Is endoscopic necrosectomy the way to go?

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necrotic cavity and debridement with endoscopic accessories. In 2005 Seewald et al. described their experience of using an aggressive endoscopic approach incorporating DEN for treatment of pancreatic necrosis and abscess, generating significant clinical interest in this technique. Alternative methods for obtaining access for drainage and combined modality treatment have also been reported.5,10

This review aims to evaluate the current role of DEN in the treatment of symptomatic WOPN, with an emphasis on DEN in the treatment of infected WOPN.

**Literature Search**

A rapid literature search strategy was employed for all English language literature published from 2000 (year when the technique of DEN was first published) to December 2015. The search was conducted on the electronic databases PUBMED and EMBASE. The search strategy included the keywords ‘endoscopic necrosectomy’, ‘endoscopic drainage’, ‘pancreatic necrosis’, ‘organized pancreatic necrosis’, and ‘walled-off pancreatic necrosis (WOPN)’. The search strategy was adjusted according to the different requirements for each database.

**Technical Aspects of Direct Endoscopic Necrosectomy**

The endoscopic approach to establishing transluminal access to the abdominal cavity without the need for surgical incision has been gaining strong interest over almost two decades, with “natural orifice transluminal endoscopic surgery (NOTES)” being explored for a variety of intra-abdominal procedures.20 DEN conceptually represents a clinical application of these transluminal endoscopic interventions.

The key indication is infected WOPN not responding to conservative treatment with appropriate antibiotics. A prerequisite for DEN is the presence of a well-defined mature wall; otherwise any endoscopic access will result in free perforation. This usually requires a timeframe of 4–6 weeks from onset of the severe necrotizing pancreatitis. The fluid collection must be accessible endoscopically, such as being located within 1 cm of the duodenal or gastric walls; para–colic collections cannot be accessed and would require adjunctive methods such percutaneous drainage. Coagulopathy, if present, should be corrected. The absence of a mature wall, presence of aneurysmal vessels within the collection, uncorrectable coagulopathy and a predominantly solid, rather than liquid collection, are contraindications for DEN.

This technique broadly consists of two steps,21 namely initial access of the WOPN, which may be performed with or without endoscopic ultrasound (EUS) guidance, and endoscopic necrosectomy if there is a lack of response following transluminal drainage. Both steps are performed in the endoscopy centre using monitored sedation, and general anesthesia is usually not required. EUS-guided access is now the preferred technique of achieving access because it provides real time ultrasonic guidance throughout the procedure, and can be successfully performed in cases of WOPN with and without luminal bulging. Randomized controlled studies performed in context of PC drainage showed that EUS-guidance had significantly higher success rates and could also successfully treat cases that non-EUS guided drainage was unsuccessful, due to its ability to visualize non-bulging PC.22,23 It involves utilizing a linear echoendoscope to visualize the WOPN (Fig. 1) and to puncture it with a 19 G needle. This is followed by insertion of guide-wires and dilatation of the puncture tract with coaxial/balloon and cautery devices. Traditionally drainage is then achieved and access maintained through the deployment of double pig-tail plastic stents. In recent years, customized large diameter lumen apposing fully covered self-expandable metallic stents (FCSEMS) have been developed. In contrast to enteral FCSEMS that were previously used, these customized FCSEMS were designed specifically for drainage of PFC and to minimize the risk of migration.24

The lumen-apposing stent (AXIOS™; Boston Scientific, Marlborough, MA, USA) is a fully covered, 10 or 15 mm diameter, nitinol, braided stent with bilateral anchor flanges. When fully expanded, the flange diameter is twice that of the “saddle” section and is designed to hold tissue layers in apposition.25 The Nagi™ stent (Taewoong Medical Co., Seoul, Korea) is another specially designed FCSEMS with a 10, 12, or 16 mm diameter in the center and 20 mm ends which can reduce the risk of migration.26 The advantages of FCSEMS are their larger diameter (15–16 mm compared to 2.8–3.3 mm [7–10 Fr] for plastic stents) and ability to maintain patency of the dilated tract (Fig. 2). This allows for ease of repeat entry into the necrotic cavity for endoscopic debridement and may even decrease the need for intervention due to more effective drainage.

DEN is carried out if there is a lack of response after conserva-

![Image](image-url)
tive treatment and drainage of the WOPN. It is performed using a gastroscope and preferably with carbon dioxide insufflation. If a large diameter FCSEMS had been inserted, the endoscope can be easily inserted into the WOPN (Fig. 3). If plastic stents had been used, then further balloon dilatation of the fistula opening to 15 to 18 mm has to be performed in order to allow endoscope passage; in fact, in between DEN sessions, there is a tendency for the opening to narrow, and thus repeat balloon dilatation may be needed. The first step in DEN is to irrigate and aspirate the smaller loose debris. Direct irrigation will help to loosen solid material partially adherent to the wall. Accessories such as Dormia basket and retrieval nets are used to gently remove the solid material within the cavity which is deposited within the gastric lumen (Fig. 4). It is crucial to perform gentle debridement, and not to forcibly pull apart solid material adherent to the wall of the WOPN, as this may lead to severe bleeding and perforation. Although it may be ideal to remove all solid material until a pink granulating wall remains (Fig. 5), it is not necessary in all instanc-

Clinical Outcome

A vast majority of published literature to date with regards to DEN comprise of studies which are retrospective in nature, with most early studies following the first report of DEN derived from case series. Seewald et al described a retrospective case series of 13 patients unfit to undergo surgery, with all patients having technical success thus avoiding surgery as the initial treatment; 12 out of 13 patients achieved complete resolution of infected pancreatic necrosis and abscesses with endotherapy alone. In the one patient requiring surgery, it was due to extension of the abscess into the right para-colic gutter, which was inaccessible by endoscopy.

The technical and clinical success rates of DEN were similar in several studies that followed with clinical resolution reported in well over 90% of patients in each of these studies. In addition, none of these earlier studies reported any mortality for DEN. With regards to other complications, bleeding was most commonly described, although majority of cases could be managed conservatively with only one of these early studies reporting uncontrollable hemorrhage during balloon dilatation requiring surgery. It should be noted, however, that percutaneous drainage was required for a few patients in addition to DEN where the cavities were inaccessible endoscopically. Recurrence and/or persistence of the necrotic cavity were also one of the issues raised in the early studies. For example, 2 out of the 12 successfully treated patients reported by Seewald et al had recurrent PC from disconnected pancreatic duct syndrome (DPDS). A mean of 4 endoscopic sessions (range, 1–10) was required in the retrospective study by Charnley et al, with necrosis successfully treated in 12 out of 13 patients. Escourrou et al reported recurrence of infection and/or persistence of a necrotic cavity in a total of 5 patients, with the mean number of DEN sessions performed per patient being 1.8 (range, 1–3) and the mean duration of each session 3.5 hours.
in patients who reported abdominal pain after initial fistula tract creation. These patients were managed non-operatively and were discharged. The overall complication rate in this series was 14%. Of the 6 mortalities reported, 5 patients died during the follow-up period after resolution and one patient died peri-procedurally. This was a 67-year-old woman who became suddenly hypotensive towards the end of the DEN session after EUS-guided transgastric access was obtained. The clinical suspicion was that of an air embolism, although no autopsy was performed to confirm this. The median number of DEN sessions were 2 (range, 1–13), which differed from the GEPARD study and will be discussed in the next session. The mean duration of the initial procedure was 87 minutes (range, 25–179 minutes), and that of all procedures was 69 minutes, with EUS guidance being used in 45% of cases. The time to cavity resolution after initial intervention was 4.1 months (range, 3.5–4.6 months). Recurrence of fluid collections was also described in 6% of patients, and this will again be touched on in the section on discussion.

Another large retrospective study looked at the immediate and long-term results of endoscopic drainage and DEN in 80 patients with symptomatic PFC. Initial technical success was reported in 97.5%, and clinical resolution was achieved endoscopically in 83.8%. Bleeding was the most common complication (12 out of 80), perforation (7 out of 80, with 4 requiring surgery), and air embolism in one patient. A further 9 patients required surgery for treatment of the fluid collections either due to its location in endoscopically inaccessible areas or inadequate drainage. The long-term success of endoscopic treatment was 72.5%, with surgery required in 4 patients over a mean follow-up of 31 months due to underlying pancreatic duct abnormalities. It should be noted, however, that not all patients in this study had infected WOPN as an indication for endoscopic therapy (24 out of 80 had infected PC with solid debris), and DEN was carried out in 49 patients in this series, the rest of whom had only transmural drainage as endoscopic therapy.

Another retrospective review of 57 patients across 16 Japanese institutions to evaluate the efficacy and safety of DEN showed that 75% of patients experienced successful resolution after a median of 5 sessions of DEN and 21 days of treatment. The complication rate reported was 33%. Six patients died in this series, 2 from multiple organ failure, one air embolism, one hemorrhage from a Mallory Weiss tear and one from an unknown cause. Recurrent PC formation occurred in 3 out of the 43 patients after clinical resolution during a median follow-up period of 27 months.

The consistently high technical and clinical success rates of DEN have spurred interest in how it performs against surgery, which is in general a morbid procedure with high complication rates. A randomized, controlled, assessor-blinded clinical trial held across 3 academic hospitals and 1 regional teaching hospital in the Netherlands compared DEN against surgical necrosectomy. It is important to note that the primary endpoint was a reduction in pro-inflammatory response between the 2 groups as measured by the cytokine interleukin-6 (IL-6) levels. This proved to be significant, with IL-6 levels increasing after surgery and decreasing after DEN (P = 0.004), and was attributed to avoiding the need for surgical dissection to reach the retroperitoneum or omental sac, as well as the fact that general anesthesia used in surgery is known to induce or prolong systemic inflammation in critically ill patients. Although the primary endpoint for efficacy was a surrogate measure and not clinical resolution, the study nevertheless offered a glimpse into the differences in complication rates between the 2 procedures when compared in a prospective trial. The compos-
ite clinical endpoint of death or major complications (defined as new onset multiple organ failure, bleeding requiring intervention, enterocutaneous fistula, perforation of a visceral organ requiring intervention, and pancreatic fistula) was significantly lower in the group undergoing DEN compared to surgery (20% vs 80%, \( P = 0.03 \)). In particular, there was decreased incidence of multiple organ failure (0% vs 50%, \( P = 0.03 \)) and pancreatic fistulas (10% vs 70%, \( P = 0.02 \)). No patients in the DEN group required pancreatic enzymes at 6 months follow-up, while 50% in the surgery group required pancreatic enzyme replacement (\( P = 0.04 \)). There was one death in the DEN group in this study, compared to 4 in the surgical arm. A median of 3 sessions of DEN were reported in the group receiving endoscopic therapy.

A two-center retrospective comparison of 32 patients comparing 21 surgical necrosectomy cases in one centre with 11 DEN cases in another also showed an increased risk of pancreatic fistula formation following surgical necrosectomy compared to DEN (86% vs 27%, \( P = 0.002 \)). This was also associated with a longer intensive care unit (84 days vs 4 days, \( P = 0.008 \)) and hospital (58 days vs 15 days, \( P = 0.005 \)) stay, although long term complications did not differ between groups. This is in keeping with other studies which show a low complication rate with DEN in addition to a high clinical and technical success rate.\(^\text{37}\)

**Discussion**

The number of cases of DEN reported in the literature has been increasing steadily over the last two decades. The technical and clinical success rates have been consistently high in most case series. However, it is also important to recognize the limitations and risks of DEN. For instance, surgery and percutaneous drainage were required in a few cases where the infected collections were inaccessible endoscopically or when endoscopic therapy proved inadequate to achieve or maintain clinical resolution of the infected WOPN despite initial technical success.\(^\text{17,21–31}\)

Many of the studies also reported recurrence and/or persistence of the necrotic cavity or cyst formation on follow-up.\(^\text{15,17–34}\) In cases of pancreatic duct disruption or DPDS the underlying pancreatic duct abnormalities must be addressed to prevent recurrent PFC.

Bleeding is the most commonly reported complication of DEN, but it is assuring that most cases encountered could be controlled endoscopically. It occurs mainly during the necrosectomy process, and not during the initial EUS-guided puncture and fistula creation. It is interesting to note that only the larger case series from multicenter studies reported severe bleeding requiring surgery or angiographic embolization, and in a small number of cases, resulting in mortality.\(^\text{31,32,34}\) This indicates that even though the risk of clinically life-threatening bleeding is currently low from the literature, the numbers may rise as individual centers perform DEN in increasing numbers. Retroperitoneal perforation may occur with DEN\(^\text{36,17,32}\) and conservative treatment may be feasible in selected patients. The reported mortality is much lower than bleeding, with only one mortality in the GEPARD study,\(^\text{11}\) albeit in a patient who had an underlying inoperable state. Thus it is crucial that centers performing DEN should have multi-disciplinary support from both interventional radiologists and pancreaticobiliary surgeons.

Air embolism is another feared complication with DEN,\(^\text{31,32,34}\) accounting for mortality in certain series.\(^\text{31,34}\) This has prompted the use of carbon dioxide insufflation instead of room air in many centers to mitigate this risk. Aggravation of sepsis and multiple organ failure, complications which may not have a direct link to the procedure of DEN, are also reported in many studies, emphasizing that the role of DEN in infected WOPN is to control the source of infection. A holistic treatment strategy with goal-directed therapy that encompass medical supportive therapy, systemic antibiotics and intervention, is crucial to achieve good outcomes for patients with sepsis from infected WOPN.\(^\text{38}\)

Another area which must not be overlooked is patient selection. Although not explored explicitly or in detail from the studies mentioned in this review, it is intuitive that the clinical condition of the patient undergoing DEN has a bearing on the complexity, safety and efficacy of the procedure, and this can be somewhat inferred from the results of the published literature. For example, the GEPARD study\(^\text{11}\) reported clinical success in 81% of patients compared to an overall success rate of 91.3% reported by Gardiner et al.\(^\text{32}\) Moreover, the mean number of sessions of DEN per patient was 6.2 (range, 1–35) and 2.5 (range, 1–13) respectively. When the 18% of patients who had only one session of DEN were removed from the calculation, the mean number of sessions for those requiring repeat DEN was 7.5. This could be explained by the patients included in each study, as the GEPARD study patients were seriously ill with indications for DEN being infected necrosis in patients with constant and intermittent fever, worsening inflammatory markers and deteriorating clinical condition. Moreover, these patients were already receiving intravenous antibiotics for more than one week with at least half of the study population having undergone either transluminal or percutaneous drainage with no improvement.

This can be interpreted both ways. Firstly, careful selection of patients, as with most other procedures, will most likely result in higher clinical success rates with DEN with a need for fewer sessions to achieve clinical resolution of the infected necrotic cavity. Conversely, the GEPARD study highlights that DEN is a viable and efficacious modality of treatment for ill patients whose baseline condition at the time of intervention may preclude them from surgery and for whom other alternatives such as percutaneous drainage have proven ineffective, although a larger number of sessions of DEN may be required to achieve the desired outcome.

While standard double pigtail plastic stents may be adequate for treatment of PC and fully liquefied abscess collections and indeed, may be preferred in view of their lower costs, they may not be sufficient for effective drainage and to maintain access to the necrotic cavity for DEN in the context of infected WOPN. Data is emerging for the utility of FCSEMS in this context.\(^\text{24,39}\) Lee et al\(^\text{39}\) recently demonstrated in a prospective randomized study that FCSEMS could reduce the median procedure time for transmural drainage of PFC under EUS guidance compared to plastic stents (15.0 minutes vs 29.5 minutes, \( P < 0.01 \)). There was also a statistically significant decrease in the number of stents and guide-wires used, pointing indirectly to a more simplified procedure using FCSEMS. A retrospective single centre comparative study showed no statistically significant differences in technical and clinical success rates, as well as adverse events between FCSEMS and plastic stents.\(^\text{40}\) However, there was again a significantly shorter mean procedure time for EUS-guided drainage (28.8 minutes vs 42.6 minutes, \( P < 0.001 \)) and shorter mean procedure time for re-intervention (34.9 minutes vs 41.8 minutes, \( P < 0.001 \)). The total cost of the procedures were similar in both the FCSEMS and plastic stent groups ($6,274 vs $5,352, \( P = 0.25 \)).

Lastly, it should also be noted that most of the evidence to date on the topic of DEN is derived from tertiary and academic medical centers, which may also account for their high technical and clinical success rates. The learning curve and quality indicators for DEN have not been formally established. DEN should only be performed by skilled and experienced therapeutic endoscopists.
who have a strong foundation in therapeutic endoscopic retrograde cholangiopancreatography and interventional EUS.

Conclusion

DEN has been shown to be an effective and safe minimally invasive option in the treatment of symptomatic WOPN in carefully selected patients. However, these challenging cases should ideally be managed in a multi-disciplinary setting, involving both the interventional radiologists and pancreaticobiliary surgeons, since complementary drainage procedures in context of inaccessible sites, and salvage treatment in context of major complications or inadequate drainage may occur. The greater use of large diameter FCSEMS may potentially reduce the need for aggressive DEN, but will certainly facilitate the process DEN when it is indicated. It is the opinion of the authors that DEN is indeed the way to go in the future.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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