Communication from the ASGE Technology Committee

TECHNOLOGY STATUS EVALUATION REPORT

ASGE American Society for Gastrointestinal Endoscopy

Endoscopic therapies for walled-off necrosis

Prepared by: American Society for Gastrointestinal Endoscopy Technology Committee

Monica Saumoy, MD, MS,[1,*] Arvind J. Trindade, MD, FASGE,[2,*] Amit Bhatt, MD,[3] Juan Carlos Bucobo, MD, FASGE,[4] Vinay Chandrasekhara, MD, FASGE,[5] Andrew P. Copland, MD,[6] Samuel Han, MD, MS,[7] Allon Kahn, MD,[8] Kumar Krishnan, MD, FASGE,[9] Nikhil A. Kumta, MD, MS,[10] Ryan Law, DO,[5] Jorge V. Obando, MD,[11] Mansour A. Parsi, MD, MPH, MBA, FASGE,[12] Guru Trikudanathan, MD,[13] Julie Yang, MD, FASGE,[14] David R. Lichtenstein, MD, FASGE,[15] (American Society for Gastrointestinal Endoscopy Technology Committee Chair)

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Background and Aims: Management of walled-off necrosis (WON) has focused on a step-up approach using minimally invasive drainage and debridement techniques. This document reviews the technical aspects of endoscopic management of WON, technical and clinical success, adverse event rates for endoscopic drainage, and dedicated endoscopic devices for direct endoscopic necrosectomy (DEN).

Methods: The MEDLINE database was searched through April 2022 for relevant articles using the key words walled-off necrosis, endoscopic necrosectomy, interventional EUS, severe acute pancreatitis, necrotizing pancreatitis, and lumen-apposing metal stent. The manuscript was drafted by 2 authors and edited by members of the American Society for Gastrointestinal Endoscopy Technology Committee and subsequently by the American Society for Gastrointestinal Endoscopy Governing Board.

Results: Multiple studies have demonstrated acceptable outcomes of primary cystenterostomy for drainage, performed with either plastic double-pigtail stents or fully covered self-expandable metal stents including lumen-apposing metal stents. Subsequent procedures for clearance of necrotic debris can be facilitated with hydrogen peroxide lavage, nasocystic flushing catheters, multiple transluminal gateway technique, dual-modality therapy, and novel DEN devices. Novel DEN devices include EndoRotor Powered Endoscopic Debridement (Interscope, Inc, Northbridge, Mass, USA), waterjet necrosectomy device, and the over-the-scope grasper (Ovesco AG, Tübingen, Germany). These devices were designed to reduce procedural time and the number of necrosectomy sessions for clearance of necrotic debris when compared with traditionally used devices such as polypectomy snares, biliary baskets, and retrieval nets.

Conclusions: EUS-guided endoscopic drainage and debridement has become a well-established method for treatment of WON in a step-up paradigm. The use of adjunctive technologies requires further evaluation to define the optimal methods for WON treatment. Further improvements in dedicated DEN devices should lead to improved outcomes and more widespread utilization of endoscopic treatment options. (iGIE 2023;2:226-39.)

The American Society for Gastrointestinal Endoscopy Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methods are used, with a MEDLINE literature search to identify pertinent clinical studies on the topic and a Manufacturer and User Facility Device Experience (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases data from randomized controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and web-based publications, proprietary publications, and informal communications with pertinent vendors. Technology status evaluation reports are drafted by 1 or 2 members of the American Society for Gastrointestinal Endoscopy Technology Committee, reviewed and edited

by the committee as a whole, and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through April 2022 for relevant articles by using key words such as "walled-off necrosis," "endoscopic necrosectomy," "interventional EUS," "severe acute pancreatitis," "necrotizing pancreatitis," and "lumen-apposing metal stent," among others. Technology status evaluation reports are scientific reviews provided solely for educational and informational purposes. Technology status evaluation reports on emerging technologies are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

Acute pancreatitis is an inflammatory disorder that results in intra- and peripancreatic fat lipolysis, immunologic responses, and microvascular dysfunction.[1] Clinical outcomes range from self-limited pain to the development of peripancreatic fluid collections, end-organ damage, and death. Severe acute pancreatitis and/or necrotizing pancreatitis have high rates of morbidity from local and systemic adverse events (AEs).[2] The predominant local AE is the development of pancreatic fluid collections (PFCs), which can be divided into 4 categories: acute peripancreatic fluid collection, acute necrotic collection, pancreatic pseudocyst, and walled-off necrosis (WON). WON is characterized by a collection of pancreatic and/or peripancreatic necrosis that develops a mature inflammatory wall after an episode of acute necrotizing pancreatitis. Drainage with selective debridement of pancreatic necrosis is necessary for patients with infected necrosis given the improvement in the already high morbidity and mortality rates.[3] Indications for intervention on necrosis in the absence of infection are necrotic collection with ongoing organ failure despite optimal medical therapy, biliary obstruction, symptomatic intestinal obstruction, intractable pain from mass effect, and disconnected pancreatic duct syndrome (DPDS) with ongoing symptoms.[4]

Open surgical debridement was historically the preferred treatment for symptomatic necrotic collections, but there has been an evolution to current management favoring a minimally invasive approach with initial endoscopic debridement and/or percutaneous catheter drainage (PCD). The PANTER trial compared upfront primary open necrosectomy with this "step-up" paradigm of minimally invasive techniques using PCD and endoscopic drainage while reserving video-assisted retroperitoneal dissection for patients without clinical improvement. The step-up approach was associated with a lower rate of major AEs, such as multisystem organ failure.[5] This focus on minimally invasive techniques led to the TENSION trial, which favored the endoscopic step-up approach as compared with the surgical step-up approach, particularly with a reduction in enteral or pancreaticocutaneous fistula formation, shorter length of hospital stay, lower costs without a reduction of major AEs, or death.[6-8]

Individual randomized controlled trials have not demonstrated a reduction in mortality with the endoscopic or PCD first approach compared with upfront minimally invasive surgery, but 1 recent meta-analysis[9] and a large international risk-adjusted study involving 1980 patients[10] suggested otherwise. The purpose of this technology status evaluation report is to review the current endoscopic devices and techniques used in managing pancreatic necrosis.

TIMING AND PREPARATION FOR DRAINAGE AND DEBRIDEMENT

Guidelines based on open surgical necrosectomy recommend delayed intervention until 4 weeks after pancreatitis onset to allow for maturation of the necrotic collection and liquefaction of internal debris.[11] Earlier drainage in the minimally invasive era with a percutaneous catheter or endoscopic approach can be considered and appears to be safe with favorable, but not superior, outcomes to delayed intervention for infected necrosis.[12,13] The POINTER study was a randomized controlled trial for treatment of infected necrosis that compared prompt drainage within 24 hours to delayed drainage after waiting 4 weeks for WON maturation. Over 33% of the delayed drainage group improved with antibiotic therapy alone and never required intervention.[13] Moreover, the early drainage group required more necrosectomies (51% vs 22%; RR, 2.27; 95% confidence interval, 1.27-4.06) and more combined endoscopic and radiologic drainage procedures (4.4 vs 2.6).

Because of the complexity of managing patients with necrotizing pancreatitis, a multidisciplinary approach is recommended to optimize outcomes, taking into consideration the patient's comorbidities, anesthesia risk, and surgical candidacy with input from stakeholders often including gastroenterologists, interventional radiologists, and surgeons. Preprocedural cross-sectional imaging should include contrast-enhanced CT or magnetic resonance imaging to assess WON size, location, wall maturity, amount of intracavitary debris, proximity to the gastric or duodenal wall, and presence of intervening vascular structures. Magnetic resonance imaging is superior to CT for quantifying the amount of intracavitary necrotic debris.[14] Quantifying the amount and location of solid debris allows for proper planning of the drainage procedures. A retrospective study of 136 patients showed that collections over 10 cm, paracolic extension, or greater than 30% necrosis may benefit from step-up therapy. This consists of endoscopic necrosectomy, subsequent percutaneous drainage (especially in cases of paracolic extension) if needed, additional endoscopic drainage if needed, and finally surgical intervention if needed.[15]

Pseudoaneurysm formation may result from necrotizing pancreatitis, typically including branches of the pancreaticoduodenal, gastroduodenal, and splenic arteries secondary to autodigestion and weakening of the arterial wall by pancreatic juices. Pseudoaneurysms contain a wall of mostly fibrous (not arterial) tissue that is at risk of a potentially fatal hemorrhage.[16] Pseudoaneurysm formation can result from pancreatitis itself or from vascular trauma related to endoscopic necrosectomy or percutaneous drain placement. If a pseudoaneurysm is detected, embolization is warranted before transmural drainage of the fluid collection because of the risk of spontaneous rupture. Additionally, endoscopic debridement may cause an iatrogenic hemorrhage. After embolization of the pseudoaneurysm, patients can be reevaluated to determine whether they should undergo endoscopic or other drainage procedures.[17]

Broad-spectrum antibiotic coverage can be considered depending on the clinical scenario when performing endoscopic WON drainage. Routine antibiotics to prevent infection is not recommended. However, broad-spectrum antibiotics are recommended when infected necrosis is suspected, particularly if culture proven. Intravenous antibiotics with good pancreatic parenchymal penetration include quinolones, extended-spectrum cephalosporins, carbapenems, and metronidazole.[3]

Endoscopic transmural drainage (ETD) is typically performed using general anesthesia or monitored anesthesia care. Intubation and mechanical ventilation may be preferred for airway protection from aspiration, because a large amount of intracystic fluid is anticipated to extrude into the stomach during the procedure.

Discontinuation of proton pump inhibitor (PPI) use before necrosectomy can be considered, because gastric acid may facilitate liquefaction of necrotic debris and reduce bacterial proliferation after ETD. A multicenter retrospective study of 272 patients using lumen-apposing metal stents (LAMSs) for drainage and debridement of WON noted that non-PPI use compared with continuous PPI use was associated with fewer necrosectomy sessions (4.6 vs 3.2, respectively; $P < .01$).[18] However, there was no difference in overall technical or clinical procedural success rates. Thus, the efficacy of PPI discontinuation remains uncertain.

The American Society for Gastrointestinal Endoscopy and European Society of Gastrointestinal Endoscopy advise the use of CO_2 instead of air for insufflation during transmural endoscopic necrosectomy. CO_2 is absorbed from the GI tract about 160 times faster than nitrogen (the major component of room air), resulting in less postprocedural pain and potentially reducing the incidence of air embolism or tension pneumoperitoneum.[11,19-23] Before the use of CO_2, air embolism was reported in .9% to 2% of cases of endoscopic necrosectomy; however, after the introduction of CO_2, air embolism during endoscopic necrosectomy has not been reported. CO_2 embolism has been reported in rare instances associated with other endoscopic techniques (eg, cholangioscopy).[24,25] Therefore, a gas embolism should still be considered in the differential diagnosis of a patient with abrupt clinical status change after the procedure.

TOOLS AND TECHNIQUES FOR ENDOSCOPIC THERAPY

Cystenterostomy and Stent Placement

The initial step for ETD of a PFC and/or peripancreatic fluid collection is creation of a cystenterostomy (Fig. 1). Historically, this has been a challenging and time-consuming procedure with high rates of AEs, resulting in considerable evolution of the technique over the years.[26] ETD was first performed in 1996 through a fistulotomy with a thermal device (ie, needleknife) at the site of extrinsic compression by the WON on the stomach or duodenum[27] with concurrent placement of a nasocystic drain or double-pigtail plastic stent (DPPS).

The procedure rapidly evolved to the current standard of EUS-guided drainage because of the ability of EUS to identify drainage sites with the WON in close apposition to the intestinal lumen (typically <1 cm) and in the absence of a visible bulge, to avoid intervening vessels using Doppler imaging, and to determine the presence and amount of internal debris.[26] Two randomized controlled trials noted significant improvement in technical success with EUS-guided access compared with visual endoscopic targeting at the site of extrinsic luminal compression (100% vs 33% and 94% vs 72%, respectively).[28,29] Although both studies were performed for patients with pancreatic pseudocysts, the results have been extrapolated to patients with WON.

The site of drainage should be chosen when possible to allow direct passage of a forward-viewing endoscope into the collection to facilitate necrosectomy.[30] The drainage procedure can be performed using the Seldinger technique (Table 1) with a 19-gauge needle used to puncture the necrotic collection followed by guidewire insertion (.025- to .035-inch), guidewire-assisted dilation of the cystenterostomy, and stent(s) placement. The diameter of the dilation depends on the type of stent placed and the decision to perform immediate versus delayed necrosectomy. Dilation width is typically chosen based on the caliber of stent chosen by the endoscopist for cystenterostomy and is typically 4 to 6 mm for fully covered self-expandable metal stents (FCSEMSs) or 10- to 15-mm for multiple DPPSs.

LAMSs are FCSEMSs with terminal flanges in a dumbbell configuration and a central tubular saddle and large variable luminal diameter and allow for ease of debridement through the stent lumen. These design features are intended to provide sufficient axial force to place the walls of the bowel and necrotic cavity in close apposition, thereby reducing leakage and perforation along the tract while simultaneously minimizing stent migration and

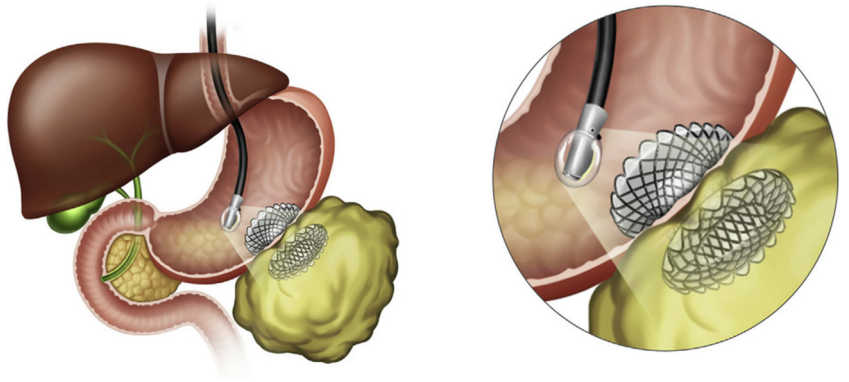


Figure 1. Creation of a cystgastrostomy with EUS-guided placement of a lumen-apposing metal stent.[31]

TABLE 1. WON drainage techniques

Noncautery-enhanced LAMS
1. EUS identification of drainage site
a. Without intervening vessels
b. Close apposition to gastric/duodenal wall (<1 cm)
c. Location to facilitate direct endoscopic necrosectomy
2. 19-Gauge FNA needle puncture of WON
3. Aspirate of WON contents for microbiologic analysis when indicated
4. Guidewire (.025- to .035-inch) placement into the WON cavity
5. Cystenterostomy tract dilation (dilating catheter, balloon, or cystotome)
a. 10-20 mm for multiple plastic pigtail stents
b. 4-6 mm for fully covered self-expandable metal stent or cold LAMS)
6. Stent placement (double-pigtail plastic stent, self-expandable metal stent, or cold LAMS)
7. Direct endoscopic necrosectomy (immediate or delayed)
Cautery-enhanced LAMS
1. Identification of drainage site analogous to cold LAMS placement
2. Single-step access of the WON cavity
a. Without need for guidewire, tract dilation, or fluoroscopy

WON, Walled-off necrosis; *LAMS*, lumen-apposing metal stent.

allowing for debridement through the stent lumen. Dilation of the LAMS is performed after stent placement, and the chosen size is based on the LAMS diameter. The electrocautery-enhanced LAMS system enables the single-step access (Table 1, Video 1, available online at www.igiejournal.org) favored by most endoscopists over the previously described Seldinger technique. The addition of DPPSs through the lumen of non-LAMS FCSEMSs or LAMSs is intended to reduce stent migration and intracystic wall trauma, but this benefit remains unclear. We refer the reader to the American Society for Gastrointestinal Endoscopy technology status evaluation report on LAMSs for a detailed description and discussion of EUS-guided LAMS placement.[31]

Stent selection and clinical outcomes. Historically, DPPSs were initially placed for drainage of WON.[32] However, their small luminal diameters (7F or 10F) resulted in incomplete drainage, particularly of the solid necrotic component.[33] In an effort to promote better drainage, reduce stent occlusion from debris, and create a larger diameter of the cystenterostomy for debridement, FCSEMSs were used (Table 2).[26,34,35] Limitations of these stents are a lack of an anchoring mechanism to reduce migration, inability of apposition of the intestinal and collection walls to reduce leakage, and long stent length predisposing to AEs (stent occlusion, bleeding, and perforation). As a result, LAMSs were used (Axios stent [Boston Scientific, Marlborough, Mass, USA] and Nagi or Spaxus stent [Taewoong, Seoul, South Korea]). The Axios stent is the only U.S. Food and Drug Administration–cleared LAMS in the United States for the indication of WON drainage, with labeling specifically cleared for lesions ≥6 cm in size, with ≥70% fluid content, and in close proximity to the enteric wall.[36] Comparative data between DPPSs, FCSEMSs, and LAMSs are heterogenous because of a variety of clinical and procedural factors, including the significant variability in WON characteristics (size, location, extension into gutters, duration since onset, infected or sterile, amount of intracavitary necrosis) and treatment options (drainage technique, stent type and number, debridement and timing, adjunctive tools).

One large retrospective multicenter series of 124 patients with WON treated by EUS-guided transmural drainage with LAMSs reported a technical success rate of 100%, clinical success rate of 86%, and requirement for direct endoscopic necrosectomy (DEN) in 30.6% using a median of 2 procedures. [37] AEs requiring intervention occurred in 18.5% of patients, with short-term (within 30 days) and long-term rates of 11.3% and 7.2%, respectively. The AEs included bleeding (1.6%), infection (5.6%), stent migration (5.6%), and occlusion (5.6%), and most were treated with stent clearance, repositioning, or replacement. Both bleeding episodes occurred during necrosectomy and required angiographic embolization.

Uncertainty remains as to the superiority of metal stents compared with plastic stents and LAMSs compared with traditional FCSEMSs for WON drainage. A meta-analysis of 41 studies totaling 2213 patients showed that metal

TABLE 2. Stent choice for cystenterostomy

Stent type	Advantages	Disadvantages	References
Double-pigtail plastic stent (DPPS)	• Lower risk of bleeding compared with metal stents	• Small luminal diameters • Increased overall procedure time • Multiple revision of stents when performing direct endoscopic necrosectomy	35, 37
Fully covered self-expandable metal stent	• Larger diameter allows for improved stent patency • Possible improved walled-off necrosis resolution compared with DPPS	• Lack of anchoring mechanism risks stent migration compared with lumen-apposing metal stent • Increased risk of bleeding compared with DPPS	35, 36
Lumen-apposing metal stent	• Larger diameter allows for improved stent patency • Possible improved walled-off necrosis resolution compared with DPPS • Shorter procedure time compared with DPPS • Possible fewer direct endoscopic necrosectomy sessions	• Increased risk of bleeding and buried stent as compared with DPPS	35-38

DPPS, Double-pigtail plastic stent.

stents (FCSEMSs and LAMSs) were superior to plastic stents in regard to WON resolution (92.1% and 80.9%, respectively; odds ratio [OR], 2.8; 95% confidence interval, 1.7-4.6; $P < .001$) with fewer resultant bleeding events (5.6% vs 12.6%, $P = .02$), a nonstatistically significant trend toward less occlusion and perforation, but increased migration rates.[38] A subgroup analysis of LAMSs alone compared with plastic stents showed improved rates of WON resolution (91.5% vs 80.9%, respectively; OR, 2.5; 95% confidence interval, 1.4-4.3; $P = .001$), with indirect evidence suggesting no difference in resolution with LAMSs (87.7%) versus non-LAMSs (77.6%).[38]

A multicenter retrospective trial compared outcomes among 313 patients who underwent drainage of WON with DPPSs (n = 106), FCSEMSs (n = 121), and LAMSs (n = 86).[39] At the 6-month follow-up, the rate of complete resolution was lowest in the DPPS group (81%) compared with the groups treated with metal stents (95% and 90% for FCSEMSs and LAMSs, respectively; $P = .001$). The mean number of procedures was lowest in the LAMS group (DPPS group, 3.6; FCSEMS group, 3; LAMS group, 2.2, respectively; $P = .04$). In contrast, the only randomized controlled trial comparing EUS-guided drainage of WON with plastic stents (n = 29) and LAMSs (n = 31) demonstrated no difference with regard to the number of procedures, clinical success, length of hospital stay, readmission rate at 6-month follow-up, and overall treatment costs, although procedure duration was shorter in the LAMS group (15 vs 40 minutes, respectively; $P < .001$).[40]

Of note, an interim analysis noted a higher AE rate (bleeding, distal common bile duct obstruction, and buried stent) in the LAMS group when the stent was left in place for more than 3 weeks (32.3% vs 6.9%, $P = .01$). It was hypothesized that prolonged dwelling of LAMSs leads to abutment of the end of the metal stent against the wall of the collapsing cavity, resulting in vascular erosion, bleeding, and, during transduodenal drainage, biliary obstruction from stent compression of the distal common bile duct. An amendment to the study protocol led to LAMS removal at 3 weeks if WON had resolved on CT, with subsequent similar AE rates between the 2 cohorts.[40] Thus, we advise removal of LAMSs within 3 to 4 weeks after placement when technically feasible. In contrast, it appears to be safe to leave plastic stents in place for prolonged periods, essentially until the WON resolves and potentially indefinitely in those with disconnected pancreatic duct anatomy.

Another important question is whether a larger luminal stent diameter is better. When comparing the diameter of LAMSs used for drainage of WON, a retrospective case-matched study of 306 patients demonstrated comparable results for 20-mm and 15-mm LAMSs in terms of clinical success and safety profile, with the larger-diameter LAMS requiring fewer necrosectomy sessions for WON resolution (mean 1.3 vs 2.1, respectively; $P < .001$).[41]

Multiple transluminal gateway and dual-modality drainage techniques. The multiple transluminal gateway technique (MTGT) (Fig. 2) refers to the creation of more than 1 tract into the necrotic pancreas collection. Usually, 2 or 3 tracts are used depending on the size of the collection.[42] This technique allows improved drainage and access to perform debridement. Two retrospective uncontrolled studies comparing MTGT with single-access drainage noted higher clinical resolution with the MTGT (91.7% vs 52.1% [$P = .10$] and 94.4% vs 62.1% [$P = .009$]).[2,33,43,44] Creation of more than 1 tract may be technically challenging as there may not be an EUS window after the initial WON decompression, depending on the proximity of the necrotic cavity to the bowel wall.[16] In 1 case report, EUS-guided fine-needle injection of sterile saline solution aided the expansion of the collection for the

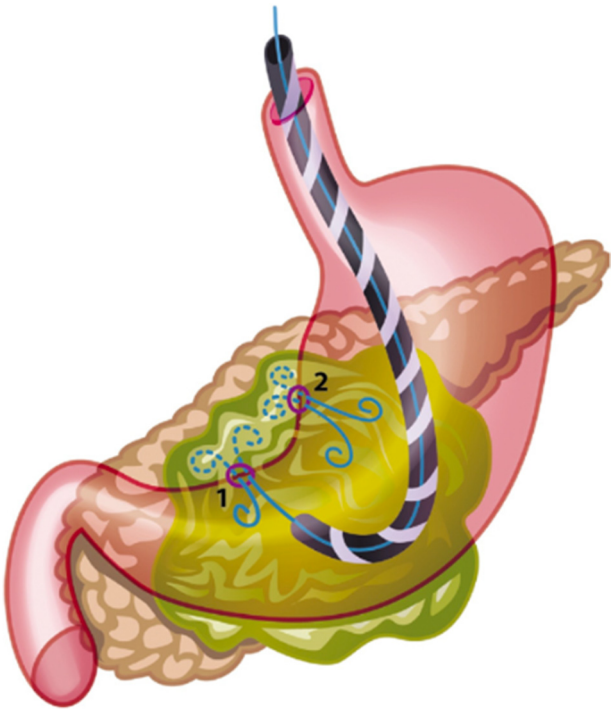


Figure 2. Multiple transluminal gateway technique for drainage of walled-off necrosis.[42]

second site of EUS targeting and stent deployment.[45] The optimal candidate for MTGT requires further study with current practice selectively using MTGT when the cyst cavity is large (eg, >12 cm), is multiseptated with undrained cavities, contains a large necrotic debris burden, or is refractory to single-tract drainage.

Dual-modality drainage (DMD) refers to combined PCD and ETD and debridement of WON. This can be accomplished with initial percutaneous catheter placement in a step-up fashion followed by selective ETD or as simultaneous PCD and ETD. A single-center retrospective study compared patients who underwent same-day DMD (n = 49) versus percutaneous drainage alone (n = 46).[6] The DMD group had a shorter length of hospital stay (24 days vs 54 days, $P < .002$) and a decreased need for adjunctive radiologic procedures (7.8 vs 14, $P < .001$); however, overall mortality and subsequent surgical intervention were similar in both groups. This study was limited by the absence of a comparator group of ETD alone. Another group prospectively evaluated treatment results of same-day DMD for 107 patients with infected and noninfected WON. None of the patients required surgical management for necrosectomy or AEs.[46] Furthermore, percutaneous drains were removed successfully in all patients, and none developed pancreaticocutaneous fistulas. DMD is often used for collections that extend into the paracolic gutters or pelvis, with endoscopic cystenterostomy allowing for mechanical debridement of the superior dominant area of necrosis and percutaneous catheter placement for irrigation and drainage of the more distant paracolic gutter and pelvic collections.[7]

Poststent follow-up. Follow-up cross-sectional imaging with CT is typically obtained 2 to 4 weeks after stent placement to assess for improvement in WON contents and size. In those with collapsed necrotic collections, metal stents are typically removed by week 4 to prevent AEs that may result from the collapse of the necrotic cavity onto the internal end of the stent. At the time of metal stent removal, the residual cavity can be assessed for size and contents. DPPSs can be placed to maintain cystenterostomy patency for ongoing drainage and future necrosectomy. On-demand imaging with CT should also be considered for the development of suspected AEs such as signs of sepsis, drop in hemoglobin suggestive of bleeding, increased abdominal pain, or organ failure. Plastic stents, unlike their metal counterparts, can be left in place until WON resolution or selectively long term for management of DPPSs, as discussed below.

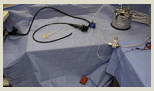
Direct endoscopic necrosectomy

After EUS-guided transgastric or transduodenal drainage, the WON cavity can be entered with a standard forward-viewing endoscope to perform DEN. DEN was first described in a series of patients who had failed transluminal stent placement.[23] Initially, this was performed by balloon dilation of the cystenterostomy tract (up to 20 mm) after DPPS placement with subsequent debridement of necrotic tissue. The currently favored approach is to perform DEN through the lumen of the LAMS used to create the cystenterostomy, either concurrent with WON drainage or in a delayed approach if transluminal stent drainage alone fails to resolve the WON.[47] This delayed approach allows for transmural tract maturation before DEN[47] and, if resolution of WON occurs, may obviate the need for DEN.[48-50]

A large multicenter retrospective study (n = 271) compared immediate DEN (n = 69) with delayed DEN (n = 202) performed 1 week after the initial LAMS-assisted drainage procedure.[51] Clinical success was the same in each group (91.3% immediate compared with 86.1% delayed, $P = .3$); however, the immediate DEN group required fewer necrosectomy sessions (3.1 vs 3.9, $P < .001$). Additionally, no significant difference was seen in the overall procedural AEs between the 2 groups (7.2% vs 9.4%, $P = .81$). Stent dislodgement during the index endoscopy occurred in 3 patients in the immediate DEN group compared with no patients in the delayed DEN group ($P = .016$).

Immediate DEN appears to be an emerging preferred strategy for WON patients with large collections or containing a large amount of solid debris.[47] Current practice for follow-up of debridement is variable, with DEN often performed on a scheduled basis at 1- to 2-week intervals in the setting of infected necrosis or alternatively on demand with an ultimate endpoint of involution of the necrotic cavity based on cross-sectional imaging and endoscopic assessment.

TABLE 3. Devices for direct endoscopic necrosectomy

	Lumen-apposing metal stent	EndoRotor Powered Endoscopic Debridement	Waterjet necrosectomy device	Over-the-scope grasper (Xcavator)	Examples of other off-label devices used for direct endoscopic necrosectomy (snare, biliary basket, food bolus net)
Device	 Law et al.[31]	 Van der Wiel et al.[56]	 Yachimski et al.[52]	 Brand et al.[60]	
Company	Boston Scientific, Marlborough, Mass, USA	Interscope, Inc, Northbridge, Mass, USA	Not yet commercially available	Ovesco AG, Tübingen, Germany	Multiple commercially available
Cost,* U.S.$	4500	EndoRoter console: 28,000 EndoRoter catheter: 1450	Not yet commercially available	299	Snare: 10 Biliary basket: 263 Food bolus net: 95
References	25, 27-32	56-58	52	60	19

*Note that costs are approximate and can vary.

Devices for DEN. Until recently, debridement of necrotic tissue was performed using instruments designed primarily for other endoscopic purposes without a U.S. Food and Drug Administration indication for DEN (Table 3). These devices included stone retrieval baskets, grasping forceps, polypectomy snares, distal attachment caps, and retrieval nets[23] (Video 2, available online at www.igiejournal.org), with such limitations as accessories not specifically designed or evaluated for DEN, limitations in their ability to fragment and remove necrotic debris, multiple devices often used in 1 session resulting in excess cost, and multiple sessions often required to achieve complete debridement.[35,52] There is great variability in cavity size and amounts of necrotic material, with 2 meta-analyses reporting that the median number of DEN sessions for clearance of necrotic material is 4 (range, 1-15).[53,54] Development of dedicated devices for DEN are aimed at reducing the complexity and time required for debridement.

EndoRotor. A dedicated instrument for endoscopic necrosectomy, the EndoRotor Powered Endoscopic Debridement system (Interscope, Inc, Northbridge, Mass, USA) recently received a primary indication to resect and remove necrotic tissue in patients with symptomatic WON. This device was first cleared by the U.S. Food and Drug Administration for the removal of tissue from the peripheral margins of an endoscopic resection site.[55] The system components include a power console, foot control, specimen trap with a preloaded filter, and a disposable catheter. The EndoRotor Powered Endoscopic Debridement catheter is compatible with therapeutic endoscopes with a working channel of at least 3.2 mm. The catheter is motorized and simultaneously cuts (by a rotating blade with small teeth attached to the inner cannula) and suctions target tissue into the specimen trap (Fig. 3 and Video 3, available online at www.igiejournal.org). The cutter opening is directed to face and contact the necrotic material. Negative pressure is used to suction necrotic tissue into a 4.0-mm^2 opening at the tip of the catheter. Blade rotation and suction are controlled by the endoscopist using 2 separate foot pedals. The EndoRotor console can be set to either high speed (1700 RPM) or low speed (1000 RPM), and the vacuum is set between 50 mm Hg and 550 mm Hg of negative pressure.

A prospective feasibility and safety study was performed with the EndoRotor Powered Endoscopic Debridement system for 12 patients with WON, 9 of whom were previously untreated and 3 of whom were refractory to standard endoscopic methods.[56] Twenty-seven procedures were performed with an average cavity diameter of 11.8 cm. The median number of procedures to achieve complete removal of necrotic material was 2 with a median procedure time of 38 minutes.[56] No AEs were recorded within 24 hours of the EndoRotor-assisted debridement. Three patients developed AEs as a result of their infected necrosis, and 2 patients died from events unrelated to the debridement.

An international, multicenter, prospective study evaluated the EndoRotor Powered Endoscopic Debridement system for

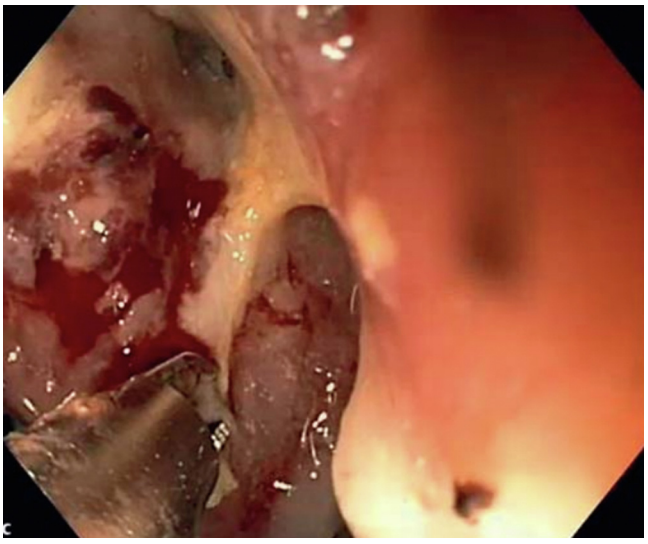


Figure 3. EndoRotor catheter in walled-off necrosis cavity performing direct endoscopic necrosectomy.[56]

DEN.[57] Thirty patients with WON measuring 6 to 22 cm with at least 30% necrosis based on CT were enrolled. Successful clearance was achieved in 29 of 30 patients (97%), defined as ≥70% debris removal. Fifteen of 30 patients (50%) achieved complete debridement in 1 session, and 21 of 30 patients (73%) achieved complete debridement after 2 sessions. The mean number of procedures per patient was 1.5 (range, 1-7) with a mean EndoRotor procedure time of 71 minutes (standard deviation, 36). A significant improvement was found in 4 quality of life 36-Item Short Form Health Survey domains between baseline and postprocedure follow-up: physical functioning (36 vs 58, $P = .002$), energy/fatigue (28 vs 37, $P = .040$), emotional well-being (61 vs 68, $P = .024$), and pain (32 vs 55, $P = .001$). No device-related AEs were noted throughout the 21-day postnecrosectomy follow-up period. Another case series of 4 patients showed similar high success rates for clearance of necrotic debris without device-related AEs.[58]

Waterjet necrosectomy device. A prototype device, the waterjet necrosectomy device (WAND) (Fig. 4), is a single-use disposable endoscopic instrument capable of selective tissue fragmentation for debridement of WON.[52] The device consists of a handle mechanism, biocompatible polytetrafluorethylene tubing, and device tip that fits through a 2.8-mm working channel of a standard adult endoscope. The WAND is designed to allow a controllable waterjet force (maximum surface pressure of 1.3 bar) that can fragment necrosis without causing damage to the underlying healthy tissue. The device tip articulates over a range of 120 degrees to provide accurate targeting. Preclinical testing has been performed in benchtop and porcine models of necrosis.[52] Unintended tissue trauma was not observed on nontarget, non-necrotic tissue. Planning is underway for use of the WAND in human safety and efficacy studies.

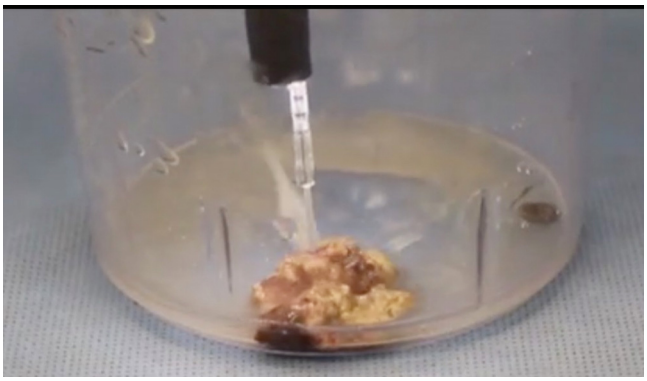


Figure 4. Waterjet necrosectomy device in ex vivo model performing fragmentation of explanted pancreatic necrosis.[52]

Clinical studies are lacking. A case series of 4 patients demonstrated technical success of DEN using a noncommercially available high-flow waterjet system.[59] Each patient underwent cystgastrostomy with SEMSs, placement of a nasobiliary drain with irrigation for 5 days, and DEN with the high-flow waterjet system through a therapeutic gastroscope using a water pump attached to a flush knife (Fujinon, Lexington, Mass, USA) to fragment debris. Necrotic debris was then removed with the simultaneous application of the flush knife, stone retrieval basket, and hot biopsy forceps.

Over-the-scope grasper. The over-the-scope grasper (Xcavator; Ovesco AG, Tübingen, Germany) (Fig. 5) was recently developed to remove necrotic debris, blood clots, and foreign bodies. It is an extra-large transparent plastic cap with distal graspers that attaches to a standard endoscope without blocking the instrument channel, allowing for simultaneous flushing and suctioning. The device is 14 mm in diameter and can be passed through a 15-mm LAMS. The opened jaws are 31 mm wide, allowing grasping of large pieces of debris. A recent report described 2 patients in which the over-the-scope grasper was used to facilitate DEN through a 15-mm LAMS.[60] In both patients, complete necrosectomy was achieved in 3 sessions with a procedure duration of 53 to 60 minutes.

ADJUNCTIVE THERAPIES FOR DEBRIDEMENT

Hydrogen peroxide lavage

Diluted hydrogen peroxide (H_2O_2) is an inorganic agent that has been used medically for wound debridement because of its antimicrobial, hemostatic, and wound-healing characteristics. It has recently been used to facilitate the debridement of necrotic material in WON. The mechanism of action is mediated through the physical agitation of debris as catalase, an enzyme found in living

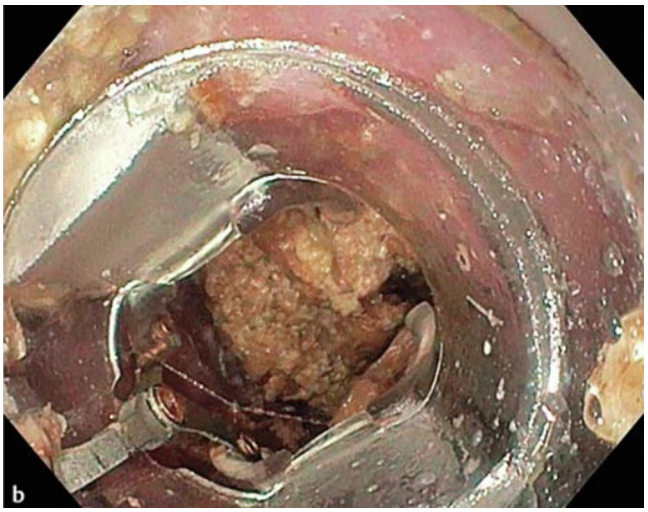


Figure 5. Over-the-scope grasper (Xcavator) used to extract a food bolus in the esophagus.[60]

tissue, converts H_2O_2 to water and oxygen. Three percent H_2O_2 is usually diluted with normal saline solution in a ratio ranging from 2:1 to 10:1.[61] It is infused during debridement or with a nasocystic catheter passed through the cystgastrostomy tract.

Several retrospective studies have been published showing a potential benefit for the treatment of WON with H_2O_2.[61-64] In the largest retrospective study, the use of H_2O_2 was associated with a higher clinical success rate (OR, 3.3; $P = .03$) and earlier resolution (OR, 2.3; $P < .001$) but with a greater number of necrosectomy procedures and no difference in AEs.[61] However, there was bias in favor of the H_2O_2 group because of a disproportionately greater use of large-diameter LAMSs (15 mm and 20 mm) in the ETD treatment group. The only randomized controlled trial demonstrated the superiority of H_2O_2 when infused in combination with plastic stent ETD; however, the control group without H_2O_2 infusion was an unmatched group undergoing ETD performed with LAMSs.[65] A meta-analysis of 7 retrospective studies involving 186 patients evaluated the pooled outcomes of hydrogen peroxide–assisted DEN of WON.[66] The pooled technical success rate for necrosectomy was 95.8%, with a clinical success rate of 91.6% after a range of 2 to 5 treatment sessions. However, the studies did not have a comparator control group to assess the incremental benefit of H_2O_2.

Although the safety profile for H_2O_2-assisted WON debridement has been favorable, with no AEs directly attributable to H_2O_2 in the meta-analyses, there is a theoretic concern of gas embolism, because oxygen is liberated from catalase activity on H_2O_2. This AE has occurred in non-GI procedures (eg, irrigation of a surgical breast wound, lumbar cavity, orthopedic).[33] Prospective studies need to be performed with a control population comparing clinical outcomes in well-defined WON patient groups (timing, size, indication) before H_2O_2 can be widely recommended.[67]

Nasocystic catheter irrigation

A nasocystic catheter can be inserted at the time of initial drainage, placed parallel to the plastic stents or through the lumen of a metal stent. The catheter can promote constant irrigation of the cavity between DEN sessions, usually through a 5F or 7F catheter at a daily volume of 500 to 1000 mL.[11] Lavage with antibiotic-containing irrigation has been used but is of uncertain benefit. Nasocystic catheters can be considered when a collection is large and if PCD is not feasible to provide continuous irrigation because patients are typically intolerant of nasal catheters.

Prospective trials evaluating the use of a nasocystic catheter are lacking. A single-center retrospective study found that nasocystic catheters decreased plastic stent occlusion rates by 3-fold (12% vs 33%, $P = .03$).[68] However, the nasocystic tube may not offer an advantage when used in conjunction with LAMSs, as 1 retrospective study demonstrated no difference in WON resolution (91% vs 96%, $P = .59$).[69]

DISCONNECTED PANCREATIC DUCT SYNDROME

Pancreatic necrosis in the central portion of the pancreas often results in a functioning pancreas on both sides of a transected duct or DPDS. This anatomic condition provides a unique clinical situation, in that after initial ETD and debridement of the WON the presence of DPDS can lead to recurrent symptomatic PFCs. Initial ETD and resolution of WON is followed by some endoscopists with the exchange of SEMSs for long-term DPPSs.[43]

A retrospective study of 149 WON patients demonstrated DPDS was present in 68% of WON patients and that PFC recurrence is lower with long-term DPPSs (17.4% vs 1.7%).[70] A subsequent randomized control trial compared the recurrence of PFCs among 104 patients with DPDS who underwent long-term DPPS placement (n = 52) versus no stent placement (n = 52) on removal of large-caliber SEMSs for WON.[71] Plastic stents subsequently migrated in 19.2% of patients during the 8 months of follow-up. Recurrent PFCs were seen in 7 patients (13%) with stents and in 13 patients (25%) without stents, which was not statistically different. In this study, most recurrences were asymptomatic and did not require further therapy. Among the 20 recurrent PFCs, only 7 patients required reintervention, 5 with EUS-guided plastic stent placement and 2 with surgical therapies.

Because of conflicting clinical data, the optimal long-term strategy for DPDS remains uncertain; therefore, the decision of whether to leave plastic stents in situ indefinitely is left to the discretion of the endoscopist pending

additional studies with longer-term outcomes. Alternatively, definitive therapy with a distal pancreatectomy can be considered in good surgical risk patients.

FINANCIAL CONSIDERATIONS

Treatment cost comparisons

Given the complexity of managing severe acute pancreatitis complicated by WON, these patients typically have prolonged hospital stays that translate into significant morbidity and costly medical care. As minimally invasive techniques have become first-line treatments for WON, there is a concern that this shift in therapeutic paradigm with a requirement for repeated endoscopic debridement procedures may add to expenses. A small randomized controlled trial involving 98 patients (TENSION trial) directly compared clinical outcomes (surgical vs endoscopic) and economic impact for treatment following a step-up algorithm. The endoscopic approach consisted of EUS-guided drainage followed by necrosectomy versus the surgical step-up of PCD followed by video-assisted retroperitoneal dissection.[7] The mean costs of the index treatments and subsequent 6-month follow-up were similar. Another clinical trial (MISER) demonstrated an economic advantage for the endoscopic step-up approach (ETD with or without necrosectomy) compared with minimally invasive surgery (laparoscopic or video-assisted retroperitoneal debridement). In contrast to the TENSION study, the MISER trial comprised a more severely ill WON patient population as patients that improved with upfront PCD were excluded and 95% were American Society of Anesthesiologists class III and IV compared with 30% in the TENSION trial.[8] Global costs were calculated based on expenses for the procedure, inpatient hospitalization, anesthesia, medications, readmissions, and imaging studies. The mean total medical costs per patient during initial hospitalization and the subsequent 6-month follow-up were $75,830 for the endoscopic approach and $117,492 for the surgical approach, for a mean absolute difference of $41,662 per patient ($P = .039$). Other studies reviewing the total costs for patients admitted with acute pancreatitis and WON were not significantly impacted by the procedure-related costs. Rather, the hospital ward, particularly intensive care unit–related costs, was the greatest contributing factor to total treatment costs.[72,73] Therefore, methods that directly target length of stay should decrease overall disease-related costs.

There is great variability in endoscopic drainage options for the treatment of WON; however, the use of EUS-guided drainage with LAMS insertion is the dominant approach for WON therapy because of the advantages of ease of stent insertion without the need for wire insertion, tract dilation, or fluoroscopy. Does this translate into improved cost efficacy? A randomized control trial comparing LAMSs with DPPSs for drainage of WON demonstrated a shorter procedure duration with LAMSs but failed to demonstrate superiority in clinical outcomes and overall treatment costs.[40] A decision analysis model compared plastic stents with LAMSs for the incident procedure and then over a 6-month time horizon, taking into account the need for subsequent DEN and AEs requiring unplanned endoscopy, PCD, or surgery.[74] The use of LAMSs was more costly at $20,029 per patient compared with that of DPPSs at $15,941 per patient. However, the clinical efficacy was superior for LAMSs versus DPPSs with rates of 92.2% and 83.9%, respectively, resulting in an incremental cost per patient of $4089. Overall, the use of LAMSs was more cost-effective because of rates of unplanned endoscopy (LAMSs, 19.4%; plastic stents, 45.2%) and surgery (LAMSs, 4.5%; plastic stents, 19.8%). The LAMS strategy had an incremental cost-effectiveness ratio of $49,214 per additional successful drainage compared with plastic stents.

Professional reimbursement

When performing ETD for patients, Current Procedural Terminology (CPT) code 43240 should be used because it applies to EUS-guided transmural drainage of a pseudocyst with LAMSs (EGD, flexible, transoral; with transmural drainage of pseudocyst [includes placement of transmural drainage catheter(s)/stent(s), when performed, and EUS, when performed]). CPT code 43247 (EGD, flexible, transoral; with the removal of foreign body[s]) can be used when the LAMSs is endoscopically removed.

A specific CPT code for endoscopic debridement of WON does not exist. The use of code 48999 (unlisted procedure, pancreas) can be used, either as a single code for the entire drainage and debridement procedure or together with the base service(s) CPT code 43240 to which it is added. When submitting the unlisted procedure code 48999, submission to the insurance carrier should include a cover letter that provides content containing the nature of the procedure, indication, time allocated, and equipment used with accompanying supportive medical literature. This can also address the major components related to these procedures: cost, physician expertise, and patient complexity. For example, the costs related to these procedures are not only for the intraprocedure disposable devices (such as stents and debridement tools) but also required multiple high-capital platforms (EUS, fluoroscopy). Additionally, managing these complex and high-risk patients requires training, expertise, risk, and competence from the endoscopist. The cover letter should also state why billing cannot be addressed with the standard CPT codes and suggest a reasonably comparable CPT code based on work relative value units and/or percentage of a reasonably comparable CPT.

TRAINING ISSUES AND ESTABLISHMENT OF COMPETENCY

Unlike standardized competency thresholds for routine endoscopic procedures, learning curves and competency

criteria for the performance of EUS-guided WON drainage and debridement are lacking. Endoscopists performing EUS-guided WON drainage with transmural LAMS placement are expected to have achieved competence in upper endoscopy, ERCP with guidewire manipulation, and fluoroscopic interpretation (Shutz I and II) in addition to proficiency in diagnostic EUS with fine-needle sampling techniques.[75,76]

Ideally, competency should be defined by the provider's independent ability to assess the need, approach, and performance of these procedures with proficiency measured by clinical outcomes and AEs.[75] The use of a procedure number as a surrogate marker of competency is likely an inaccurate endpoint because of great individual variability in acquiring procedural skills, although a minimum number is often recommended. Studies evaluating clinical and procedural outcomes for endoscopic management of PFCs demonstrated improvement in technical proficiency with a reduction in procedural time, days to resolution, and resolution rates after a minimum of 20 to 25 procedures.[76,77] However, these studies were performed during the developmental stages of endoscopic PFC treatment, and thus the Asian EUS Working Group consensus guidelines suggest the performance of a lower threshold of 5 to 10 supervised procedures to gain competency in pseudocyst drainage, a procedure that is equivalent to the drainage component of WON therapy.[78] This number does not address the criteria for achieving competency for DEN, with evolving techniques because of the recent development of dedicated devices. The European Society of Gastrointestinal Endoscopy recommends that at least the first 25 cases of any EUS intervention should be performed under the supervision of an endoscopist experienced in that intervention.[75]

Current approaches to achieving competency in endoscopic treatment of WON include structured courses with balanced combinations of formal cognitive self-directed study and "hands-on" courses using simulator-based training and ex vivo/live animal models, vendor-supported education, and observership or hands-on training at select high-volume medical centers of expertise.[75,76] Many fourth-year advanced endoscopy training programs provide exposure but not necessarily adequate experience to attain proficiency, with the maturation of these skills ultimately acquired in clinical practice. Future studies will better define optimal training pathways and competency assessment for EUS-guided treatment of WON.

FUTURE AREAS FOR RESEARCH

Management of necrotizing pancreatitis has improved significantly; however, additional research is necessary to optimize patient care. Questions remain about timing and type of drainage, particularly related to direct and overall disease-related costs and outcomes. Additional studies are needed to evaluate combination therapy for necrosis clearance using H_2O_2 lavage, nasocystic flushing catheters, MTGT, and novel DEN devices. Future studies must demonstrate that these novel devices and techniques for DEN reduce the number and duration of DEN sessions and length of hospital stay and thus favorably impact overall treatment costs.

CONCLUSION

Management of patients with pancreatic necrosis is complex and requires a multidisciplinary approach with input from medical intensivists, advanced endoscopists, interventional radiologists, and pancreatic surgeons. EUS-guided cystenterostomy in a step-up paradigm has become the preferred approach for the treatment of WON because of similar clinical efficacy to initial minimally invasive surgical techniques and reduction in fistula formation and length of hospital stay, with a favorable economic impact. Recent developments of dedicated DEN devices such as the EndoRotor have facilitated necrosectomy, leading to shorter and fewer procedures to achieve WON resolution. Other adjunctive therapies such as nasocystic catheter drainage, H_2O_2 lavage, discontinuation of PPI therapy, and waterjet necrosectomy cannot be recommended at this time. The development of new drainage and debridement technologies and the refinement of existing treatment algorithms are forthcoming. Because of the great variability in patient characteristics and clinical presentations, these advances will necessitate prospective comparative clinical trials focusing on procedural efficacy and safety.

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Abbreviations: AE, adverse event; CPT, Current Procedural Terminology; DEN, direct endoscopic necrosectomy; DMD, dual-modality drainage; DPDS, disconnected pancreatic duct syndrome; DPPS, double-pigtail plastic stent; ETD, endoscopic transmural drainage; FCSEMS, fully covered self-expandable metal stent; LAMS, lumen-apposing metal stent; MTGT, multiple transluminal gateway technique; PCD, percutaneous catheter drainage; PFC, pancreatic fluid collection; PPI, proton pump inhibitor; WAND, waterjet necrosectomy device; WON, walled-off necrosis.

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*Drs Saumoy and Trindade contributed equally to this article.

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Current affiliations: Department of Gastroenterology, University of Pennsylvania, Philadelphia, Pennsylvania, USA (1), Department of Gastroenterology, Zucker School of Medicine at Hofstra/Northwell, Long Island Jewish Medical Center, New Hyde Park, New York, USA (2), Department of Gastroenterology, Hepatology & Nutrition, Cleveland Clinic, Cleveland, Ohio, USA (3), Division of Gastroenterology and Hepatology, Stony Brook Medicine, Stony Brook, New York, USA (4), Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA (5), Division of Gastroenterology and Hepatology, University of Virginia Health Systems, Charlottesville, Virginia, USA (6), Division of Gastroenterology, Hepatology and Nutrition, The Ohio State Wexner Medical Center, Columbus, Ohio, USA (7), Department of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona, USA (8), Division of Gastroenterology, Department of Internal Medicine, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts, USA (9), Division of Gastroenterology, Mount Sinai Hospital, New York, New York, USA (10), Division of Gastroenterology, Duke University Health System, Raleigh, North Carolina, USA (11), Division of Gastroenterology and Hepatology, University of Tennessee Health Sciences Center, Memphis, Tennessee, USA (12), Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, Minneapolis, Minnesota, USA (13), Division of Gastroenterology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA (14), Division of Gastroenterology, Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts, USA (15).