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TOPIC

Endoscopic management of walled-off pancreatic necrosis

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Abstract Endoscopic management of infected walled-off pancreatic necrosis is increasingly being performed. Although the role of the interventional endoscopist in treating necrotizing pancreatitis is growing, a multidisciplinary team including dedicated surgeons and interventional radiologists is a condition sine qua non for optimal patient management. Optimal management starts with a correct diagnosis with accurate description of the extent and nature of the inflammatory changes according to the recently updated criteria. This is important to consequently select the correct patients for the correct intervention at the correct interval after onset. When a decision is made to endoscopically intervene in a patient with (infected) pancreatic necrosis, the actual endoscopic technique does not differ much from the first retrospective series published a decade ago. Although endoscopic intervention for pancreatic necrosis is increasingly performed, evidence for superiority of endoscopic treatment over other techniques is still lacking. Dedicated endoscopic accessories for optimal drainage and necrosectomy are still lacking as well. This review provides an overview of current status, technique and recent innovations of endoscopic treatment of walled-off pancreatic necrosis.

Keywords Acute necrotizing pancreatitis · Acute necrotizing pancreatitis, surgery · Acute necrotizing pancreatitis, therapy · Endoscopic transluminal necrosectomy · Infected pancreatic necrosis

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Introduction

Acute pancreatitis is a common and potentially lethal disease. Approximately 80% of patients develop edematous pancreatitis, in which the clinical course is mild and the disease usually resolves spontaneously within several days to weeks. Approximately 20% of patients, however, develop necrotizing pancreatitis, which is associated with a mortality rate of 15% [1]. About 30% of patients with necrotizing pancreatitis develop infected necrosis and generally need an intervention during the course of their disease [1, 2]. The vast majority of sterile collections can be managed conservatively.

According to the recently updated Atlanta classification, acute pancreatitis associated collections can be subdivided into acute necrotic collections, walled-off necrosis (WON), acute peripancreatic fluid collections, and pseudocysts [3]. It is important to distinguish necrotic collections from other types of pancreatitis associated fluid collections, since management is substantially different.

During the last decade, minimally invasive interventions have essentially replaced traditional open necrosectomy in an attempt to reduce morbidity and mortality associated with open necrosectomy. Besides percutaneous drainage and minimally invasive surgery, endoscopic transluminal drainage and necrosectomy has been described in multiple reports as an alternative for open surgery [4–13]. This review provides an overview of the current status of endoscopic treatment of WON.

Indications for and timing of intervention

Optimal management of infected necrotizing pancreatitis requires a multidisciplinary team including dedicated surgeons, interventional radiologists and gastrointestinal endoscopists. Such a multidisciplinary team needs to be involved from the onset of the disease to decide if, when, and how an intervention needs to be performed. Feasibility of transgastric or transduodenal, as well as percutaneous

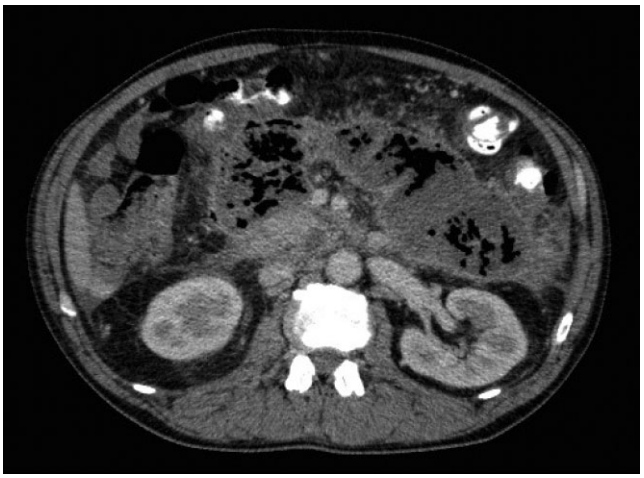

Fig. 1 Infected walled-off pancreatic necrosis as evidenced by presence of gas bubbles in the collection

(retroperitoneal) drainage, needs to be assessed. Before drainage is initiated, one should consider different interventions in case not all (infected) collections are expected to be adequately drained by just one approach.

Cases eligible for (endoscopic) intervention can be subdivided into infected and sterile necrotic collections.

Infected (walled-off) necrosis

The major cause of death, next to early organ failure, is infection of (peri)pancreatic necrosis leading to sepsis and multiple organ failure. Secondary infection of pancreatic necrosis develops in approximately 30% of patients with necrosis [1, 2]. Infected necrosis is virtually always an indication for intervention. Fine needle aspiration to prove infection is rarely necessary since interventions are postponed and infection becomes obvious on clinical and radiological criteria, avoiding the risk of a false negative result and secondary infection [13]. Infection is proven by detecting gas in the necrotic collection on computed tomography (CT). Suspicion of infection is usually based on ongoing clinical deterioration despite maximal support, high fever with rising inflammatory markers and/or positive blood cultures.

Currently, (suspected) infected necrosis is not always an indication for immediate intervention. A longer period of time between onset of the disease and intervention is suggested to be associated with lower mortality and intervention is delayed if the clinical condition allows [1]. This allows the collection to become more organized and walled-off, which optimizes conditions for intervention (Fig. 1). In case of proven or suspected infected necrotizing pancreatitis, intervention should be delayed where possible until at least 4 weeks after initial presentation [1, 14]. In the meantime patients should be treated with broad-spectrum antibiotics.

Sterile (walled-off) necrosis

In around 70% of patients with necrotizing pancreatitis, the (peri)pancreatic necrosis remains sterile. The vast majority of sterile necrotic collections can be treated conservatively as most collections will resolve spontaneously [14]. An intervention for sterile (peri)pancreatic collections is only indicated in patients with persistent gastric outlet, intestinal, or biliary obstruction due to mass effect of WON at least 4–8 weeks after onset of symptoms [14]. In case of persistent symptoms such as pain and "failure to thrive" intervention is more debated and current guidelines suggest that in such cases, intervention can be considered 8 weeks after onset [14].

Technique of endoscopic transluminal drainage

Endoscopic drainage and necrosectomy may lead to acute or delayed bleeding. Therefore, anticoagulant or antiplatelets drugs should preferably be discontinued. In case of severe bleeding during the procedure, which cannot be treated endoscopically, immediate assistance of an interventional radiologist should be requested.

Endoscopic drainage and necrosectomy are preferably performed with patients under deep sedation or general anesthesia. Routine antibiotic use is recommended for those not already receiving broad-spectrum antibiotics for presumed or documented infection. All procedures should be performed with carbon dioxide (CO_2) insufflation since fatal gas embolism has been described. Endoscopic transluminal necrosectomy (ETN) is performed according to similar protocols around the world with small technical variations between centers. We did not change our protocol much since our report concerning ETN almost a decade ago [12].

Initial EUS guided drainage

First, the feasibility of endoscopic drainage is assessed with endoscopic ultrasound (EUS). This mainly consists of verifying the presence of a collection as seen on CT or magnetic resonance imaging (MRI) and subsequent determination of the optimal site for drainage, ensuring a minimal distance and avoiding vessel interposition by use of color-flow Doppler (Video S1). Rarely, initial drainage is performed by blind puncture at the site of maximum impression on the gastric or duodenal wall. However, EUS guidance is shown to increase technical success rate and in our opinion also vital in decreasing the number of complications and misdiagnosis [15, 16].

After determining the optimal puncture site, the collection is punctured under EUS guidance with either a 19-gauge EUS needle or a cystotome (Video S2). After

withdrawal of the stylet or inner needle wire, some fluid is aspirated to confirm the correct position of the needle in the collection. Correct positioning can also be confirmed by contrast injection into the collection under fluoroscopy. The aspirated fluid is sent for fluid analysis including at least a Gram stain and culture. Next, a standard 0.035 guidewire is introduced through the 19-gauge needle or cystotome into the collection, after which the needle is removed. The tract is dilated with either a 10 Fr cystotome, a balloon of between 8 and 15 mm, or both. Finally at least two double-pigtail stents and a naso-cystic catheter are inserted into the collection. The latter will be used for continuous flushing with 1 l of sterile fluid per 24 h. In case of clinical improvement, subsequent necrosectomy can be avoided. In case a patient does not improve after 48–72 h and the collection is deemed inadequately drained as observed on repeat contrast enhanced computed tomography, additional ETN is performed. Since it is expected that about 60% of patients need additional necrosectomy, an experienced endoscopic team needs to be available 48 to 72 h after initial drainage.

Some authors have advocated dilating the tract further during the initial procedure to perform direct ETN aiming to reduce the number of procedures needed [17]. In line with the success of percutaneous catheter as definitive treatment, which is successful in avoiding the need for additional surgical necrosectomy in about 40% of patients with infected WON, we reserve ETN for cases that do not clinically improve [13]. For endoscopic drainage this concept has, however, not been proven yet.

Endoscopic transluminal necrosectomy

Endoscopic transluminal necrosectomy is a time-consuming procedure. Enough time needs to be allocated on the endoscopy suite when the procedure is started, which is another strong argument for deep sedation or general anesthesia. In general ETN procedures take between 60 and 120 min. Optimal circumstances prevent multiple suboptimal necrosectomy procedures, frustrating the patient as well as the endoscopy staff. Before entering the necrotic collection, recent abdominal imaging needs to be carefully studied to improve anatomical orientation during the procedure and to prevent that subcavities of the collection remains unrevealed and untreated.

At the start of the procedure the naso-cystic catheter is removed and, after introducing the therapeutic gastroscope, all but one of the pigtail stents are removed as well. The remaining stent is used as a visual guide to the opening of the cavity and as an escape route for air or fluids in case of aggressive insufflation or rinsing. Next, the fistula usually needs dilation under radiologic guidance up to 18 or 20 mm using a dilation balloon. The cavity is entered and

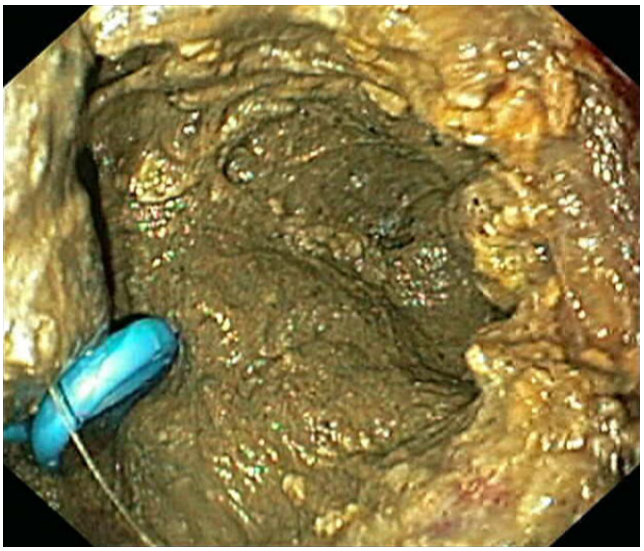

Fig. 2 Endoscopic image showing pancreatic necrosis before endoscopic necrosectomy. One transluminal stent is left in situ

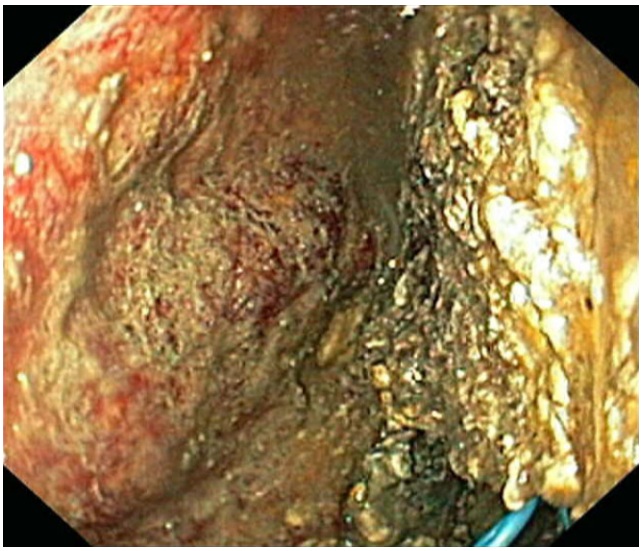

Fig. 3 Endoscopic image showing necrosis (right) and a vital, pink wall (left)

necrosectomy is performed using a polypectomy snare, Dormia basket, Roth net, or other endoscopic device at the discretion of the endoscopist (Fig. 2, Video S3). Some novel techniques are discussed below under "innovations". The procedure is completed when most adherent necrotic tissue is removed until a vital, pink wall becomes visible (Fig. 3). Again at least two double pigtail stents and a naso-cystic catheter for continuous lavage are inserted into the collection. In our centre the procedure is repeated in case there is no clinical improvement within 48 to 72 h or when multiple necrotic parts could not be removed in the previous procedure. Before re-intervention one should always consider

whether additional collections are not adequately drained and should be drained as well via a different route i.e. percutaneous drainage of endoscopically inaccessible collections.

Follow up

In the early days of ETN, stents were removed in case the collection was collapsed about 10 weeks after the final procedure. The majority of recurrences seem to be related to persistent disruptions of the pancreatic duct [18]. Consequently, the tendency is to leave the stents in for a longer period to theoretically provide time in which potential disruptions of the pancreatic duct can heal. There still is debate whether duct anatomy needs to be determined by ERCP or MRCP during the course of the disease to, in case of a disruption, place either a stent in the pancreatic duct or leave the transluminal stents in situ for a long period. Small studies suggest that leaving the stents in situ results in less recurrence without complications related to leaving the "foreign" stents in situ [18, 19].

Complications

In a recently published systematic review of ETN, complications occurred in 36% of patients (163/455 patients) [20]. The most common complication was bleeding, which occurred in 18% of patients. The majority of bleeding episodes (93%) could be treated endoscopically by coagulation, epinephrine injections, or clips. In 7% of patients, an angiography with coiling or surgery was required to stop the bleeding. The described major bleedings requiring additional intervention that consisted of bleeding form pseudoaneurysmata in the collection and from the fistula created to enter the necrotic collection [20].

Perforations to the (retro)peritoneum occurred in 4% [20]. The majority of perforations occurred during dilation of the initial puncture site for drainage, probably because the necrotic collection was not adherent enough to the stomach or duodenal wall at the puncture site. In general, at least in our experience, such perforations can be treated conservatively. However, in the mentioned systematic review, 67% of perforations appeared to be treated surgically. On the other hand, in case of a perforation of the wall of the collection itself, surgery is usually indicated.

A feared complication is gas embolism, which is described in three case series and one case report [10, 17, 21, 22]. Gas embolism is a rare, but well known severe complication of especially therapeutic endoscopy [23]. Gas embolism results from a direct communication between a source of gas and the bloodstream. Risk factors included the use of interventional techniques and local inflammation, which are both present during an ETN [23]. It has been advised to use CO_2 instead of air because CO_2 is better absorbed and therefore would decrease the risk of air embolism [10, 17, 21]. However, fatal gas embolism when using CO_2 insufflation is described as well [22].

Besides (theoretically) decreasing the risk by using CO_2 insufflation, it is important to consider and recognize gas embolism if cardiovascular and/or respiratory symptoms develop abruptly during the procedure without another explanation [23]. Protocols should be available to manage these critical situations. Gas in the venous portal system beforehand may contraindicate additional endoscopic necrosectomy.

Evidence

The earlier mentioned recent systematic review shows that ETN is a safe and effective minimally invasive treatment in (infected) necrotizing pancreatitis [20]. More than 80% of patients were treated successfully with endoscopic management alone. This was associated with a mortality rate of 6% and complication rate of 36%. Of note, 14 of a total of 15 included studies were retrospective in nature and the methodological quality of the vast majority of included studies was moderate to low. Furthermore, the vast majority of included studies did not report on the most relevant parameters of disease severity (e.g. preprocedural organ failure and presence of infected necrosis) or outcome measures. Only two studies reported clear definitions for organ failure. Just little more than half of the patients had proven infected necrosis. Therefore, the favorable results of this systematic review should be regarded in the light that the pooled data comprise mostly moderately ill patients and the methodological quality of the included studies is limited [20].

Recently updated guidelines already state that if an intervention is indicated in patients with (infected) necrotizing pancreatitis, initial treatment should consist of either image-guided percutaneous catheter drainage or endoscopic transluminal drainage [14]. If catheter drainage does not lead to clinical improvement, the next step is minimally invasive drain-guided retroperitoneal necrosectomy or ETN [14]. Endoscopic management is, since the underlying evidence is moderate, not proven to be as effective as the minimally invasive surgical step up approach. A recently performed pilot multicentre randomized controlled trial of 22 patients does suggest that ETN reduces the number of major complications [6]. Results from a currently performed multicentre randomized controlled trial comparing ETN to minimally invasive surgical step up approach are eagerly awaited for higher level of evidence (TENSION trial; ISRCTN09186711) [24].

Innovations

One relatively small modification of the above-described technique is dual-modality drainage combining endoscopic drainage and percutaneous drainage in all cases when feasible [25]. This approach combines relatively large percutaneous drains in combination with transluminal stents, theoretically decreasing the need for additional necrosectomy. Moreover, the risk of a pancreatic fistula complicating the percutaneous drain in case of a disrupted pancreatic duct is theoretically decreased by the presence of a transluminal drain as compared to only percutaneous drainage. The potential benefits of this approach needs to be evaluated in comparative trials.

Another modification is the use of multiple transluminal stents aiming to increase adequate drainage of the often multiseptated necrotic collections. This can be either done by creating multiple transluminal tracks in case the collections seem not to communicate or by placing multiple double pigtail stents and a nasocystic catheter in the different subcavities via the same track [26, 27]. The latter modification can be easily adapted into current standard ETN without the risk of additional complications or risks.

Recently, various case reports and small case series described the use of a self-expandable metal stent for transluminal drainage of pancreatic fluid collections combined in some cases with direct necrosectomy [28–34]. The larger diameter of the metal stents in comparison to the plastic pigtail stents aims to improve drainage and avoiding the need for re-dilatation if an additional ETN procedure is necessary. However, migration and mechanical compression of the end of the metal stent into the collapsed fluid collection has been reported to cause massive bleeding and could be one of the major drawbacks of using metal stents [29]. Metal stents specially designed for drainage of pancreatic fluid collections, are meant to overcome these complications [28, 32, 33]. Results regarding safety and superior efficacy are awaited before the use of these innovative metal stents can be adapted into clinical practice.

One of the biggest challenges of ETN is to effectively remove large amounts of necrotic material from within the collection in a limited time. Currently used endoscopic accessories are designed for other purposes and are far from optimal in achieving adequate necrosectomy. Recently, two small case series describe the use of hydrogen peroxide (H_2O_2) to facilitate the removal of necrotic debris [5, 35]. Benefits and potential complications needs to be further investigated in prospective series.

The final reported potential innovation is the use of a vacuum assisted closure system, widely used in treating patients with anastomotic leaks after rectal surgery. A recent case report describes the use of this system transgastrically in two patients with infected necrotizing pancreatitis [36]. Since the sponge has to be frequently exchanged, the potential benefits of using the vacuum assisted closure system seem to be limited, in our opinion.

Future

Endoscopic transluminal necrosectomy is widely performed in tertiary referral centers for patients with infected necrotizing pancreatitis. Although endoscopic management is believed to be associated with fewer complications, morbidity, and costs, superiority or at least non-inferiority to minimally invasive surgery has not been proven yet in high quality comparative trials. It is expected that the abovementioned TENSION trial results will be available in 2015 [24]. Until then, the selection of the modality used in patients with infected necrotizing pancreatitis largely driven by local expertise and tradition.

Besides necessary evidence, the biggest improvement in efficacy of ETN would be achieved by an innovative endoscopic device that facilitates efficient removal of necrotic tissue. The innovations mentioned above are potentially small improvements but still seem not to result in real effective removal of the necrotic tissue. Especially, an endoscopic high pressure water blasting system to pulverize the necrosis without damaging surrounding structures would be welcomed.

The trend towards minimally invasive therapy for (infected) pancreatic necrosis has led to the development and optimization of endoscopic treatment of pancreatic necrosis with primary endoscopic EUS-guided drainage supplemented with ETN. This trend is expected to further reduce the procedure-related morbidity and mortality and thereby improving patients' prognosis. Care for the very ill patients needs to be delivered in a multi-disciplinary fashion and includes the most advanced part of the spectrum of therapeutic endoscopy. Many parts of the procedures can be improved further. The relative low number of patients that need ETN per center per year, makes collecting good evidence for innovations challenging and this can only be done in high quality multicentre research.

Conflict of interest None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Video S1 Video showing endoscopic ultrasound (EUS) guided determination of the optimal site for drainage, ensuring a minimal distance and avoiding vessel interposition by use of color-flow Doppler.

Video S2 Video showing endoscopic ultrasound (EUS) guided puncture with a cystotome.

Video S3 Video showing a walled-off necrotic collection and different techniques of endoscopic transluminal necrosectomy using a polypectomy snare, Roth net and Dormia basket.