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Endoscopic treatment of infected necrosis

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1. Introduction

Acute pancreatitis is complicated by necrosis of the pancreas or peripancreatic tissue in around 20% of patients (6, 30). Necrotizing pancreatitis can often be treated successfully with a conservative approach, without the need for invasive intervention (21, 33, 34). In a subset of patients, however, there is a need for a more aggressive regimen which includes invasive intervention. The primary indication for this is bacterial infection of peripancreatic collections with walled-off necrosis, which occurs in around 30% of patients with necrotizing pancreatitis (21, 33, 34). Indications for invasive intervention in sterile necrosis include mechanical obstruction of the biliary or gastrointestinal tract, persisting abdominal discomfort and failure to thrive caused by persisting necrotic collections beyond 8 weeks after onset of the acute attack (21, 34).

The traditional approach to infected walled-off necrosis has long been primary laparotomy with complete debridement of pancreatic and peripancreatic necrosis. This surgical approach of primary 'open necrosectomy' is associated with a high risk of complications and death (12). In the last decade, minimally invasive procedures have gained popularity. Recent guidelines now advocate the use of a step-up approach, consisting of catheter drainage, followed, only if necessary by necrosectomy (21, 34). The aim of catheter drainage as a first step is to temporize sepsis by releasing infected fluid from the peripancreatic collections. This may improve the patient´s clinical condition and thereby postpone or even obviate the need for further intervention (25, 31). Catheter drainage can be performed percutaneously under guidance of ultrasound or computed tomography, or endoscopically through the wall of the stomach or duodenum (21, 33, 34).

If the patient's clinical condition does not improve after catheter drainage, necrosectomy can be performed through laparotomy, laparoscopy, a minimally invasive retroperitoneal approach or by an endoscopic transluminal approach. This chapter focuses on the technique and the results of published studies on endoscopic drainage and necrosectomy.

2. Technical aspects

Endoscopic drainage and necrosectomy can be performed under conscious sedation using midazolam or propofol and fentanyl. As a first step, linear-array endoscopic ultrasound is performed to visualize the collection of walled-off necrosis and to determine the optimal route for puncture through the posterior wall of the stomach

or duodenum. This is facilitated by the finding of the collection bulging into the stomach or duodenum. Under endoscopic ultrasound guidance, the collection is punctured using a 19 gauge needle. The stylette is withdrawn and the content of the collection is aspirated to confirm the correct position. A guidewire is then advanced through the needle under fluoroscopic guidance. The outer sheath of a cystgastrostomy is advanced using electrocautery, and balloon dilatation of the puncture tract is performed up to 15 mm. The aspirate is sent for microbiological culturing, after which rigorous irrigation of the collection is performed using normal saline. As a next step, for the traditional approach, 2 or more double-pigtail plastic stents (size varying from 5 to 10 Fr) are placed in the cystgastrostomy. A nasocystic catheter may be positioned in the space of the walled-off necrosis which can be used for continuous irrigation of the collection with at least 1 liter of normal saline per 24 hours in order to secure the patency of the cystgastrostomy. Although obvious, it must be stressed that flushing with large amounts of fluid is not possible as the nasocystic catheter is for inflow only: i.e. all fluids are considered as intake and must be accounted for as such. Many centers do not routinely place nasocystic drains, rather repeating endoscopic intervention, or flushing via an adjunctive retroperitoneal percutaneous catheter, which allows “one way” irrigation through the endoscopic cystenterostomy into the stomach or duodenum (24).

The results of endoscopic drainage on the clinical condition of the patient is followed for the next 72 hours. A new endoscopic procedure is planned if there is no clinical improvement: i.e. a decrease in the need for organ supportive therapy on the intensive care unit, disappearance of fever and improvement of vital signs, or a decrease in serum C-reactive protein and white blood cell count (31).

If a subsequent endoscopic procedure is performed, and a traditional style of double pigtail stents is utilized, the endoluminal access site is dilated up to 15 - 20 mm using a dilatation balloon. A forward-viewing endoscope is advanced in the collection and the necrosectomy is performed. The pancreatic and peripancreatic necrotic tissue can be evacuated with several instruments such as a basket, a polypectomy snare or grasping forceps. At the end of the procedure, several double-pigtail plastic stents (5 to 10 Fr.) are placed in the collection and irrigation is continued. Endoscopic necrosectomy is repeated as needed in the subsequent days, depending on the amount of necrosis left in the collection and the clinical condition of the patient. The steps of transgastric necrosectomy are illustrated in **Figure 1** and a video of the procedure is available at http://www.jama.com (2).

3. Results from published studies

Case series

Since endoscopic necrosectomy was introduced in treatment of necrotizing pancreatitis numerous case series have been published. Two systematic reviews on endoscopic necrosectomy including these cohorts state that it is an effective and safe treatment option (8, 28). The most recent of the two systematic reviews included 14 studies published up to June 2013, with a total of 455 patients (28). Primary intervention was endoscopic drainage of the necrotic collection in 92% of patients at a mean of 57 days after diagnosis of acute pancreatitis. Drainage was followed by endoscopic necrosectomy at a mean of 7 days. Complications occurred in 36% of patients, with bleeding (18%), perforation of a hollow organ other than the stomach or duodenum due to the intervention itself (4%) and pancreatic fistula (5%) being the most predominant. Endoscopic necrosectomy was clinically successful; i.e. the condition was treated by endoscopic procedures alone, in 81% of patients with a mean of 4 endoscopic procedures per patient. The remaining patients needed additional percutaneous or surgical intervention for treatment of the pancreatic necrosis or complications of endoscopic necrosectomy. Overall mortality was 6% (range 0% - 15%) (28).

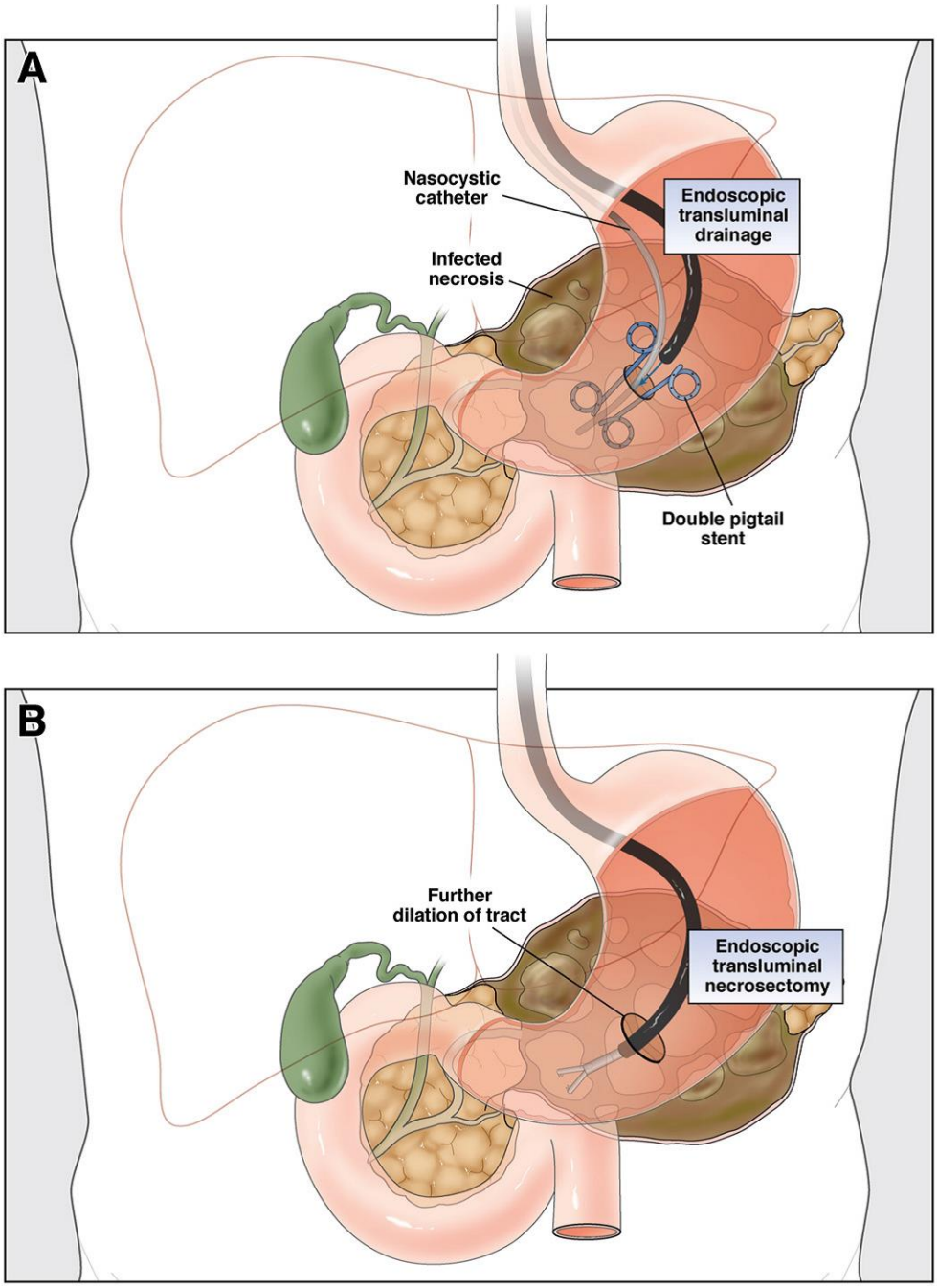

Figure 1. Endoscopic drainage and necrosectomy. Shown is a peripancreatic collection of walled-off fluid and necrosis. The collection is identified behind the posterior gastric wall through bulging into the gastric lumen and endoscopic ultrasound. (A) Endoscopic drainage: The collection is punctured and balloon dilated. Double pigtail stents and a nasocystic catheter drain are placed for continuous irrigation and to secure patency of the cystgastrostomy. (B) Endoscopic Necrosectomy: The tract is dilated up to 15-20mm and endoscopic necrosectomy is performed by grasping forceps (shown) or other endoscopic necrosectomy instruments.

More recent and relatively large case series (N=57 to N=176) on endoscopic treatment of necrotizing pancreatitis report similar results on a number of endoscopic procedures (2 to 5), clinical success rate (76% to 94%) and mortality (0% to 11%) to those reported in the systematic review (5, 9, 16, 22, 35). Type of complications in these newer series are also similar and include bleeding, pneumoperitoneum, perforation of a hollow organ and infection, but their occurrence

seem to decrease with a reported incidence of 3% to 33% (5, 9, 16, 22, 35).

A limitation of most case series is selection bias. Series on endoscopic necrosectomy often include only patients felt to be suitable for endoscopic drainage and necrosectomy; i.e. with well demarcated necrotic collections, which are in close apposition to the gastric or duodenal lumen and without deep retroperitoneal or pelvic extension.

Comparative studies

Few studies compare endoscopic treatment with percutaneous / surgical treatment for necrotizing pancreatitis and indications for intervention between studies are diverse. A retrospective analysis of 20 patients undergoing endoscopic necrosectomy compared with 20 patients undergoing surgical necrosectomy for symptomatic sterile pancreatic necrosis showed no mortality or significant difference in complications (10). Patients in the endoscopic group underwent more re-interventions (9 vs. 3 patients), had a shorter length of hospital stay (3 vs. 7 days) and a longer time to resolution of the necrotic collection (3.6 vs. 0.4 months). Another retrospective analysis included 62 patients (30 open necrosectomy, 14 minimally invasive retroperitoneal necrosectomy and 18 endoscopic necrosectomy) and showed lower severe complication and mortality rates for endoscopic necrosectomy (7). However, significant baseline differences on severity of disease and infection of necrosis were evident which restricts judgment on comparisons.

One prospective registry study matched 12 patient undergoing endoscopic necrosectomy with 12 patients undergoing the surgical step-up approach for suspected or confirmed infected walled-off necrosis (11). In the surgical step-up group, 3 patients required catheter drainage only and 9 underwent subsequent minimally invasive surgical necrosectomy. One patient in the endoscopic group needed additional percutaneous drainage of an endoscopically inaccessible necrotic collection. Patients in the endoscopic necrosectomy group experienced fewer severe complications (1 vs. 7) and less post-procedural new-onset organ failure. Furthermore, endocrine insufficiency was less frequent during follow-up in the endoscopically treated group (0 vs. 7). One patient in the surgical group died (11).

A randomized trial that included a total of 20 patients and compared endoscopic necrosectomy with surgical necrosectomy for infected walled-off necrosis showed that the primary end-point of post procedural pro-inflammatory response measured by serum interleukin 6 was significantly lower in the endoscopically treated group. The trial also reported lower incidence of post procedural new-onset organ failure (0% vs. 50%) and pancreatic fistulas (10% vs. 70%) in the endoscopic group (4).

Innovation

The endoscopic techniques are subject to rapid development. Recently, several series have been published using single, lumen-apposing, self-expandable metal stents as a substitute for the multiple 5 to 10 Fr. pigtail stents that are placed in the cystgastrostomy (14, 17-19, 32). The stents are saddle shaped and are equipped with bilateral double-walled anchoring flanges which are designed to hold the gastrointestinal wall in direct apposition to the wall of the pancreatic collection (**Figure 2**) (1, 19). Their length is 10 mm and they are available at 10 mm or 15 mm in diameter, the latter being more suitable if necrosectomy is anticipated. These stents, specifically designed to be delivered via endoscopic ultrasound, are easily deployed and after primary drainage of the pancreatic collection, direct endoscopic necrosectomy can be performed through the stent if necessary. The stent can be left in situ for additional necrosectomies in the following days or weeks (18, 19). Clinical outcome is similar to recent studies using traditional endoscopic approach, with 86-88% clinical success rate with endoscopic intervention alone.

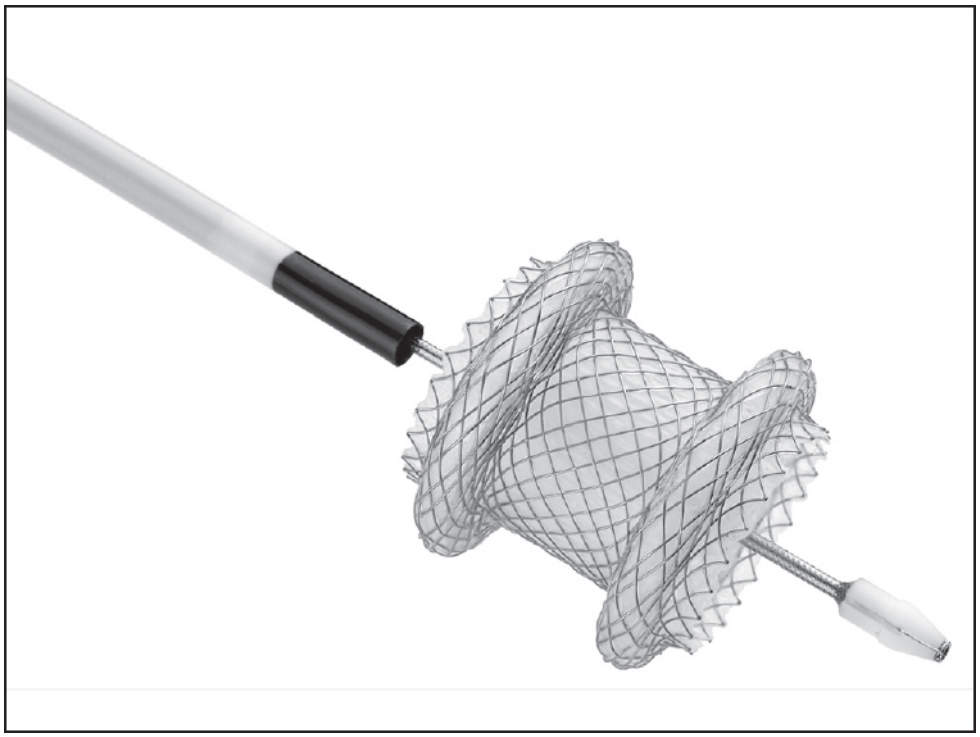

Figure 2. Lumen apposing self-expandable metal stent

Major complications include bleeding, infection, stent migration and stent occlusion, and occur in 7-13% of patients. Two large retrospective studies (N = 124 and N = 68) reported no mortality in their series (18, 19). The advantages of metallic stents are of particular interest in the treatment of necrotizing pancreatitis in children. Specifically this young and fragile patient group may benefit from the high patency of the stent, easy access to the collection, possible need for less interventions and absence of external fistula (23). Given the fact that these interventions are infrequently performed in children, treatment is reserved for specialist centers (23).

Another alternative to the traditional approach of endoscopic drainage and placement of double pigtail stents is the use of a fully covered, large-bore, esophageal metal stent. The stent is placed directly following primary endoscopic ultrasound guided drainage of large necrotic collections. The flares at both ends of the stent limit migration and the large diameter (up to 23 mm) facilitate drainage and instrumental access for necrosectomy. Due to its size, the stent is limited to transgastric (as opposed to transduodenal) drainage and necrosectomy. Results of case series are preliminary but suggest these stents are of particular use for larger necrotic collections when the need for repeated endoscopic intervention can be expected (3, 15).

4. Discussion

In this chapter we have presented an overview of the indication, the technique and primary structured results of the latest and most innovative invasive treatment strategy for necrotizing pancreatitis. The endoscopic approach of necrotizing pancreatitis appears to measure up to surgical techniques in terms of choice of primary and definitive treatment, number of complications, health care utilization and costs (10, 11, 26, 28). Available studies even suggest lower mortality rates and lower incidence of new onset endocrine insufficiency (5, 9, 11, 16, 22, 28, 35).

Endoscopic intervention carries a number of advantages over surgical techniques. First, the

procedure can be performed under conscious sedation and thereby obviates the need for general anesthesia, which is known to induce or prolong systemic inflammatory response syndrome in critically ill patients (20). Second, by creating an internal fistula between the necrotic collection and the gastrointestinal lumen as a drainage and necrosectomy gateway, a lumbotomy or laparotomy is avoided. External fistula, which can be cumbersome to reverse, are thereby non-existent if endoscopic therapy is successful without additional percutaneous or surgical interventions. Special interest to endoscopic approach goes out to treatment of disconnected pancreatic duct syndrome with pancreatic fluid collections obstructing the biliary tree or gastrointestinal tract. By internally bypassing the disrupted natural drainage canal of the exocrine pancreas to the stomach or duodenum, the pancreatic juices are not lost, bothersome external fistula from percutaneous catheters are prevented and extensive surgery with alteration of the intestinal anatomy and loss of functional pancreatic tissue is avoided (13). It must be stressed however, that interventions for sterile collections after necrotizing pancreatitis are preferably delayed to beyond 8 weeks after the acute attack as symptoms are known to regress spontaneously over time (34). Third, with endoscopic intervention the integrity of the abdominal wall remains intact which prevents wound infections, debilitating incisional hernias and unsightly scars. As opposed to surgical procedures such as video-assisted retroperitoneal debridement and sinus tract necrosectomy, endoscopic treatment of necrotizing pancreatitis can therefore be called ‘truly minimally invasive’.

A limitation of the endoscopic approach is that, in order for the endoscopist to safely enter, the necrotic collection must adjoin the lumen of the stomach or the duodenum. Not every patient with necrotizing pancreatitis in need for invasive intervention is therefore suited for endoscopic treatment. However, due to the anatomic relation of the pancreas to the stomach and duodenum, it is likely that the vast majority of necrotic collections can be reached endoscopically. The positive side of this limitation is that in some cases the endoscopic route is preferred, as kidney, spleen, stomach, large vessels and intestine can complicate the surgical route towards the centrally located walled-of necrosis. A second limitation of the endoscopic technique is that complications such as perforations and bleeding can be difficult to manage. Perforation often requires additional surgical intervention which partly nullifies the benefits of primary endoscopic treatment (5, 28). Small bleedings can often be controlled endoscopically by clipping, thermal coagulation or local epinephrine injection. Persistent bleeding needs more definite treatment, in which angiographic coiling of the artery is the treatment of choice after which emergency laparotomy, with its associated surgical disadvantages, is the last resort (28). Thirdly, endoscopic drainage and necrosectomy is challenging due to the small anatomical space in which the endoscopist must operate, indirect vision and limited options for tools to be used simultaneously. The procedure can therefore only be executed by an experienced endoscopist with access to advanced endoscopic instruments. This, combined with the fact that necrotizing pancreatitis is relatively rare and invasive interventions are not performed frequently, means that the endoscopic approach is reserved for specialist centers only. Finally, for treatment success with endoscopic necrosectomy, an average of four procedures per patient are necessary as opposed to 1 - 3 for the minimally invasive surgical and open necrosectomy (26, 28, 31). Although not necessarily associated with higher costs, this can be a significant burden on the patient and its relatives, as well as on health care resources.

Advantages and options for improving technical aspects of the endoscopic approach are evident and outcomes in treatment of necrotizing pancreatitis are promising (24). This seems to justify the increasing role of endoscopy in treatment of necrotizing pancreatitis. However, reports on endoscopic treatment for necrotizing

pancreatitis included patients that are generally less ill than patients treated in studies reporting on surgical procedures. This is indicated by lower APACHE-II scores, less organ failure and less infected necrosis in the endoscopic studies (26, 28). These differences may in part explain the more favorable outcomes of endoscopy. On the other hand, it is likely that less invasive interventions in necrotizing pancreatitis induce less surgical, pro-inflammatory stress and could thereby lead to better outcomes. This lower pro-inflammatory response after less invasive intervention was already shown in a randomized trial comparing endoscopic with surgical necrosectomy (4). This trial also showed less complications for the endoscopy group but was not powered for clinical endpoints. Another randomized controlled multicenter trial, adequately powered for clinical endpoints, compared minimally invasive surgical step-up approach with primary open necrosectomy in infected necrotizing pancreatitis. Patients in the (less invasive) step-up group experienced less post-procedural new-onset organ failure, underwent fewer operations, had fewer incisional hernias and less new-onset endocrine and exocrine insufficiency at 6 month follow-up (30). It could very well be that the less invasive nature of endoscopic treatment translates to equal or even better outcome than minimally invasive surgical necrosectomy. Comparative studies on this matter are scarce, include small numbers of patients and bias is likely due to the mostly retrospective study design (4, 7, 10, 11). A randomized controlled multicenter (TENSION) trial in the Netherlands compares the transluminal endoscopic step-up approach with the minimally invasive surgical step-up approach (controlled trials ISRCTN09186711) (29). This direct comparison in 98 patients with infected necrotizing pancreatitis will answer the question if endoscopic step-up treatment is superior to surgical step-up treatment on the combined end-point of death or major complications. A randomized controlled trial on the outcome death alone will most likely never be performed due to the complexity and rare nature of the disease. Therefore an international collaboration between pancreatic specialist centers worldwide was founded to pool the results of individual participant data undergoing necrosectomy for necrotizing pancreatitis. The protocol for this study is prospectively registered at the POSPERO registry for systematic reviews (CRD42014008995) and is available online (27). Both the randomized TENSION trial and the individual participant data meta-analysis are currently being finalized and results are expected by the end of 2016.

In conclusion, endoscopic transluminal drainage and necrosectomy is a rapidly developing and increasingly popular technique in the treatment of necrotizing pancreatitis. Results from numerous case series and small comparative studies are promising, but evidence from adequately powered trials or studies with robust methodological quality are needed. Results of a large multicenter randomized controlled trial and an international meta-analysis of individual participant data are pending.

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