Interventions for Necrotizing Pancreatitis: A Multidisciplinary Approach

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Introduction

Acute pancreatitis (AP) is a dynamic inflammatory process involving the pancreas, peripancreatic tissues, and less commonly remote organ systems [1–6]. The most widely used definitions for acute pancreatitis are derived from the recently revised Atlanta classification, which has undergone extensive revision by an international panel of experts from multiple disciplines [7]. According to these revisions, AP is either interstitial or necrotizing. Pancreatic necrosis is typically defined by non-enhancement of pancreatic parenchyma on contrast-enhanced computed tomography (CECT). Necrosis can involve either pancreatic parenchyma alone (less commonly), both the pancreatic parenchyma and the peripancreatic tissues (more commonly), or isolated peripancreatic tissue alone (least commonly). Isolated peripancreatic or extrapancreatic necrosis may be associated with improved long-term outcomes compared to pancreatic necrosis [8]. However, peri- or extrapancreatic necrosis carries a worse prognosis than acute interstitial pancreatitis. Both pancreatic and peripancreatic necrosis can be either sterile or infected. Mortality of necrotizing pancreatitis has traditionally varied from approximately 15 % in patients with sterile necrosis, to as much as 39 % in patients with infected necrosis, which occurs in approximately 40–70 % of patients.

According to the recent revisions, there are only four kinds of collections associated with interstitial and necrotizing pancreatitis [7] (Table 17.1). Of importance is that many walled-off collections formerly referred to as pseudocysts in fact represent walled-off necrosis (WON), a distinction that has major implications for management [9]. Simple drainage is almost always effective for pseudocysts, but only for the minority of WON. In general, sterile necrosis does not require intervention, while infected necrosis usually requires evacuation. The traditional management of infected necrosis has centered on open surgical debridement, with additional percutaneous drainage and peritoneal lavage, all of which usually require multiple operative sessions and interventions. Open surgical debridement is accompanied by significant risk of perioperative stress, organ failure, and

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Table 17.1 Revised Atlanta Criteria terminology for collections in acute pancreatitis

Interstitial edematous pancreatitis
Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognizable tissue necrosis
CECT criteria
• Pancreatic parenchyma enhancement by intravenous contrast agent
• No findings of peripancreatic necrosis (see below)
Necrotizing pancreatitis
Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis
CECT criteria
• Lack of pancreatic parenchymal enhancement by intravenous contrast agent and/or
• Presence of findings of peripancreatic necrosis (see below—ANC and WON)
1. APFC (acute peripancreatic fluid collection)
Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. Applies only to areas of peripancreatic fluid seen within first 4 weeks after onset, not a pseudocyst
CECT criteria
• Occurs in the setting of interstitial edematous pancreatitis
• Homogeneous collection with fluid density
• Confined by normal peripancreatic fascial planes
• No definable wall encapsulating the collection
• Adjacent to pancreas (no intrapancreatic extension)
2. Pancreatic pseudocyst
An encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis. This entity usually occurs more than 4 weeks after onset
CECT criteria
• Well circumscribed, usually round or oval
• Homogeneous fluid density
• No nonliquid component
• Well-defined wall; that is, completely encapsulated
• Maturation usually requires >4 weeks after onset of acute interstitial edematous pancreatitis
3. ANC (acute necrotic collection)
A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues
CECT criteria
• Occurs only in the setting of acute necrotizing pancreatitis
• Heterogeneous and nonliquid density of varying degrees in different locations (some appear homogeneous early in their course)
• No definable wall encapsulating the collection
• Location—intrapancreatic and/or extrapancreatic
4. WON (walled-off necrosis)
A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. WON usually occurs >4 weeks after onset of necrotizing pancreatitis CECT criteria
• Heterogeneous with liquid and nonliquid density with varying degrees of loculations (some may appear homogeneous)
• Well-defined wall, that is, completely encapsulated
• Location—intrapancreatic and/or extrapancreatic
• Maturation usually requires 4 weeks after onset of acute necrotizing pancreatitis

long-term complications including external fistulas, diabetes, pancreatic exocrine insufficiency, and incisional hernias [5, 10–18]. Over the past decade, the management of pancreatic necrosis has evolved substantially with introduction and refinement of a variety of minimally invasive approaches to drainage and evacuation of necrosis. The aim of the current review is to give an insight into the various minimally invasive modalities available for necrosectomy. Regardless of approach, in order to achieve optimal outcomes, emphasis is placed on the necessity for multidisciplinary management in advanced medical centers with specialized expertise in the management of severe acute pancreatitis. Such an approach involves routine coordinated involvement of dedicated interventional endoscopists, surgeons, and interventional radiologists, all with specific understanding of and experience with management of necrotizing pancreatitis. Ongoing consultation and ideally weekly conferences are essential to the systematic management of these challenging patients.

Diagnosis of Pancreatic, Peripancreatic, and Infected Necrosis

CECT remains the "gold standard" for imaging in severe acute pancreatitis [1–6] (Figs. 17.1 and 17.2). CECT aids in the diagnosis of pancreatic parenchymal necrosis, in determining the extent

Fig. 17.1 CECT (coronal image) showing very large walled-off necrotic collections involving the pancreas itself (central collection outlined by *arrows*) and peripancreatic tissues extending deep into left pelvis (*arrows* to screen *lower right*). These types of complex WON will often fail to resolve using a single approach and require adjunctive techniques

Fig. 17.2 CECT (coronal image) showing complete resolution of WON in Fig. 17.1, after combined dual entry endoscopic transmural drainage and necrosectomy, combined with left flank retroperitoneal percutaneous catheter drainage (PCD) and sinus tract endoscopic necrosectomy (see Fig. 17.7)

of necrosis, and can identify local complications including venous thrombosis and pseudoaneurysm. Complete evolution of pancreatic necrosis may take up to 5 days. Hence, CECT can underestimate or underdiagnose necrosis if performed before this interval. Disadvantages of CECT include radiation exposure, especially with repeated imaging, and contrast-induced nephropathy. MRI with MRCP is considered as an alternative for the diagnosis of necrosis. Even without the use of intravenous gadolinium, MRI can demonstrate the presence of pancreatic necrosis, based on fat-suppressed T1-weighted images, enabling its use in renal insufficiency. Avoidance of radiation exposure, enhanced detection of non-liquid material in pancreatic and peripancreatic fluid collections, and ability of MRCP to detect bile duct stones and image the pancreatic duct above and below any disruption make MR imaging attractive when compared to CT imaging. Comparative drawbacks of MR include more variable quality and interpretation, longer acquisition times, difficult patient tolerance in the setting of critical illness, toxicity of gadolinium in patients with chronic kidney disease, and contraindication of MRI in pacemakers and other metallic objects. EUS can be performed at bedside in critically ill patients, allows the most precise identification of gallbladder and bile duct stones, and, if necrosis is present, enables the combination of imaging with intervention and drainage with the same procedure. On the other hand, EUS has potential for adverse events in profoundly ill patients, especially cardiopulmonary risk in patients who are not on ventilator support, and may overestimate the necrotic debris content of pancreatic collections.

The peak incidence of infection of pancreatic or peripancreatic necrosis is between 2 and 4 weeks after presentation, but can occur at any time during the clinical course [1–6]. Clinically, infected necrosis should be suspected when there is new onset of sepsis in a previously stable patient, or progressive clinical deterioration such as worsening renal function, rising white blood cell count, or persistent tachycardia despite maximal support, and without an alternate source for infection.

In a minority of patients, there are characteristic findings on CT including intra- or peripancreatic gas due to gas-forming organisms or fistulous communication with the stomach, small intestine, or colon (with introduction of organisms and air). The microbial spectrum in infected necrosis includes monomicrobial flora in 60–87 % of patients and polymicrobial flora in 13–40 % of patients with a predominance of gram-negative aerobic organisms [19, 20]. In the past, a positive aspirate from a diagnostic image-guided fine-needle aspiration (FNA) was considered an indication for immediate surgical intervention, and such procedures were commonly performed [21]. However, FNA has been demonstrated to have a false-negative rate of 10 % or more and with the acceptance of the "step-up" approach to intervention, diagnostic FNA has largely been deemed unnecessary. Rather, the decision to intervene is made on clinical grounds including strong suspicion of infected and symptomatic necrosis. Once minimally invasive intervention is undertaken, cultures for bacteria and fungi can be obtained to further guide antimicrobial therapy. Using a clinical strategy for management of infected necrosis in the PANTER trial, cultures obtained during minimally invasive intervention yielded a definitive evidence for infected necrosis in over 90 % of patients [16]. Currently, one of the few remaining indications for diagnostic FNA in necrotizing pancreatitis is to detect fungal superinfection when a patient remains febrile despite ongoing treatment with broad-spectrum antibiotics [1, 4].

Indications and Timing for Intervention

Indications for intervention including endoscopic, percutaneous, or surgical in necrotizing pancreatitis are shown in Table 17.2. The primary indication for intervention in necrotizing pancreatitis is presence of infected necrosis. Sterile acute necrotic collections almost never warrant intervention early in the course of the disease, i.e., in the first 4 weeks. Interventions should be considered later in the course of sterile necrotizing pancreatitis only in the presence of persistent organ failure, disabling symptoms such as persistent pain requiring narcotics or preventing oral intake, gastric outlet or biliary obstruction, or presence of disconnected pancreatic duct. In order to optimize outcomes, interventions should be delayed as much as possible until there is "walled-off" necrosis (WON), which typically takes 4 weeks or more, but may be highly variable. Asymptomatic WON does not mandate intervention, regardless of the size and extension of the collection, and may resolve spontaneously over time.

Table 17.2 Indications for intervention (endoscopic, radiologic, or surgical) in necrotizing pancreatitis

1.	Clinical suspicion or documented infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled off
2.	In absence of documented infection, ongoing organ failure for several weeks after the onset of acute pancreatitis, preferably when the necrosis has become walled off
3.	In sterile necrosis: ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect
4.	In sterile necrosis: persistent symptoms (e.g., intractable pain, "persistent unwellness") in patients with walled-off necrosis
5.	Disconnected duct syndrome (i.e., transection of the pancreatic duct in the presence of pancreatic necrosis) with persisting symptomatic collection(s)

Adapted from Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis

Interventions of any kind, whether endoscopic, percutaneous, or surgical, for pancreatic or peripancreatic necrosis within the first few weeks are generally associated with adverse outcomes and are typically reserved for infected necrosis in severely deteriorating patients [4, 5]. The primary exception is in the setting of abdominal compartment syndrome, wherein surgical or image-guided decompression is potentially lifesaving, but involves primarily fasciotomy and does not include debridement or drainage of acute necrotic collections [5].

Minimally Invasive Approaches to Necrosectomy

The presence of infected necrosis has traditionally been thought to be an indication for debridement or necrosectomy [21]. Recently, several studies have suggested the possibility of treatment of infected necrosis without formal drainage or necrosectomy; several studies have described nonsurgical treatment of infected necrosis by management in an ICU setting with targeted antibiotics (third-generation cephalosporin with beta-lactamase inhibitors and carbapenems), aggressive nutritional support, and judicious percutaneous intervention in the event of infected WON [22–26]. They have suggested significantly decreased length of hospitalization, duration of external drainage, and number of radiological procedures, and a mortality that was comparable to surgery. It is, however, unclear which patients could be safely and effectively managed without any form of necrosectomy, as these studies do not consider percutaneous drainage as an intervention, or consider endoscopic methods at all.

Traditional approaches to debridement involve open surgery, either via an anterior transperitoneal approach or via retroperitoneal approach through a flank incision [5, 10–18]. Alternative techniques continue to evolve and undergo refinement, and are collectively referred to as minimally invasive necrosectomy. They can be classified based on the method of visualization (open, radiologic, endoscopic, hybrid, or other) and route (per oral, transpapillary, or transmural, percutaneous retroperitoneal, percutaneous transperitoneal, percutaneous transmural, or other) according to a taxonomy developed by Windsor and colleagues [27] (Fig. 17.3). Minimally invasive procedures are thought to induce less physiological stress as compared with open surgical debridement.

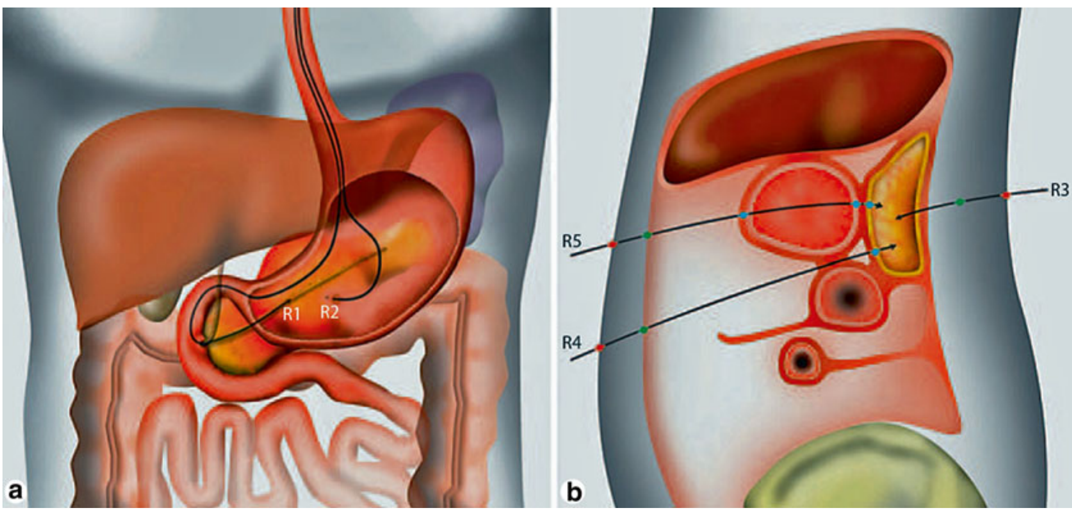

Fig. 17.3 Illustrations of a comprehensive classification of invasive procedures for treating the local complications of acute pancreatitis, as described by Loveday, Windsor, and coauthors at University of Auckland, Auckland, New Zealand. R1, Per-os transpapillary; I, internal route traversing duodenal papilla to enter pancreatic duct; R2, Per-os transmural; External orifice entry point, internal route traversing gastrointestinal wall; R3, Percutaneous retroperitoneal; Skin-external entry point, internal route traversing retroperitoneum; R4, Percutaneous transperitoneal; Skin-external entry point, internal route traversing peritoneum; R5, Percutaneous transmural; Skin-external entry point, internal route traversing gastrointestinal wall. Reprinted from Pancreatology, 11/4, Loveday BPT, Petrov MS, Connor S, Rossaak JI, Mittal A, Phillips ARJ, et al., A comprehensive classification of invasive procedures for treating the local complications of acute pancreatitis based on visualization, route, and purpose, 406–13, Copyright 2011, with permission from Elsevier

Percutaneous Catheter Drainage

Percutaneous catheter drainage (PCD) of pancreatic and peripancreatic necrosis involves placement of single or multiple catheters, which are subsequently upsized, irrigated, and manipulated, sometimes along with direct percutaneous necrosectomy (Figs. 17.4 and 17.5). Freeny et al. first described a series of 34 patients with infected acute necrotizing pancreatitis who were treated primarily with imaging-guided PCD as an alternative to primary surgical necrosectomy, using PCD with active percutaneous necrosectomy by placement of multiple large-bore catheters and vigorous irrigation [28]. PCD was successful in postponing surgical intervention for a median of 4 weeks in 9 months and in obviating the need for surgical necrosectomy in 47 % of patients. Over the past two decades, PCD has been increasingly utilized to stabilize critical patients both as "a bridge to surgery" and sometimes as definitive therapy. The preferred route for PCD is via a flank approach through the retroperitoneum, because it avoids enteric leaks and dissemination of infected material into the peritoneal cavity. In addition, a retroperitoneal approach for PCD allows the tract to be used as guidance for surgical video-assisted retroperitoneal necrosectomy (VARD) or sinus tract endoscopy (Figs. 17.6 and 17.7). The Dutch Pancreatitis group recently reported a nationwide multicenter prospective study primarily of patients with infected necrosis. In that study, 63 % ($n = 130$) of patients underwent PCD as a primary intervention [30]. Of this group 35 % of patients recovered without additional necrosectomy. Further a comprehensive systematic review of 11 retrospective studies involving 384 patients (both sterile and infected) showed that 56 % of patients who underwent PCD for sterile or infected necrosis did not need surgical intervention [31]. However care should be taken with interpretation of the conclusions of this systematic review, as selection bias and the design of the included studies may lead to overestimation of the proportion of patients who could be treated with PCD alone. The authors acknowledged the wide variation in techniques with drains varying from 8 to 28 Fr; only one study utilized routine stepwise dilation for upsizing the drains. Prospective studies have suggested a more realistic primary success rate of PCD of approximately 33 % [16].

PCD is a relatively simple and well-established radiologic procedure. It is beneficial especially as

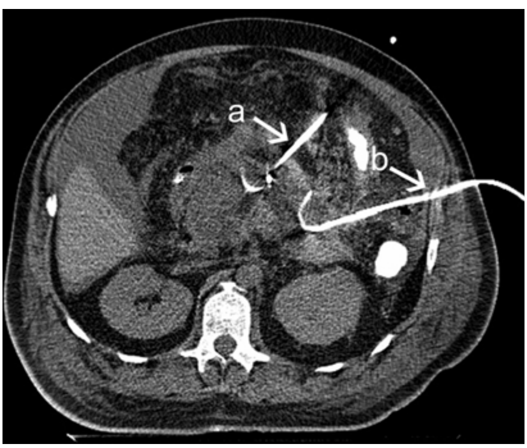

Fig. 17.4 CECT (axial image) showing dual PCD of WON; (*a*) shows anterior transperitoneal (R4) approach; (*b*) shows retroperitoneal (R3) approach

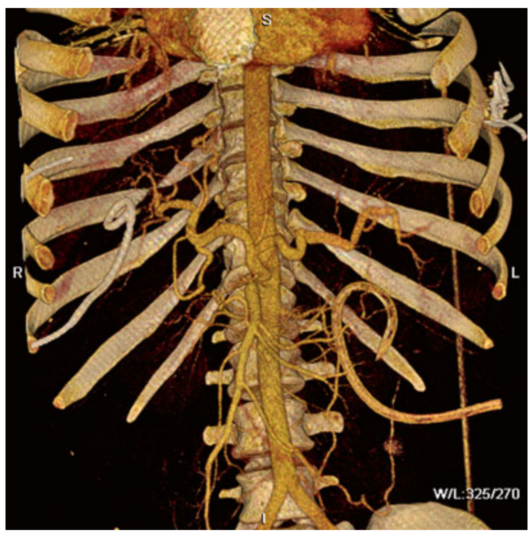

Fig. 17.5 CT angiogram showing two percutaneous catheters placed to treat patient with infected peripancreatic necrosis that was poorly encapsulated and extending deep into left retroperitoneum and intraperitoneally under liver; catheter through left flank is retroperitoneal (R3), and catheter in right upper quadrant is transperitoneal (R4)

Fig. 17.6 Patient (same patient as Figs. 17.1 and 17.2) in prone position under general anesthesia showing left flank retroperitoneal percutaneous catheter (*red tube*) about to undergo minimally invasive retroperitoneal debridement via sinus tract endoscopy

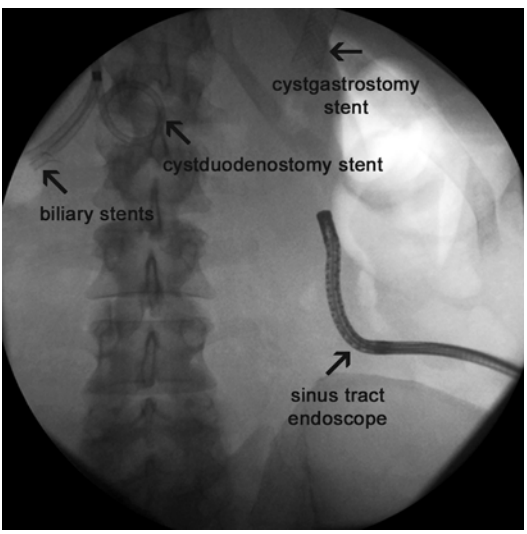

Fig. 17.7 Fluoroscopic image of patient (same patient as in Figs. 17.1, 17.2, and 17.6) showing maximal combined multimodality approaches to extensive WON including minimally invasive retroperitoneal debridement via sinus tract endoscopy, after dual endoscopic transluminal drainage and necrosectomy via cystogastrostomy and cystoduodenostomy, plus biliary stenting; *arrows* from *left* to *right*: biliary stents, cystoduodenostomy stent, endoscope passed from left flank tract through retroperitoneum into lesser sac; self-expanding metallic stent in cystogastrostomy

a prelude to definitive necrosectomy or when combined with another modality of treatment such as endoscopic drainage. It remains an adjunctive treatment in situations where the collection cannot be accessed endoscopically, such as deep retroperitoneal extension, or when the collection is poorly demarcated or walled off. Of note, percutaneous drains placed before 3 weeks are associated with a prolonged course and more frequent drain exchanges, underscoring the importance of maturation of WON before intervention. PCD is technically not adequate or feasible when retroperitoneal hemorrhage, bowel necrosis, or duodenal/biliary obstruction further complicates necrotizing pancreatitis. One of the main drawbacks of PCD is persistent external fistulae, which occur in up to 27 % of patients [5]. Other drawbacks include limited ability to remove necrotic debris. Dilatation of the percutaneous tract up to 26 Fr and use of grasping forceps to extract the debris have been described, as has the use of assist devices such as stone retrieval baskets, but these techniques are seldom performed in clinical practice [29, 32]. A dedicated team of radiologists willing to assiduously follow

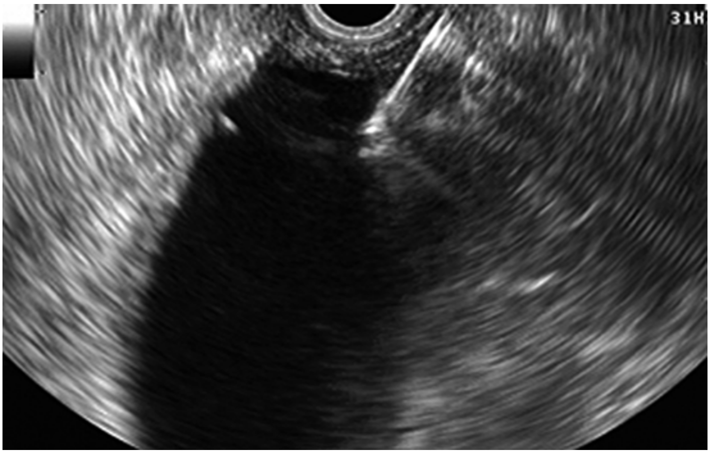

Fig. 17.8 Endoscopic ultrasound-guided transgastric puncture of WON

these patients and perform meticulous catheter care, with frequent upsizing of drainage catheters and frequent imaging to localize the loculated undrained areas is critical for successful percutaneous management of necrotizing pancreatitis as a primary strategy.

Endoscopic Transluminal Drainage and Necrosectomy

Endoscopic transluminal drainage and necrosectomy represent true natural orifice transluminal endoscopic surgical (NOTES) approaches (Figs. 17.8, 17.9, 17.10, 17.11, 17.12, 17.13, 17.14, 17.15, and 17.16). Endoscopic necrosectomy is increasingly gaining traction as primary therapy for infected pancreatic necrosis in carefully selected patients. Transmural drainage of chronic pancreatic pseudocysts is a well-established modality particularly when performed by experienced interventional endoscopists [33–35], and has been extrapolated to the management of WON [36, 37]. However, the principal difference is that unlike with pseudocysts, endoscopic necrosectomy involves direct debridement of solid debris [38]. Endoscopic approaches also offer simultaneous ability to treat biliary obstruction and also to treat disconnected pancreatic duct by performing transpapillary and/or internal cystenterostomy stenting.

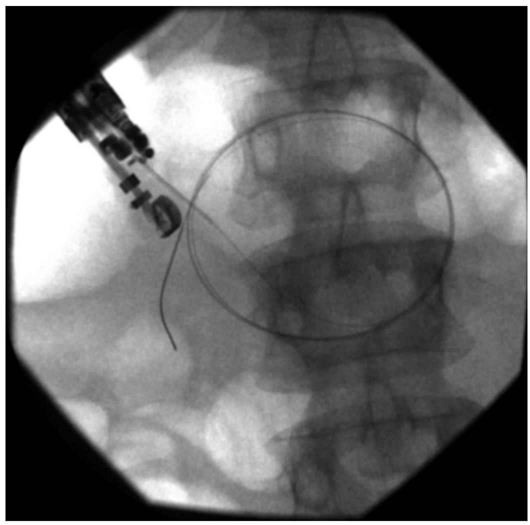

Fig. 17.9 Endoscopic ultrasound-guided transgastric puncture of WON; fluoroscopic view showing guidewire coiled in cavity

Endoscopic transmural necrosectomy (ETN) was first reported by Seifert and colleagues [39]. ETN involves creation of a cystenterostomy, followed by large-diameter (10–20 mm) balloon dilation, and direct entry into the necrotic cavity using a forward-viewing endoscope. Necrosectomy is performed under direct endoscopic vision using forceful irrigation, suction, snares, rat toothed-forceps, tripod retrieval, stone removal baskets, and a range of other endoscopic accessories. Endoscopic necrosectomy is generally repeated

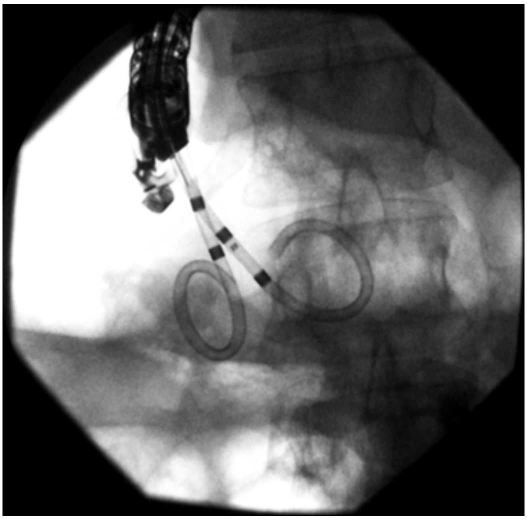

Fig. 17.10 Endoscopic ultrasound-guided transgastric puncture of WON; fluoroscopic view showing two double pigtail 10F stents placed through cystogastrostomy

Fig. 17.11 Endoscopic transgastric view of freshly accessed infected WON, demonstrating obviously purulent partially liquefied necrosis poorly amenable to mechanical debridement, and prompting endoscopic drainage, plus minus lavage, with attempts at debriding solid necrosis best deferred

until the necrotic cavity is thoroughly evacuated and healthy granulation tissue is evident.

Several retrospective studies of ETN have been reported [39–51]. It must be emphasized that these represent selected groups of patients with endoscopically accessible collections that were deemed feasible to treat by this route, and

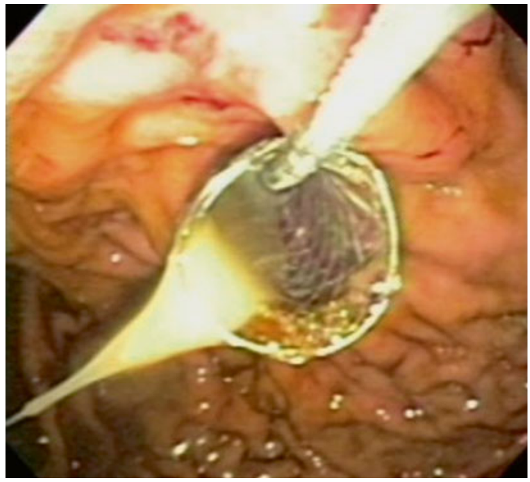

Fig. 17.12 Endoscopic view of initial placement of fully covered metallic stent into infected WON via a transgastric route, with drainage of obviously purulent contents

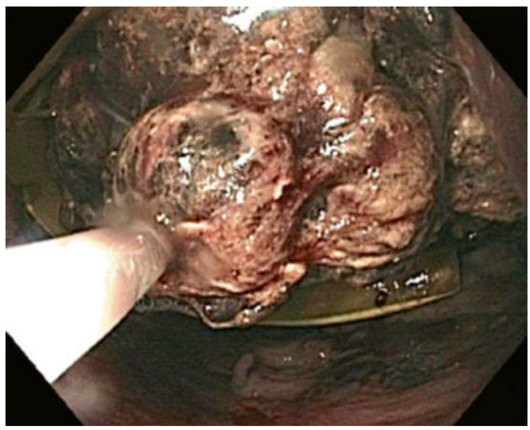

Fig. 17.13 Endoscopic view of transluminal necrosectomy using an endoscopic net. Just below the necrosis, a percutaneous large-bore drain is visible, which has flushed away the liquid component, leaving only solid debris for necrosectomy

are thus not directly comparable to series of surgical or PCD without adjustment for other variables. Some but not all series of ETN/ETD involve selective use of adjunctive techniques such as nasocystic lavage or PCD. The GEPARD study involved 93 patients at six centers in Germany, with 6-year follow-up. Initial clinical success was reported in 80 % of patients, with an overall complication rate of 26 and a 7.5 % mortality rate at 30 days [41]. At a mean follow-up

Fig. 17.14 Another view showing careful net debridement of solid necrosis just underneath a very large vessel, possibly the splenic artery

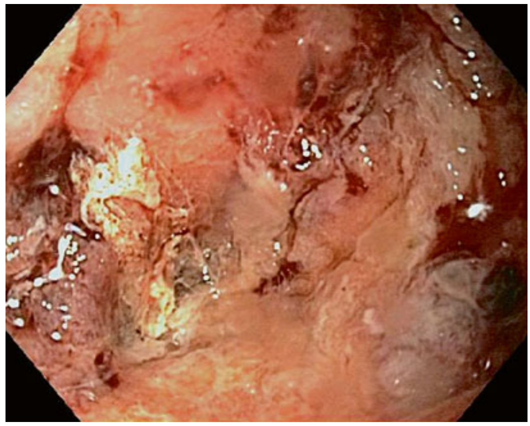

Fig. 17.15 Endoscopic view of clean cavity after successful endoscopic transluminal necrosectomy

of nearly 4 years, 84 % of initially successful patients had a sustained clinical improvement, with 10 % needing further endoscopic drainage and only 4 % needing surgery. An American multicenter study included 104 patients at six American centers undergoing endoscopic necrosectomy for symptomatic WON. A minority of patients had infected necrosis, and like other series included only patients selected as suitable for endoscopic necrosectomy, rather than as "intent-to-treat" [42]. Successful resolution was achieved in 91 % of patients, with a mean duration of treatment of 4 months. Two patients underwent operative drainage for persistent WON, one required surgery for massive bleeding on fistula tract dilation, and one died during intraprocedure presumably due to an air embolus. The study by Gardner and colleagues confirmed ETN to be an efficacious and reproducible technique with an acceptable safety profile. Overall, retrospective studies of endoscopic necrosectomy report a

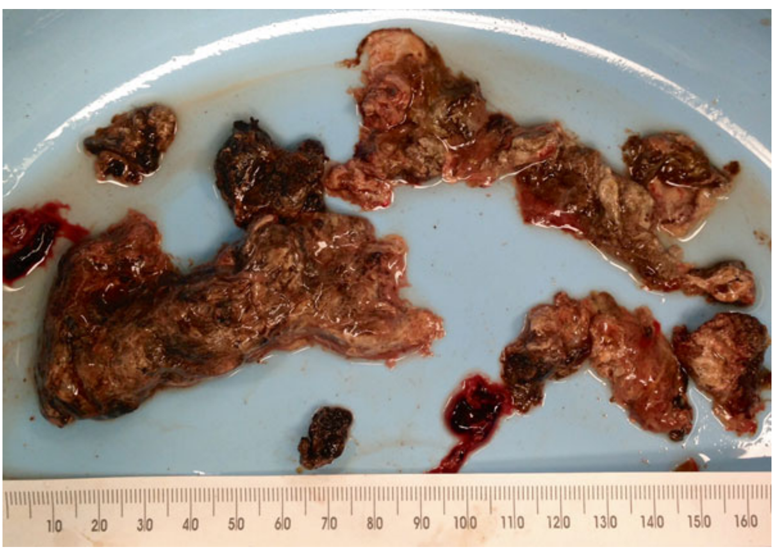

Fig. 17.16 Pan containing large amounts of solid necrotic material extracted through cystenterostomy after combined endoscopic transluminal and PCD and lavage of very large infected WON

clinical success rate of approximately 70–95 %, requiring typically three to six sessions for completion with surgery required in anywhere from 2 to 25 % of cases, a morbidity of 11–70 %, and a mortality from 0 to 15 % [52]. As with all retrospective series of a single technique, case selection may be a primary determinant of outcome.

The Dutch Pancreatitis Study Group recently reported the results of the first randomized control trial comparing endoscopic transgastric necrosectomy ($n=10$) and surgical necrosectomy (video-assisted retroperitoneal debridement or, if not feasible open necrosectomy, $n=10$) in patients with infected necrotizing pancreatitis [53]. Patients underwent PCD, via a step-up approach, and if that failed, were randomized either to endoscopic necrosectomy or VARD. In the PENGUIN trial, the investigators utilized a surrogate marker post-procedural serum interleukin as the primary outcome rather than clinical endpoints due to small sample size. Secondary outcomes included a composite clinical endpoint of death or major morbidity including new-onset multi-organ failure, intra-abdominal hemorrhage, perforation of a visceral organ needing intervention, enterocutaneous or pancreatic fistula. IL-6 rose rapidly within the first 24 h after surgical necrosectomy, but did not increase in the endoscopic group ($p=0.004$). There were also strikingly improved clinical outcomes in the endoscopic group. Major complications were significantly reduced in the endoscopic group (20 % vs. 80 %, risk difference 0.6, $p=0.03$). New-onset multi-organ failure did not occur in the endoscopic group and fewer patients developed pancreatic fistula. The authors attributed the superior outcome to the use of a natural orifice as access route to the retroperitoneal cavity as compared to surgical dissection which contributed to more physiological stress. Endoscopic interventions were performed under moderate conscious sedation, obviating the need for general anesthesia. General anesthesia is known to provoke or prolong systemic inflammation in critically ill patients, but is widely utilized for ETD/ETN in the United States. These promising results need to be replicated in larger trials before being extrapolated into routine clinical practice.

There are many variations of technique and approaches for endoscopic necrosectomy. Varadarajulu et al. described a multi-gateway approach which uses multiple transmural entry sites created under EUS guidance, to facilitate rapid drainage in large symptomatic WON (measuring >80 mm in diameter) [54] (see Fig. 17.6). Through the creation of two to three fistulous tracts from the enteric lumen to the necrotic collection, one tract may serve as a channel for irrigation while the other acts as an egress conduit for drainage of the necrotic contents and also minimizes the probability of closed-space infection. However, the authors cautioned that this technique may not be feasible in smaller sized WON and those which are not in close approximation to the lumen. The Virginia Mason group has advocated another variation consisting of combining percutaneous large-bore catheter drainage and debridement with internal transmural endoscopic drainage, in order to blend the advantages of both techniques, and in particular to avoid external fistulas [55, 56]. Lavage through the percutaneous approach with egress through the transmural fistula theoretically facilitates more rapid debridement than either technique alone. Combined modality therapy was retrospectively compared with standard PCD alone, suggesting significantly decreased hospitalization (26 vs. 55 days, $p<0.0026$), duration of external drainage (83.9 vs. 189 days, $p<0.002$), number of CECTs (8.95 vs. 14.3, $p<0.002$), drain studies (6.5 vs. 13, $p<0.0001$), and lower rate of external fistula (0 vs. 3 patients) in favor of the combined modality therapy over percutaneous catheter-based management alone [56]. The authors postulated that the decreased need for external drainage and fistula was the result of luminal exit for pancreatic secretions in those patients with disconnected pancreatic ducts, which was maintained by leaving cystogastrostomy stents in place indefinitely. A major advantage of combining PCD and endoscopic internal drainage is the ability to perform "one-way" flushing of the percutaneous catheter on the floor at regular intervals (up to once every 8 h) that washes debris out of the cystenterostomy into the bowel lumen, rather than requiring egress through sometimes limited

Fig. 17.17 Fluoroscopy showing "one way" flushing possible via left flank percutaneous catheter drain that communicated with endoscopic cystogastrostomy. *Arrows* show direction of flow of contrast through left flank drain, through cavity, and out into stomach

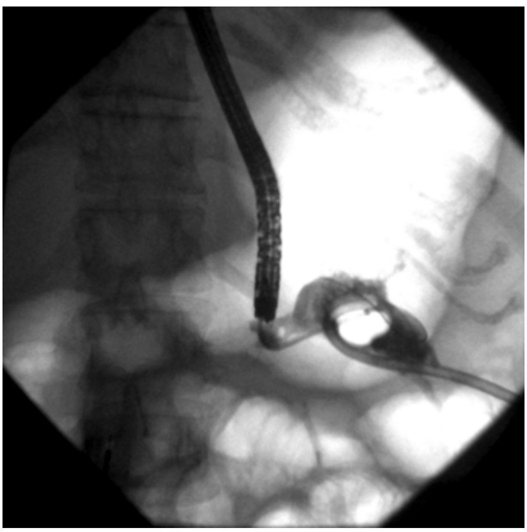

Fig. 17.18 Fluoroscopy showing "rendezvous" between endoscopic transluminal necrosectomy with endoscope passed though cystogastrostomy and meeting with percutaneous left flank retroperitoneal catheter

size of percutaneous catheters (Figs. 17.17, 17.18, 17.19, and 17.20). Limitations of any technique based primarily on PCD are difficulty reaching central collections and long duration of external drainage catheters, which may be quite

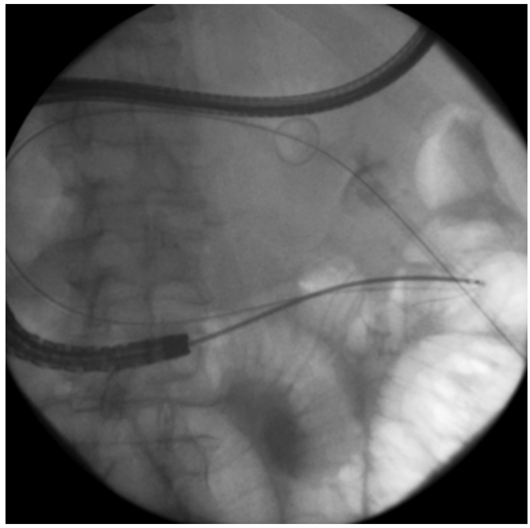

Fig. 17.19 Endoscopic placement of jejunal feeding tube to ligament of Treitz through percutaneous endoscopic gastrostomy tube that was just inserted during same procedure. Enteral feeding is a critical component of treatment of WON in ill patients and may interfere with or delay endoscopic treatments unless stomach is fixated to abdominal wall using sutures or T-tacks

limiting for ambulatory patients once discharged. However, the principle of combining endoscopic and percutaneous techniques is a sound one that deserves wider application.

Two factors render endoscopic visualization of the contact point with a collection and GI tract difficult. One is the location in the tail of the pancreas. The second is the low serum albumin which is prevalent in profoundly moribund patients and results in diffuse edema of the gastrointestinal mucosa. The use of endoscopic ultrasound-guided drainage has been shown in two randomized controlled trials involving pseudocysts to significantly increase rate of successful access to the collection, with a trend towards reduced complications, likely because of enhanced visualization and transluminal targeting of the collection, and because of ability to identify and avoid vascular structures [57, 58] (see Figs. 17.8 and 17.9).

Complications are relatively common with endoscopic transluminal necrosectomy. A recent systematic review of endoscopic necrosectomy pooling the results of ten studies involving 260 patients (60 % infected necrosis) showed a

Fig. 17.20 External view of same patient in Fig. 17.19 showing gastrostomy tube (*red* clamp to screen left) with jejunal extension receiving jejunal feeds, because of inability to tolerate oral nutrition. To screen right (posterior left flank) is retroperitoneal percutaneous catheter with drainage of purulent contents placed as adjunct to endoscopic transmural drainage and necrosectomy for very large WON extending to left flank and pelvis

Fig. 17.21 Different patient than Fig. 17.20, showing bleeding through left flank percutaneous drain in very large infected WON after aggressive endoscopic transluminal necrosectomy. This proved to be herald bleeding from a pseudoaneurysm of the splenic artery requiring angiographic embolization (see Fig. 17.22)

procedure-related morbidity in 27 % of patients. The most commonly reported complication was bleeding, which may occur during access to the collection, particularly if a vessel is punctured during dilatation of the transmural tract, and during the actual debridement of the necrotic material [52] (Figs. 17.21 and 17.22). Other serious and occasionally fatal complications have been reported [39–58]. Perforation may be due to dissection of air (or preferably carbon dioxide used for insufflation during necrosectomy) (Fig. 17.23). Stents or untreated necrosis may fistulize to vessels, bowel,

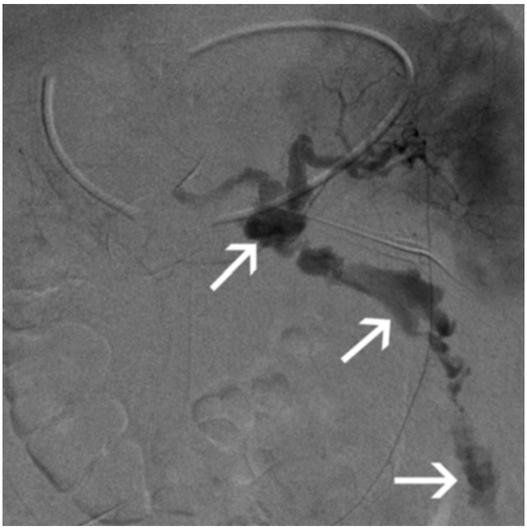

Fig. 17.22 Angiography showing very large extravasation of contrast from splenic artery due to pseudoaneurysm (same patient as Fig. 17.21)

Fig. 17.23 CECT (axial image) showing extensive intraperitoneal free air after final session of endoscopic transluminal necrosectomy (cystogastrostomy stents and collapsed necrotic cavity can be seen to screen right). Patient was managed conservatively with nasogastric suction, bowel rest, and antibiotics

or even through the diaphragm (Fig. 17.24). Air embolism is a very rare but potentially fatal complication due to dissection of air through retroperitoneal veins into the systemic circulation. Carbon dioxide is increasingly used for insufflation during necrosectomy and endoscopy in general for many reasons, and is thought to reduce risk of embolism.

Fig. 17.24 CECT (coronal image) showing complication of endoscopic transmural drainage of infected WON just under diaphragm: a large fistula has developed (*arrows*) through the diaphragm into the left pleural space resulting in empyema. The defect was thought to be due to erosion of the stent through the diaphragm, combined with unresolved infected necrosis. The patient recovered fully after requiring two chest tubes and one session of video-assisted thoracic surgery to close the diaphragmatic defect

Not all necrotic collections are amenable for endoscopic necrosectomy; when necrosis is poorly organized, does not abut the lumen of the stomach or duodenum, or extends deeply into the retroperitoneum or other areas, use of substitute or adjuvant approaches needs to be considered. Although the balloon size utilized to dilate the cystenterostomy may be correlated with the success of the procedure [38], the ideal balloon size is yet to be determined. Probably the aspect most in flux is which type of stent to use in the cystenterostomy. While two or more 10F double pigtail stents have been utilized traditionally, increasingly large bore (10-20 mm) fully covered metallic stents, including even larger covered esophageal stents, are being used more commonly. A newly designed "spool-shaped" shallow wide bore stent specifically designed for cystenterostomy have also been developed, one of which (Axios) has recently become available in the US [59–63]. Potential advantages of large-bore fully covered metallic stents include creation of a very large (up to 2 cm) cystenterostomy, allowing spontaneous digestion and egress of necrotic material with less need for mechanical debridement.

The optimal schedule for endoscopic debridement, the completeness of required necrosectomy required once undertaken, and need for repeat imaging remain uncertain. ETD/ETN is a time-consuming and labor-intensive process, which demands a special commitment by the patient and the entire team of physicians. It is best to undertake these procedures either in the operating room or in the endoscopic suite in close proximity to the operating room. Since the training requirement and the learning curve are unknown, this procedure is best performed by highly experienced and specialized endoscopists with the support of surgeons, interventional radiologists, and intensivists. Despite these limitations, the promising outcomes and the safety profile suggest that endoscopic necrosectomy is a central addition to the evolving techniques for the management of WON.

Laparoscopic Debridement

Laparoscopic-assisted pancreatic debridement is performed with laparoscopic visualization followed by hand-assisted or laparoscopic necrosectomy through a separate port, or alternatively by creation of a cystenterostomy via a transgastric or retrogastric approach [5, 64–69]. Laparoscopic debridement, although conceptually appealing, has gained little acceptance, especially in ill patients with infected necrosis, because it usually involves a transperitoneal route and thus risk of disseminating retroperitoneal infection into the peritoneal cavity [5].

Gagner and colleagues pioneered the treatment of pancreatic necrosis using three different minimally invasive approaches: transgastric, retrogastric retrocolic, and a full retroperitoneoscopic technique in eight patients [65]. Bucher et al. demonstrated the successful use of single-port laparoscopic necrosectomy in 8 patients with infected WON patients not responding to radiological drainage [64]. The authors reported that the use of a single large port laparoscopic trocar enabled good visualization for debridement and extraction. Only one patient needed a repeat minimally invasive necrosectomy. No perioperative complications or postoperative morbidity was reported. Parekh and colleagues reported on a series of 19 patients undergoing laparoscopic hand-assisted necrosectomy through a transperitoneal infracolic approach [66]. Only 1 of the 19 patients needed conversion to open necrosectomy. The authors demonstrated a significantly reduced local peritoneal and systemic immune response following laparoscopic approach compared to open necrosectomy, as well as no postoperative complications such as wound dehiscence or external bowel fistulae, and a shorter hospital stay. Fischer et al. described a novel laparoendoscopic rendezvous maneuver which was successful in five out of six cases of symptomatic WON [69].

Overall, laparoscopic necrosectomy has a clinical success rate of 70–95 %, morbidity of approximately 20 %, and mortality of 0–18 %. Laparoscopic debridement through a transgastric route via cystenterostomy is less likely to injure major vessels and thus may avoid the associated risk of visceral ischemia and bleeding. A transperitoneal approach enables access to areas inaccessible through endoscope to the lesser sac, right and left paracolic gutters, perinephric space, retroduodenal space, and root of the mesentery. Single large-port laparoscopic necrosectomy permits resection of a large amount of necrotic debris and may obviate the need for repeated interventions. It also permits simultaneous laparoscopic cholecystectomy in patients with biliary pancreatitis. However, it is unclear if the pneumoperitoneum created during laparoscopy has deleterious effects in hemodynamically unstable patients. The laparoscopic approach to WON should be undertaken by highly experienced minimally invasive surgeons, and the transgastric approach only in cases in which the collection closely abuts the stomach lumen. Laparoscopic debridement appears to be a valid therapeutic option which definitely warrants further refinement and investigation. At present, it may be most widely applicable for patients with well-organized necrosis who are scheduled to undergo simultaneous cholecystectomy late in the course of the disease [5].

Minimally Invasive Retroperitoneal Approach

Once a radiological image-guided percutaneous tract is established by a retroperitoneal route, a wide array of minimally invasive techniques are available to perform necrosectomy [5, 32, 70–75]. Minimally invasive necrosectomy via a flank tract has evolved from an adjunct to open debridement through lumbar incision (as guided by the percutaneous drain) to a primarily endoscopic technique for thorough irrigation and debridement (see Figs. 17.6 and 17.7). All variants of retroperitoneoscopy are collectively known as either sinus tract endoscopy or VARD [32, 70–76]. Sinus tract endoscopy involves intraoperative dilatation of the percutaneous drain tract followed by irrigation, lavage, and suction using a nephroscope or flexible endoscope. Gambiez et al. was the first to report this technique by using a mediastinoscope in a series of 20 patients with infected necrosis, and reported a success rate of 75 % with 10 % mortality [71]. Carter et al. used a nephroscope and long grasping forceps for debridement and continuous irrigation after serial dilation to 30F tract under fluoroscopic guidance [74]. Multiple sessions were needed to adequately evacuate all of the necrotic debris. Horvath et al. subsequently described the VARD technique, which involved a small subcostal incision (5 cm or less) to access the retroperitoneal necrotic collection, followed by limited blunt dissection and then placement of a port through which a videoscope was inserted [70, 72]. Debridement was achieved with hydrodissection and a long laparoscopic spoon forceps inserted through a second port. Only loosely adherent debris was removed, thereby minimizing the risk of trauma to underlying blood vessels and other structures. Following irrigation with normal saline, the percutaneous drain was replaced by two large-bore single-lumen drains, one placed at the deepest point of the cavity, and the other positioned closer to the incision. Continuous postoperative lavage was performed with normal saline until the effluent was clear. A repeat CECT was performed to evaluate resolution of the collection.

While theoretically appealing, the benefits of a minimally invasive retroperitoneal approach were not initially apparent. The Liverpool pancreas group retrospectively compared 137 patients who underwent retroperitoneal minimally invasive techniques to a cohort of patients who underwent open necrosectomy during the same period. The reported complications and mortality rates were lower in the minimally invasive group than in the open surgically treated group (55 % vs. 81 %, and 19 % vs. 38 %, $p = 0.009$, respectively) [73]. A Taiwanese group recently proposed a "delay until liquefaction" strategy wherein surgery was delayed until the retroperitoneal necrosis liquefied and reached the left flank [75]. A sump drain was placed via a small left flank incision that remained in place for an average period of 4 months. They reported success in 17 out of 19 patients without the need for multiple dilations and debridement procedures. Other case series of minimally invasive retroperitoneal approaches have estimated periprocedural complication rates to be less than 5 %, median number of interventions to be less than 3, and mortality ranging from 0 to 20 %.

VARD and sinus tract endoscopy are relatively simple and cost-effective techniques that can be performed by any gastrointestinal surgeon with basic laparoscopic or endoscopic skills. Utilizing minimal or no incisions, surgeons have been able to perform large necrosectomies, resulting in shorter operating time and lesser need for repetitive procedures. These techniques are particularly suitable for collections extending deep into the left side of the retroperitoneum that are partly liquefied. Collectively, minimally invasive retroperitoneal debridement techniques have a clinical success rate of 60–84 %, morbidity of up to 90 %, and mortality of 0–40 % [5]. As in all series, case selection and patient comorbidity are likely dominant factors in outcomes.

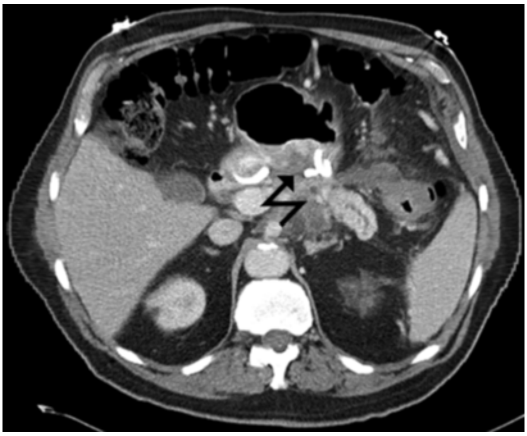

Fig. 17.25 CECT (axial image) showing disconnected pancreatic duct (*arrow*) 2 years after endoscopic transluminal necrosectomy, with dual double pigtail stents left in place indefinitely to prevent recurrent fluid collections. The patient developed inflammatory pancreatitis around the disconnected tail after the central end of the remnant pancreatic duct closed off, with subsequent ischemic colitis and requiring distal pancreatectomy and left hemicolectomy

Limitations of minimally invasive retroperitoneal approaches include limited applicability to WON of the head and the uncinate process, which may not be readily amenable for percutaneous drainage via a retroperitoneal approach. Also, any technique that involves an external percutaneous approach is associated with a substantial risk of external pancreatic fistula, especially in patients with disconnected pancreatic duct (Fig. 17.25). Sinus tract endoscopy involves the use of C-arm fluoroscopy and thereby additional risks of radiation exposure and possible increased costs. Although a reduction in morbidity has been clearly demonstrated using these techniques in comparison to open necrosectomy, a reduction in mortality or reduction in hospital stay has not been clearly demonstrated for minimally invasive retroperitoneal techniques.

Step-Up Approach

The Dutch Pancreatitis Study Group recently published the findings of a landmark trial comparing a minimally invasive "step-up" approach with traditional open necrosectomy for patients with infected necrosis [16]. The PANTER trial involved seven university and 12 major teaching hospitals across the Netherlands. Eighty-eight patients with proven or suspected infected necrosis were randomly assigned to undergo either primary open necrosectomy with continuous postoperative lavage ($n=45$) or the step-up approach ($n=43$). Step-up approach consisted of initial percutaneous (or in a few cases endoscopic) drainage, and if there was no clinical improvement within 72 h, a second drainage was performed followed by VARD; patients then underwent open necrosectomy if that strategy failed. Combined endpoints of death or major morbidity were significantly lower in the step-up approach than in the open surgery group (40 % vs. 69 %, $p=0.006$). Similarly, rates of new-onset multi-organ failure (12 % vs. 40 %), incisional hernia (7 % vs. 24 %), new-onset diabetes mellitus (16 % vs. 38 %), and pancreatic enzyme use (7 % vs. 33 %) were all significantly lower in the step-up group. The PANTER trial provides compelling evidence for a minimally invasive strategy for patients with suspected or confirmed infected necrosis. The same group has recently embarked on a nationwide randomized trial comparing the outcomes of the percutaneous and the endoscopic step-up approach, with initial drainage and debridement as needed both performed by the same route as the initial drainage, i.e., VARD or endoscopic necrosectomy (TENSION trial, registration number ISRCTN09186711) [76].

Disconnected Pancreatic Duct

Disconnected pancreatic duct represents isolation of an upstream portion of viable pancreas caused by dissolution or disruption of a central portion of the pancreas either by necrosis or by surgical or instrumental intervention. Subsequent fistulas either to internal organs or to the skin are common, as are recurrent pancreatic fluid collections after necrosis is evacuated. Management of disconnected duct represents a challenge for all disciplines involved [5]. Options include endoscopic transpapillary stenting, which often fails in the long term, leaving cystenterostomy stents in place indefinitely, endoscopic and/or percutaneous rendezvous to reconnect the duct, percutaneous techniques for gluing or occluding fistulas, and surgery including internal drainage operations, or resection of remaining upstream isolated pancreas with or without islet cell autotransplantation [77]. As such, careful consideration of all options should be evaluated with input from all relevant specialties.

Overall Strategy for Interventions in Necrotizing Pancreatitis

As there are now so many options for interventions in necrotizing pancreatitis, in reality the strategy at any center tends to be led by the specialist or specialists with the most interest and experience, be they surgeons, interventional radiologists, or endoscopists. A center focused on necrotizing pancreatitis should have all three specialists available and collaborating in management decisions regarding all incoming patients with necrotizing pancreatitis.

Our center's approach has been to individualize the approach depending on the acuity and stability of the patient, and the size, location, extent, and maturity of the collection or collections. All decisions for intervention are made in collaboration between interventional endoscopy, critical care surgery, and interventional radiology. Ill patients are generally managed in the surgical intensive care unit. All active patients are reviewed at a weekly interdisciplinary conference specifically dedicated to acute pancreaticobiliary disease management.

One of the central challenges is providing early and adequate nutrition. Enteral nutrition has been shown consistently to be superior to parenteral nutrition, with best outcomes when started within first day or two of hospitalization for severe acute pancreatitis. Nasojejunal or nasogastric tube feeding is limited for long-term nutrition, especially once patients become ambulatory. Percutaneous endoscopic gastrostomy with jejunal tube extension is advisable for many patients. However, conventional passive gastrostomy allows risk of dehiscence or leakage, especially during repeated endoscopic interventions. As such, use of T-fasteners as commonly performed by interventional radiology, or a newly described endoscopic full-thickness suturing technique for gastrostomy is advised if the patient is to undergo endoscopic necrosectomy (Attam R, personal communication) see (Figs. 17.19 and 17.20).

For walled-off collections abutting the stomach or duodenum, and especially central collections, endoscopic approach is recommended as the primary technique. For very large collections, two separate cystenterostomies, usually transgastric and transduodenal, are recommended. However, many situations call for combining percutaneous techniques. Especially if collections require early intervention because of infection but are poorly demarcated, or extend deeply into the abdomen, typically into the pelvis, percutaneous techniques should be primarily utilized, followed by minimally invasive retroperitoneal necrosectomy if insufficient. It is always preferable for a percutaneous catheter to be placed via a retroperitoneal posterior route rather than anterior/transperitoneally, as that will allow subsequent sinus tract endoscopy or VARD without dissemination of infection throughout the peritoneal cavity. Endoscopic transluminal drainage can be performed as an adjunct to avoid external fistulae, which then provides a major advantage in that aggressive flushing of percutaneous catheter on the floor results in one-way lavage of necrotic material through the cystenterostomy, rather than requiring egress out the percutaneous catheter.

For deep collections that persist after PCD, retroperitoneal flexible endoscopic approaches through the percutaneous tract are ideal, and are essentially identical to those performed via an endoscopic transluminal route but with greater reach into the pelvis, and can be performed during the same anesthesia as the per-oral necrosectomy.

Consensus Recommendations and Future Directions

Results of a multidisciplinary consensus conference on interventions for necrotizing pancreatitis have been published recently, representing the first contemporary consensus guidelines incorporating minimally invasive interventions for necrotizing pancreatitis. Subsequently, a consensus meeting was convened by the International Association of Pancreatology and the American Pancreatic Association regarding management of acute pancreatitis. Both consensus meetings included leading surgeons, endoscopists, radiologists, and medical pancreatologists with special interest and expertise in severe acute pancreatitis. Findings and recommendations were similar between both. When intervention was indicated, a step-up approach utilizing percutaneous or endoscopic drainage followed by minimally invasive or endoscopic necrosectomy was recommended, with traditional open necrosectomy reserved as a second-line intervention for patients who fail minimally invasive approaches. No specific recommendations were made as to combining approaches.

In the future, areas of further studies include improved ways for recognizing and predicting patients at risk for developing pancreatic necrosis, optimal early strategies to minimize risk of progression to pancreatic necrosis, and identifying factors associated with development of infection and organ failure in patients who develop necrosis. On the technical front, refinements in endoscopic and minimally invasive retroperitoneal necrosectomy will likely include larger removable covered stents for cystenterostomy, and hopefully devices allowing performance of secure large-bore stapled cystenterostomy. In addition, there will no doubt be improved devices for direct endoscopic debridement, and perhaps dissolution agents to facilitate liquefaction and evacuation of solid necrosis. Most importantly, combinations of techniques such as endoscopic transluminal and minimally invasive retroperitoneal necrosectomy may prove superior to single techniques for very extensive collections. Laparoscopic and percutaneous techniques will also progress to the point that any minimally invasive intervention will likely become definitive rather than require repeated procedures as is currently typical.

It should be emphasized that no single approach can be applied universally to all patients with necrotizing pancreatitis, so that the ideal approach for a particular patient should be determined based on the individual clinical scenario. Combinations of techniques in the same patient may prove superior to any single approach. Given the complexity associated with minimally invasive techniques for necrosectomy, patients with severe acute pancreatitis should be managed by a multidisciplinary team consisting of specialists from surgery, interventional endoscopy, interventional radiology, and critical care.

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