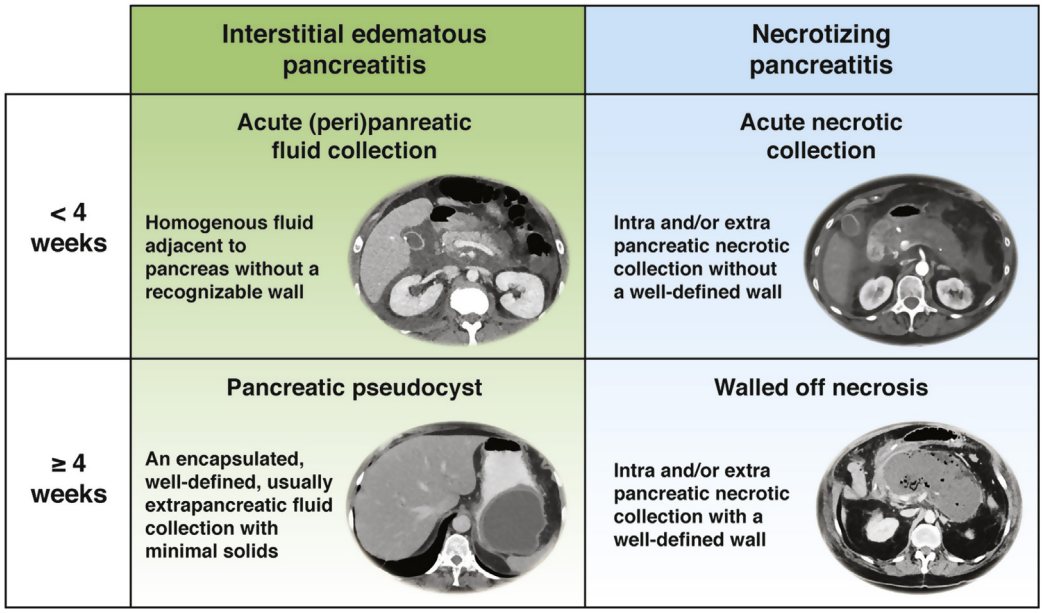
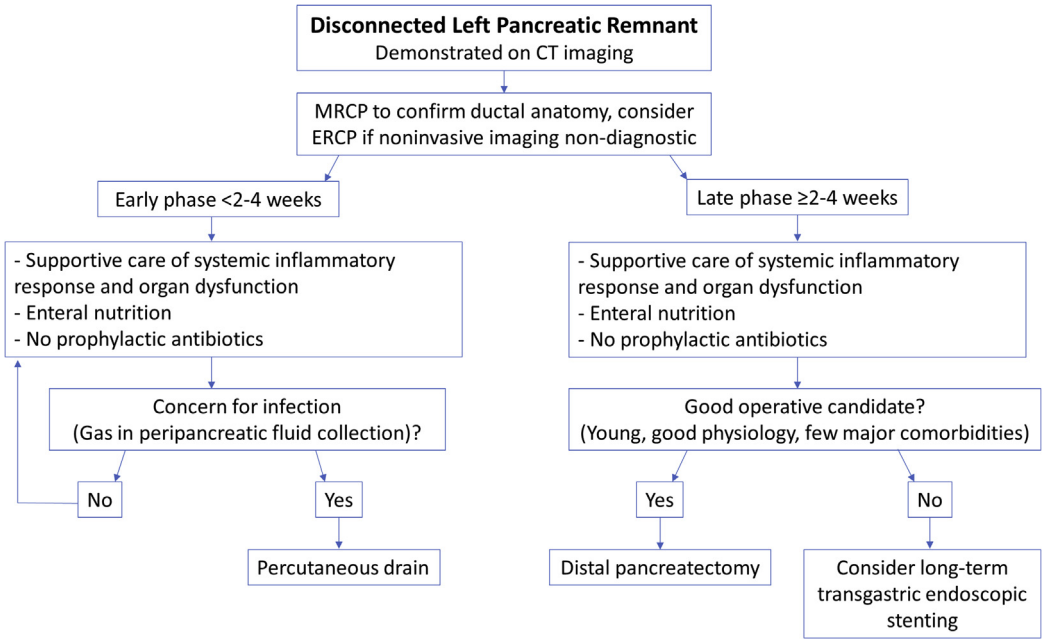
Conflicts of interest
These authors disclose the following: Todd H. Baron is a consultant and speaker for Boston Scientific, Cook Endoscopy, Medtronic, Olympus, and W.L. Gore. Christopher J. DiMaio is a consultant and speaker for Boston Scientific and Medtronic. The remaining authors disclose no conflicts.



Supplementary Figure 1. Classification of acute pancreatitis and associated fluid collections. Based on international consensus according to the Acute Pancreatitis Classification Working Group (revised Atlanta criteria).[2] From Trikudanathan et al,[1] reprinted with permission.



Supplementary Figure 2. Approach to the patient with severe acute pancreatitis and a disconnected left pancreatic remnant. CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.