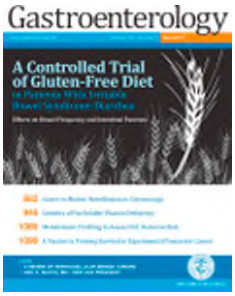
Journal Pre-proof



American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis

Todd H. Baron, Christopher J. DiMaio, Andrew Y. Wang, Katherine A. Morgan

PII: S0016-5085(19)41293-6
DOI: https://doi.org/10.1053/j.gastro.2019.07.064
Reference: YGAST 62864

To appear in: *Gastroenterology*
Accepted Date: 31 July 2019

Please cite this article as: Baron TH, DiMaio CJ, Wang AY, Morgan KA, American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis, *Gastroenterology* (2019), doi: https://doi.org/10.1053/j.gastro.2019.07.064.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 by the AGA Institute

Journal Pre-proof

Title: American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis

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

Affiliations:

1. Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, NC, USA

2. Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY

3. Division of Gastroenterology and Hepatology, University of Virginia, Charlottesville, VA, USA

4. Division of Gastrointestinal and Laparoscopic Surgery, Medical University of South Carolina, Charleston, SC

*** Corresponding author:**

Andrew Y. Wang, MD, AGAF, FACG, FASGE

Professor of Medicine

Division of Gastroenterology and Hepatology

Box 800708

Journal Pre-proof

University of Virginia

Charlottesville, VA 22908

Tel: 434-924-1653

Fax: 434-244-7590

E-mail: ayw7d@virginia.edu

Disclosures:

Dr. Todd Baron is a consultant and speaker for Boston Scientific, Cook Endoscopy, Medtronic, Olympus, and W.L. Gore.

Dr. Christopher DiMaio is a consultant and speaker for Boston Scientific and Medtronic.

Dr. Andrew Wang has nothing to disclose.

Dr. Katherine Morgan has nothing to disclose.

Funding: None

Authors' contributions:

Each of the four authors contributed to drafting of the manuscript and critical revision of the manuscript for important intellectual content.

Journal Pre-proof

Word count: 3,928 (not including Best Practice Advice statements, references, figure/video captions, or tables)

Description: The purpose of this 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 (CPUC) 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 CPUC 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 manuscripts 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.

Journal Pre-proof

Keywords: Pancreatitis; necrosis; nutrition; antibiotics; percutaneous; endoscopic; necrosectomy; step-up; surgery

Secondary keywords: Walled-off; WON; drainage; cystgastrostomy; debridement; endoscopic; direct endoscopic necrosectomy; DEN; lumen-apposing metal stents; LAMS; videoscopic; minimally-invasive

Journal Pre-proof

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 (i.e. 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 (e.g. carbapenems, quinolones, metronidazole). Routine use of antifungal agents is not recommended. CT-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 parental 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 (SIRS).

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 only performed earlier when there is an organized collection and a strong indication.

Best Practice Advice 7: Percutaneous drainage or transmural endoscopic drainage are both appropriate first-line, non-surgical 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 strongly be 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 (SEMS) in the form of lumen-apposing metal stents (LAMS) appear to be superior to plastic stents for endoscopic transmural drainage of necrosis.

Best Practice Advice 10: The use of direct endoscopic necrosectomy (DEN) should be reserved for those patients with limited necrosis who do not adequately respond to endoscopic transmural drainage using large bore SEMS/LAMS alone or plastic stents combined with irrigation. DEN 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.

Journal Pre-proof

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 a SEMS/LAMS alone, followed by DEN, and then surgical debridement is reasonable, although approaches may vary based on the available clinical expertise.

Journal Pre-proof

Abbreviations

PFCs – pancreatic fluid collections

SIRS – systemic inflammatory response syndrome

WON – walled-off pancreatic necrosis

CT – computed tomography

TEN – total enteral nutrition

TPN – total parental nutrition

PEG – percutaneous endoscopic gastrostomy

PEJ – percutaneous endoscopic jejunostomy

VARD – video-assisted retroperitoneal debridement

EUS – endoscopic ultrasound

SEMS – self-expandable metal stents

LAMS – lumen-apposing metal stents

DEN – direct endoscopic necrosectomy

DPDS – disconnected pancreatic duct syndrome

Journal Pre-proof

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 (PFCs) are defined, noting the importance of not only the length of time a PFC 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 was 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 (SIRS).

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, intravenous fluids and, as such, variability exists among practitioners and institutions regarding the preferred management approach.

We refer the reader to the AGA 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 AGA Clinical

Practice Update is 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%. Thus, 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 SIRS, 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 the pancreas is recommended. These include carbapenems, quinolones, metronidazole, and third- or higher-generation cephalosporins. Computed tomography (CT)-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 CT-guided biopsy 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 anti-fungal therapy in patients with pancreatic necrosis, and thus routine administration is not recommended.

Journal Pre-proof

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 and remaining nil per os. However, these theories have largely been disproven.

Most patients with severe and/or necrotizing pancreatitis are acutely ill, in a hypercatabolic state, and are 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 a significantly lower rate of pancreatic infectious complications (20% vs. 47%), multiorgan failure (20% vs. 50%), and death (6% vs. 35%) compared to patients receiving total parental nutrition (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%), pancreatic septic 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 in terms of 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] Thus, either route is acceptable, though nasogastric (or nasoduodenal) tubes are easier to place and maintain.

For those patients in whom nasoenteric feeding is not tolerated (e.g., 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 (PEG) 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 (PEJ) tube is a reasonable option. For those patients with gastric outlet obstruction, delayed gastric emptying and/or prolonged ileus, placement of a PEG 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 (e.g. 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 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 8 Fr to 24 Fr) 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 24 Fr or larger percutaneous drain reduces the need for dissection at the time of VARD. Lastly, for patients in the early phase of acute necrotizing pancreatitis (<2-4 weeks) who have suspected or confirmed infected necrosis but 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%, $P<0.01$).[15] However, the risk of fistula formation

may be eliminated by combining percutaneous drainage with simultaneous endoscopic drainage using two 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 most often used, 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 in regards to avoidance of bleeding. Plastic stents and self-expandable metal stents (SEMS) have been used for transmural drainage. Since plastic stents were used prior to 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 increasingly used 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, though patients are less tolerant of nasal irrigation. Similarly, whether the approach to DEN should be upfront (at the time of LAMS placement) or delayed, and whether to perform scheduled versus "on-demand" DEN are unknown. DEN has been shown to improve the outcome of endoscopic therapy when 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 is 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 they 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 recently 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 videoscopic-assisted retroperitoneal debridement (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.

Journal Pre-proof

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% to 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 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 lend 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 showed 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 diffusely distributed 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, 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 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-approach demonstrated recently at long-term (mean duration of 86 months) follow-up.[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, though 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 7-Fr 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 or an endoscopic step-up approach (transluminal drainage with or without necrosectomy) starting with two 7-Fr stents or later use of a 15-mm LAMS, when it became commercially available.[43] The primary endpoint, 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% CI: 0.11-0.80; P=0.007). While 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=0.001).[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.

References

1. **Trikudanathan G**, **Wolbrink DRJ**, van Santvoort HC, et al. Current Concepts in Severe Acute and Necrotizing Pancreatitis: An Evidence-Based Approach. Gastroenterology 2019;156:1994-2007 e3.
2. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.
3. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13:e1-15.
4. Vege SS, DiMagno MJ, Forsmark CE, et al. Initial Medical Treatment of Acute Pancreatitis: American Gastroenterological Association Institute Technical Review. Gastroenterology 2018;154:1103-1139.
5. Crockett SD, Wani S, Gardner TB, et al. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology 2018;154:1096-1101.
6. Isenmann R, Runzi M, Kron M, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology 2004;126:997-1004.
7. Dellinger EP, Tellado JM, Soto NE, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg 2007;245:674-83.

8. Garcia-Barrasa A, Borobia FG, Pallares R, et al. A double-blind, placebo-controlled trial of ciprofloxacin prophylaxis in patients with acute necrotizing pancreatitis. J Gastrointest Surg 2009;13:768-74.

9. Petrov MS, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. Dig Surg 2006;23:336-44; discussion 344-5.

10. Wu XM, Ji KQ, Wang HY, et al. Total enteral nutrition in prevention of pancreatic necrotic infection in severe acute pancreatitis. Pancreas 2010;39:248-51.

11. Singh N, Sharma B, Sharma M, et al. Evaluation of early enteral feeding through nasogastric and nasojejunal tube in severe acute pancreatitis: a noninferiority randomized controlled trial. Pancreas 2012;41:153-9.

12. Eatock FC, Chong P, Menezes N, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. Am J Gastroenterol 2005;100:432-9.

13. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 2011;141:1254-63.

14. van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362:1491-502.

15. van Brunschot S, van Grinsven J, van Santvoort HC, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet 2018;391:51-58.

16. Nemoto Y, Attam R, Arain MA, et al. Interventions for walled off necrosis using an algorithm based endoscopic step-up approach: Outcomes in a large cohort of patients. Pancreatology 2017;17:663-668.

17. Bang JY, Holt BA, Hawes RH, et al. Outcomes after implementing a tailored endoscopic step-up approach to walled-off necrosis in acute pancreatitis. Br J Surg 2014;101:1729-38.

18. Ross AS, Irani S, Gan SI, et al. Dual-modality drainage of infected and symptomatic walled-off pancreatic necrosis: long-term clinical outcomes. Gastrointest Endosc 2014;79:929-35.

19. Baron TH, Thaggard WG, Morgan DE, et al. Endoscopic therapy for organized pancreatic necrosis. Gastroenterology 1996;111:755-64.

20. Baron TH, Kozarek RA. Endotherapy for organized pancreatic necrosis: perspectives after 20 years. Clin Gastroenterol Hepatol 2012;10:1202-7.

21. Abu Dayyeh BK, Mukewar S, Majumder S, et al. Large-caliber metal stents versus plastic stents for the management of pancreatic walled-off necrosis. Gastrointest Endosc 2018;87:141-149.

22. Sharaiha RZ, Tyberg A, Khashab MA, et al. Endoscopic Therapy With Lumen-apposing Metal Stents Is Safe and Effective for Patients With Pancreatic Walled-off Necrosis. Clin Gastroenterol Hepatol 2016;14:1797-1803.

23. Bang JY, Hasan MK, Navaneethan U, et al. Lumen-apposing metal stents for drainage of pancreatic fluid collections: When and for whom? Dig Endosc 2017;29:83-90.

24. Gardner TB, Chahal P, Papachristou GI, et al. A comparison of direct endoscopic necrosectomy with transmural endoscopic drainage for the treatment of walled-off pancreatic necrosis. Gastrointest Endosc 2009;69:1085-94.

25. Trikudanathan G, Tawfik P, Amateau SK, et al. Early (<4 Weeks) Versus Standard (>/= 4 Weeks) Endoscopically Centered Step-Up Interventions for Necrotizing Pancreatitis. Am J Gastroenterol 2018;113:1550-1558.

26. van der Wiel SE, Poley JW, Grubben M, et al. The EndoRotor, a novel tool for the endoscopic management of pancreatic necrosis. Endoscopy 2018;50:E240-E241.

27. Freeny PC, Hauptmann E, Althaus SJ, et al. Percutaneous CT-guided catheter drainage of infected acute necrotizing pancreatitis: techniques and results. AJR Am J Roentgenol 1998;170:969-75.

28. Horvath K, Freeny P, Escallon J, et al. Safety and efficacy of video-assisted retroperitoneal debridement for infected pancreatic collections: a multicenter, prospective, single-arm phase 2 study. Arch Surg 2010;145:817-25.

29. Munene G, Dixon E, Sutherland F. Open transgastric debridement and internal drainage of symptomatic non-infected walled-off pancreatic necrosis. HPB (Oxford) 2011;13:234-9.

30. Gibson SC, Robertson BF, Dickson EJ, et al. 'Step-port' laparoscopic cystgastrostomy for the management of organized solid predominant post-acute fluid collections after severe acute pancreatitis. HPB (Oxford) 2014;16:170-6.

31. Worhunsky DJ, Qadan M, Dua MM, et al. Laparoscopic transgastric necrosectomy for the management of pancreatic necrosis. J Am Coll Surg 2014;219:735-43.

32. Howard TJ, Patel JB, Zyromski N, et al. Declining morbidity and mortality rates in the surgical management of pancreatic necrosis. J Gastrointest Surg 2007;11:43-9.

33. Parikh PY, Pitt HA, Kilbane M, et al. Pancreatic necrosectomy: North American mortality is much lower than expected. J Am Coll Surg 2009;209:712-9.

34. Rodriguez JR, Razo AO, Targarona J, et al. Debridement and closed packing for sterile or infected necrotizing pancreatitis: insights into indications and outcomes in 167 patients. Ann Surg 2008;247:294-9.

35. Kozarek RA, Ball TJ, Patterson DJ, et al. Endoscopic transpapillary therapy for disrupted pancreatic duct and peripancreatic fluid collections. Gastroenterology 1991;100:1362-70.

36. Nealon WH, Bhutani M, Riall TS, et al. A unifying concept: pancreatic ductal anatomy both predicts and determines the major complications resulting from pancreatitis. J Am Coll Surg 2009;208:790-9; discussion 799-801.

37. Howard TJ, Moore SA, Saxena R, et al. Pancreatic duct strictures are a common cause of recurrent pancreatitis after successful management of pancreatic necrosis. Surgery 2004;136:909-16.

38. Fischer TD, Gutman DS, Hughes SJ, et al. Disconnected pancreatic duct syndrome: disease classification and management strategies. J Am Coll Surg 2014;219:704-12.

39. Nadkarni NA, Kotwal V, Sarr MG, et al. Disconnected Pancreatic Duct Syndrome: Endoscopic Stent or Surgeon's Knife? Pancreas 2015;44:16-22.

40. Varadarajulu S, Wilcox CM. Endoscopic placement of permanent indwelling transmural stents in disconnected pancreatic duct syndrome: does benefit outweigh the risks? Gastrointest Endosc 2011;74:1408-12.

41. Rana SS, Bhasin DK, Rao C, et al. Consequences of long term indwelling transmural stents in patients with walled off pancreatic necrosis & disconnected pancreatic duct syndrome. Pancreatology 2013;13:486-90.

42. Hollemans RA, Bakker OJ, Boermeester MA, et al. Superiority of Step-up Approach vs Open Necrosectomy in Long-term Follow-up of Patients With Necrotizing Pancreatitis. Gastroenterology 2019;156:1016-1026.

43. Bang JY, Arnoletti JP, Holt BA, et al. An Endoscopic Transluminal Approach, Compared With Minimally Invasive Surgery, Reduces Complications and Costs for Patients With Necrotizing Pancreatitis. Gastroenterology 2019;156:1027-1040 e3.

Author names in **bold** designate shared co-first authorship.

Journal Pre-proof

Figure Captions:

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, TEN: total enteral nutrition, PEG: percutaneous endoscopic gastrostomy, PEG-J percutaneous endoscopic gastrostomy with jejunal extension, PEJ: percutaneous endoscopic jejunostomy).

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 (LAMS: lumen-apposing metal stent, DEN: direct endoscopic necrosectomy). ***** 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.

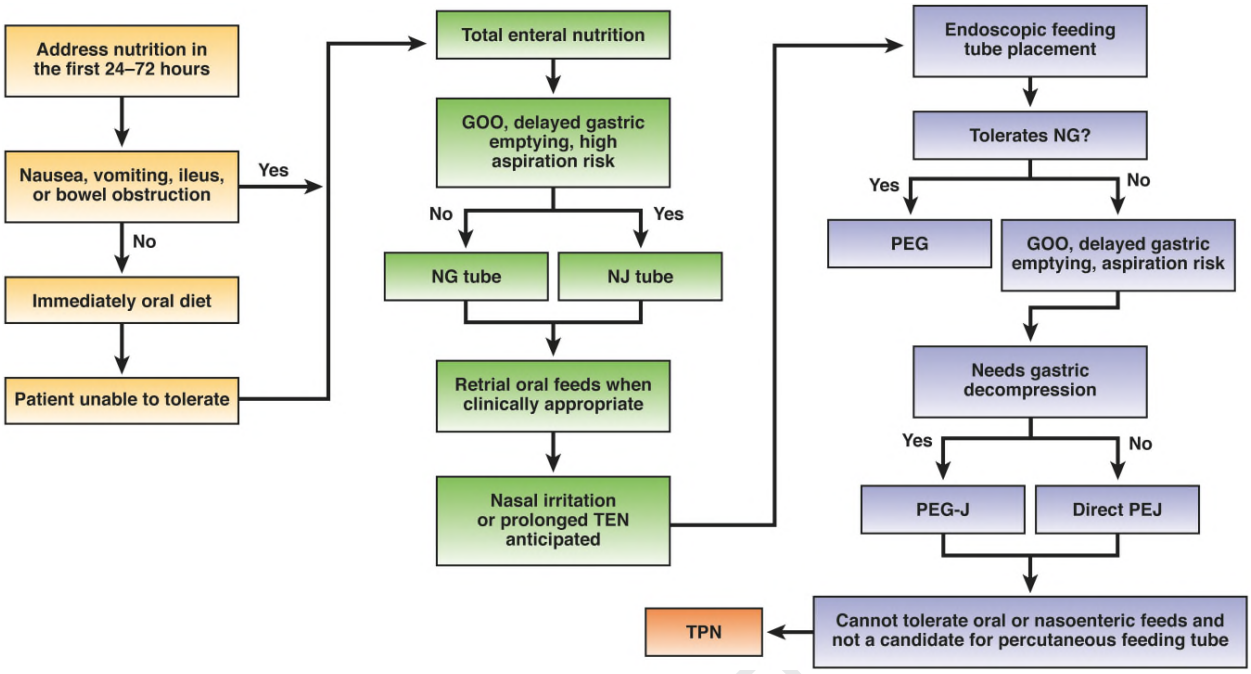
Figure 3. Decision tree outlining the acute- and late-phase management of patients with severe acute pancreatitis and necrosis including a multidisciplinary approach to drainage and/or debridement when required.

Journal Pre-proof

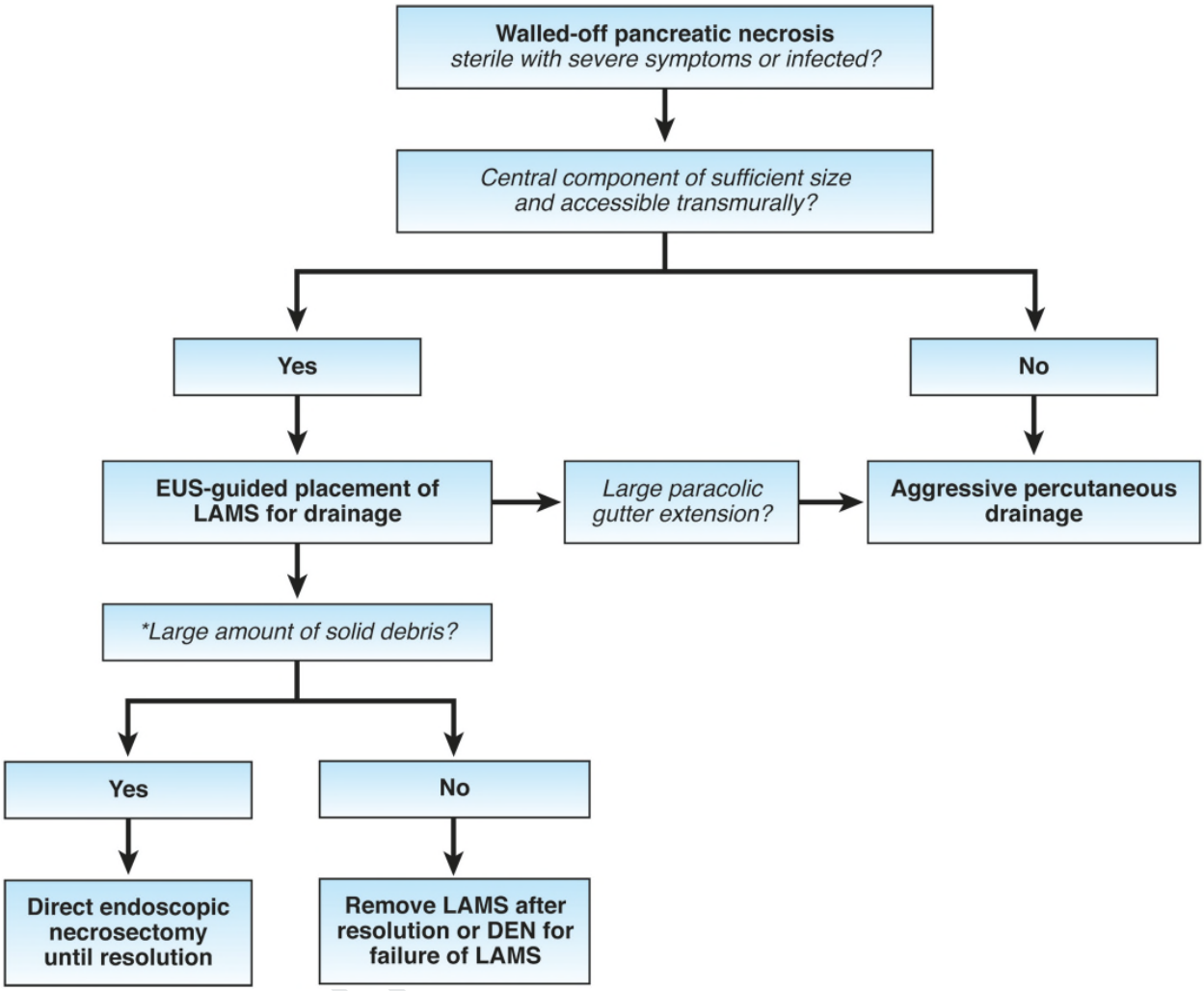
Supplementary Figure 1. Classification of acute pancreatitis and associated fluid collections. Based on international consensus according to the Acute Pancreatitis Classification Working Group (revised Atlanta criteria).[2] This figure was taken from Trikudanathan et al[1] with permission from Elsevier.

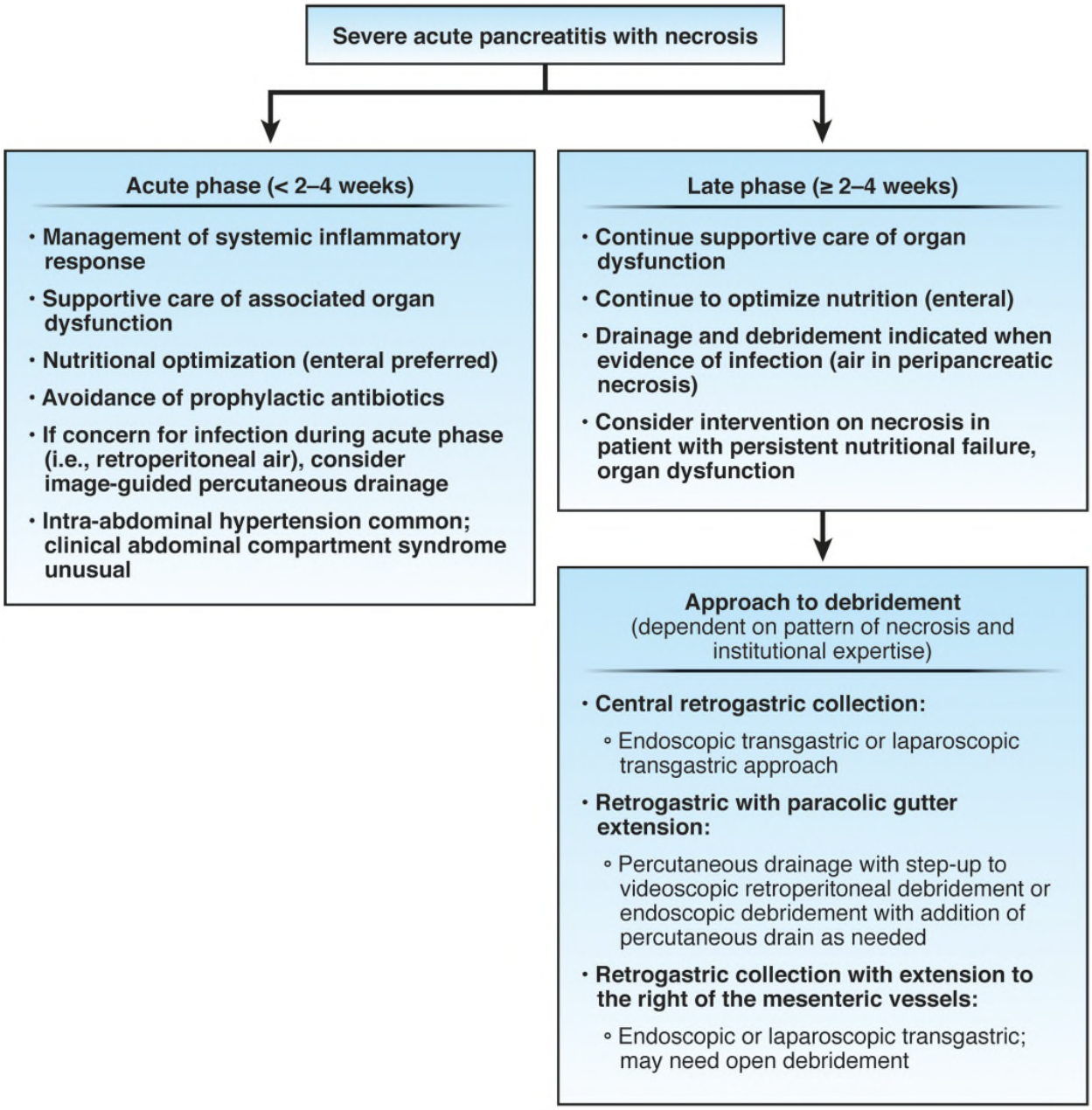
Supplementary Figure 2. Approach to the patient with severe acute pancreatitis and a disconnected left pancreatic remnant.

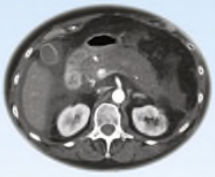
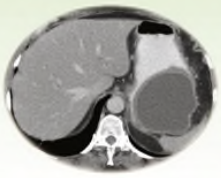
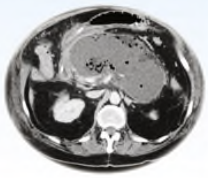
Journal Pre-proof



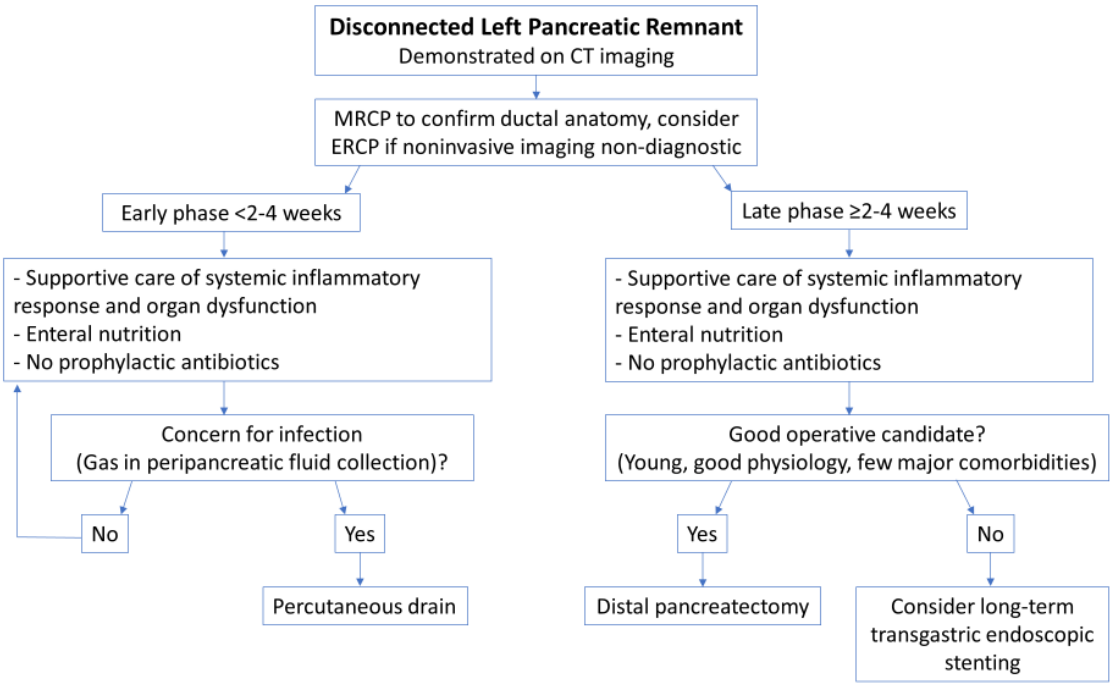
Journal Pre-proof


Walled-off pancreatic necrosis
sterile with severe symptoms or infected?
Central component of sufficient size and accessible transmurally?
Yes
No
EUS-guided placement of LAMS for drainage
Large paracolic gutter extension?
Aggressive percutaneous drainage
*Large amount of solid debris?
Yes
No
Direct endoscopic necrosectomy until resolution
Remove LAMS after resolution or DEN for failure of LAMS


Severe acute pancreatitis with necrosis
Acute phase (< 2–4 weeks)
• Management of systemic inflammatory response
• Supportive care of associated organ dysfunction
• Nutritional optimization (enteral preferred)
• Avoidance of prophylactic antibiotics
• If concern for infection during acute phase (i.e., retroperitoneal air), consider image-guided percutaneous drainage
• Intra-abdominal hypertension common; clinical abdominal compartment syndrome unusual
Late phase (≥ 2–4 weeks)
• Continue supportive care of organ dysfunction
• Continue to optimize nutrition (enteral)
• Drainage and debridement indicated when evidence of infection (air in peripancreatic necrosis)
• Consider intervention on necrosis in patient with persistent nutritional failure, organ dysfunction
Approach to debridement
(dependent on pattern of necrosis and institutional expertise)
• Central retrogastric collection:
◦ Endoscopic transgastric or laparoscopic transgastric approach
• Retrogastric with paracolic gutter extension:
◦ Percutaneous drainage with step-up to videoscopic retroperitoneal debridement or endoscopic debridement with addition of percutaneous drain as needed
• Retrogastric collection with extension to the right of the mesenteric vessels:
◦ Endoscopic or laparoscopic transgastric; may need open debridement

	Interstitial edematous pancreatitis	Necrotizing pancreatitis
< 4 weeks	**Acute (peri)panreatic fluid collection** Homogenous fluid adjacent to pancreas without a recognizable wall 	**Acute necrotic collection** Intra and/or extra pancreatic necrotic collection without a well-defined wall 
≥ 4 weeks	**Pancreatic pseudocyst** An encapsulated, well-defined, usually extrapancreatic fluid collection with minimal solids 	**Walled off necrosis** Intra and/or extra pancreatic necrotic collection with a well-defined wall 

Journal Pre-proof


Disconnected Left Pancreatic Remnant
Demonstrated on CT imaging
MRCP to confirm ductal anatomy, consider ERCP if noninvasive imaging non-diagnostic
Early phase <2-4 weeks
Late phase ≥2-4 weeks
- Supportive care of systemic inflammatory response and organ dysfunction
- Enteral nutrition
- No prophylactic antibiotics
- Supportive care of systemic inflammatory response and organ dysfunction
- Enteral nutrition
- No prophylactic antibiotics
Concern for infection (Gas in peripancreatic fluid collection)?
Good operative candidate? (Young, good physiology, few major comorbidities)
No
Yes
Yes
No
Percutaneous drain
Distal pancreatectomy
Consider long-term transgastric endoscopic stenting

Journal Pre