

# Endoscopic transmural drainage and necrosectomy in acute necrotizing pancreatitis: A review

Linlin Feng, Jintao Guo, Sheng Wang, Xiang Liu, Nan Ge, Guoxin Wang, Siyu Sun

<sup>1</sup>Department of Gastroenterology, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China

## ABSTRACT

Acute necrotizing pancreatitis occurs in 10%–20% of patients with acute pancreatitis (AP) which is one of the most important acute abdominal diseases that require hospital admission. Pancreatic necrosis is also associated with high mortality and morbidity. In the past 20 years, the treatment of pancreatic necrosis has shifted from open necrosectomy to minimally invasive techniques, such as endoscopic interventions. With the development of endoscopic techniques, the safety and effectiveness of endoscopic interventions have improved, but there exist several unresolved problems. Currently, there is no unified standard approach for endoscopic treatment of pancreatic necrosis that takes into account local expertise, anatomical features of necrosis, patients' preferences, and comorbidity profile. We reviewed the current status of endoscopic therapy for acute necrotizing pancreatitis, focusing on the new endoscopic drainage technique and necrosectomy protocol.

**Key words:** acute necrotizing pancreatitis, endoscopic ultrasound, direct endoscopic necrosectomy, percutaneous endoscopic necrosectomy

## INTRODUCTION

Acute pancreatitis (AP) is one of the most important acute abdominal diseases that require hospitalization in most parts of the world. About 10–20% of patients with AP develop necrotizing pancreatitis that significantly worsens their prognosis, may be associated with several complications, and could lead to severe morbidity and mortality.<sup>[1–3]</sup> In recent years, the treatment options of pancreatic necrosis have changed from open surgical debridement to minimally invasive methods, such as laparoscopic, radiologic, endoscopic, and hybrid techniques that combine these methods if required. Laparotomy is only used to treat rare complications of AP, such as abdominal compartment syndrome, intestinal ischemia and necrosis, among others.<sup>[4]</sup> Endoscopic interventional therapy for pancreatic necrosis is becoming more popular, with promising results

and acceptable complication rate. In this review, we focus on the latest advances and controversies concerning endoscopic therapy for patients with acute necrotizing pancreatitis, and we also focus on the new endoscopic drainage technique and necrosectomy protocol.

## MANAGEMENT OVERVIEW

Over the years, endoscopic techniques for pancreatic necrosis have improved dramatically, including endoscopic transluminal drainage via placement of plastic stents, EUS-guided transluminal drainage, drainage by creating multiple tracts with plastic or metal stents, placement of nasal-cyst drainage tube at the same time, using an endoscope to mechanically debride necrotic tissue, combined with other drainage approaches, such as percutaneous drainage (PCD), and the use of specially designed instruments.<sup>[5–9]</sup> With

**Address for Correspondence:**  
Prof. Siyu Sun, Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Shenyang, Liaoning Province, China, 110004. E-mail: sunsy@sj-hospital.org; sun-siyu@163.com

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these improvements, the curative effect and safety of endoscopic techniques have gradually improved. Current data show a clinical success rate of 80–94%, an incidence of adverse event between 8% and 25%, and a mortality rate <10%.<sup>[10–16]</sup>

The endoscopic treatment of pancreatic necrosis is less invasive with similar outcomes, requiring shorter hospital stays and lower costs than open surgery.<sup>[17–19]</sup> Recent evidence also suggests that endoscopic necrosectomy is superior to minimally invasive retroperitoneal necrosectomy.<sup>[20, 21]</sup> A 2019 study has shown that endoscopic therapy should be the preferred treatment strategy for patients with severe infectious necrotizing pancreatitis, taking into account the overall clinical, health, and economic situation, which significantly reduced the incidence of major complications and the cost of treatment and improves the quality of life of patients compared to minimally invasive surgery.<sup>[20]</sup>

EUS-guided therapy, without external drainage, minimizes the risk of pancreatic fistula and prevents fluid and electrolyte loss. A 2018 systematic review of 490 patients concluded that compared with PCD, endoscopic drainage for symptomatic pancreatic fluid collections (PFCs) had a significantly better clinical success rate, a lower reintervention rate, and a shorter duration of hospital stay.<sup>[22]</sup> Furthermore, in critical situations, it may be safer to perform the EUS-guided puncture in the intensive care unit without moving the patient to the radiology department for CT-guided drainage.

## ENDOSCOPIC TRANSMURAL DRAINAGE

If feasible, the interventions should be delayed until the inflammatory response becomes more organized and walled-off pancreatic necrosis (WOPN) appears.<sup>[23]</sup> A clear transgastric window into the necrotic cavity is preferable if most of the necrosis burden is contiguous with the posterior part of the stomach or if the patient is at a particularly high risk of intestinal or pancreatic fistulas.<sup>[24]</sup> A CT scan should be done 2–3 days after drainage to assess the adequacy of drainage, and assessment should also include a combination of patient's symptoms and signs. In the case of failure, endoscopic necrosectomy should be performed.

Because of the wide availability and possible safety benefits of fluoroscopy, traditional endoscopic-guided drainage is performed under fluoroscopy; however, it is associated with radiation exposure and is not mandatory.<sup>[25]</sup> Recent studies have shown that stents can be successfully placed without fluoroscopic assistance just under the guidance of EUS and the technical incidences were similar as well as the technical incidences.<sup>[26, 27]</sup>

Endoscopic-guided drainage is usually performed with an oblique-viewing echoendoscope, which is difficult to perform and requires endoscopists with sufficient experience in the use of linear endoscopic ultrasonography. Some endoscopists suggest that a forward-viewing echoendoscope may be used to overcome these difficulties and have tried to use an echoendoscope with a working channel aligned with the axis of the endoscope for drainage of PFCs. However, the results of a multicenter randomized controlled trial did not show a significant difference between the two echoendoscopes in terms of ease of drainage or safety and efficacy of the procedure.<sup>[28]</sup>

Because of the variable amounts of necrotic debris in WOPN which may prevent complete drainage, endoscopic drainage of WOPN is less successful and requires more frequent endoscopic interventions than pseudocysts.<sup>[29, 30]</sup> To improve the success rates in patients with WOPN, some endoscopists choose to insert a nasocystic tube (NCT) for irrigation to optimize treatment. An NCT is used to provide continuous irrigation and drainage of the cystic cavity to prevent or treat infections. In studies on WOPN, placement of the NCT to irrigate the necrotic cavity with saline has been shown to reduce the rate of stent occlusion, potentially shortening the time required for resolution and ultimately resulting in higher short-term success rates.<sup>[31–33]</sup> However, in another retrospective study,<sup>[34]</sup> similar results were observed even without any endoscopic or external irrigation, as seen in our previous experience.<sup>[35, 36]</sup> It is not clear from current studies whether using the NCT in conjunction with the newer lumen-apposing metal stent (LAMS) offers any advantages.<sup>[37]</sup> Lastly, many patients may not be able to tolerate the NCT. Based on available evidence, we strongly recommend irrigation of the necrotic cavity with the NCT if there are signs of infection; however, more high-quality studies are still required to demonstrate this.

## SELECTION OF DRAINAGE STENT

Currently available stents for transmural drainage mainly include plastic stent (PS), fully covered self-expanding metal stent (FCSEMS), and LAMS. Their characteristics and associated adverse events are listed in Table 1.<sup>[38–48]</sup> These three types of stents are used extensively in practice. There have been limited studies comparing their clinical efficacy and safety, and produced inconsistent results, leaving stent selection a contentious topic.

Traditionally, PSs are used for PFC transmural drainage, which has achieved good results for pseudocysts. However, these were less effective for more complex PFCs, such as WOPN,<sup>[39]</sup> which is thought to be because of their small diameter which can be easily occluded by necrotic debris,

**Table 1: Available transmural placed stents for drainage of PFC**

Stent	Diameter	Characteristic features	Stent-associated adverse event(s)
Double-pigtail plastic stent	7–10 Fr	Made of polyethylene double-pigtail form small diameter low risk of stent migration facilitates easy removal economical	Stent occlusion and cavity infection
FCSEMS	6–10 mm	time-consuming and relatively challenging to deploy Initially designed for biliary or esophageal stenting tubular shape larger lumen non-availability of appropriately sized stents expensive easy to deploy low risk of stent occlusion and superimposed infection biliary self-expanding metal stents does not permit direct debridement access	High risk for migration
LAMS	8-20 mm	Bi-flanged shape for tissue apposition higher tensile force easy deployment expensive wider diameter lumen drain more efficiently and quickly provides direct debridement access allows for a single-maneuver procedure through an incorporated electrocautery-enhanced delivery system (Hot AXIOS stent) act as a tamponade in case of bleeding	Buried stent syndrome delayed bleeding biliary stricture stent dislodgement

PFC: pancreatic fluid collection; FCSEMS: fully covered self-expanding metal stent; LAMS: lumen-apposing metal stent.

requiring further interventions to achieve adequate drainage. Metal stents (FCSEMS and LAMS) with wider diameter overcome the problem of draining high consistency liquid and are used mainly in the drainage of WOPN. They can be placed under EUS only without fluoroscopy.<sup>[27]</sup> The tube shape of FCSEMS involves a higher migration risk; however, it has been reported that placing a double-pigtail PS in the lumen can immobilize FCSEMS, thereby preventing migration and extending patency time.<sup>[40]</sup> The double-walled flanges on both ends of LAMS can anchor the position and the self-expansion design with complete silicone covering can avoid leakage along the tract. Besides, because of its large diameter, the LAMS can allow direct endoscopic necrosectomy through the stent if required. Recently, a study reported that EUS-guided drainage of PFCs having lumen-apposing metal stents with electrocautery (EC-LAMS) involves less procedure time and appears to be easier and safer, thereby simplifying and streamlining EUS-guided management of PFCs.<sup>[41]</sup>

In a large retrospective study conducted in China<sup>[42]</sup> involving 160 patients with PFCs (129 pancreatic pseudocysts, 31 WOPNs), 62 patients drained with PS, 28 with FCSEMS, and 70 with LAMS. The clinical outcomes were similar in all the groups, with the technical success

being 93.5% *vs* 96.4% *vs* 94.3% ( $P = 1.000$ ) and treatment success rates being 84.6% *vs* 85.2% *vs* 89.2% ( $P = 0.763$ ) between PS, FCSEMS, and LAMS, respectively. Four patients (FCSEMS:  $n = 2$  and LAMS:  $n = 2$ ) developed severe bleeding because of pseudoaneurysms, among which three were detected within 2 weeks after the intervention. The two patients in the LAMS group died. The authors emphasized that we should be watchful for severe (or even fatal) bleeding during early stages after metal stent placement, and consider performing CT angiography or EUS examination 1 week after the intervention to detect pseudoaneurysms around PFCs. A study comparing the cost-effectiveness of LAMSs to PSs in managing WOPN showed that LAMSs were more effective than PSs (92% *vs.* 84%) but were also more expensive.<sup>[43]</sup> Some retrospective studies show that FCSEMS and LAMS have similar success rates in managing WOPN, but FCSEMS requires more procedures, and LAMS is more likely to have early adverse events,<sup>[44, 45]</sup> which should not be ignored and careful consideration should be given before using these stents. Another worrisome complication of LAMS is buried stent syndrome, which can make it difficult to remove a stent, introducing a risk of perforation and bleeding on removal.<sup>[46]</sup> De Angelis CG *et al.*<sup>[47]</sup> analyzed all eligible articles reporting timing and complications of LAMS

removal. Their conclusion supported the 4-week timing for LAMS removal, as recommended by European Society of Gastrointestinal Endoscopy (ESGE) guidelines.<sup>[48]</sup> More high-quality studies are still needed to prove the relationship between removal timing, outcome, and adverse events related to LAMS.

## DIRECT ENDOSCOPIC NECROSECTOMY

Concerning WOPN debridement, currently, there are two main types of endoscopic necrosectomy procedures preferable for surgical necrosectomy: direct endoscopic necrosectomy (DEN) and percutaneous endoscopic necrosectomy (PEN). Studies have shown that DEN is more efficacious than minimally invasive surgery, with lower mortality, lower risk of pancreatic fistula, and shorter hospital stays.<sup>[21, 49]</sup> DEN involves cystogastric tract dilatation with a balloon, followed by endoscopic insertion into the cavity of WOPN, detachment and removal of necrotic pieces from the cavity, and flushing of the cavity with saline. There are no effective tools designed specifically for this purpose, and therefore, a variety of endoscopic tools, such as snares, baskets, and rat-toothed forceps are used to remove the necrotic debris.<sup>[50]</sup> The new metal stent has a wide lumen and allows multiple DEN operations without the need to repeatedly dilating the cystogastric tract, making the task of DEN relatively easy.

Recent studies reported the clinical success of DEN between 75% and 95% and the incidence of complications ranged from 7.2% to 33%, with a mortality rate of less than 12%.<sup>[13, 51–55]</sup> The most common complication of DEN was hemorrhage, followed by perforation and infection,<sup>[13, 51–55]</sup> with occasional reports of air embolism, which could be prevented using carbon dioxide insufflation. Most cases of bleeding can be cured by endoscopic treatment. However, severe bleeding required surgical intervention. There are different opinions on the timing, frequency, and interval of DEN. Some experts prefer to perform DEN simultaneously with stent placement which can reduce the number of necrosectomy sessions as well as the problem-solving and resource utilization time.<sup>[13]</sup> However, other experts prefer to wait, stating that direct necrosectomy should only be performed if individual transmural drainage is not successful. The frequency of debridement depends on the size of the cavity, the amount of solid debris, and the degree of adhesion to the adjacent wall.<sup>[56]</sup> Some experts recommend that DEN should be repeated every 48–72 hours until all necrotic tissue has been cleared and granulation tissue is visible on the inner walls of the necrotic cavity.<sup>[57]</sup> However, the need for complete removal of necrotic material is still debatable,

since a thorough removal of necrotic material increases the risk of bleeding.

Although there are no effective tools available, various additional therapies have been investigated for increasing the effectiveness and safety of DEN. Some examples include a high-flow water jet system<sup>[58]</sup> and the endoscopic vacuum-assisted therapy.<sup>[59]</sup> However, only a few small case series have been published describing such efforts. Some researchers suggested the advantage of using hydrogen peroxide to loosen up the necrotic tissue. A dilution between 1:5 and 1:20 can be injected into the cavity under endoscope to assist with chemical debridement to improve efficiency.<sup>[60]</sup> Some endoscopists tried stopping the proton pump inhibitor (PPI) therapy to promote the auto-digestion of necrosis by gastric acid. In theory, stomach acid might enter the WOPN through the stent and promote the auto-digestion of solid necrotic debris, reducing the need for DEN procedures. A multicenter retrospective study<sup>[61]</sup> involving a group of 272 patients with WOPN showed that although withholding PPI increases the risk of early stent occlusion, the overall adverse event rates appeared similar and it could reduce the number of DENs required to achieve a complete resolution. Recently, a novel automated mechanical endoscopic resection system called EndoRotor has been developed for use in gastrointestinal tract for tissue dissection and resection.<sup>[62]</sup> In a prospective study, the endoscopists performed a total of 27 endoscopic necrosectomies using EndoRotor in 12 patients for complete removal of necrotic tissue. Their initial results suggest that the EndoRotor can remove necrotic tissue safely, quickly, and effectively and is easy to use.<sup>[63]</sup> In the future, the development of newer necrosectomy instruments may help achieve a complete solution of WOPN by shortening the operation time and reducing the number of debridements.

## PERCUTANEOUS ENDOSCOPIC NECROSECTOMY

DEN is not possible if the WOPN is located deeply into the retroperitoneum or in the paracolic and pelvic areas away from the stomach or duodenum. This often requires surgical treatment; however, recent studies have shown that PEN (also known as sinus tract endoscopy) provides a safe and effective alternative.<sup>[64–70]</sup> Meanwhile, PEN is also suitable for patients with poor health conditions or other cases where direct endoscopic or surgical treatments are not suitable. PEN was first described in 2000,<sup>[64]</sup> and some studies have demonstrated several potential advantages of PEN including high clinical success rate with minimal adverse events when performed in the regular endoscopy suite (even by the bedside).<sup>[64–70]</sup>



PEN required only moderate sedation, obviating the need for general anesthesia. The same percutaneous track of PCD can be used for PEN by dilating it to approximately 10–12 mm, or a metal stent (such as FCSEMS) can be placed. A flexible endoscope can then be introduced inside the cavity through the tract, and instrumentation established for DEN such as a snare, a basket, and/or a net basket can be used to perform mechanical debridement. There have been reports of PEN with nephroscope, tracheoscope, choledochoscope, and pediatric gastroscope; however, in recent years, debridement using standard gastroscope has been mainstream.<sup>[66–67]</sup> Compared to a rigid nephroscope or laparoscope, a flexible endoscope is more effective in necrosectomy, manipulating the scope to different areas of the cavity to remove debris. We can also use both upper endoscope and nephroscope to perform multiport debridement procedure in patients with a large volume of peripancreatic necrosis, which was shown efficiently in some cases.<sup>[66, 67]</sup> Also, similar to DEN, researchers suggest that this procedure should not be used for cystic lesions in the acute phase when it is extensive, diffuse, or poorly located.<sup>[68]</sup> It is instead best to use carbon dioxide for insufflation during the surgery and avoid overinflation by deflating the cavity intermittently. This procedure can be repeated every 2–3 days until sepsis is controlled and cavities are cleared. Some experts recommend that lavaging the cavity with hydrogen peroxide and/or povidone-iodine solution might help the discharge of necrotic debris.<sup>[67]</sup> However, Jain *et al.*<sup>[69]</sup> reported that it could contribute to the development of peritonitis and recommended that its regular use must be avoided.

Based on the results of relevant studies, the success rate of PEN was 67–93% and procedure-related complication rate was no more than 20%,<sup>[64–75]</sup> with minor complications such as bleeding and pancreatico-cutaneous fistulae. Because of the small operating space, even minor bleeding during PEN operation can be problematic and should be avoided as much as possible. In order to avoid bleeding, surgeons should slowly and carefully grasp the loose necrotic debris while avoiding the blood vessels and should continue lavaging with sterile saline solution. If the necrotic tissue is difficult to remove, it should not be forcibly removed. Although the larger diameter of the tract involves the risk of fistula formation, studies have shown that less than 10% of patients developed pancreatico-cutaneous fistulae after PEN and most fistulas could be healed by conservative management.<sup>[64, 69, 70]</sup>

In recent years, covered metal stents have also been used in PEN operations because of their large caliber, providing a reproducible pathway for necrosectomy. The use of metal stents has been reported to improve safety and reduce the incidence of complications such as site

infection.<sup>[66, 70–72]</sup> Unlike transgastric stents, percutaneous stents are not easily moved as they are fixed to the skin after placement. Currently, there are several problems associated with the use of percutaneous metal stents, such as the time of stent placement and procedure time, which require more prospective studies. Even for this large covered stent, larger necrotic debris can still clog the passage, resulting in prolonged procedure time. A 2019 study<sup>[73]</sup> first reported the use of laparoscopic Babcock forceps under fluoroscopy to remove lodged debris from the midstent. They found that the small and dull “teeth” of Babcock forceps can enter and relieve the obstruction in the stent, simplifying the procedure without any additional complications.

PEN is an advanced interventional technique that requires collaboration between endoscopist and an interventional radiologist, as well as some backup from a pancreatic surgeon for potentially fatal adverse events such as bleeding. Only a few reports on the topic are available, most of which are case or series reports. Larger datasets from large-sample randomized controlled studies are needed to demonstrate its feasibility, safety, and efficacy, as well as to develop the optimal management strategies about PEN. Although the technique has shown promising results, it still has several drawbacks, such as the risk of radiation, lack of specialized endoscopes for necrotic debridement, the possibility of persistent fistula, and the risk of hemorrhage, which is difficult to control. Therefore, it is still debatable whether PEN is superior to surgical necrosectomy in patients with WOPN and more trials are needed in this direction.

## TIMING OF ENDOSCOPIC INTERVENTION

Current international guidelines recommend postponing endoscopic interventions for pancreatic necrosis, ideally at least 4 weeks after the onset of pancreatitis, to encapsulate and define the necrosis. However, some cases of infectious pancreatic necrosis with clinical deterioration may demand earlier (<4 weeks) intervention. Some experts advise less invasive techniques, such as PCD. However, some of these patients require early endoscopic or surgical management in case of no clinical improvement. Trikudanathan *et al.*<sup>[76]</sup> first reported the outcomes of an early (<4 weeks) endoscopically centered step-up approach for necrotic collections in 2018, showing that for patients with infection and organ failure, early intervention can achieve good outcome even before 4 weeks, with similar complications and relatively low mortality compared to a standard intervention after 4 weeks. More than half of the patients who underwent early interventions had only a partial degree of encapsulation. Another recent study<sup>[77]</sup> identified 19 patients with early intervention and showed that early

endoscopic intervention of necrotic lesions 15–27 days after the onset of pancreatitis had similar efficacy and safety as the regular endoscopic intervention in WOPN. They concluded that early endoscopic intervention in pancreatic necrosis at the third and fourth weeks after the onset of pancreatitis is safe and effective if there are indications necessitating urgent clinical intervention and enhanced CT showing a partial or complete wall of collection.

## STRATEGY OF ENDOSCOPIC INTERVENTION

The management strategy for pancreatic necrosis requires a tailored endoscopic technique, based on the specific characteristics of each cyst, size, location, and the number of debris, presence of infection, response to intervention, the general condition of the patient, skill level of the physician, and the availability of equipment.<sup>[4]</sup> In addition to transmural drainage and necrosectomy, several complementary procedures could be used to improve outcomes in pancreatic necrosis patients. Equipment and technological innovations in this area include multiple transluminal gateway technique (MTGT), dual-mode drainage, and minimally invasive step-by-step approach.<sup>[15, 69, 78–80]</sup> An MTGT technique involves the creation of 2–3 transmural tracts between the necrotic cavity and the gastrointestinal tract guidance of EUS. One of the tracts is used for saline flushing through the NCT, while the others are used to place multiple plastic stents to help drain the necrotic debris. Several studies have shown that patients with WOPN treated with MTGT have a higher success rate than those treated with conventional drainage.<sup>[78]</sup> The dual-modality drainage where endotherapy is performed in addition to PCD has been demonstrated as an effective option for the treatment of WOPN with low mortality and morbidity.<sup>[79–80]</sup> The minimally invasive step-by-step approach includes PCD, followed by a minimally invasive resection of retroperitoneal necrosis, if necessary. With the development of various endoscopic techniques, doctors started paying attention to the use of endoscopic treatment strategies to yield the greatest clinical benefits. Bang's study<sup>[15]</sup> compared the traditional endoscopic approach for WOPN to an algorithmic approach, which was based on the collection size, location, and stepwise response to intervention. For larger WOPN (greater than 12 cm), the approach is tailored to the size and location of the debris, and a step-by-step approach is used based on the intervention, the variations of multichannel technique, nasal canal irrigation and drainage, percutaneous catheter irrigation and drainage, percutaneous sinus endoscopic necrosectomy, *etc.* The results show that the algorithmic approach has a higher success rate and less surgery-related

morbidity compared to conventional treatment, and the algorithm-based management was the only predictor of treatment success. Although this finding still needs to be verified in a random setting, preliminary data suggest that the algorithmic approach improves overall outcome.

## CONCLUSION

Endoscopic transdural drainage and necrosectomy are being used widely for management of acute necrotizing pancreatitis, offering the advantages of internal drainage with comparable success rate and low incidence of complications. Current data suggest that endoscopic treatment of pancreatic necrosis requires tailored protocols and more integrated multidisciplinary approach, with the need of further studies to improve the strategy.

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## Conflict of Interest

Siyu Sun is an Associate Editor-in-Chief of the journal. This article was subject to the journal's standard procedures, with peer review handled independently of this editor and his research groups.

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