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EXPERT REVIEWS

Minimally invasive intervention for infected necrosis in acute pancreatitis

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Infected necrosis is the main indication for invasive intervention in acute necrotizing pancreatitis. The 2013 IAP/APA guidelines state that percutaneous catheter drainage should be the first step in the treatment of infected necrosis. In 50–65% of patients, additional necrosectomy is required after catheter drainage, which was traditionally done by open necrosectomy. Driven by the perceived lower complication rate, there is an increasing trend toward minimally invasive percutaneous and endoscopic transluminal necrosectomy. The authors present an overview of current minimally invasive treatment options for necrotizing pancreatitis and review recent developments in clinical studies.

KEYWORDS: acute pancreatitis • drainage • endoscopic • laparoscopy • minimally invasive • necrosectomy • necrotizing pancreatitis • surgery • VARD

Acute pancreatitis is an acute inflammatory condition of the pancreatic gland. It is currently the most common gastrointestinal cause of acute hospital admission with an incidence of 15–45 per 100,000 in Europe and the US [1–4]. Each admitted patient costs an average of US$6000–10,000 and these costs can exceed US$130,000 per patient when the patient is treated with open necrosectomy for infected necrosis [1,5–7]. Eighty percent of patients with acute pancreatitis have mild disease and symptoms resolve within a week with medical treatment following the current guidelines [8,9]. The remaining 20% develop a more severe form of pancreatitis (i.e., moderately severe or severe acute pancreatitis; TABLE 1) which is typically associated with persisting systemic inflammatory response syndrome (TABLE 2), (multiple) organ failure and necrosis of the pancreatic gland or peripancreatic tissue (i.e., necrotizing pancreatitis; TABLE 3). Despite maximal supportive care in the intensive care unit, the mortality of patients with severe acute pancreatitis with persistent organ failure (i.e., more than 48 h) in the first week of their disease is around 40% [8,10,11]. However, in most patients with (moderately) severe acute pancreatitis, the initial systemic inflammatory response syndrome and/or (multiple) organ failure resolve during the first 2 weeks with maximal supportive care. Full recovery results in discharge without the need for additional clinical treatment.

If the patient develops necrotizing pancreatitis (FIGURES 1 & 2, TABLE 3), in around 30% the necrosis gets infected [12]. Infected necrosis should be suspected when a patient deteriorates clinically and biochemically after a period of initial clinical improvement. This also applies to patients who do not show signs of clinical improvement from their initial systemic inflammatory response syndrome or organ failure. Contrast-enhanced computed tomography (CECT) may show an acute necrotic collection or walled-off necrosis (FIGURES 1 & 2, TABLE 3) [8,9]. Gas bubbles may be present in the collections, caused by gas-forming bacteria or by spontaneous fistula formation from the necrotic cavity into the intestinal lumen. Gas bubbles are pathognomonic for infected necrosis [13,14]. When the diagnosis of infected necrosis is not clear, fine needle aspiration (FNA) can be obtained to confirm infection. However, false-negative results of FNA up to 20% are reported and in most cases, clinical signs and radiologic imaging suffice to diagnose infected necrosis [7,14–16]. Proven or suspected infected necrosis requires immediate start of intravenous broad-spectrum antibiotics. If infection is diagnosed after a positive culture

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Table 1. Grades of severity.

Mild acute pancreatitis	• No organ failure • No local or systemic complications
Moderately severe acute pancreatitis	• Less than 48 h of organ failure and/or • Local or systemic complications
Severe acute pancreatitis	• Persistent (single or multiple) organ failure lasting more than 48 h

Adapted from [8].

coming from FNA, other or additional organisms were cultured after subsequent intervention in 27% (12/44 patients) of cases in a Dutch study [14]. This should be taken into consideration when tailoring antibiotic treatment. It is worth mentioning that prophylactic antibiotic treatment is not indicated in the early phase of the disease, as it has not clearly shown positive effects on prevention of secondary infections, surgical interventions or mortality [17,18].

In general, infected necrosis requires invasive treatment. Recovery with non-invasive measures and antibiotics alone has been reported, but occurs only in a rare subgroup of patients with an exceptionally good clinical condition [12,19,20]. Invasive intervention is currently postponed in many centers until CECT shows obvious signs of walled-off necrosis and as long as the clinical condition of the patient is stable. Usually it takes 3–4 weeks before a collection becomes completely walled off [13]. Intervention at this point probably reduces the risk of complications and mortality, compared with intervention at an earlier stage (i.e., the first 2 weeks) [12,21]. A rather rare indication for invasive intervention in the late phase of (moderately) severe acute pancreatitis is mechanical obstruction of the gastrointestinal or biliary tract caused by walled-off necrosis, without signs of infection. Other indications for intervention in sterile necrosis are symptoms such as pain and persisting unwellness. A disconnected pancreatic duct, caused by central pancreatic necrosis, potentially causes an outflow problem of the viable remnant tail of the pancreas and may lead to symptomatic collections. Intervention for these sterile collections should generally be postponed for at least 8 weeks, as the symptoms may resolve spontaneously, preventing the intervention altogether [9]. The risk of introducing infection into an initially sterile collection, with its associated morbidity and mortality, should be minimized [22].

Table 2. Systemic inflammatory response syndrome criteria.

Temperature	<36°C or >38°C
Respiratory rate	>20 breaths/min or P_aCO_2 <32 mmHg
Pulse	>90 beats/min
White blood cell count	$<4\times10^9$/l or $>12\times10^9$/l or >10% immature bands

Systemic inflammatory response syndrome is defined as the presence of two or more systemic inflammatory response syndrome criteria.

The mortality rate of patients with sterile pancreatic necrosis was reported at 12% [12]. Mortality rates of patients with infected necrosis vary from 20 to 30% [12,23], and if infected necrosis is concomitant with organ failure, the mortality increases to around 40% [23].

Invasive treatment

Open necrosectomy

Traditionally, patients with progressive clinical deterioration due to necrotizing pancreatitis were treated surgically. Laparotomy with complete necrosectomy of all non-viable tissues was performed at an early stage of the disease. This strategy was associated with high morbidity (34–95%) and mortality (11–39%) rates [24,25]. More recent reports show lower mortality rates (11–19%) for open necrosectomy [7,15,26]. This is attributed to better understanding of the clinical course of the disease, optimal timing of intervention and better supportive measures [12,21].

In the last decade, new interventional possibilities have emerged and results from (randomized controlled) trials have shown that later and less-invasive intervention improves the clinical outcome compared with early open necrosectomy (Figure 3). Early open necrosectomy is, therefore, no longer considered the standard of treatment in acute necrotizing pancreatitis [7,21,27,28].

Indications for early laparotomy, however, remain, and include acute abdominal catastrophes such as abdominal compartment syndrome and bowel ischemia. These complications are rare in acute pancreatitis, but when present, are associated with high mortality rates exceeding 50% in most reports [12,29–32]. Other rare complications of acute pancreatitis which might require early laparotomy are bowel perforation and acute hemorrhage [33–35]. These emergency interventions generally do not require simultaneous necrosectomy; the necrosis is usually still sterile in these early intra-abdominal catastrophes.

Minimally invasive intervention

Currently, several minimally invasive interventions are available for (infected) necrotizing pancreatitis, namely, percutaneous drainage and percutaneous necrosectomy, laparoscopic necrosectomy, video-assisted retroperitoneal debridement (VARD), and endoscopic transluminal drainage and necrosectomy.

The rationale for the beneficial effect of minimally invasive approaches is that less surgical injury lowers the risk of complications and shortens postoperative recovery in these already critically ill patients. The initial goal is removal of pus under pressure. The next step is to remove non-adherent necrotic tissue, rather than complete removal of necrosis. Limited necrosectomy reduces the risk of bleeding from viable tissue during the procedure. Necrosectomy can be repeated during the following days and weeks, if deemed necessary for full clinical recovery. This line of thinking is in contrast with classic open necrosectomy, where complete debridement of all non-viable tissues was considered essential for success [36].

In the past two decades, the share of minimally invasive interventions in the treatment of infected necrosis has

Table 3. Morphological features of acute pancreatitis.

Interstitial edematous pancreatitis	• Acute inflammation of the peripancreas • CECT: Pancreatic enhancement (i.e. no necrosis) by intravenous contrast
Necrotizing pancreatitis	• Pancreatic parenchymal necrosis and/or necrosis of peripancreatic tissue • CECT: Pancreatic non-enhancement (partly)
Acute peripancreatic fluid collection	• Associated with interstitial edematous pancreatitis, less than 4 weeks after the onset of disease • CECT: Confined by normal fascial planes without intrapancreatic extension • CECT: Homogenous fluid density without definable encapsulating wall
Pancreatic pseudocyst	• Associated with interstitial edematous pancreatitis, after 4 weeks of the onset of disease • CECT: Usually round or oval with well-defined encapsulating wall • CECT: Homogenous fluid density without non-liquid component
Acute necrotic collection	• Associated only with necrotizing pancreatitis • CECT: Heterogeneous density (liquid and non-liquid) without definable encapsulating wall • CECT: Located intra- and/or extrapancreatic (Figure 1A & 1B)
Walled-off necrosis	• Develops after maturation of an acute necrotic collection • Usually requires 4 weeks after the onset of disease • CECT: Heterogeneous density (liquid and non-liquid) with well-defined encapsulating wall (Figure 2)

CECT: Contrast-enhanced computed tomography.
Adapted from [8].

increased [37]. Based on pre-procedural imaging, most cases of infected necrosis are suitable for minimally invasive intervention [38]. The following overview describes the different minimally invasive techniques and their outcomes.

Percutaneous catheter drainage

The least invasive procedure in the treatment for infected pancreatic necrosis is drainage. Percutaneous catheter drainage (PCD) of infected necrosis was first reported by Freeny and colleagues [39]. The theoretical basis is that drainage of infected fluid under pressure could help patients to recover, or at least let them improve as a bridge to further surgery. Since its introduction, the technique has become more widely used. Recent systematic reviews and meta-analyses report success rates of PCD of little more than 50%, which means no additional necrosectomy is needed for complete recovery [28,40]. The multicenter Dutch randomized PANTER trial compared a surgical 'step-up approach' with primary open necrosectomy in 88 patients with (suspected) infected necrotizing pancreatitis. The step-up approach consisted of PCD and if the patient did not show clinical improvement after 72 h, this was followed by VARD. The PANTER trial showed that 35% of

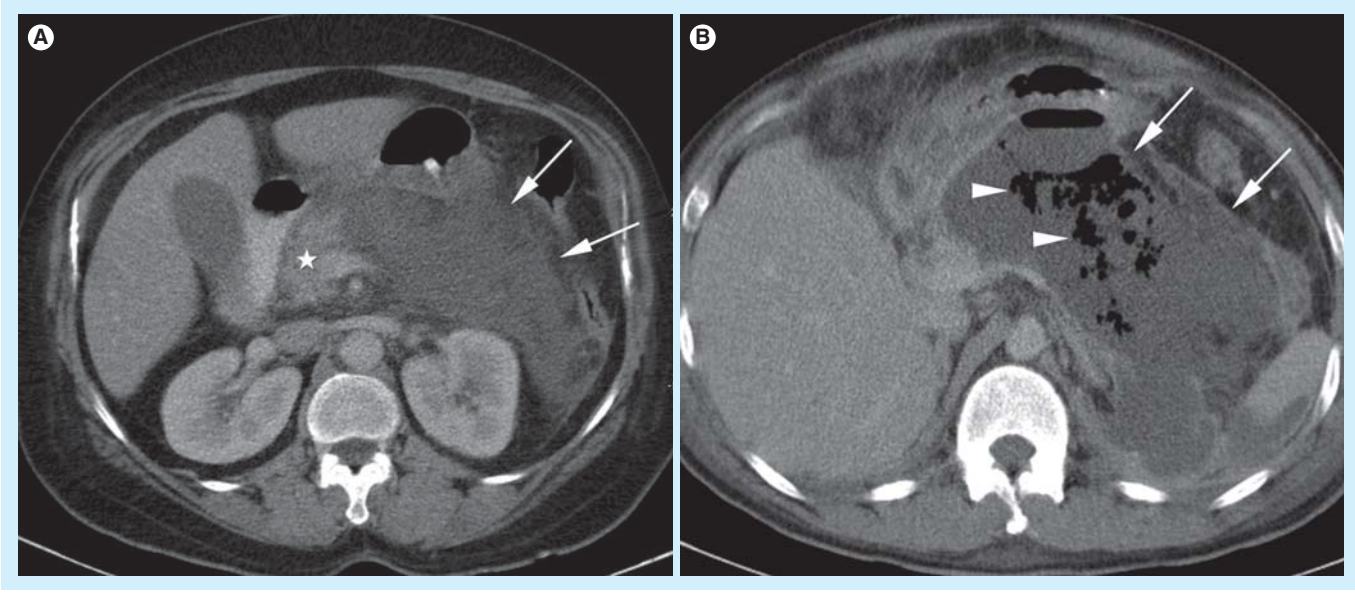

Figure 1. Acute necrotic collection. (A) Arrows point out the necrotic collection of the body and tail of the pancreas. The asterisk shows normal enhancement of the viable head of the pancreas. **(B)** Gas bubbles (arrowheads) in the collection (arrows), pathognomonic for infection.

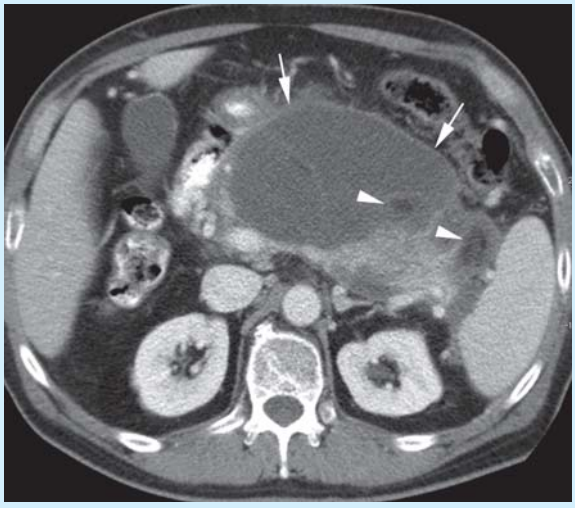

Figure 2. Walled-off necrosis. Necrotic collection with a well-defined encapsulating wall (arrows), clearly showing a heterogeneous density (arrowheads).

patients in the step-up group were successfully treated with PCD alone [7].

Reversal of sepsis after PCD was seen in 62–84% of patients [20,41], creating a time interval during which either the patient recovers or the necrosis matures and becomes more encapsulated. This has proven to be beneficial in terms of outcome after subsequent necrosectomy [21]. A complication rate for PCD of around 20% was reported in a systematic review that included 384 patients [28]. Formation of pancreaticocutaneous and pancreaticoenteric fistula is the most common complication and often can be treated non-operatively. Less common complications are abdominal pain, catheter dislodgement and self-limiting pneumothorax. Potentially life-threatening, although rare, complications of PCD are laceration of the splenic artery and colonic perforation, which demand immediate intervention (e.g. angiographic coiling/loop ileostomy) when present.

Most peripancreatic collections are considered accessible for PCD by retroperitoneal or transperitoneal route [38]. The retroperitoneal route is preferred because it prevents advancement of the infection intraperitoneally. Also, a retroperitoneal drain can be used as guidance in case necrosectomy is needed at a later stage. Technical success rates of drain placement of near 100% are attributed to accurate imaging for assessing the optimal route (computed tomography [CT]-guided placement), combined with experienced and skilled radiologists performing the procedure [7,38,42].

If one pancreatic collection is seen on CECT, placing a single drain may suffice. More than one infected collection justifies the placement of additional drains [28]. One retrospective study suggested that drain size is not necessarily associated with the success of PCD. In this study, the drain size varied from 8 to 24 French in 80 patients, of whom 34 (43%) recovered without further necrosectomy [43].

To prevent occlusion, drains should be flushed with normal saline, typically every 8 h. Some authors advocate aggressive flushing of drains during multiple procedures, thereby irrigating the necrotic cavity and removing small pieces of loose necrotic material [20]. This can be regarded as a step toward percutaneous necrosectomy, also referred to as sinus tract necrosectomy. If the collections are inadequately drained, drains can be changed or additional drains may be placed, in an attempt to avoid further necrosectomy.

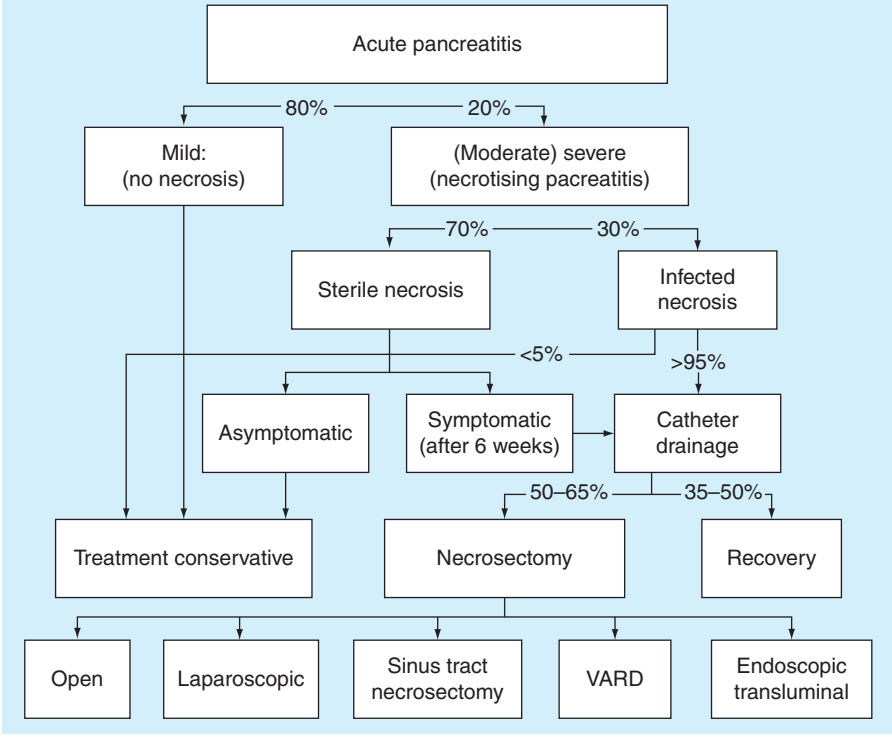

Figure 3. Treatment of acute pancreatitis [12].
Emergency laparotomy is left out because this intervention is regarded as a treatment of complications, rather than a treatment of the pancreatic disease itself.
VARD: Video-assisted retroperitoneal debridement.

Sinus tract necrosectomy

Sinus tract necrosectomy was first described in 2000 by Carter *et al.* [44] and was subsequently termed 'minimally invasive/access retroperitoneal pancreatic necrosectomy' by others [45–47]. This technique comprises the placement of a small (i.e., 8–12 French) retroperitoneal drain under CT guidance in the necrotic collection. Subsequently, under fluoroscopic guidance, the drain tract is stepwise dilated up to 30 French and an Amplatz

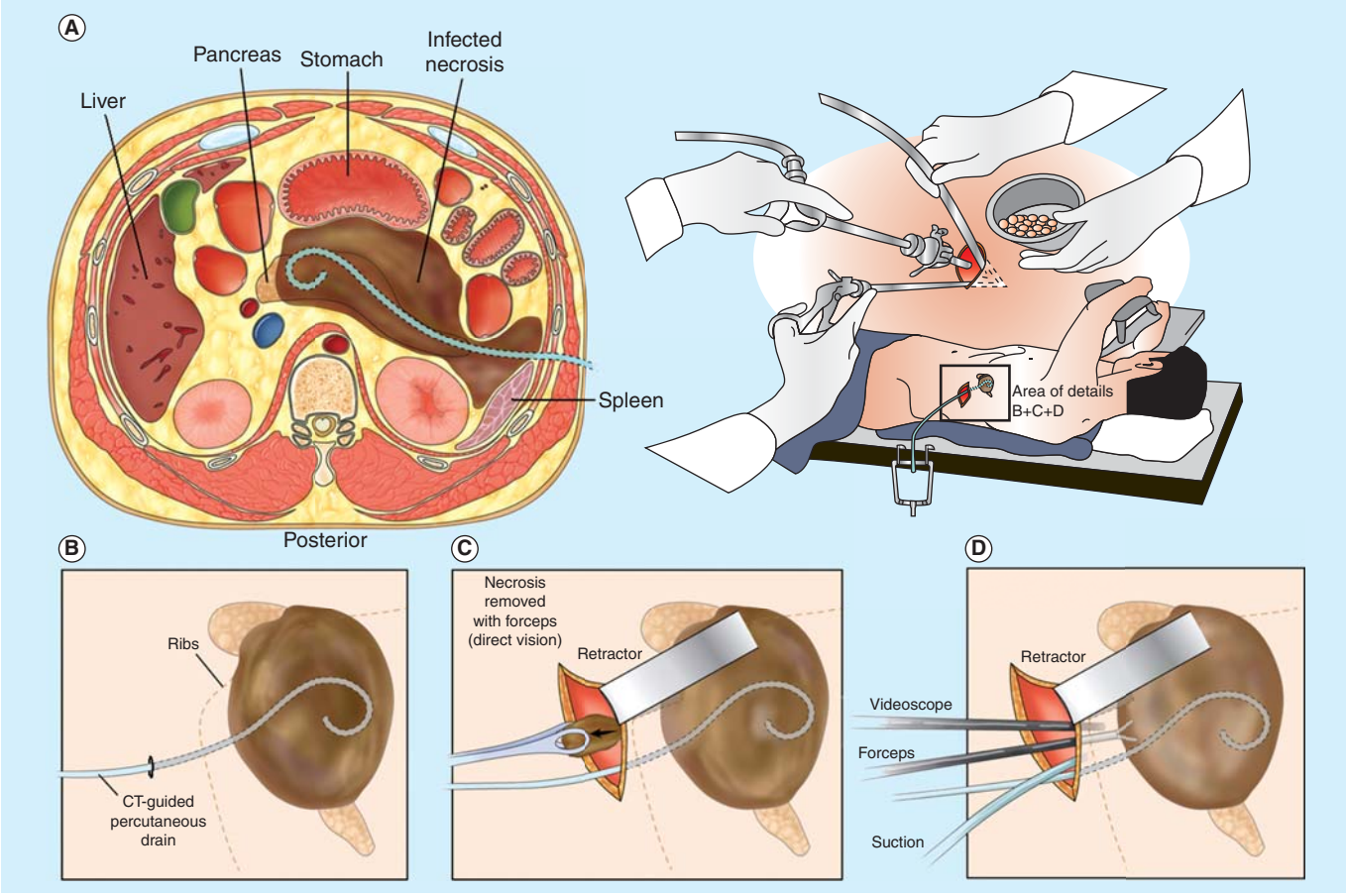

Figure 4. Percutaneous catheter drainage and video-assisted retroperitoneal debridement. (A) Cross-sectional image and torso depicting a peripancreatic collection with fluid and necrosis. The preferred access route is through the left retroperitoneal space between the left kidney, dorsal spleen and descending colon. A percutaneous drain is inserted in the collection to mitigate sepsis and postpone or even obviate necrosectomy. **(B)** The area of detail. **(C)** A 5-cm subcostal incision is made, and the previously placed percutaneous drain is followed into the retroperitoneum to enter the necrotic collection. The first necrosis is removed under direct vision with a long grasping forceps. **(D)** This is followed by further debridement under videoscopic assistance.
CT: Computed tomography.
Adapted with permission from [96,97].

sheath is placed. An operating nephroscope is used to advance through the sheath and enter the collection. Loosely adherent parts of necrosis are removed from its cavity with grasping forceps. Post-procedural lavage of the cavity is continued until clearance of the lavage fluid or until the next necrosectomy [44].

A median number of three [48] to four [47] procedures are necessary per patient. Conversion to open surgery for further necrosectomy or treatment of complications was needed in 14–26% of patients [46,47]. Fistula formation (4–22%) and bleeding (10–17%) are the most prominent procedure-related complications. Mortality of patients treated with sinus tract necrosectomy was reported between 9 and 19% [46–48].

Video-assisted retroperitoneal debridement

In general, before a VARD is performed, a percutaneous drain is placed in the peripancreatic collection in order to optimize the clinical condition of the patient. This two-step treatment modality is referred to as the step-up approach [7]. As mentioned before, PCD prevents the need for further necrosectomy in 35–50% of patients. Therefore, performing a VARD procedure without preceding PCD is not recommended [16,49].

VARD (Figure 4) was first described by Horvath and colleagues in 2001 and in subsequent years, it was used by others [50,51]. Under general anesthesia, the patient is placed in a supine position with the left flank raised to 30–40°. A mid-axillary, subcostal incision of 5 cm is made close to the exit point of the drain. Guided by the drain and the CT images, the surgeon enters the retroperitoneum and clears purulent material by suction. Grasping forceps are used to remove the first necrosis under irrigation and suction. When the directly visible necrosis is removed, a videoscope is introduced and CO_2 can be infused through the initial drain to inflate the cavity and enhance vision. With a laparoscopic forceps or long grasping clamp, more necrosis is removed. By limiting the debridement to only the loosely adherent necrosis, the risk of bleeding from viable underlying tissue is brought to a

minimum. The initial drain is removed and careful irrigation of the cavity performed. After placement of two large-bore single-lumen drains for postoperative lavage, the fascia and skin are closed. Lavage with normal saline (up to 10 l/24 h) is continued until the effluent is clear. Videos of the VARD procedure can be seen on YouTube under the search term 'VARD pancreatitis' [52].

In the PANTER trial, the surgical step-up approach scored significantly lower on the combined clinical endpoint of major complications and death, compared with open necrosectomy (40 vs 69%, respectively; p = 0.006). Complications of the step-up approach included intra-abdominal bleeding (16%), fistula formation (28%) and incisional hernia (7%). Mortality rate was 19% [7]. Other studies have reported lower complication and mortality rates of the VARD procedure [20,53]. In only three (12%) patients randomized to the step-up approach in the PANTER trial, the retroperitoneal collection with pancreatic necrosis could not be reached retroperitoneally and open necrosectomy was therefore performed. In a prospective, multicenter study on VARD, 16 out of 31 patients (52%) requiring necrosectomy eventually underwent open necrosectomy due to retroperitoneal inaccessible collections [53].

In line with the described VARD technique, others have implemented similar methods for retroperitoneal necrosectomy of infected necrosis. Castellanos *et al.* described a technique in which a flexible endoscope is used to visualize and remove necrosis with the aid of irrigation [54]. Also, three-port retroperitoneoscopic necrosectomy [55,56] and single-port retroperitoneoscopic necrosectomy with three trocars [57] have been described in a small series (eight and nine patients). Primary results seem to be similar with 'traditional' VARD; however, further research is necessary.

Laparoscopic approach

Several reports use the term 'laparoscopic necrosectomy' for either a transperitoneal or a retroperitoneal approach [56,58,59]. We will refer to 'laparoscopic' when the necrosectomy is performed transperitoneally, as opposed to the previously described retroperitoneal approaches. A variety of techniques are described, from guidance by percutaneous drains and single-port access [60] to hand-assisted procedures [61]. The laparoscopic cystgastrostomy is most frequently used. In this procedure, three or four ports are used for operating instruments. After insertion and inflation of the abdomen, an anterior gastrostomy is made and the pancreatic collection located. Access to the collection or 'cyst' is made through the posterior gastric wall and a cystgastrostomy is created by four to five firings of an endo GIA stapler. Fluid and/or necrotic debris can then be removed from the collection. Once adequate debridement and hemostasis are achieved, the anterior gastrostomy is closed with sutures [62]. A video of a laparoscopic cystgastrostomy can be seen on YouTube under the search term 'laparoscopic cystgastrostomy' [63].

A number of retrospective studies reported good outcomes after laparoscopic necrosectomy of necrotizing pancreatitis, all with minor morbidity and mortality [60–62,64–66]. The largest series, however, fail to mention whether collections were proven to be infected before intervention; nor were any pre-procedural disease severity indexes mentioned [61,62,64,65]. These patients might have been less ill than those treated with other modalities and, therefore, comparison cannot easily be made. A recent retrospective study in 76 patients with infected necrosis showed significant advantages of laparoscopic necrosectomy compared with open surgery with regard to postoperative complications (fistula, pulmonary infection and incisional infection). No differences in mortality were seen [67]. A downside of this technique is that it requires two gastrostomies and might offer less overview of the infected collection as compared to VARD.

Endoscopic approach

The endoscopic approach toward pancreatic collections was introduced in the mid-1980s. Endoscopically placed nasocystic tubes were used to drain pancreatic fluid collections. In 2000, Seifert and colleagues reported successful endoscopic transluminal necrosectomy in three patients with infected pancreatic necrosis [68]. Over the years, the endoscopic approach gained popularity through good results and evolved to a widely accepted treatment method, even in extensive infected collections [16,19,49,69–71]. The step-up strategy can also be applied to the endoscopic approach. In this treatment modality, endoscopic transluminal drainage is, if necessary, followed by endoscopic transluminal necrosectomy.

Endoscopic transluminal drainage and necrosectomy (Figure 5) can be considered if the infected collection lies within several centimeters of the gastric or duodenal lumen. The procedure can be performed under deep sedation. However, sudden drainage of large amounts of fluid could cause reflux and subsequent aspiration. Therefore, to prevent complications, some advocate general anesthesia for the first procedure [72]. It is recommended to use endoscopic ultrasound to establish the best puncture site of the posterior gastric or duodenal wall [16]. Endoscopic ultrasound can aid in locating the collection, confirm its contents, measure the distance to the intestinal lumen, trace vascular structures in the intended puncture site and distinguish the collection from other structures (e.g. gall bladder) [73]. Randomized trials have shown higher technical success rates of endoscopic ultrasound-guided endoscopic drainage when compared with conventional drainage [74,75].

Most endoscopists use a 19 gauge FNA needle to puncture the collection through the intestinal wall. The content is subsequently aspirated, or contrast injected, to confirm access into the collection. A standard-sized guide wire is advanced into the cavity. This is generally done under fluoroscopic guidance, although Rana and colleagues reported good results without fluoroscopic guidance in 20 patients [76]. A fistula tract between the intestinal lumen and the necrotic cavity is then created using electrocautery. The tract is dilated to approximately 10 mm using balloon dilators. After control of potential bleeding, two double pigtails and a nasocystic flushing catheter are placed. The nasocystic catheter is rinsed with 1 l normal saline

per 24 h, solely to keep the cystgastrostomy open. If necessary, multiple non-communicating collections can be drained in one session. Varadajulu [77] and Bang [78] have described this multiple transluminal gateway technique in two retrospective studies. Patients with walled-off necrosis undergo multiple (up to six) endoscopic cystgastrostomies in one procedure. The authors reported good initial treatment outcomes. Obviously, these results are to be confirmed by well-designed trials in the future.

In case the patient does not improve clinically within the first 72 h after drainage, an endoscopic necrosectomy is performed. A forward viewing endoscope is used to balloon dilate the tract up to 15–20 mm (Figure 6) and the endoscope is advanced into the collection. Necrosectomy can be performed using various instruments including snares, waterjets, nets, baskets and grasping forceps to pull the necrotic tissue out of the collection and into the stomach [16,72,79]. Irrigating the cavity with hydrogen peroxide might loosen necrosis, but there is no convincing evidence for this method [80]. After removing the loosely adherent necrosis, again multiple double pigtail stents and a nasocystic catheter are placed to maintain the fistula tract. Over time, the infected fluid and potentially necrotic tissue drain to the intestine and the cavity collapses [72]. A video and case description of an endoscopic procedure is shown on YouTube under the search term 'endoscopic necrosectomy' [81].

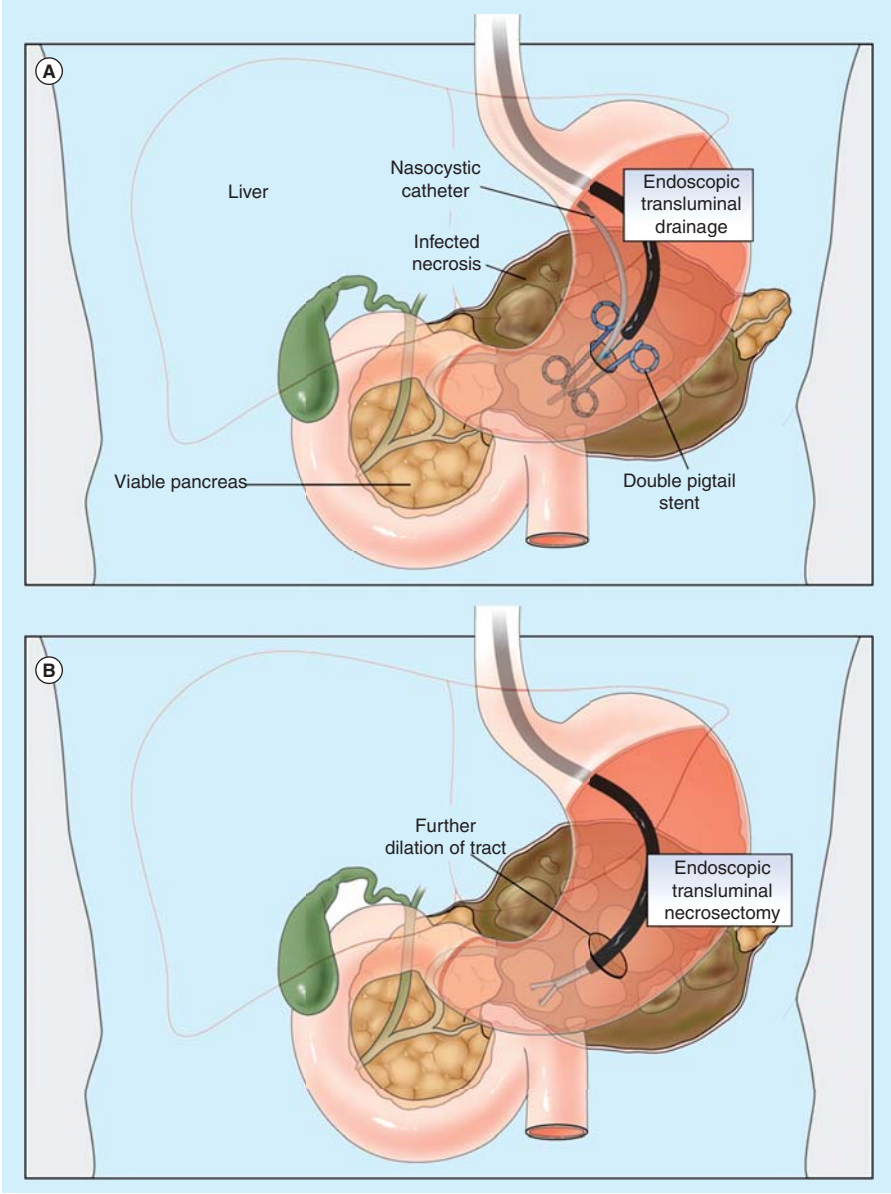

Figure 5. Endoscopic transluminal drainage and endoscopic transluminal necrosectomy. A large peripancreatic collection containing fluid and necrosis is shown. The preferred access route for endoscopic transluminal treatment is through the posterior wall of the stomach. The necrotic collection often bulges into the stomach, facilitating endoscopic transluminal treatment. **(A)** The collection is punctured through the gastric wall, followed by balloon dilatation of the tract. Two double-pigtail stents and a nasocystic catheter are placed for continuous postoperative irrigation. **(B)** The cystostomy tract is further dilated, the collection is entered by a forward viewing endoscope, and necrosectomy is performed.
Adapted with permission from [96].

A review on endoscopic transluminal drainage of pancreatic fluid collections in 1134 cases reported a technical and clinical success rate of 97 and 91%, respectively. However, data on the percentage of patients with infected necrosis were lacking [73]. A recent systematic review on endoscopic transluminal necrosectomy of studies published in the last 9 years included 455 patients from 14 studies [82]. Infected necrosis was diagnosed in 57% of patients, and on average, four endoscopic interventions were performed per patient. Clinical success, defined by successful treatment and clinical recovery with endoscopic necrosectomy alone, was achieved in 81% of patients. Complication and mortality rates of 36% and 6%, respectively, were reported, with the major complications being bleeding (18%), pancreatic fistula (5%) and spontaneous perforation of a hollow organ (4%). A rare but possibly fatal complication is an air embolus due to over-insufflation of the collection and intestine during the procedure. To reduce the risk, although not proven effective in preventing this complication, CO_2 instead of normal air insufflation should be used [83]. A small randomized controlled trial (RCT) of 28 patients found that stent retrieval within

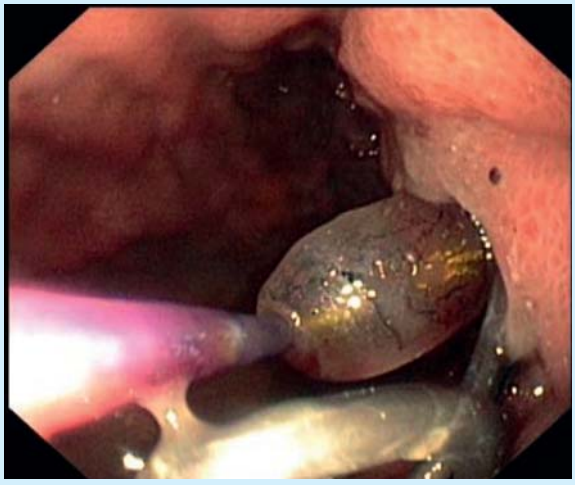

Figure 6. An endoscopy view of balloon dilatation of a fistula tract between the stomach and the necrotic collection. A previously placed pigtail drain can be seen coming out of the collection.

2 weeks after successful endoscopic drainage of a symptomatic pancreatic fluid collection was related to higher recurrence rate of the same symptomatic pancreatic fluid collection. In the control group, stents were left *in situ* without major complications. This RCT included patients with acute and chronic pancreatitis and did not report results separately. The authors suggested that long-term stent maintenance could be applied for most patients, but further prospective trials are necessary [84].

Recent developments have shown that it is feasible to place fully covered self-expandable metallic stents in the fistula tract during the first procedure, through which nasocystic irrigation and necrosectomy are possible. Initial reports used a variety of stents, sized from 16 × 30 mm [85] upward to 23 × 105 mm [86], for the treatment of pancreatic fluid collections and infected walled-off necrosis. A mean of five interventions per patient were needed and the reported clinical success rates are promising at 88%, with minor morbidity and no mortality [85,86]. The use of metal stents might facilitate the endoscopic procedure and improve drainage of the cavity.

A rather new technique combines percutaneous drainage and endoscopic transluminal drainage. Reports from this technique have originated from the Virginia Mason Medical Center in Seattle, Washington, USA, and the authors have named it 'dual modality drainage' [87–90]. The necrotic collection is percutaneously drained under CT guidance, directly followed by endoscopic drainage. The technique was developed in order to reduce the 20% pancreaticocutaneous fistula the authors experienced with percutaneous drainage alone [90]. Forty-nine [87], 23 [88] and 15 [89] patients treated with the dual modality drainage strategy were retrospectively analyzed. Initially, the authors compared dual modality drainage with percutaneous drainage alone and reported that the length of hospital stay and the amount of radiologic procedures were reduced in dual modality drainage [87–89]. Their most recent analysis retrospectively included 117 patients treated with dual modality drainage for infected necrosis (n = 55; 47%) and failure to clinically progress or experiencing gastric outlet obstructive symptoms (n = 62; 53%). In this group, which was partly still under treatment during analysis (n = 14; 12%), all patients recovered clinically without additional surgical necrosectomy and a disease-related mortality rate of 3.4% was reported. No pancreaticocutaneous fistula were reported and three patients needed late surgery for pain (n = 2) and gastric outlet obstruction (n = 1) [90].

One can imagine the dual modality drainage being performed with subsequent necrosectomy, if necessary. Varadarajulu reported such a case of successful dual drainage followed by sinus tract necrosectomy through a metal stent in a patient with suspected infected necrosis [91].

Discussion

Knowledge of necrotizing pancreatitis has increased considerably over the last two decades. Recently, experts from across the world have joined forces in order to reach consensus on several treatment questions. This resulted in the IAP/APA evidence-based guidelines for the management of acute pancreatitis [9]. Twelve multidisciplinary review groups performed systematic literature reviews to answer a set of predefined clinical questions. Overall agreement of the working group followed after a joint meeting. Based on the current evidence, these guidelines advocate catheter drainage (percutaneous or endoscopic transluminal) as the first step in the treatment of infected necrosis and preferably delay the drainage at least 4 weeks after the initial presentation. Intervention in sterile necrosis is best avoided to reduce secondary infection. However, when patients experience ongoing symptoms, intervention can be considered in a late phase, beyond 8 weeks after the initial presentation [9,92].

If necrosectomy is indicated, no definitive evidence exists as to what procedure should be the treatment of choice. Although many suggest that minimally invasive interventions are superior to open necrosectomy, this has not yet been proven by well-designed trials. The only RCT in this area, the PANTER trial, compared a step-up approach with primary open necrosectomy [7]. The obvious advantages of this step-up approach over open necrosectomy cannot blindly be attributed to the minimally invasive surgery alone because the primary open necrosectomy was not preceded by drainage of the collection. Laparoscopic (i.e. transperitoneal) necrosectomy may be superior to open necrosectomy when considering the postoperative complications [67]. However, because of lack of well-designed prospective and comparative studies, and the fact that a laparoscopic necrosectomy requires extensive surgical experience, it should not be recommended as a standard approach to infected pancreatic necrosis [16].

Sinus tract necrosectomy is most popular in the UK [44,46,47,93]. Disadvantages of this technique are conversion rates to open surgery reported in up to 26% and the fact that

only small pieces of necrosis can be removed. As a result, there is need for three to four sinus tract procedures for the patient to recover [47,48]. VARD is a relatively simple procedure in which standard surgical instruments are used. Complication and mortality rate are comparable to those of sinus tract necrosectomy. However, incisional hernias are reported in 7% of patients undergoing VARD [7]. Usually, one VARD is sufficient for recovery [7,53]. These aspects could favor VARD over sinus tract necrosectomy.

A pilot RCT (PENGUIN trial), including 22 patients, which compared VARD with endoscopic transluminal necrosectomy as treatment for infected necrosis, showed that endoscopic necrosectomy reduced the pro-inflammatory response postoperatively, measured by interleukin-6 levels [94]. Also, the combined clinical endpoint of major complications and death was significantly lower in the endoscopic group. These results suggest an advantage of endoscopic transluminal necrosectomy over VARD, but larger studies are needed to support these results. The TENSION trial, a multicenter Dutch RCT, is currently ongoing in the Netherlands (registration number: ISRCTN09186711). This study compares an endoscopic with a surgical step-up approach for (suspected) infected necrotizing pancreatitis. In one arm, endoscopic transluminal drainage is (if necessary) followed by endoscopic necrosectomy. In the other arm, percutaneous drainage is (if necessary) followed by minimally invasive surgery (i.e. VARD). The primary endpoint is a composite of death and major complications.

The complication rate of 36% for endoscopic necrosectomy [82] is comparable to VARD (28–50%) [7,53]. Mortality rates (6% for endoscopic necrosectomy and 3–19% for VARD) may suggest that the endoscopic approach is safer, but bias through patient selection is likely [7,53,82]. Endoscopic necrosectomy is performed without a cutaneous incision. Therefore, no risk of incisional hernia exists and no physical signs of an operation can be seen. A downside of endoscopic necrosectomy compared with VARD is that the procedure is reserved for highly specialized endoscopists having the right instruments at their disposal. VARD is a relatively simple procedure performed with basic instruments and, therefore, is more widely accessible. With an average of four endoscopic necrosectomies [82] needed per patient compared with one VARD [7], it should be noted that endoscopic treatment of infected necrosis depends on a dedicated team of physicians.

With dual modality drainage, an interesting new technique in the treatment of infected and symptomatic necrosis is introduced. With percutaneous drains for optimal drainage of infected fluid/necrosis and parallel endoscopic transmural drainage in order to prevent secondary pancreaticocutaneous fistulae, Ross *et al.* have reported a remarkable fistula rate and additional necrosectomy rate of 0% for both and a mortality rate of 3.4% [90]. In their systematic review on percutaneous drainage in necrotizing pancreatitis, van Baal *et al.* reported a need for further necrosectomy of just below 50%, a subsequent fistula rate of 15% and a mortality rate of 17% [28]. These results, together with an infected necrosis rate of 47% in the study of Ross *et al.* and 71% in the systematic review, suggest a selected patient group which was less sick in the dual modality drainage study. This could possibly explain the preferable outcome of dual modality drainage compared to percutaneous drainage alone. Nevertheless, the technique is promising and the results deserve further comparing research.

Most literature on the treatment of necrotizing pancreatitis focuses on the early course (i.e. the first weeks) of the disease. Few reports are known to evaluate long-term outcome [92,95]. Common problems are pancreatic exocrine and endocrine insufficiency, abdominal pain, intolerance to oral intake, recurrent episodes of acute pancreatitis and main pancreatic duct disruption due to central pancreatic necrosis. A report of 197 patients with necrotizing pancreatitis revealed that patients with main pancreatic duct disconnection need operative debridement more often compared to patients with normal ductal anatomy (82 vs 35%). Subsequently, the same group had more persistent fluid collections (70 vs 16%), persistent fistula (82 vs 22%) and postprandial pain/poor intake (70 vs 0%) after debridement [92]. For these complications, the disconnected duct group underwent significantly more interventions during follow-up, varying from drainage to pancreatic tail resection.

Expert commentary & five-year view

A little more than 5 years have passed since the PANTER trial concluded in 2008. A follow-up study to evaluate the long-term results of the step-up approach is ongoing. This study will investigate whether patients who were initially treated with only percutaneous drainage require additional interventions in the follow-up. Also, it will evaluate the long-term complications of necrotizing pancreatitis in general.

It is well-known that retrospective cohorts are subject to patient selection bias, which is a limiting factor in comparing the results between various techniques. Ideally, comparative studies should be carried out in a randomized controlled setting. However, this will be difficult to achieve since patients developing infected necrotizing pancreatitis (being the main indication for an invasive intervention) are relatively rare. The TENSION trial (registration number: ISRCTN09186711) has the potential of showing superiority of one of the two step-up approaches, surgical versus endoscopic.

Several studies on acute pancreatitis are currently performed according to the International Clinical Trials Registry Platform. An RCT comparing laparoscopic cystgastrostomy to endoscopic transluminal drainage of non-infected post-pancreatitis fluid collections is being performed in India (registration number: CTRI/2012/09/002969). This RCT should provide better comparing evidence concerning the laparoscopic approach toward pancreatic fluid collections. These and other studies to come will further increase knowledge about acute pancreatitis and its treatment. It must be stressed that the most valuable results will come from well-designed studies, with predefined inclusion criteria based upon the revised Atlanta Classification and accurately described treatment modalities. This will eventually result in more comparable outcome measures [8].

Acute pancreatitis remains a challenging disease with potentially debilitating and fatal complications such as necrosis and infection. These patients demand a dedicated team of physicians consisting of surgeons, gastroenterologists, radiologists, intensivists and microbiologists, assessing each separate case. An individualized strategy regarding the best intervention and the timing of intervention should be made. With the available evidence at hand, a minimally invasive and retroperitoneal (percutaneous or endoscopic) approach seems justified as the initial step toward drainage and necrosectomy.

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Key issues

- Sterile asymptomatic necrotizing pancreatitis can be treated non-invasively.
- Necrosectomy is best postponed until necrosis is walled off.
- Catheter drainage should be the first step in the treatment of infected necrosis.
- Minimally invasive necrosectomy seems superior to open necrosectomy in terms of complications and resource utilization.
- The 2013 evidence-based IAP/APA guidelines reflect the increasing international consensus on the treatment of acute pancreatitis.

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