Management of Pancreatic Fluid Collections

An Evidence-based Approach

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Abstract: Managing pancreatic fluid collections (PFCs) remains a challenge for many clinicians. Recently, significant progress has been made in the therapy of PFCs, including improvements in technology and devices, as well as in the development of minimally invasive endoscopic techniques, many of which are proven less traumatic when compared with surgical options and more efficacious when compared with percutaneous techniques. This review will explore latest developments in the management of PFCs and how they incorporate into the current treatment algorithm.

Key Words: pancreatitis, pancreatic fluid collection, pancreatic necrosis, walled-off pancreatic necrosis, gallstone pancreatitis

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Pancreatic fluid collections (PFCs) are a common complication of acute pancreatitis, with a reported incidence of 43%.[1] PFCs form in the setting of pancreatic injury such as in the setting of acute pancreatitis, pancreatic trauma, postsurgery, posttransplant, and pancreatic duct (PD) obstruction. Classification of PFCs, based on acuity and presence of necrosis, is imperative to guiding their management. Traditionally, the management of PFCs has been surgical drainage. However, recent advances in endoscopic instruments and techniques have shifted the paradigm in favor of approaches involving minimally invasive drainage and endoscopic intervention.

CLASSIFICATION OF PFCs

The first international consensus on classification of PFCs was developed in 1993 and became known as the Atlanta criteria.[2] On the basis of the original Atlanta criteria, PFCs were classified as either acute (formed within 4 wk of pancreatitis onset) or chronic (formed after 4 wk of pancreatitis onset). Chronic PFCs were further subdivided into either pancreatic necrosis, pancreatic pseudocysts (PPs), or pancreatic abscesses (Table 1).

Recent advances in pathophysiology and diagnostic tools warranted a revision to these criteria. The most important distinction to arise from the new classification system, known as the revised Atlanta criteria,[3] is the delineation between collections containing only fluid versus collections containing necrotic tissue with or without accompanying fluid. The criteria for acute versus chronic PFCs is preserved, but new additions have been made based on the presence of necrosis. Acute collections are divided into acute peripancreatic fluid collections and acute necrotic collections. Chronic collections are divided into PPs and walled-off pancreatic necroses (WOPNs). These distinctions have helped guide the development of treatment strategies tailored to the acuity and contents of a given collection.

ENTERAL FEEDING

In addition to fluid resuscitation, nutritional support is a vital early intervention in the management of any PFC. Traditionally, oral intake in symptomatic acute pancreatitis has been avoided based on concern that pancreatic stimulation would worsen inflammation. In the setting of severe or prolonged pancreatitis, extended periods of NPO (nil per os) have been found to be associated with increased mortality due to functional impairment of other vital organs.[4,5] As such, total parenteral nutrition arose as a solution to continue providing patients nutritional support while simultaneously avoiding pancreatic stimulation. Recently, several meta-analyses have demonstrated the efficacy, safety, and superiority of enteral feeding over total parenteral nutrition.[6,7] Early initiation of enteral feeds in acute pancreatitis, within 48 hours of admission, has been shown to be associated with significantly reduced mortality, organ failure, and infectious complications compared with delayed enteral feeds.[8–14] Currently, there is not sufficient data to suggest whether nasojejunal feeding can serve as a bedside alternative to nasojejunal tube placement.[15] Similarly, data are lacking to suggest any mortality or cost benefit when using elemental or semielemental enteral nutrition formulations over the standard formulation.[16,17]

INDICATIONS FOR DRAINAGE OF PFCs

The original Atlanta criteria recommended drainage for PFCs based on the size of the collection, as well as the presence of symptoms including abdominal pain, gastrointestinal (GI) or biliary obstruction, vascular compression, or infection. With recent advances in diagnostic tools and interventional techniques, indications for the drainage of PFCs have been revised to emphasize the presence of symptoms or infected collection:[18,19]

(1) Symptomatic sterile collections with or without the presence of necrosis; symptoms include persistent abdominal pain, ileus, and gastric outlet obstruction with or without fever.

(2) Proven or suspected infected PFCs with or without the presence of necrosis.

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TABLE 1. Pancreatic Fluid Collection Nomenclature Based on Revised Atlanta Criteria[3]

Type of collection	Timing (wk)	Description
Acute peripancreatic fluid collection (APNC)	≤4	Homogenous, nonencapsulated, fluid filled with no liquefaction
Acute necrotic collection (ANC)	≤4	Heterogeneous, nonencapsulated, with necrotic tissue
Pancreatic pseudocyst (PP)	>4	Homogenous, encapsulated, fluid filled with no liquefaction
Walled-off pancreatic necroses (WOPN)	>4	Heterogeneous, encapsulated, with necrotic tissue

Asymptomatic sterile necrotic collections and asymptomatic WOPN are not recommended for drainage, as they may undergo spontaneous resolution given time.[20] In 2011, a step-up approach utilizing radiologic or endoscopic drainage was shown to be preferred over open surgery, which is associated with higher morbidity and mortality.[21] In addition, timing of intervention should ideally be at least 4 weeks after onset of pancreatitis. However, in the presence of sepsis or suspected infected fluid collection, drainage before the 4-week period might be mandated in an attempt to decrease morbidity or mortality. Trikudanathan et al[22] compared early intervention (intervention before 4 weeks of initial onset of pancreatitis) via "step-up approach," with standard intervention (intervention after 4 weeks of initial onset) for necrotizing pancreatitis. During this study, early intervention was more often performed for infection (91% vs. 39%, $P<0.05$) and end organ dysfunction. The study demonstrated a significant increase in mortality (13% vs. 4%, $P=0.02$) and need for rescue open necrosectomy (7% vs. 1%, $P=0.03$) within the early intervention group. This is related to the fact that substantial number of patients undergoing early intervention had infected necrosis associated with new-onset organ failure or shock, refractory to medical therapy. The 13% mortality rate in the early intervention group is relatively low by comparison to a recent meta-analysis showing that infected necrosis with organ failure is associated with 30% mortality rate.[23] Finally, there was no increased risk of procedure-related complications and both early and standard intervention showed significant improvement in organ dysfunction. Therefore, endoscopic intervention when required should be offered earlier than the standard 4 weeks, and may be especially beneficial in the setting of multiorgan failure and sepsis.

ABDOMINAL COMPARTMENT SYNDROME AND ACUTE PANCREATITIS

Abdominal compartment syndrome (ACS) is defined as an elevation in intra-abdominal pressure (IAP) >20 mm Hg, associated with new organ dysfunction or failure.[24] Ileus from acute pancreatitis is often mistaken for ACS. Differentiation between the 2 conditions is crucial for appropriate management. The pathophysiology of ACS is similar to that of compartment syndrome, where an increase in pressure within a fixed compartment impairs adequate blood flow, leading to cellular hypoxia and lactic acidosis.[25] Although the incidence of ACS in pancreatitis is relatively low (1% incidence in a study of 218 patients with acute pancreatitis[26]), it is crucial to be able to identify the condition because of its acuity and potential complications.

Predisposing conditions and risk factors for the development of ACS, according to the World Society for the Abdominal Compartment syndrome, include reduced abdominal wall compliance, increased intraluminal contents, increased extraluminal/intra-abdominal contents, and capillary leak/fluid resuscitation.[24]

In pancreatitis, ACS is extremely rare and seems to be related to the underlying inflammatory process leading to the buildup of pancreatic and visceral edema, peri-PFCs, and capillary leakage causing ascites.[27,28] These fluid collections can be drained through endoscopic intervention or percutaneously if inaccessible. In the event that conservative measures fail, a decompressive laparotomy is typically offered.[29] However, in a recent systematic review and meta-analysis reviewing the surgical management of ACS, the mortality rate was 49.7% in adults and even higher in children after decompressive laparotomy.[30] Interestingly, recent data demonstrated that decompression with percutaneous catheter drainage is as effective as open laparotomy with fewer complications.[31]

Treatment of ACS should be done in a systematic manner and tailored depending on the cause.[32,33] Measurement of IAP is usually done through the measurement of the bladder pressure.[24] The diagnosis of ACS is made with an IAP >20 mm Hg, along with evidence of organ dysfunction.[24] Once ACS is diagnosed or there is evidence of elevated IAP >12 mm Hg, next steps are taken to reduce IAP through nasogastric and/or rectal decompression, along with ensuring adequate sedation/analgesia and paralysis, and avoiding excess fluid resuscitation. Next, efforts must be made to minimize or discontinue enteral nutrition to avoid further increasing intraluminal contents, and fluid removal through diuresis or resuscitation with hypertonic fluids may be considered. If the above methods of medical management fail, further intervention is warranted to drain fluid collections through the endoscopic or percutaneous route. If these less invasive routes fail to relieve IAP, decompression may be considered. A percutaneous approach should be preferred keeping in mind the high mortality associated with surgery in this setting.[29,30]

MANAGEMENT OF PPs

On the basis of the revised Atlanta criteria, PPs are defined as a matured, encapsulated fluid collection without the presence of solid necrosis that forms at least 4 weeks after initial pancreatitis.

Surgical Drainage

Surgical drainage, either open or laparoscopic, of PPs is performed by creating an anastomosis between the PFC and the GI tract. The location of the PFC dictates whether drainage into the stomach via cystogastrostomy or drainage into the small bowel via cystenterostomy is more appropriate.[34]

Surgical drainage of PPs was pioneered in 1921 and was the gold standard for management of PPs. These procedures have been reported to have a mortality rate of 2% and a recurrence rate of 2.5% to 5% after drainage.[35] However, further studies have found complication rates to range from 24% to 40%.[36] More recently, studies directly comparing surgical versus endoscopic approaches to pseudocyst drainage have demonstrated a preference for the latter, newer approach.[37] A meta-analysis Zhao et al[38] in 2016 compiled the results from comparative trials and showed that although surgical and endoscopic treatment had comparable rates of treatment success, adverse events, and recurrence, endoscopic treatment was associated with shorter length of hospital stay and lower cost to the patient. In a randomized trial comparing endoscopic versus surgical drainage of PFCs, endoscopic drainage was associated with a lower cost than surgical drainage.[37] This lower cost is in part because of shorter hospital stay for patients who undergo endoscopic drainage.[39] In the abovementioned randomized trial, the mean cost for patients undergoing endoscopic drainage was less than half that of patients undergoing surgery ($7011 vs. $15,052, $P=0.003$).[37]

Percutaneous Drainage

Percutaneous drainage for treatment of PPs developed with advances in real-time radiography, in particular computed tomography or ultrasound with fluoroscopy. Percutaneous drainage is performed with the insertion of an external catheter into the pseudocyst via a Seldinger technique.

Initial studies comparing the surgical to percutaneous drainage found both techniques to be efficacious, and percutaneous drainage was, in some studies, shown to be associated with reduced mortality compared with surgical drainage.[40] A 2020 meta-analysis by Szako et al[41] compared rates of clinical success, recurrence, complications, mortality, and length of hospital stay between pseudocysts drained percutaneously versus endoscopically. PD resulted in higher rate of recurrence [odds ratio: 4.91; 95% confidence interval (CI), 1.82 to 13.22; $P=0.002$] and lower rate of clinical success (odds ratio: 0.13; 95% CI, 0.07 to 0.22, $P<0.001$). In another study with 129 patients undergoing either percutaneous or endoscopic drainage of PFCs, endoscopic drainage was associated with lower rates of reintervention, adverse events, and a shorter hospital stay.[42]

EGD-Guided Transmural Drainage

Advancements in endoscopic instruments and techniques allowed for the development of internal transmural approaches to access and drain PFCs. Traditionally, endoscopy was utilized to visualize a bulge in the gastric wall formed from external compression by the fluid collection. A tract between the gastric lumen and the PFC is then created and cannulated via Seldinger technique, with the insertion of a pigtail stent to maintain access.[43]

The efficacy and safety of esophagogastroduodenoscopy (EGD)-guided transmural drainage have been validated by several studies.[44–47]

The technique, however, is limited by its need for direct visualization of an endoluminal bulge. It is estimated that somewhere between 42% and 48% of PPs do not present with gastric wall bulges and are therefore not suitable for transluminal drainage.[48,49] The development of endoscopic ultrasound (EUS) therapy has allowed this limitation to be surmounted.

EUS-Guided Transmural Drainage

EUS-guided drainage benefits from the ability to visualize both bulging and nonbulging pseudocysts. Additional benefits of EUS-guided drainage include identification of vascular structures interposed between the gastric wall and the PFC, as well as confirmation of the lack of solid necrotic tissue contained within the collection.

As its first reported cases in 1992, EUS-guided drainage has been validated as efficacious and safe in several studies. A 2018 systemic review by Teoh et al[50] evaluated 6 studies that compared EUS-guided to EGD-guided and surgical drainage. When compared with EGD-guided drainage, EUS-guided drainage was associated with higher clinical success rate in 2 prospective randomized studies. Compared with surgical drainage, EUS-guided drainage was associated with reduced hospital stay, cost to patient, and improved quality of life in 1 randomized clinical trial and 1 prospective randomized trial.

The most recent guidelines on management of acute necrotizing pancreatitis from the European Society of Gastrointestinal Endoscopy recommend EUS-guided access over conventional EGD-guided access, further cementing EUS-guided endoscopy as the current gold standard for access and drainage of PFCs.

Fully Covered Self-Expanding Metal Stents

Fully covered self-expanding metal stents (FCSEMSs) are a recent addition to existing endoscopic stent options. Compared with traditional plastic stents, covered metal stents offer a larger lumen for drainage. This feature both reduces the risk for stent occlusion and subsequent need for revision, as well as reduces the procedure time by replacing the need to place multiple plastic stents (MPSs). Furthermore, insertion of a double-pigtail biliary stent through the FCSEMS allows for its anchoring to reduce the risk of migration.

A prospective study by Penn et al[51] in 2012 evaluated a cohort of 20 patients with symptomatic PPs to assess the feasibility and safety of FCSEMS in EUS-guided drainage of PFCs. They reported a technical success rate of 100% (20/20) and a resolution rate of 70% (14/20) in which there were no known recurrences, adverse events, or need for surgery. There were 3 patients in whom EUS-guided drainage with FCSEMS placement did not result in pseudocyst resolution; all the 3 required eventual surgery for drainage. Another 3 patients experienced pseudocyst recurrence after stent removal.

More recent case series continue to demonstrate high rates of technical and clinical success using FCSEMS in pseudocyst drainage[52–55] (Table 2). Complication rates in these studies have ranged from 4% to 16%. In addition to perforation and infection, stent migration and occlusion account for the majority of remaining causes of procedure complication. Yao et al[52] in 2019 compared a new biflanged antimigratory metal stent against the traditional tubular metal stent for use in pseudocyst drainage and found significantly lower rates of stent migration with the biflanged design with no differences in technical or clinical success rates.

Dhir et al[53] in 2015 evaluated the presence of PD disruption in patients who receiving EUS-guided pseudocyst drainage with FCSEMS. Technical and functional success was reported in 43 patients (92%). At 3 weeks follow-up, pancreatic ductal leak was found in 3 patients and disconnected duct was found in 2 patients on magnetic resonance imaging–magnetic resonance cholangiopancreatography (MRCP). Endsocopic Retrograde Cholangiopancreatography (ERCP) with stenting successfully treated all 3 patients with ductal leak. Only 2 recurrences (4.7%) among 42 patients was found on median follow-up of 306 days, both recurrences were in patients with disconnected ducts. Importantly, multivariate analysis demonstrated that pancreatic ductal leak or disconnection were independent factors that affected pseudocyst resolution at 3 weeks.

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TABLE 2. Pseudocyst: Plastic and Metal Stent Drainage

Study	Cases	Procedure Performed	Stent Device Used	Clinical Success Rate (%)	Technical Success Rate (%)	Complications
Plastic stent drainage						
Hookey et al[56]	116	EGD-guided transmural drainage	Stents	88	88	11% complication rate
Antillon et al[48]	33	EUS-guided transmural drainage	Double-pigtail stent	94	82	2 major, 3 minor complications
Azar et al[57]	23	EUS-guided transmural drainage	Double-pigtail stent	91	91	—
Lopes et al[58]	51	EUS-guided transmural drainage	Straight/double-pigtail stent	94	94	17.7% stent migration, obstruction
Barthet et al[59]	50	EUS-guided transmural drainage	Double-pigtail stent/straight polyethylene	90	98	18% morbidity, 5 superinfections
Varadarajulu et al[37]	20	Endoscopic cystogastrostomy	Plastic stent	95	90	—
Lee et al[60]	50	EUS-guided drainage	25 plastic stent/25 FCSEMS	91 for plastic, 87 for FCSEMS (ns)	100 for both	10 complication rate
Sharaiha et al[61]	230	EUS-guided drainage	118 double-pigtail stent (DP)/112 FCSEMS	89 for DP, 98 for FCSEMS	92 for DP, 98 for FCSEMS (ns)	31 complication rate in DP, 16 complication rate in FCSEMS
Ang et al[62]	36	EUS-guided drainage	24 double-pigtail stent (DP)/12 FCSEMS	65 for DP, 92 for FCSEMS	100 for Both	18 stent migration in DP, 6 stent migration in FCSEMS
Metal stent drainage						
Talreja et al[63]	50	EUS-guided drainage	Covered self-expanding metal stent	95	78	5 superinfections, 2 bleed, 1 stent migration
Berzosa et al[64]	7	Single-step EUS-guided drainage	Single self-expanding metal stent	100	83	—
Fabbri et al[65]	22	EUS-guided drainage	Covered self-expanding metal stent	77	77	—
Penn et al[51]	20	EUS-guided drainage	Fully covered self-expanding metal stent	70	70	2 pseudocyst infection, 1 post-ERCP pancreatitis and fever
Itoi[66]	15	EUS-guided drainage	Lumen apposing metal stent	100	100	—
Weilert et al[55]	18	EUS-guided drainage	Fully covered self-expanding metal stent	78	78	—
Shah et al[67]	33	EUS-guided drainage	Lumen apposing metal stent	91	93	1 stent migration, 1 access-site infection and stent dislodgement
Walter et al[68]	61	EUS-guided drainage	Lumen apposing metal Stent	93	98	3 stent migration, 3 stent dislodgement during necrosectomy
Mukai et al[69]	2	EUS-guided drainage/direct endoscopic necrosectomy	Novel flared biflanged metal stent	100	100	—
Rinninella et al[70]	18	EUS-guided drainage	Lumen-apposing metal stent	100	—	—
Dhir et al[53]	47	EUS-guided drainage	Fully covered self-expanding metal stent	94	91	2 cyst infection
Raijman et al[54]	47	EUS-guided drainage	Fully covered self-expanding metal stent with antimigratory fins	77	100	3 fever, 2 stent migration, 1 abdominal pain
Yao et al[52]	125	EUS-guided transmural drainage	76 self-expanding biflanged metal stent (BFMS)/49 tubular metal stent (TMS)	88 for TMS, 92 for BFMS (ns)	98 for TMS, 97 for BFMS (ns)	15 stent migration in TMS, 0 stent migration in BFMS

EUS indicates endoscopic ultrasound; FCSEMSs, fully covered self-expanding metal stents.

To date, no comparative studies have been conducted to investigate the ideal timing for stent removal. In their prospective study, Penn et al[51] used a study protocol in which FCSEMS placement was followed by abdominal CT in 4 to 10 weeks to assess for pseudocyst resolution. If resolution was achieved, the stent was removed, and if resolution was not achieved, abdominal CT was repeated in 2 to 4 weeks intervals until resolution was observed and the stent was removed. At this moment, interval CT imaging to assess for pseudocyst resolution seems to be the most reliable indicator for FCSEMS removal.

More recently, an improved stent design known as lumen apposing metal stents (LAMS) has been gaining popularity over FCSEMS for use in PFC drainage. The LAMS design incorporates large, biflanged metal ends to protect against stent migration, as well as apposed the lumens of the GI tract and PFC to facilitate more effective drainage.

Plastic Stents Versus Metal Stents

Several recent comparative studies have compared the efficacy and safety of plastic versus metal stent usage in PP drainage (Table 2).[60,61,71] The results from these studies are in favor of metal over plastic stents with regard to shortened procedure time, decreased rates of stent migration, decreased rates of repeat drainage, and increased rates of clinical success.

These trends were confirmed in a 2019 meta-analysis by Saunders et al.[72] Their group evaluated 681 patients across 7 studies comparing plastic to metal stents in PFC drainage. In the metal stent group, pooled risk ratios demonstrated significantly higher rates of clinical success and lower rates of adverse events compared with plastic stents. Pooled risk also showed lower reintervention rates in the metal group, but did not reach significance.

Yoon et al[73] included procedure time and overall cost as outcomes in their meta-analysis of 7 trials, including 905 patients. Again, pooled analysis demonstrated metal stents having significantly higher rates of clinical success and lower rates of adverse events compared with plastic. Three of their included trials reporting on procedure time consistently demonstrated significantly shorter durations when metal stents were used. There were no significant differences in overall cost when using metal versus plastic stents.

There is still a need for further randomized, controlled studies directly comparing plastic to metal stents, but current evidence supports a preference for metal over plastic given its higher clinical success rate and lower rate of adverse events.

LAMSs

A new FCSEMS stent design incorporating 2 flanged ends received Food and Drug Administration approval in 2013 and became known as LAMSs.[67] The flanges were designed to improve on the antimigratory features of existing FCSEMS.

Several case series and comparative studies have demonstrated evidence validating the utility of LAMS in PP drainage (Table 2).[52,54,66,68–70]

The safety and efficacy of LAMS usage in draining PPs was further supported in Hammad et al's[74] 2018 meta-analysis of 11 trials including 688 patients. LAMS demonstrated pooled technical success rates and clinical success rate of 98% and 95%, respectively. The pooled adverse event rate was 5%. Data from trials comparing LAMS against MPSs was also synthesized. LAMS was favored over MPSs for higher clinical success and lower adverse event rates.

In addition, LAMS has demonstrated significantly lower rates of stent migration with no difference in procedure time, technical success clinical success, or bleeding and infection when compared with traditional tubular metal stents.[52]

Several case reports have noted embedding of LAMS within the gastric lumen after the placement for PP drainage.[75,76] The buried stents were discovered 4 to 6 weeks after their placement, when endoscopic retrieval was being performed. In 1 patient, endoscopic retrieval resulted in massive hemorrhage requiring interventional radiology embolization. Another patient required surgical intervention for stent removal. Further studies are required to determine predictors of stent embedment and optimal timing of follow-up and retrieval to minimize risk of embedment.

MANAGEMENT OF WOPN

WOPN is a mature collection of solid necrotic debris, encapsulated by a clearly defined capsule. Fluid may or may not be present within the collection.

Surgical Drainage

As with PPs, surgical debridement has traditionally been the standard approach to the management of WOPN. The presence of solid necrotic tissue in WOPN necessitates not only stent placement for drainage but often debridement of the contained necrosis to facilitate drainage. Access to the collection is first achieved via open laparotomy or retroperitoneal incision, and then necrosectomy is performed via blunt dissection. After necrosectomy, there are 4 approaches to completing the debridement: (1) packed open abdomen with repeated debridement, (2) planed and staged repeat laparotomies with lavage, (3) packed and closed abdomen with external drain placement and repeat open necrosectomy, and (4) closed abdomen with continuous lavage.[20]

Videoscopic-assisted retroperitoneal debridement (VARD) has emerged as a minimally invasive alternative to laparoscopic debridement. VARD is performed with a 5-cm subcostal incision in the left flank followed by fascial dissection to access the retroperitoneum and WOPN. Debridement is then performed via irrigation, grasping forceps, and suction device. A laparoscopic port and videoscope are introduced once debridement under direct vision is no longer feasible. Once debridement is complete, 2 percutaneous drains are placed before closure of the fascia and skin.[77]

Open necrosectomy has been reported to be associated with both high rates of mortality (6% to 25%) and morbidity (34% to 95%).[78–81] Complications of open necrosectomy are varied and include organ failure, perforation, local infection, hemorrhage, creation of pancreatico-cutaneous or entero-cutaneous fistulae, and abdominal wall hernias.[78,82–84]

van Brunschot and colleagues demonstrated that VARD alone had success rates ranging from 50% to 83% for treatment of WOPN. Furthermore, VARD was associated with high rates of overall mortality (13%) and complications (35%). In their review, the 2 most common complications associated with VARD were pancreatic fistulae and bleeding, occurring in 17% and 13% of patients, respectively.[85]

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The results from the 2012 PENGUIN[86] trial demonstrated patients undergoing necrosectomy via VARD had increased risk for a composite of postprocedural organ failure, bleeding, and fistula compared with patients undergoing endoscopic necrosectomy (risk difference: 60%, 95% CI, 0.16 to 0.80).

Advances in minimally invasive surgery have prompted the development of laparoscopic approaches to necrosectomy. To unify descriptions of these varied approaches, a system was developed based on 3 characteristics: (1) method of visualization (open, radiologic, endoscopic, hybrid, or other), (2) route (transpapillary/transmural, percutaneous retroperitoneal, percutaneous transperitoneal, percutaneous transmural, or other), and (3) purpose (drainage lavage, fragmentation, debridement, excision, or other).[20] Laparoscopic approaches were found to be associated with lower rates of systemic complications and lower rates of new organ failure compared with open necrosectomy.

Percutaneous Drainage

Percutaneous techniques for WOPN drainage involve radiographic-guided placement of drains ranging from single, small-caliber to multiple, large-bore catheters. Repeated irrigation and necrosectomy is then performed via these catheters, which can range in diameter from 12 Fr to 30 Fr. Two approaches have been described for catheter placement: transperitoneal or retroperitoneal. The retroperitoneal approach is preferred, as it decreases risk for enteric leaks and subsequent contamination.[87]

Percutaneous drainage as primary management for necrotic debridement has been shown to have clinical success rates of only 33% and 35% in 2 prospective studies, and complications including external pancreatico-cutaneous fistulae were found to occur in up to 27% of patients.[88,89]

In 2010, van Santvoort et al[89] published their results from the PANTER multicenter trial. Eighty-eight patients with necrotizing pancreatitis were randomly assigned to either open necrosectomy or a step-up approach consisting of percutaneous drainage, following by minimally invasive retroperitoneal necrosectomy if necessary. Patients in the step-up group were found to have a decreased rate of major complications (including new-onset multiple-organ failure, organ perforation, or bleeding) compared with the open surgery group (40% vs. 69%, OR: 0.57; 95% CI, 0.38 to 0.87). However, mortality did not differ significantly between the 2 groups.

The Dutch Pancreatitis Study Group, who published the PANTER trial, are currently leading the POINTER trial to investigate whether immediate catheter drainage is superior to the current standard of postponed intervention in patients with infected necrotizing pancreatitis.[90] The results from this trial will contribute to determining when and how to incorporate percutaneous drainage into step-up approaches to necrotizing pancreatitis drainage.

Endoscopic Necrosectomy

An endoscopic approach to WOPN drainage was first described by Baron et al[91] in 1996 when an enterocystic fistula was created and stented with plastic to facilitate irrigation through a nasocystic drain.

Carter and colleagues described the first use of percutaneous endoscopic necrosectomy as an alternative to enterocystic endoscopic necrosectomy. Additional case series have demonstrated clinical success ranging from 54% to 100% and technical success ranging from 86% to 100%[84,92–101] (Table 3). This procedure has been associated with complication rates as high as 88% and has largely been supplanted by a new endoscopic technique for necrosectomy.

The current endoscopic approach to WOPN drainage is known as direct endoscopic necrosectomy (DEN). This technique involves EUS-guided localization and puncture of the collection (Fig. 1), creation of a fistulous tract for access, and then tract dilation and stent placement to allow for direct endoscopic access (Fig. 2) into the necrotic collection (Figs. 3, 4). Debridement is then carried out via a variety of endoscopic mechanical techniques (Figs. 5, 6) and irrigation.[71] Multiple sessions are often required with weekly cross-sectional imaging (Figs. 7, 8).

Data from several case series have demonstrated that EUS-guided drainage and DEN have high technical and clinical success rates in treatment of WOPN, ranging between 80% and 100% and 64% to 100%, respectively[102–118] (Table 4). Complication rates have ranged from 4 to 38, typically involving either bleeding, perforation, or suprainfection. Stent occlusion and migration are also noted as late-occurring complications.

The multicenter, randomized Transluminal endoscopic step-up approach in patients with infected necrotising pancreatitis (TENSION) trial including 98 patients was recently completed in 2018 by van Brunschot et al[125] comparing endoscopic step-up to surgical step-up approaches for the treatment of WOPN. Endoscopic step-up involved EUS-guided transluminal drainage followed by DEN if necessary. Surgical step-up involved percutaneous drainage followed by VARD if necessary. The rates of major complications and mortality did not differ significantly between the 2 groups. The trial concluded that endoscopic step-up was not superior to surgical step-up in reducing major complications but was associated with significantly lower rates of pancreatic fistula formation and shorter length of hospital stay.

The timing of necrosectomy in WOPN drainage continues to be debated. A 2019 trial by Yan et al[126] demonstrated no significant differences in technical success, clinical success, and adverse event rates between early intervention (at time of stent placement) versus delayed intervention (1 wk after stent placement). The mean number of total necrosectomy sessions was significantly lower in the early intervention group (3.1 vs. 3.9, $P < 0.001$). Ultimately, DEN at the time of stent placement was found to be an independent predictor for fewer DEN sessions until WOPN resolution [odds ratio (OR): 2.3; $P = 0.004$].

The use of hydrogen peroxide as a chemical debriding agent in DEN has been increasingly reported. Messalam et al[127] performed a retrospective review of 204 patients comparing the efficacy and safety of DEN with and without hydrogen peroxide. The use of hydrogen peroxide in addition to standard necrosectomy was found to be associated with higher rates of clinical success (93.8% vs. 78.9%, $P = 0.002$; OR: 3.30; $P = 0.033$), as well as earlier resolution (OR: 2.27; $P < 0.001$). The rates of postprocedure bleeding, perforation, infection, and overall complication rate were not significantly different with and without hydrogen peroxide. Further studies are required to standardize optimal concentrations, volume, and specific technique for use of hydrogen peroxide in DEN.

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TABLE 3. Percutaneous and Transcutaneous Necrosectomy

Study	Cases	Procedure Performed	Tract Diameter	Clinical Success Rate ()	Technical Success Rate ()	Complications
Carter et al[92]	14	10 percutaneous necrosectomy (PN), 4 percutaneous sinus tract endoscopic necrosectomy (STE)	30 Fr for PN, 45 Fr for STE	80 for PN, 100 for STE	100	1 enteric fistula, 1 gastric ileus requiring gastrojejunostomy, 2 pancreatic pseudocyst formation
Connor et al[93]	24	Minimally invasive retroperitoneal necrosectomy		54	88	88 complication rate
Mui et al[94]	13	Percutaneous drainage (PD) or open necrosectomy (ON), followed by sinus tract endoscopy	18 Fr for PD group, 30 Fr for ON group	67 in PD group, 100 in ON group	100	1 transverse colon perforation, 1 spontaneous colon fistula, 1 SIRS, 1 tract catheter dislodgement
Cheung et al[95]	4	Percutaneous sinus tract endoscopic necrosectomy	32 Fr	75	100	1 subphrenic fluid collection
Connor[96]	47	Minimally invasive pancreatic necrosectomy	—	—	—	—
Lakshmanan et al[97]	5	Minimally invasive retroperitoneal necrosectomy	28-30 Fr	100	100	2 pancreatic fistula, 1 left renal contusion,
Raraty et al[84]	137	Minimal access retroperitoneal pancreatic necrosectomy	30 Fr	81	86	34 organ failure, 19 mortality
Ahmad et al[98]	32	Minimally invasive retroperitoneal necrosectomy		88	100	3 bleeding, 7 fistula formation, 3 myocardial infarction, 2 thromboembolism
Dhingra et al[99]	15	Percutaneous endoscopic necrosectomy	28 Fr	93	100	1 minor bleeding, 1 pancreatic fistula which spontaneously closed
Trikudanathan et al[22]	19	Percutaneous sinus tract endoscopic necrosectomy	24 or 28 Fr	100	100	1 bleed during percutaneous tract dilation
Goenka et al[100]	10	Percutaneous sinus tract endoscopic necrosectomy	32 Fr	90	100	2 pneumoperitoneum
Jain et al[101]	53	Percutaneous drainage with step-up to percutaneous endoscopic necrosectomy	36 Fr	64	100	2 aspiration pneumonia, 2 peritonitis, 1 ileus, 1 bleeding, 1 subcutaneous emphysema

For WOPN extending to the paracolic gutter, transcutaneous endoscopic necrosectomy can be offered. In these cases, a previously placed percutaneous drain allows for wire access to the collection. Further tract dilation and metal stent placement allow endoscopic access and subsequent necrosectomy. Several studies have reported on the use of transcutaneous endoscopy to access retroperitoneal and paracolic WON and have shown high rates of technical and clinical success[128–131] (Table 5). These techniques are a promising new solution for draining fluid collections not localized to the paragastric or paraduodenal areas.

Multiple Transluminal Gateway Technique

The multiple transluminal gateway technique (MTGT) has emerged in the last decade as a new EUS-based approach to improve drainage of necrotic collections.[132] MTGT expands upon conventional drainage by creating 2 to 3 transmural tracts between the necrotic cavity and GI tract, rather than the conventional single tract.

In a review of 3 retrospective case series comparing MTGT to conventional drainage across 204 patients, MTGT demonstrated improved rates of treatment success (92% to 100% vs. 52% to 70%), with no significant difference in rates of complications.[133]

Of note, MTGT has a longer procedure duration compared with the conventional technique (37 vs. 22 min, $P=0.017$).[132] The use of a Hot AXIOS System (Xlumena Inc., Sunnyvale, CA) in MTGT, however, has improved procedure time by offering single-step tract creation.[134,135] MTGT represents a promising technique that is both more effective than single transmural drainage, as well as less invasive than DEN.

FCSEMS

Before the development of biliary and esophageal metal stents, DEN was performed through a cystenterostomy tract created via needle puncture and balloon dilation to 6 to 8 mm with the placement of double-pigtail plastic stents. The additional deployment of FCSEMS into these tracts has allowed for larger stent lumens for the passage of the endoscope. Initially, biliary FCSEMS were used and were later improved on by esophageal FCSEMS, which have an even larger lumen diameter.[64,65]

Antillon et al[136] in 2009 described the first case of esophageal FCSEMS used in WOPN drainage. Further studies continued to support the efficacy and safety of FCSEMS in DEN[113–117] (Table 4). A comparative study by Siddiqui et al[137] evaluated the usage of plastic stents versus FCSEMS in WOPN drainage, finding significantly higher resolution rates and lower adverse event rates in the latter group with no difference in technical success rates.

LAMSs

Large diameter LAMSs have recently gained favor in the management of WOPN, in addition to their use in pancreatic pseudocyst drainage. The short stent length and biflanged design allows for the close approximation of the

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FIGURE 1. Endoscopic ultrasound–guided location of a pancreatic fluid collection. MI indicates mechanical index; TIS, thermal index for soft tissue.

enteric and WOPN lumens, as well as offers increased security against stent migration.

Numerous case series have demonstrated high rates of clinical and technical success, ranging from 64% to 100% and 81% to 100%, respectively[67–70,116–124] (Table 4). Complication rates have been reported to range from 7% to 16%, largely involving bleeding and infection.

Comparative studies evaluating the usage of LAMS versus plastic stents and LAMS versus FCSEMS in management of WOPN have continued to provide evidence in favor of LAMS. Compared with plastic stents, LAMS has shown higher rates of clinical success and lower rates of eventual surgical drainage.[138] And compared with FCSEMS, LAMS has shown equivocal clinical success with lower mean number of necrosectomy procedures to achieve resolution, as well as lower rates of stent occlusion and migration.[137] Lower rates of stent occlusion and migration in the LAMS group reduced the need for repeat intervention to address complications, ultimately decreasing morbidity and cost to the patient.

Of note, delayed bleeding has been noted in cases where LAMS remained in place beyond 3 weeks.[139–141] Indeed, LAMS removal after 4 weeks was found to be an independent predictor of hemorrhage in a study by Bang et al.[142] Therefore, current recommendations are for early LAMS removal, ideally within 3 or 4 weeks of placement, when clinically possible.[143]

FIGURE 2. Endoscopic ultrasound–guided placement of the inner flange of a lumen apposing metal stent.

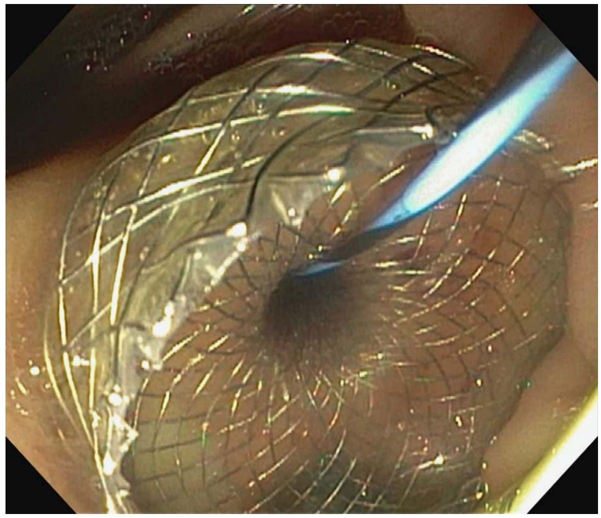

FIGURE 3. Endoscopic deployment of the second flange of the lumen apposing stent in the stomach lumen.

PD DISRUPTION

PD disruption is an important component of PFC management. PD injuries and leaks are not only associated with increased risk of recurrent pancreatitis and increased severity of pancreatitis[144–147] but also with decreased rates of PFC resolution even after drainage is attempted.[145] A PD leak with PP can sometimes be treated with drainage alone; however, oftentimes, PD disruption in cases of necrotizing pancreatitis with walled-off necrosis need to be treated with ERCP.[132]

In recent years, PD stenting has emerged as a means of PD disruption management. Case reports and case series have established the transpapillary approach with

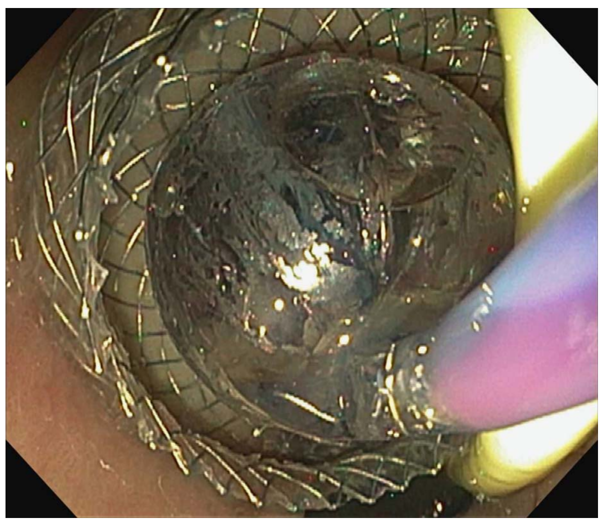

FIGURE 4. Endoscopic dilation of the lumen apposing metal stent to facilitate access into the cavity.

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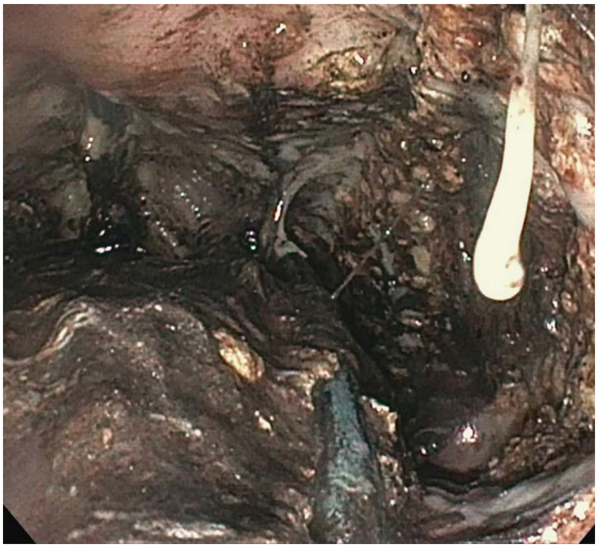

FIGURE 5. Endoscopic access into the necrotic cavity.

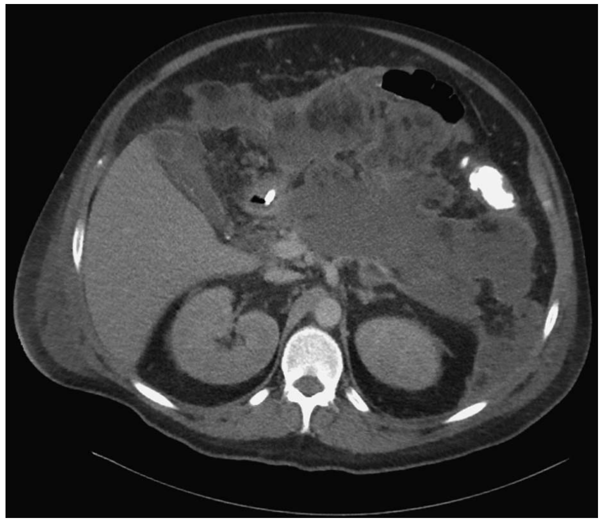

FIGURE 7. Computed tomography abdomen of the collection before drainage.

drain insertion has been successful in the treatment of pancreatic ascites,[148–150] localized fluid collections,[151,152] and both internal and external fistulae within the duct.[153] The impact of stenting in PD disruptions was investigated in several studies, which have demonstrated the success of PD stenting in the setting of partial disruptions.[147,154] Furthermore, Trevino et al[147] determined those who underwent PD stenting were significantly more likely to have improvement in symptoms and resolution of PFC than those who did not undergo PD stenting. PD stenting and leak sealing is crucial for improving resolution and recurrence of PFC.

DISCONNECTED DUCT SYNDROME

Disconnected duct syndrome (DDS) represents an important, but often overlooked, complication of acute necrotizing pancreatitis. It results from segmental necrosis of the main PD and causes disconnection between the pancreas and duodenum. Pancreatic fluid from viable tissue continues to drain, but into peripancreatic and extrapancreatic tissues rather than the GI tract. This has the potential to lead to further PFCs, pancreatic fistulae, and recurrent pancreatitis.[155]

Timely detection of DDS is imperative for dictating endoscopic management. Although ERCP remains the gold standard for diagnosis, recent studies evaluating EUS, magnetic resonance cholangiopancreatography (MRCP), and secretin-enhanced MRCP have demonstrated sensitivities ranging from 92% to 100%.[156] Given the noninvasive nature of these imaging modalities, further studies should be conducted to confirm using imaging as a first diagnostic in detecting DDS.

FIGURE 6. Endoscopic necrosectomy with basket.

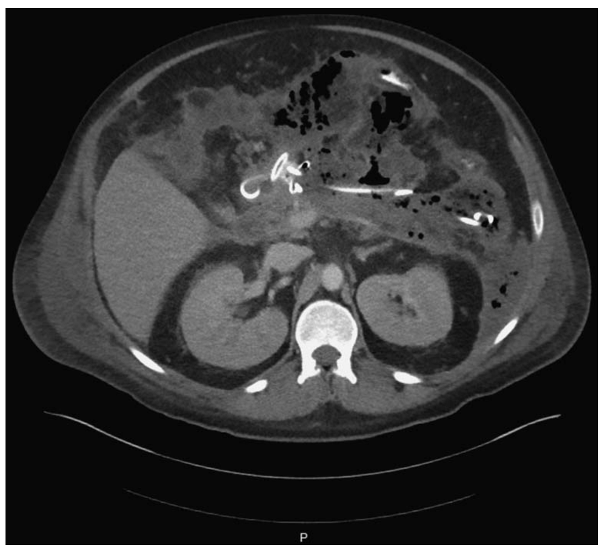

FIGURE 8. Computed tomography abdomen of the collection after drainage.

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TABLE 4. WOPN: Non-LAMS and LAMS Drainage

	Cases	Procedure Performed	Stent Device Used	Clinical Success Rate (%)	Technical Success Rate (%)	Complications
Non-LAMS drainage						
Seewald et al[102]	13	Direct endoscopic necrosectomy	Double-pigtail stent	91	91	4 minor bleeding
Charnley et al[103]	13	Direct endoscopic necrosectomy	Double-pigtail stents	92.30	92.30	—
Voermans et al[104]	25	Direct endoscopic necrosectomy	Double-pigtail stents	93	93	2 eventual surgery, 1 hemorrhage, 1 cyst wall perforation
Papachristou et al[105]	53	Direct endoscopic necrosectomy	Double-pigtail stents	81	81	23 eventual surgery
Escourrou et al[106]	13	Direct endoscopic necrosectomy	Double-pigtail stents	100	100	3 bleed, 3 transient aggravation of sepsis
Seifert et al[107]	93	Transmural endoscopic necrosectomy	Multiple stents	80	80	13 bleed, 5 perforation, 2 fistula perforation, 2 air embolism
Gardner et al[108]	45	25 direct endoscopic necrosectomy, 20 conventional endoscopic drainage	Multiple stents	45	88 for DEN, 45 for conventional drainage	—
Gluck et al[109]	23	Percutaneous drain placement, followed by EUS-guided drainage	Double-pigtail stents	100	—	1 abscess, 2 percutaneous drain dislodgment, 1 duodenal edema
Varadarajulu et al[110]	57	EUS-guided drainage	Double-pigtail stents	63	100	1 perforation, 5 WOPN infection, 2 stent migration
Bang et al[111]	76	58 conventional EUS-guided drainage, 18 multiple transluminal gateway technique	Double-pigtail stents	62 in conventional drainage, 94 in MTGT	—	1 perforation, 1 bleeding, 6 infection
Gardner et al[112]	104	Direct endoscopic necrosectomy	Multiple stents	91	91	14 complication rate, 5 retrogastric perforation
Attam et al[113]	10	Endoscopic transluminal necrosectomy	Large-bore, fully covered metal esophageal stent	90	100	—
Smoczynski et al[114]	112	Conventional endoscopic drainage	Multiple stents	84	93	19 stoma bleed, 4 GI perforation, 2 cyst perforation, 1 sepsis, 3 stent migration
Sarkaria et al[115]	17	EUS-guided drainage	Fully covered esophageal self-expanding metal stents	83	83	—
Mukai et al[69]	27	EUS-Guided Drainage	Plastic Stents	93	100	1 stent migration, 3 bleed
Siddiqui et al[116]	227	EUS-guided drainage and direct endoscopic necrosectomy	106 plastic stents, 121 fully covered self-expanding metal stents	81 for plastic, 95 for FCSEMS	99 for plastic, 100 for FCSEMS	Plastic: 38 complication rate, FCSEMS: 29 complication
Bansal et al[117]	64	EUS-guided drainage and direct endoscopic necrosectomy	Fully covered self-expanding metal stents	91	100	3 life-threatening bleed, 2 minor bleed, 3 stent migration
Bang et al[118]	29	EUS-guided drainage and direct endoscopic necrosectomy	Double-pigtail stents	97	100	2 stent migration, 1 bleed
LAMS drainage						
Mukai et al[69]	19	EUS-guided drainage and direct endoscopic necrosectomy	Novel flared biflanged metal stent	100	100	—
Rinninella et al[70]	52	EUS-guided drainage	Axios LAMS	90	100	3 requiring surgery for infection, 1 perforation
Walter et al[68]	46	EUS-guided drainage	Axios LAMS	81	81	9 complication rate
Albers et al[119]	13		Nagi flared biflanged metal stent	92	100	1 migration, 1 bleed, 2 perforation

TABLE 4. (*continued*)

	Cases	Procedure Performed	Stent Device Used	Clinical Success Rate (%)	Technical Success Rate (%)	Complications
		EUS-guided drainage and DEN, additional percutaneous drainage in 5 patients				
Shah et al[67]	11	EUS-guided drainage	Axios LAMS	64	82	15 complication rate
Siddiqui et al[116]	86	EUS-guided drainage	Axios LAMS	90	98	16 complication rate
Vazquez-Sequeiros et al[120]	33	EUS-guided drainage	Axios LAMS	91	97	—
Gornals et al[121]	12	EUS-guided drainage	Axios LAMS	100	100	2 bleed, 2 infection
Bang et al[122]	13	EUS-guided drainage	Hot axios LAMS	92	100	15 complication rate
Teoh et al[123]	39	EUS-guided drainage	Niti-S LAMS	97	100	7 complication rate
Bang et al[124]	31	EUS-guided drainage	Hot axios LAMS	94	100	1 stent migration, 1 bleed

DEN indicates direct endoscopic necrosectomy; EUS, endoscopic ultrasound; FCSEMSs, Fully covered self-expanding metal stents; LAMS, lumen apposing metal stents; MTGT, multiple transluminal gateway technique; WOPNs, walled-off pancreatic necroses.

TABLE 5. Transcutaneous Endoscopic Necrosectomy for Drainage of Paracolic WON

	Cases	Procedure Performed	PFC Location	Transcutaneous Stent Diameter	Clinical Success Rate (%)	Technical Success Rate (%)	Complications
Kedia et al[128]	1	Transcutaneous endoscopic necrosectomy	Right paracolic gutter	18 mm	100	100	—
Jürgensen et al[129]	14	Flexible percutaneous endoscopic retroperitoneal necrosectomy	1 distal pancreas, 5 left paracolic, 2 right paracolic, 6 other*	20 mm	93	100	1 abdominal compartment syndrome, 1 minor bleeding
Ke et al[130]	1	Stent-assisted percutaneous endoscopic necrosectomy	Left paracolic gutter	18 mm	100	100	—
Saumoy et al[131]	9	Transcutaneous endoscopic necrosectomy	3 left retroperitoneal, 6 right retroperitoneal	18 mm	89	100	—

*Other including 2 infrahepatic, 1 left subpancreatic and right paracolic, 1 left infrarenal, 2 left subphrenic.
PFC indicates pancreatic fluid collection; WON, Walled-off necrosis.

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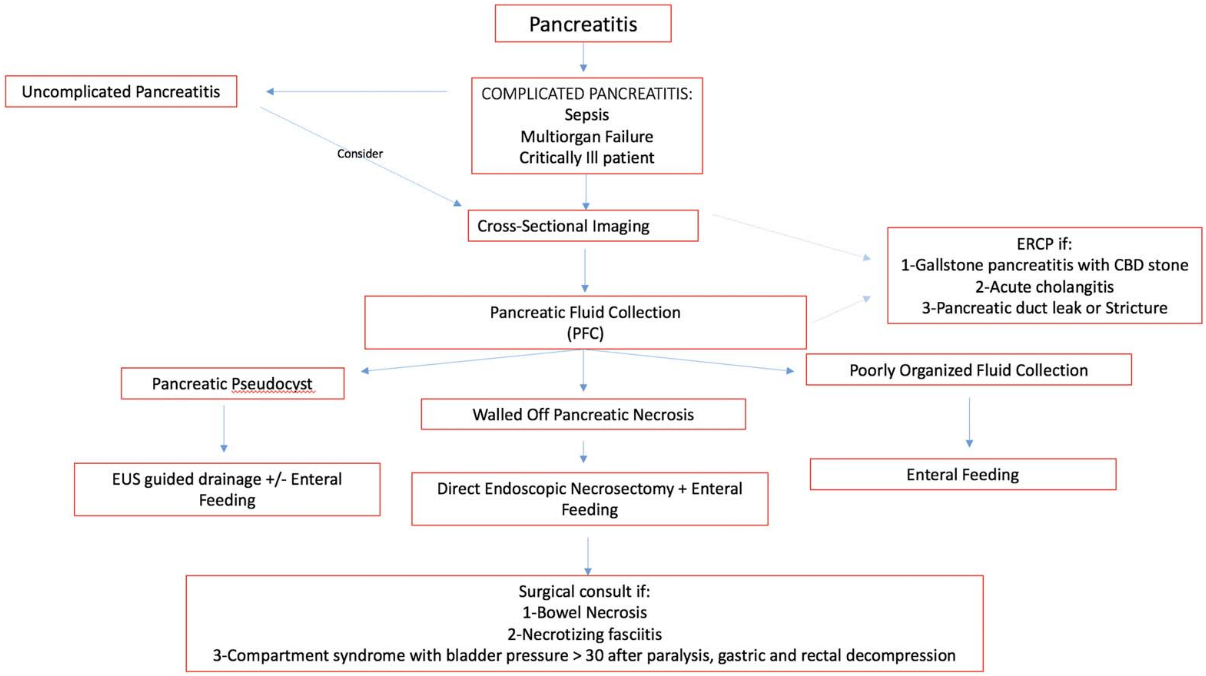

FIGURE 9. Algorithm for modern management of pancreatic fluid collections. ERCP indicates Endoscopic retrograde cholangio-pancreatography.

TABLE 6. RCTs Comparing Surgery to Step-up Approach for Necrosectomy

Study	No. Patients	Interventions	Step-up Therapy	Mortality (%)	% of Adverse Events	Type of Adverse Events
PANTER 2010[89]	88	Open necrosectomy vs. percutaneous or endoscopic	Minimally invasive retroperitoneal necrosectomy	16 (open) vs. 19 (step-up) ($P=0.70$)	40 (open) vs. 12 (step-up) ($P=0.002$)	Organ failure, perforation, fistula, bleeding
PENGUIN 2012[86]	20	Surgical vs. endoscopic necrosectomy	Video-assisted retroperitoneal necrosectomy	Composite outcome of adverse events + death	80 (surgery) vs. 20 (endoscopic) ($P=0.03$)	Organ failure, bleeding fistula, death

Management of DDS varies depending on whether there is concurrent PFC. If present, the PFC can be used as a site for EUS-guided transmural drainage. If not, more complex techniques, including stenting via EUS-PD, are necessitated for drainage of pancreatic fluid.[155]

In some studies, the prevalence of DDS has been reported in as many as 30% to 50% of cases of necrotizing pancreatitis.[157] The frequency of DDS and its potential to be a major complication should prompt further study regarding the utility of excluding it in all patients with necrotizing pancreatitis.

CONCLUSIONS

PFCs management has seen a dramatic shift toward minimally invasive interventions, with dominance of endoscopic therapy. This paradigm shift is not only related to improved understanding of the pathophysiology of pancreatitis, recognition of the importance of early enteral feeding, and drainage of infected fluid collections, but also to the development of novel devices such as LAMSs and providing biliary or pancreatic therapy at the appropriate time (Fig. 9) (Table 6).

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