—Review Article—

# Controversies in EUS-guided treatment of walled-off necrosis

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## ABSTRACT

This review gives an overview of different techniques in the treatment of post-acute complications of acute pancreatitis. The endoscopic treatment of those complications is currently standard of care. EUS opened up the broad implementation of internal drainage methods to make them safe and effective. Due to different endoscopic approaches worldwide, controversies have arisen that are pointed out in this paper. The main focus was placed on weighing up evidence to find the optimal approach. However, if no evidence can be provided, the authors, experienced in the field, give their personal advice.

**Key words:** pancreatitis, ultrasound, intervention, complication

## INTRODUCTION AND HISTORY

Endoscopic treatment of local complications of postacute pancreatitis such as peri-pancreatic fluid collections (PFCs) and pancreatic or peripancreatic necrosis has evolved to become a standard of care in clinical practice.[1,2] Since its introduction as a treatment option for patients suffering from conditions mentioned above, the mortality and

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morbidity rates for these procedures have dropped significantly.[2,3] Multiple techniques of drainage are currently in use due to lack of standardization during the early phases of their development. As institutions explored different ways to achieve optimal drainage of the walled-off necrosis (WON) into the gastrointestinal (GI) tract, they learned from their own mistakes and those of others. As a result, there currently exist variable approaches and a number of technical controversies, which this paper intends to address, with the aim to further improve an already very effective modality.[4] Looking closer, the reader will realize that these different techniques do not exclude each other since they approach the necrotic collection in different ways. However, knowing the different technical options and approaches with their advantages and disadvantages will help an operator identify the optimal treatment strategy in each individual case.

## WHY DO WE NEED PROCEDURES BEYOND OPEN SURGERY?

Before the popularization of percutaneous and endoscopic therapy, the approach to WONs after acute pancreatitis was typically open surgery in combination with high-end intensive care. The Pancreatitis Working Group around Besselink *et al.* investigated the different invasive approaches in 2004 and divided their patients into four groups: one group received an open abdomen strategy; another group received laparotomy with continuous postoperative lavage; the third group received minimally invasive surgical approaches; and the fourth group underwent primary abdominal closure. Surprisingly, the group with the least invasive approach was the group with the lowest mortality rate. The authors concluded that a minimally invasive approach was the safest and most effective treatment.[5] This study came parallel to a publication by Seifert *et al.*, who showed that endoscopic transgastric treatment in patients with WON was possible.[6] Technical advances such as the development of therapeutic echoendoscopes with longitudinal scanning accelerated the introduction of endoscopic treatment of WONs with astonishing results worldwide. Today, there is no doubt that the endoscopic approach of patients suffering from complications of acute pancreatitis is the method of choice, resulting in less mortality and morbidity, and surgery is only reserved for cases who cannot be treated endoscopically, for example, where EUS guidance might not reach the extension of WONs into the paracolic gutters or in peripheral parts of the abdomen where video-assisted retroperitoneal debridement might be the preferred approach. Of particular note, all percutaneous drainage techniques carry the risk of persistent pancreatic or enterocutaneous fistulae.

## WHAT DIAGNOSTIC MANAGEMENT IS REQUIRED BEFORE INTERVENTIONAL THERAPY FOR WOPN?

Before therapeutic intervention, three essential questions must be addressed:

1. Differential diagnosis: Is the lesion really a pancreatitis-associated fluid accumulation?
2. Is there an indication for intervention?
3. Are there contraindications or risk factors that can be influenced?
4. Which possible access routes exist?

Several cases have been described in the literature in which EUS-guided drainage treatment was performed under the assumption of an inflammatory PFC, but pancreatic cystic neoplasia turned out to be present in the further course of treatment.[7] In a large prospective cohort of 320 patients who were referred to a tertiary center for EUS examination and drainage of PFCs, four cases were identified with an associated malignancy.[8]

Case studies and this series highlight that all patients referred for EUS-guided intervention of PFCs require a complete and thorough EUS pancreatic examination to exclude cystic pancreatic neoplasia or underlying malignancy before proceeding with transmural drainage and stent placement.[9]

Before performing interventional treatment of PFCs, indication has to be evaluated carefully. 64% of all WONs can be managed conservatively with low mortality.[10] Up to 50% of WONs remains asymptomatic, most of them resolving spontaneously.[11] Asymptomatic and noninfected PFCs, among them also some cases of WONs, do no warrant interventional treatment regardless of size or imaging features.[9] A majority of patients with asymptomatic WOPN do not suffer any complications in their further clinical course.[12] Another important consideration before intervention of a WOPN or other PFCs is the analysis of risk factors. EUS-guided treatment of

WONs is associated with relevant peri-interventional morbidity.[13] The spectrum of these complications is broad, and efficacy and risk can be influenced in part by detailed knowledge of the pathologic anatomy and possible access routes, as well as optimal selection of intervention timing, intervention method, access route, and intervention materials.[13-15]

## HOW TO PERFORM EUS-GUIDED WOPN DRAINAGE?

Initially, transmural drainage of pancreatic collections causing intraluminal bulging was achieved by "blind" puncture under only endoscopic guidance. The development of EUS allowed performance of a more controlled technique under imaging guidance, resulting in a more effective, as well as safer procedure, resulting in less bleeding and perforation, and also accessibility of nonbulging collections. Thus, EUS-guided transmural drainage of pancreatic collections is presently accepted as standard of care [Figure 1].

## DO WE NEED TO WAIT 4 WEEKS FOR MATURATION OF THE WALL?

### *Yes*

In the early stages of pancreatitis, the fatty tissue surrounding the pancreas may become involved in the inflammatory process, as autodigestion follows the release of activated pancreatic enzymes into the retroperitoneum. An initial phlegmon will begin to progressively liquefy, with fluid tracking along various retroperitoneal planes such as the paracolic gutters.[16] This process does not show any compartmentalization, and the liquefied area can spread diffusely within the retroperitoneum. Central collections may bulge anteriorly into the lesser sac and push against the posterior wall of the stomach; however, it is important to appreciate that this fluid does not typically enter the peritoneal space unless the peritoneum is somehow breached. The concept of the necrosis and fluid initially remaining within the retroperitoneal space is key to understanding the benefits of the less invasive treatment modalities of percutaneous/endoscopic

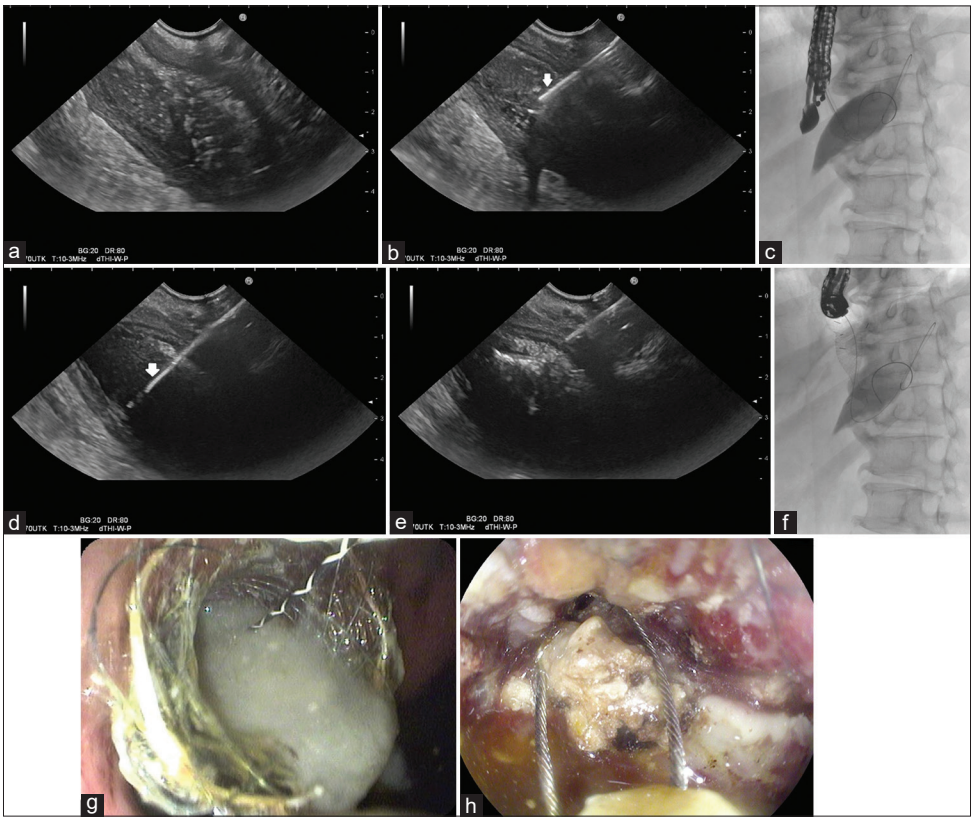


**Figure 1.** EUS-guided treatment of a walled-off necrosis (WON): A thick-walled pancreatic necrosis with heterogeneous content is visualized using a longitudinal echoendoscope at the posterior gastric wall (a). A 19-gauge aspiration needle (arrow) is inserted into the necrosis (b) and after positioning of a 25″ guidewire and wire-guided dilatation of the needle track the introducer system of a LAMS (arrow) is pushed forward into the WON (c and d). Stent release can be well controlled both by EUS (e) and by fluoroscopy (f). Pus empties into the stomach via the LAMS (g). The 14-mm diameter LAMS allows advancement of a standard gastroscope into the necrotic cavity, and several sessions of endoscopic necrosectomy are performed (h). LAMS: Lumen-apposing metal stent

drainage and minimally invasive surgery (MIS). This is one of the key disadvantages of early surgery, as it may result in peritoneal contamination and greater propensity for spreading infection. In the early stages of inflammation, the liquid is sterile because translocation of bacteria and fungi does not happen until later, usually once compensatory anti-inflammatory processes result in relative immunosuppression.[17-19] Puncturing this sterile liquid collection from the GI tract would likely result in its infection and possibly increase the risk of generalized peritonitis. Moreover, only organized liquid collections should be drained since ongoing tissue inflammation does not benefit from drainage. Finding the best moment for endoscopic intervention is one of the most important decisions for an endoscopist. To date, most interventionalists have recommended waiting a minimum of 4 weeks from the onset of pancreatitis and advise performing drainage as late as possible.

### *No*

The 4-week time limit for intervening in pancreatic-related fluid collections and infected necrosis is derived from expert surgical opinion, which has not been validated in prospective trials. Rather, this period merely indicates a probability that an organized collection has formed. On imaging, PFCs can be expected to be organised if they are approximately spherical and have a well-defined rim (walled-off). The The content can appear both fluid and (pseudo-)solid. It should be noted that computed tomography (CT) is poor at discriminating fluid from devitalized tissue and it is the authors' opinion that magnetic resonance imaging and contrast-enhanced (endoscopic) ultrasound are far superior in this regard.

Unfortunately, the optimal time for intervention cannot be determined by time alone.[20] The general condition of the patient and the clinical course have to be taken into account as well. There are two major complications of WONs that need urgent treatment. The most common is superinfection that is not responsive to conservative measures. The other, less common, but very serious complication is the development of an intra-abdominal compartment syndrome.[21] Both these complications must be treated as soon as possible. While the second complication is more a case for open surgery,[22] the first should be treated by interventional endoscopy. Meanwhile, several studies have shown that early endoscopic treatment using lumen-apposing metal stents (LAMSs) and direct endoscopic necrosectomy is justifiable when required to the clinical deterioration despite use of all conservative treatment options.[20,23-27]

Estimation of how far the process of liquefaction and organization has progressed can be done using imaging. If a wall of granulation tissue can be detected, intervention can be undertaken earlier than 4 weeks although the potential for a higher complication rate should be taken into account. If there is no detectable wall, but an intervention is required for clinical reasons, percutaneous drainage via a retroperitoneal approach can be employed; this may be definitive treatment, facilitates subsequent interventions such as minimal access surgery, or allows the collection to mature allowing delayed endoscopic intervention. This is an extremely rare event; thus, the indication for intervention would almost always be clinical deterioration related to sepsis.

Where endoscopic and percutaneous posterior retroperitoneal approaches are not deemed feasible, the often forgotten option of percutaneous transgastric drainage can be considered. This can be even performed half endoscopically by using the gastropexy device. This older modality avoids contamination and spreads within the peritoneal space, while allowing a tract to form from the gastric lumen into the developing collection and cavity. Once the cavity is more mature, this tract can be developed to allow subsequent endoscopic access and intervention if required.[18]

In general, fluid collections that have developed a wall tend to have a spherical shape. Thus, using imaging techniques such as CT and ultrasound (US), the detection of a spherical lesion of significant size (>5 cm) leads to a highly probable presence of a wall, and this situation allows the assumption of an "organized collection."[1] Likewise, when performing EUS in patients with sepsis, the experienced interventionalist visualizing a near-spherical fluid collection can be confident in performing drainage if there are no clear contraindications.

### *Conclusion*

Four weeks after the onset of symptoms, pancreatic necrosis has usually sufficiently liquefied and become walled-off for safe and effective intervention. Infection with clinical deterioration may necessitate earlier intervention.[9]

## CAUTERY DEVICES: DO WE NEED CYSTOTOMES?

### *Introduction*

Most of the initial approaches to gain access into the retroperitoneal cavity used a Seldinger technique by puncturing the cavity under US view with a 19-gauge needle followed by introduction of a guidewire through the needle. Small bougies and/or dilatation balloons can be placed over the guide wire. After dilation of the new tract, a plastic or metal stent could be deployed. As an alternative to bougies and balloon dilatation, cautery devices such as a needle knife or standard sphincterotome were used, including a one-step system like the Giovannini set.[28-30] Subsequent technical advances included incorporation of cautery instruments and LAMSs into single delivery systems, rendering the procedure easier to perform.[31,32] Cystotomes are however more flexible than stiff steel EUS needles. It is therefore important to initiate diathermy before applying pressure to advance the device in the intended direction because otherwise, instead of cutting through the gastric and cyst walls, the cystotome will encounter resistance, bend, and deviate along the gastric/cyst walls. At worst, the cystotome may pass between the stomach and cyst wall, creating a communication with the peritoneal space. This may result in peritonitis or, if not recognized, stent misplacement in the peritoneal space with the potential for dissemination of gastric content. It has to be taken into account that the salvage procedure using needle puncture might not be possible after multiple failed attempts with the cautery device due to severely reduced visibility.

### *Points in favor of cystotomes*

Under cutting diathermy, cystotomes pass through the GI wall easily and are reasonably visible when accessing the cavity by continuous US view. The heat effect of the cystotome normally produces some gas reaction, which can impair ultrasound scanning, but this normally disappears within seconds. The new tract created by the cystotome is reliable and normally does not require further dilatation to introduce a plastic or metal stent. Access through the GI wall without a cautery device is more time-consuming and technically demanding, as it requires needle puncture with subsequent dilation and exchange of tools over the wire, increasing the risk of losing the guidewire position. Since the procedure is easier and quicker to perform with a cystotome, most endoscopists prefer direct puncture with a cystotome over needle access these days.[4]

### *Points against cystotomes*

The main advantage of an atraumatic entrance into the cavity is that it avoids injury to arterial vessels in the wall. Arterial vessels cannot be punctured easily by the initial passage of a 19-gauge needle. All subsequent steps involving bougie and balloon dilatation only part the tissue further without damaging blood vessels, while diathermy effects extend to the surroundings and may cause immediate or delayed damage. Therefore, one should expect less bleeding complications using needle access than with cystotomes.[33]

## WHICH KIND OF CYSTOTOME FOR WHAT KIND OF PURPOSE?

There are multiple devices around to access WON through the gastric or duodenal wall. In general, cystotomes developed for the treatment of pancreatic collections are better than devices intended for ERCP use. Needle knife sphincterotomes tend to deviate from the axis of the guidewire. This usually makes the procedure more difficult and increases the complication rate.

Modern cystotomes produced as access tools through the GI wall can be used over a guidewire or can be used as a "hot needle" device.[34,35] These devices are easily detectable during US scanning and minimize procedural trauma. In the case of the cystotome from Cook Medical (Bloomington, IN, USA), after obtaining access with the cystotome inner tip, the tract can be enlarged with the outer most 10 Fr ring diathermy without further exchanges of tools.

## DO WE NEED BOUGIES?

### *Introduction*

After initial guidewire insertion, the next step is to widen the newly created tract through the GI wall. The outer muscle layer of the stomach is particularly resistant, such that a pointed instrument is necessary for this step if mechanical dilatation is used.

### *In favor of using bougies*

Bougies can widen the tract through the GI wall in a relatively atraumatic fashion due to the lack of a burning effect. This might lead to less bleeding during the procedure and a more controlled opening of the wall.[36]

### *Against use of bougies*

Introducing a bougie through the gastric wall can be challenging. The more or less blunt tip has to be forced through the wall, and this might lead to loss of position of either the guidewire or the endoscope. Even when using especially stiff wires, it is not always successful. To gain access, most endoscopists use first a 6 Fr followed by a 7 Fr bougie. This increases the length of the procedure as well as the risks of guidewire position loss or leakage.

### *Conclusion*

Little data exist comparing the use of bougies and balloon dilatation as opposed to cystotomes for the development of a tract in EUS-guided enteral drainage of peri-PFCs. While the risk of bleeding associated with cystotome use has been shown to be between 1% and 10%, the technical success rate (implying preserved guidewire position) of the Seldinger approach is reported to be in the region of 95%. Nevertheless, the use of cautery to achieve access to a collection has evolved as the preferred technique, due to its ease of use and shortened procedure time.

## ARE EUS NEEDLES DIFFERENT - AND IF YES, WHY?

### *EUS needles are all the same*

Needles are necessary for diagnostic puncture of a collection or the introduction of a guidewire. In case a guidewire is needed, it is preferable to use a 0.035 inch one due to the greater stability of the thicker wire. At least a 19-gauge needle is needed to accommodate such a wire. Super-stiff 0.025-gauge wires are available which would pass through a 22-gauge needle – however, the devices for opening up the stomach such as bougies, balloons, or cystotomes are not closing up nicely to the wire, and this might be a downfall in certain cases.[37] There is little difference between various 19-gauge needles available, so any needle will do.[38]

### *EUS needles are different*

Still if you look at 19-gauge needles, there are some different options available. In rare instances, the inner needle lumen is not large enough to allow a 0.035 guidewire to pass. It should be verified before the procedure that a guidewire is passing. Second, there is the issue of stiffness of the needle. Conventional 19-gauge needles are often very stiff and therefore hard to get through the instrument channel, especially when the instrument is in a curved position as in the duodenal position. Newer developments include more flexible 19-gauge nitinol alloy needles that are easier to use in difficult scope positions and that also allow a suitable guidewire to pass. Such increased flexibility may be relevant in certain procedures where accessing the collection may be challenging.[39]

## PLASTIC OR METAL STENTS

### *Introduction and review of the literature*

Initially, only plastic stents were used due to the lack of dedicated metal stents. Even in plastic stents, different options were available. It soon became apparent that straight plastic stents like the one in the Giovannini set had a very high migration rate. As a result, most authors preferred double pigtail configurations with a significantly lower migration rate.[40] The placement of at least two plastic stents (multiple plastic stenting [MPS]) was an attempt to reduce the rates of stent occlusion. Soft plastic double pigtail prosthesis can adapt nicely to the necrotic cavity and seldom cause damage to the cavity wall. Multistenting with double pigtail plastic stents (DPPSs) became the most common option employed, presenting little technical difficulty over and above single-stent placement.[41] It should be considered that MPS placement for patients with WON as opposed to pancreatic pseudocysts (PPs) has a lower success rate (63% *vs.* 93.5%) and higher adverse events (AEs) (16% *vs.* 5%).[42] Thus, MPS should be reserved for PPs where they are the treatment of choice. Due to the disappointing results presented above, the same authors adopted a different EUS-based approach for the treatment of WONs by creating multiple transluminal gateways (MTGs) to facilitate effective drainage of necrotic contents.[43] Two tracts were created in which placement of two to four 7 Fr plastic stents was performed. Finally, a 7 Fr nasocystic catheter adjacent to the first transmural stent site was placed for continuous lavage. Treatment success was more likely for patients treated by MTG than by the conventional single-tract MPS drainage technique (91.7% *vs.* 52.1%; $P = 0.01$), even though hospital stay was longer for the MTGs treatment (16.5 (4–45) *vs.* 4.5 [2–16] days). An alternative to both standard MPS placement and MTG is the use of fully covered self-expanding metal stents (FC-SEMSs), with the aim being to create a larger, stable opening, which can theoretically allow for easier spontaneous passage of necrotic tissue than plastic stents (PSs) and also the performance of direct endoscopic necrosectomy

whenever needed.[44] One systematic review[45] and one comprehensive review of the literature[46] produced conflicting recommendations about which one of these two approaches should be preferred; however, both publications have limitations. Bang *et al.*'s systematic review suggested no difference between metal and plastic stents but included only 16 patients with WON while Tyberg *et al.*'s literature review examined only a limited number of articles on FC-SEMs or LAMSs that were available at the time. A more recent systematic review and meta-analysis involving 11 studies for a total of 668 patients with both PPs and WONs treated with LAMSs found that there was no difference in clinical success for PPs *versus* WONs.[47] AEs occurred in 13% of the cases and were statistically more frequent in patients with WON ($P = 0.009$). Most common AEs requiring intervention were stent migration (4.2%), followed by infection (3.8%), bleeding (2.4%), and stent occlusion.

In five studies with 483 patients with PFCs, the efficacy of FC-LAMSs specifically designed to create an anastomosis between two hollow organs/cavities was compared with that of MPS. Greater clinical success was observed in the FC-LAMS group. With respect to adverse events, 6 studies with 504 patients compared the safety of LAMSs with MPS for the management of PFCs; LAMSs were associated with less AEs leading the authors to conclude that FC-LAMSs should be preferably used over MPS.[47] In the same year, a randomized controlled trial comparing LAMSs (Hot-Axios™) *versus* MPS for the treatment of 60 patients with WONs was published.[41] The primary outcome was the total number of procedures to achieve resolution of the WON within 6 months. Overall, there was no significant difference in the total number of procedures performed, treatment success, clinical AEs, readmissions, length of stay, and overall treatment costs between the two cohorts. In the LAMS arm, the procedure duration was shorter (15 *vs.* 40 min, $P < 0.001$), but stent-related serious AEs (32.3% *vs.* 6.9%, $P = 0.01$) and procedure costs (US$12,155 *vs.* US$6,609; $P < 0.001$) were higher, including two patients with a buried stent, three with bleeding pseudoaneurysms that required coil embolization, and another three with stent-induced biliary stricture. However, all these AEs occurred within a period of 6 weeks from stent placement, with half (2 buried stents, 1 biliary stricture) occurring in the second 3 weeks. Interim analysis made the authors change the protocol to include a follow-up CT at 3 weeks, resulting in a decrease in AE rate to 6.5% in the subsequent patients treated with LAMSs. Since all the AEs described happened in patients in whom LAMS treatment was successful, our opinion is that these AEs are related to morphological changes that occur when the necrotic collection is resolving, highlighting the need for the development of a different standardized follow-up protocol in this clinical setting. According to one guideline, MPS should be preferred, while LAMSs should only be utilized in the context of clinical research studies.[48] The strongest argument against LAMSs in these guidelines was based on the higher rate of adverse events in the LAMS group compared to the PS group in the small randomised trial by Bang *et al.* mentioned above.[41] The final outcome of this study, following the mid-study change in protocol already described, was that there was no significant difference in number of procedures (LAMSs median 2, PSs median 3; $P = 0.192$), treatment success, clinical AEs, readmissions, length of hospitalization, and overall treatment cost between the two modalities. Of further note is that two of the USA-based authors involved in the guidelines were also authors in Bang *et al.*'s randomized study.

In the same year as the above two conflicting studies, Bazerbachi *et al.* published in GI Endoscopy the study of possibly greatest significance regarding this issue. This systematic review and meta-analysis comparing metal and plastic stents specifically for treatment of WONs included 41 studies with 2213 patients. It demonstrated statistically significant increased resolution as well as fewer procedures and nonsignificant bleeding episodes with metal stents when used for WONs.[49] Three further studies are worth mentioning in this regard. Chen *et al.*, in a cost-effective analysis, evaluated 680 patients who received either a LAMS or PS and came to the conclusion that LAMSs were not only more effective but also more costly.[50] In contrast, Mohan *et al.*, in a systematic review and meta-analysis that included only data published since the emergence of the revised definitions for PFCs in the 2012 Atlanta classification, demonstrated equal clinical success and AE rates in a study that included 1264 patients with WON.[51] A systematic review and meta-analysis of 13 studies ($n = 1584$ patients) with head-to-head comparison of LAMSs and DPPSs for the EUS-guided treatment of PFCs reported a significantly lower rate of AEs for EUS-guided drainage with LAMSs, but

identical technical and clinical success rates. Interestingly, the safety profile differed between both stent types: Bleeding was the most common complication in the LAMS group, whereas infection was the most common complication in the DPPS group. Moreover, the LAMS migration rate was lower compared to DPPS.[52] It should be noted that many current guidelines and much of the available literature do not emphasize the difference between drainage of a PP *versus* WON. The content and related implications for adequate drainage as well as need for further interventions are markedly different between these two entities and should not be ignored.

## ARGUMENTS IN FAVOR OF PLASTIC STENT DRAINAGE

### *Pro*

The most important argument for still using plastic stents is the costs of the procedure. Even with multistenting using 3–4 plastic stents, it seems to be cheaper over the full course of treatment.[53] DPPSs rarely migrate and do not cause much damage to the necrotic cavity.[54,55]

A rarely mentioned disadvantage of LAMSs is that their opening may become sealed through a "valve" type effect caused by the collapse of necrotic tissue against the inner opening of the metal stent [Figure 2]. This does not occur with MPS, which in fact may be placed within a LAMS to prevent occlusion of the metal stent. Because of potential bleeding AEs, the reports have been published showing some improvement in AE rate when using coaxial DPPSs within LAMSs.[56,57] Some authors describe conflicting results showing no benefits of this approach.[58]

### *Con*

For proper treatment of necrosis, repeated endoscopic necrosectomy within the inflammatory cavity may be required. When MPS is used, the PSs may be removed or dislodged during passage of the endoscope. This increases costs sometimes higher than the costs of metal stents because the later ones can be left in place to facilitate repeated endoscopic necrosectomy.[59] Especially when performing the first few procedures, endoscopic passage into the cavity through a hole maintained by MPSs can be more difficult than through a LAMS.[60,61] Thus, for easier access and a larger lumen for drainage, metal stents

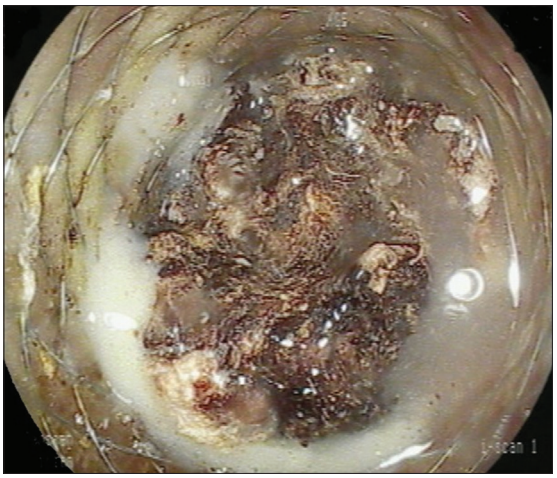

**Figure 2.** Early occlusion of an LAMS by necrotic debris: 4 h after deployment of the LAMS combined with a first session of endoscopic necrosectomy and initiation of flushing using an initially placed percutaneous drainage, the patient experienced severe abdominal pain, and clinical sepsis criteria developed. Endoscopically, the lumen of the LAMS was totally occluded by a necrotic tissue. Rescue treatment was performed by endoscopic necrosectomy. LAMS: Lumen-apposing metal stent

are preferred by most endoscopists.[62-64] Another argument in favor of metal stents is the experience that the placement of LAMSs can be easily and safely performed without fluoroscopic guidance.[65-67] This is of particular value in patients at intensive care units where fluoroscopy is much more difficult to implement [Figure 3].

An unanswered question is whether the use of fully covered enteral SEMSs may offer the same advantages as LAMSs in terms of drainage and access but without the cost of currently available LAMSs.

### *Conclusion*

In patients with PFCs, the introduction of SEMS has been driven by the assumption that their larger diameter compared with that of PS allows for faster and better drainage, decreased risk of occlusion, and reduced need for repeated procedures. Hammad *et al.*'s systematic review and meta-analysis involving 11 studies for a total 668 patients with both PPs and WONs mentioned above concluded that SEMSs should be favored over MPS.[47] These results were contradicted by Bang *et al.*'s randomized trial,[41] in which in patients with WONs, LAMSs were initially associated with a higher rate of serious AEs as compared to MPS. On interim analysis, half of the AEs developed more than 3 weeks after stent placement; however, the protocol was changed to remove the LAMS at 3 weeks if CT scan had demonstrated resolution of WON.

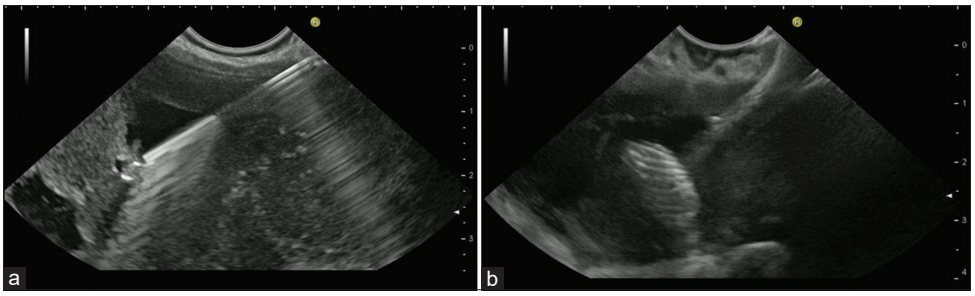


**Figure 3.** Easy and safe nonfluoroscopic deployment of an LAMS: All steps of the procedure can be monitored and guided by EUS. (a) Puncture of the WON using a 19-gauge needle; (b) deployment of the inner tulip of the LAMS. LAMS: Lumen-apposing metal stent

Subsequently, no differences in AEs have been noted *versus* the PS group, as mentioned above.[41] This latter trial is however limited by its small size. Bazerbachi *et al.*'s systematic review of 2213 patients with WON suggested that metal stents were superior to PS in terms of resolution with less bleeding, occlusion, and perforation. They were however more prone to migration. Chen *et al.*'s and Mohan *et al.*'s subsequent studies again provide opposing views but approached the question from different perspectives with different methodologies. In conclusion, lumen-apposing stents seem to be preferable to plastic stents, but to date, there are no solid data in the literature to confirm this endoscopists' choice.[68-70]

## ARE LUMEN-APPOSING STENTS BETTER THAN FULLY COVERED SELF-EXPANDING STENTS?

### *Yes*

Lumen-apposing stents have the advantage that they compress the inner wall of the cavity tightly against the stomach wall. This theoretically hinders the spillage of the cavity fluid into the peritoneal space, which occasionally happens in the drainage of PPs, especially where the cyst wall may not be adherent to the wall of the GI tract. The opening can also be used immediately for cavity inspection with an endoscope, because a sliding effect of the outer wall against the wall of the cavity is due to the stent construction basically impossible. LAMSs possess an expansion force that in the event of bleeding through the cautering effect of the device will be immediately stopped due to the mechanical effect of the stent. In the event of bleeding following the use of cautery, the mechanical expansion force of a LAMS may compress the bleeding site, thereby halting extravasation. These features do not distinguish LAMSs from FC_SEMSs – these advantages would be applicable to both. The single delivery system of LAMSs with built-in cautery and uploaded stent enables quick and simple transluminal stent insertion in one step within minutes. For endoscopic debridement, the short saddle length and wide anchoring flanches of the LAMS prevent dislodgement when the scope and debris are pulled through the stent. An international, multicenter retrospective study recently showed that EUS-guided drainage of WONs was equally effective and safe using both types of metal stents: biflanged FC-SEMSs and LAMSs. However, stent migration occurred significantly more often using the traditional type of FC-SEMSs, with all clinically significant dislodgements of traditional FC-SEMSs occurring during direct endoscopic necrosectomy.[71]

### *No*

Lumen-apposing stents are currently the most expensive option for endoscopic drainage of WONs. Specially designed FC-SEMSs are cheaper, and most have the same advantages as LAMSs.[72] Once in place, the stent can be passed with conventional endoscopes, and necrosectomy is also comfortably possible. They can similarly be used to manage bleeding at the time of transgastric access. The problem with FC-SEMSs is their more difficult deployment through the GI wall, since the inner stent opening does not stay as stable in the cavity as is the case with lumen-apposing stents. Further, there is no fixation of the cavity wall to the GI wall and therefore leakage is possible. In some designs, the coating is also not as stable as in LAMSs and therefore increases the risks of stent ingrowth and of difficulties in removing the stent.

### *Conclusion*

LAMSs are easier to insert, but this comes at much higher costs. Evidence is still needed comparing the two modalities' efficacy and safety profiles.

## SHOULD ENDOSCOPIC DEBRIDEMENT BE PURSUED DIRECTLY OR LATER?

### *Yes*

Timeous endoscopic removal of pus, debris, and necrotic tissue is critical in a patient with ongoing features of sepsis. Effective drainage increases the chance of recovery in WONs.[73] Often, LAMSs do not open fully immediately following insertion, and balloon dilatation is necessary to enter the cavity with a standard endoscope. Sometimes, a compromise can be made by draining the cavity of fluid using a slim endoscope (diameter of 5–6 mm) and reserving the necrosectomy for later. This avoids balloon dilation of the stent and keeps trauma to a minimum.[73] However, directly performing debridement at the time of initial stent insertion seems to reduce the number of necrosectomy sessions required until resolution of the WON is achieved.[73]

### *No*

Most WONs (50%–90%) do not require endoscopic debridement and will resolve with stenting alone.[74] A step-up approach therefore seems reasonable as it avoids unnecessary necrosectomy with its risks.[74-76] Maturation of the fistula tracts after EUS-guided drainage and stent deployment needs a few days. Unintended removal of a fully covered metal stent very early after deployment may result in leakage of infected contents of the WON into the peritoneal cavity in particular if EUS-guided drainage has been performed early in the course of acute necrotic pancreatitis. Therefore, most interventionalists leave the stent in place for 2–3 days before accessing the cavity with an endoscope.[77] After draining the cavity into the gastrointestinal lumen, the residual dense necrotic tissue starts disconnecting from the outer cavity wall and can then be removed more easily. As a result, delayed necrosectomy is preferable, depending on the clinical condition of the patient; a nasocystic drain for continuous irrigation of the cavity can be helpful and facilitate the necrosectomy by cleansing the cavity.

The choice between percutaneous minimal invasive surgery (MIS) MIS and endoscopy for debridement of residual necrotic tissue should be based on the patient anatomy, the location of the WON, and the local preference and expertise of endoscopists, radiologists, and surgeons.

### *Conclusion*

Direct endoscopic necrosectomy is needed only if drainage by stenting is not successful.

## DOES THE DIAMETER AND LENGTH OF THE COVERED STENT MATTER?

### *Introduction*

Covered stents are coming in different sizes. Those sizes do not differ in the size of the application system, so there is no difference for the endoscope used to perform the procedure. Different sizes in opening up diameter might be important for the procedure to follow, but even in an uncomplicated PP, it might be possible to perform an intervention later on in the treatment. The pro and contra will be argued in the following paragraphs.

### *Yes*

Stent diameter can be tailored according to the nature of the collection and the potential need for further intervention. If the content of the cavity is mainly liquid and necrosectomy unlikely to be needed, a smaller stent lumen may be chosen to limit stent trauma. Stent occlusion is more likely in the setting of large necrotic cavities and when significant debris and necrotic tissue is present. In such cases, larger stent diameters should be selected that ensure adequate drainage and facilitate the introduction of an endoscope if necrosectomy is required. The length of the stent should be adapted to the distance of the cavity from the GI tract. Caution should be exercised not to underestimate the distance to the cavity, because of the possibility of incomplete opening of either flange of the stent and primary stent dislocation. For most LAMS, the distance to bridge between stomach/duodenum and WON should be <1 cm.

### *No*

In clinical practice, a 15-mm diameter 10-mm length LAMS is sufficient in almost all WON cases. If the distance to the cavity is too long – stent displacement is possible even with longer stents. The lumen-apposing effect will not work, and this might lead to further complications. Even larger diameter stents can occlude when big pieces of solid necrotic tissue are present that not even the largest stent lumen can drain.

## DO WE NEED MULTIPLE TRANSLUMINAL GATEWAY STENTING?

### *Yes*

In multiple transluminal gateway stenting, two or three transgastric or transduodenal tracts are created under EUS guidance to enable effective drainage of

WON.[43] MTG stenting allows irrigation through one tract via a nasogastric tube and the others to drain. The constant directed flow results in more effective clearance of the necrotic content, reducing the need for endoscopic necrosectomy or MIS.[78] MTG procedures might be necessary, if the necrotic cavity is separated into different areas. In those cases, two or more openings could be made without increasing the risk of complications.

### *No*

Most WONs will resolve with insertion of one large diameter stent. The costs of metal stents may be substantial; however, each new tract creation poses its risks. Additional percutaneous drainage might exert the same effect.

### *Conclusion*

In selected cases of WONs that contain a large amount of necrotic tissue, insertion of several stents in different positions can accelerate clearance of the necrotic content. It might be necessary to have multiple gateways if the necrotic areas are not connected to each other.

## DO WE NEED $CO_2$ INFLATION DURING THE NECROSECTOMY?

### *Yes*

Pneumoperitoneum, as well as fatal cases of air embolism, has been reported following drainage of WONs as well as necrosectomy (1%). The risk of air embolism is high because of the anatomical area where the most necrotic cavities are located. In the retroperitoneum, venous vessels drain directly into the inferior vena cava by small gastric and esophageal veins. In addition, a relative negative pressure exists due to the direction of the bloodstream and negative intrathoracic pressure. Long procedure duration is a risk factor. If veins are opened during the procedure, air might directly flow into the right heart and can stop blood flow totally. This is a critical situation and might result in the death of the patient.[79] $CO_2$ gas used during the procedure might lessen the risk due to the fast absorption of the gas into the body tissue.

### *No*

The event of air embolism is a rare complication of the procedure. It is not proven that by using $CO_2$ gas embolism, it can be prevented;[3] however, the risk does seem to be smaller than with air. Using general anesthesia and patient intubation during the procedure can limit this risk even more, due to the positive thoracic pressure from the ventilation machine.

### *Conclusion*

$CO_2$ is now widely available and should be used for endoscopic drainage and necrosectomy, mainly due to its faster resorption following the procedure.

## IS THE ENDOSCOPIC APPROACH SUPERIOR TO THE PERCUTANEOUS APPROACH?

### *General considerations*

While accepting that open surgical approaches lead to higher morbidity, longer hospital stay, and more patient discomfort, the percutaneous approach (involving percutaneous drainage with/without subsequent MIS) has retained its place as an alternative modality to endoscopic therapy. Percutaneous approaches however have the tendency to lead to fistulae and result in drains through the patient's skin causing discomfort. Two important randomized trials have investigated the question of whether an endoscopic approach is superior to percutaneous step-up treatment of necrotizing pancreatitis. In the TENSION trial, the Dutch pancreatitis study group demonstrated a nonsuperiority outcome with there being no difference in the primary endpoint of major complication and death in 98 randomized patients.[80] Endoscopically treated patients did however have significantly shorter hospital stays, less direct costs, and less pancreatic fistulae. Three important aspects of the trial bear noting however: First, DPPSs were utilized for endoscopic drainage; second, pancreatic fistulae were not considered a major complication and were excluded from the primary endpoint; at last, in both treatment groups, additional endoscopic as well as percutaneous drainage and endoscopic or surgical necrosectomy was allowed. In the MISER trial, Bang *et al.*'s group randomized 66 patients; importantly, they included pancreatic fistulae as a major complication allowing this to be included in the data, contributing to assessment of the primary endpoint of major complication/death.[81] There was no significant difference between the two modalities in terms of mortality; however, there was a significant difference in terms of the primary endpoint in favor of the endoscopic approach (11.8% *vs.* 40.6%; $P = 0.007$). The mean number of major complications was $0.15 \pm 0.44$ for therapeutic endoscopy and 0.69 for $\pm$ 1.03 for MIS ($P = 0.007$). Endoscopic treatment also resulted

in better quality of life and lower cost. After including the above two studies as well as a smaller randomized trial of 20 patients performed by Bakker in 2012, Bang *et al.* completed a meta-analysis of the available data in 2020. The findings of this study were that while there was no significant difference in mortality, new-onset multiple organ failure (5.2% *vs.* 19.7%, RR = 0.34, $P = 0.045$), enterocutaneous fistula/perforation (3.6% *vs.* 17.9%, RR = 0.34, $P = 0.034$), and pancreatic fistula (4.2% *vs.* 38.2%, RR = 0.13, $P < 0.001$) were significantly lower for endoscopic interventions compared to MIS. Length of hospital stay was also significantly shorter for endoscopy.[82]

### *Yes*

EUS-guided interventions do not traverse the patient's skin and can be left in place until the lesion has resolved, recommendations differ in guidelines from 3[45] or 4 weeks[4,9] to be left indefinitely in place. Percutaneous approaches result in drains penetrating the patient's skin and are associated with a significant rate of wound infection and percutaneous fistulae.[80,83] Moreover, the endoscopic approach provides the opportunity of direct endoscopy of the cavity. This can clear out debris and has a much bigger opening into the cavity as the largest percutaneous approach could ever made. In this regard, the endoscopic approach is much more efficient however could be combined with percutaneous irrigation for faster cleansing.[84]

### *No*

In a significant subset of patients with PFCs, percutaneous approaches are successful alone.[85] In severely ill patients, catheters are already in place for the necessity of interventional ventilation, urethral catheterization, central and arterial lines, pleural drainage, and so on. The addition of percutaneous catheters in these patients does not add to the patient's discomfort; however, the drainage site needs to be carefully dressed and taken care of. Moreover, some WONs or parts of complex necrotic systems (e.g., paracolic) may not be accessible (only) by an EUS-guided approach so that percutaneous drainage may be the only or a necessary additional approach. If necessary for necrosectomy, the established percutaneous sinus tract can be dilated stepwise to allow access of small-caliber endoscopes for debridement of the necrotic cavity.[86-90]

### *Conclusion*

Percutaneous interventions:

- Result in a higher rate of fistulae and possibly new organ failure
- Do not seem to have a higher rate of additional complications
- Require less deep sedation
- Can reach locations where EUS approach is not feasible
- Still requires penetration of the skin in severely ill patients; however, this adds little additional complexity to the patient's management since these patients already have central intravenous lines, urinary catheter, arterial lines, invasive ventilation, and so on
- Can precede or complement EUS interventions
- Can be used for sinus tract endoscopy and percutaneous endoscopic necrosectomy.

In general, the EUS approach is superior in stable patients and should be preferred if possible, particularly where there has been sufficient delay for the collection to become well organized. The percutaneous approach can be less invasive, requires less sedation, and is sometimes the only alternative if EUS is not possible. In the severely ill, the percutaneous approach should be performed first, with the EUS approach undertaken after a certain level of patient recovery because of its advantage in preventing fistulae.[91] Good data to support this approach are however still awaited. It should also be appreciated that often percutaneous and endoscopic approaches may be complementary rather than competitive. What is paramount is that a tailored, individualized management plan should be drafted for each patient, with multidisciplinary input taking into account local expertise and preference.[76,92-94]

## DO WE NEED GENERAL ANESTHESIA WITH ENDOTRACHEAL INTUBATION?

### *Introduction*

#### Yes

For prolonged procedures, general anesthesia is preferred. The successful deployment of large diameter stents results in discharge of large amount of liquids within seconds into the gastric lumen, which poses a substantial risk of aspiration. Having airway protection by endotracheal intubation (ETN) is reassuring in this situation. In addition, in unstable septic patients, general anesthetics should also be considered.

No

The deployment of LAMSs often requires only a few minutes. Outpouring of fluid from the WON can be removed directly by suction through the echoscope and an elevation of the patient's head can prevent aspiration accordingly. Further, a fast switch from the longitudinal echoendoscope to a conventional gastroscope with a large suction channel can be performed. In general, this question cannot be answered in one sentence. Interestingly, neither the American nor the European guidelines refer to this topic.[1,95] ETN is generally considered in cases of high risk for peri-interventional aspiration. In the German guideline for sedation in endoscopy, ETN is suggested in cases of elevated risk for aspiration; data exist however to suggest that ETN *per se* may pose a higher risk for pneumonic infiltrates.[96]

### *Conclusion*

The duration and complexity of the procedure, the experience of the interventional team, the aspiration risk, and the comorbidities and clinical condition of the patient determine the need for endotracheal intubation.

## WHEN TO REMOVE THE STENT?

The literature is contradictory in guiding this decision. Publications vary from 4 weeks after placement to indefinitely keeping plastic stents in place.[95,97,98] It is recommended however that the stent be removed at some point to avoid tissue ingrowth and secondary complications. In general, PSs tend to survive unharmed over a longer period of time (6–12 months). LAMSs or FC-SEMSs should be removed after a maximum of 3–6 months because of the risk of tissue ingrowth. If that happens, metal stents cannot be easily removed. There is also the tendency to consider early removal within the 1st month, to avoid the serious AEs reported in the study by Bang *et al.*[41] At that point in time, if the necrotic collection is not fully resolved, removal of the LAMS should be followed by replacement with PSs, which should be left in place indefinitely in case of the disconnected pancreatic duct syndrome.

A well-formed tract typically develops between the stomach/duodenum and the collections cavity within days of stent placement. If necrosectomy is required, this should be pursued within days of original stent placement if clinically indicated and continued with repeated interventions until satisfactory debridement has been achieved. This should primarily be done via the lumen of an SEMS if this has been used or by balloon dilatation of the tract if plastic stents were deployed during initial access. If stent dislodgement occurs during necrosectomy, the stent should either be replaced to ensure continued access or further endoscopic intervention scheduled within a short period of time so that closure of the tract does not occur before necrosectomy has been completed. With the wider diameter provided by SEMSs, these tracts can remain open for some days but will ultimately close.

## MANDATORY *VERSUS* PREFERABLE *VERSUS* NOT USEFUL EUS EQUIPMENT

### *Mandatory equipment in an EUS unit for drainage procedure*

Mandatory equipment for endoscopic treatment of WONSs is:

- Longitudinal endoscopic US probe with ultrasound equipment
- 19-gauge needle suitable for an 0.035 (0.025) guidewire (flexible nitinol needle if necessary)
- 0.035 (0.025) guidewire (coated)
- Standard gastroscope
- Standard duodenoscope
- Double pigtail plastic endoprosthesis (8.5–10 Fr)
- Bougie dilatators (6 and 7 Fr)
- Balloon dilators of different sizes (6–18 mm)
- Cautery device or cystotome (10 FR ring knife)
- Lumen-apposing metal stent system or specially designed fully covered metal stent
- $CO_2$ insufflation system
- Pulse oximeter and blood pressure measurement system
- Oxygen.

### *Preferable equipment*

Preferable equipment for endoscopic treatment of walled of necrosis is:

- $CO_2$ pump for endoscopy
- Equipment for general anesthesia
- Slim gastroscope
- Flexible 19-gauge needle
- 19-gauge access needle
- X-ray machine.

### *Add-on equipment*

Add-on equipment could be:

- US system capable of performing contrast-enhanced US
- Multiple plane X-ray equipment.

### *Materials that should be avoided*

- Biliary metal stents, especially if non-covered
- Esophageal metal stents, especially if non-covered.


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### *Conflicts of interest*

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