

## CME

# Endoscopic Interventions for Necrotizing Pancreatitis

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**Interventions for necrotizing pancreatitis have undergone a paradigm shift away from open surgical necrosectomy and toward minimally invasive techniques, with endoscopic transmural drainage (ETD) and necrosectomy emerging as principle forms of treatment. Recent multicenter studies, randomized trials, evidence-based guidelines, and consensus statements have endorsed the safety and efficacy of endoscopic and other minimally invasive techniques for the treatment of walled-off necrosis. A comprehensive review of indications, standard and novel approaches, outcomes, complications, and controversies regarding ETD and necrosectomy is presented. Given the inherent challenges and associated risks, endoscopic techniques for the management of necrotizing pancreatitis should be performed at specialized multidisciplinary centers by expert endoscopists well versed in the management of necrotizing pancreatitis.**

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## REVISED DEFINITIONS FOR COLLECTIONS IN ACUTE PANCREATITIS

Acute pancreatitis (AP) is a dynamic inflammatory process involving the pancreas, peripancreatic tissues, and less commonly remote organ systems (1–5). The terminology of severe AP and its complications has been redefined by an international consensus committee based on improved understanding of the natural course of the disease and refinement of imaging techniques (3). Adoption of these standard definitions is important for the appropriate understanding and management of AP.

According to the revised Atlanta criteria, there are four types of collections associated with AP: (1) acute peripancreatic fluid collections, which occur in interstitial edematous pancreatitis; (2) pseudocysts, which are delayed (usually >4 weeks) complications of interstitial edematous pancreatitis, are typically extrapancreatic, and are rare after severe AP; (3) acute necrotic collections, which occur in the early phase of acute necrotizing pancreatitis, before demarcation; and (4) walled-off necroses (WONs), which are surrounded by a radiologically identifiable capsule, a feature that rarely develops before 4 weeks after the onset of pancreatitis (3).

About 5–10% of patients with AP develop necrotizing pancreatitis (3). Necrosis of the pancreas itself is defined by nonenhancement of pancreatic parenchyma on contrast-enhanced computed tomography (CECT) (3,4). However, necrosis may also involve peripancreatic or distant extrapancreatic tissues, particularly mesenteric fat. Larger size, extension into retroperitoneum, irregular wall definition, and the presence of fat attenuation and debris on CECT enables us to distinguish WON from pseudocysts (4,6). Patients may have combined intrapancreatic and extrapancreatic necrosis (most commonly), pancreatic necrosis

alone (less commonly), or isolated extraperipancreatic necrosis (least commonly).

Although many walled-off and at least partially liquefied collections after severe AP are referred to as pseudocysts, it has been recognized relatively recently that such collections in fact mostly represent WON (2–5). The distinction is important because of implications for treatment. Associated necrotic debris and the presence of disconnected pancreatic duct can easily be underestimated by CECT. Magnetic resonance imaging and endoscopic ultrasound (EUS) may be superior to CECT in differentiating WON from pseudocysts (1–5). Any of these collections can be intrapancreatic or extrapancreatic and can be sterile or infected (**Figure 1**). Mortality of necrotizing pancreatitis has 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 (1–5).

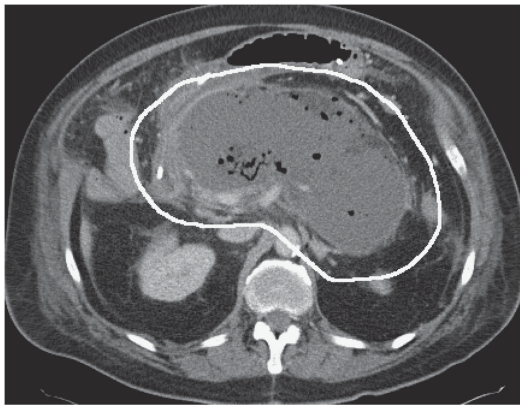
## EVOLUTION OF INTERVENTIONS FOR WON

Interventions for walled-off collections after pancreatitis have traditionally been surgical or percutaneous (1–4) (**Figure 2**). Endoscopic transmural drainage (ETD) of pseudocysts was first reported in 1985 (7) and has been widely performed (8), but until recently it had not been compared with open surgery; a randomized trial has shown substantially shorter hospital stay, lower cost, and improved quality of life for endoscopic compared with surgical drainage, with equivalent recurrence rates at 2-year follow-up (9). For infected or persistently symptomatic WON, treatment has also traditionally focused on open surgical drainage or debridement, usually requiring multiple operative sessions and

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accompanied by a significant risk of perioperative stress, organ failure, and long-term complications, including external fistulas, pancreatic exocrine and endocrine insufficiency, and incisional hernias (1–4,10).

As for pseudocysts, the management of necrotizing pancreatitis has evolved substantially with the introduction and refinement of a variety of minimally invasive approaches, which have recently been systematically categorized using a universal taxonomy (11) (**Figure 2**). Endoscopic management of necrotic collections is a relative newcomer. ETD combined with lavage of WON was first reported in 1996 (12), and endoscopic transmural necrosectomy (ETN) in 2000 (13) but are increasingly widespread and now accepted as first-line treatment for WON when intervention is indicated (1–5). As these endoscopic techniques are complex and continuously evolving, a thorough review of the current and future status of ETD and ETN was felt to be in order.

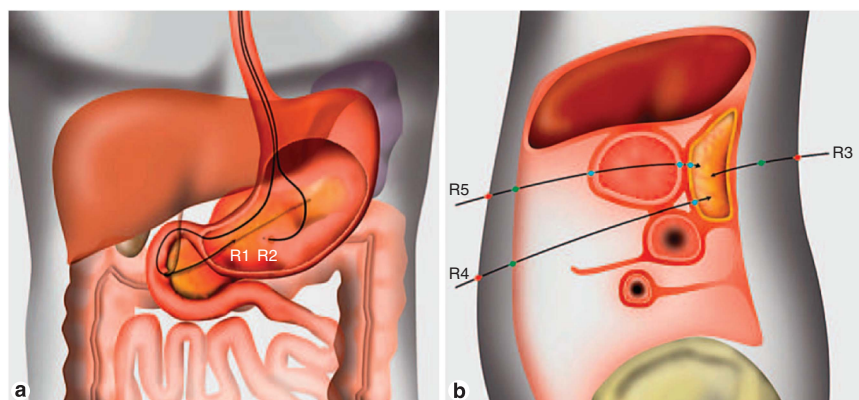


**Figure 1.** Contrast-enhanced computed tomography showing large infected walled-off pancreatic and peripancreatic necrosis accessible by endoscopic transluminal necrosectomy (by transduodenal and transgastric routes).

## INDICATION AND TIMING OF INTERVENTIONS FOR NECROTIZING PANCREATITIS

The primary indications for intervention in necrotic collections, which are similar regardless of whether they are done by endoscopic, percutaneous, or surgical routes, are listed in **Table 1**. Indications include (i) infected necrosis, which typically occurs several weeks or more into the course (1–5); infected necrosis is currently diagnosed primarily on clinical suspicion and imaging (i.e., extraluminal gas in the pancreatic and/or peripancreatic tissues on CECT) rather than by fine-needle aspiration and culture because of accuracy of clinical diagnosis and risk of false-negative cultures (5). Although systemic inflammatory response syndrome is almost universal, infected necrosis is extremely rare during the early phase (typically the first week) of severe AP, as is bacteremia unless it is due to cholangitis (3). (ii) In the absence of documented infected necrotizing pancreatitis, organ failure persists several weeks after the onset of AP, preferably when the collection has become walled off (5). (iii) Only late in the course (i.e., 4–8 weeks after onset) intervention may be indicated for the following: ongoing gastric, intestinal, or biliary obstruction; (iv) “persistent unwellness,” i.e., intractable pain, systemic illness, anorexia, and weight loss; or (v) disconnected pancreatic duct syndrome (i.e., complete transection of the pancreatic duct in the presence of pancreatic necrosis) with symptomatic and persistent collections. Asymptomatic WON does not require intervention regardless of the size and extension of the collection and may resolve spontaneously over time (5).

Several studies have suggested the possibility of treatment of infected necrosis without formal drainage or necrosectomy, either by antibiotics alone or more commonly by using selective percutaneous drainage (14–17). A recently published meta-analysis that pooled 8 studies involving 324 patients showed that primary non-operative management of infected necrosis without necrosectomy was successful in 64% of cases and was associated with a lower mortality and obviated the need for surgical necrosectomy (17). There was considerable heterogeneity among included studies,



**Figure 2.** Classification of routes taken during the treatment of local complications of acute pancreatitis. (a) Coronal view. (b) Sagittal view. R1 = per-os transpapillary; R2 = per-os transmural; R3 = percutaneous retroperitoneal; R4 = percutaneous transperitoneal; R5 = percutaneous transmural. Adapted from Loveday BT, Petrov MS, Connor S, *et al.* (11) Reproduced with permission from S. Karger AG, Basel and IAP.

**Table 1. Indications for intervention (endoscopic, radiological, 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 (5).

particularly as percutaneous drainage was considered a conservative modality, and endoscopic drainage was overlooked, raising questions about the validity of the conclusions (18). It remains unclear as to which patients with infected necrosis can be safely and effectively managed without any form of intervention, but withholding intervention is likely suitable in only a small minority of cases (19).

## OVERVIEW OF STRATEGIES FOR INTERVENTION

The best available evidence suggests that interventions for necrotizing pancreatitis should be delayed until the collections have become walled off, typically 4 weeks after the onset of pancreatitis, even if it is infected (4,5). Either endoscopic transmural or image-guided percutaneous drainage (preferably via a retroperitoneal approach) are recommended as first-line treatments for infected necrosis, followed, if necessary, by endoscopic or minimally invasive surgical necrosectomy (4,5). ETD requires proximity to the gastroduodenal lumen and a walled-off collection, whereas percutaneous drainage may be suitable for collections distant from the gut lumen and those with less demarcation. As a result, perhaps only 75–80% of necrotic collections requiring intervention can be approached at least partially by endoscopic transmural techniques, and thus flexibility in strategy and cooperation between interventional radiology, surgery, and advanced endoscopy is mandatory for successful management (1–5). Interventions of any kind 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. The primary exception is in the setting of abdominal compartment syndrome, in which surgical or image-guided decompression is potentially lifesaving, which includes primarily fasciotomy that does not involve debridement or drainage of acute necrotic collections (4). Other indications

for emergent surgery include perforation of a hollow viscus, severe bleeding which is not amenable to angiographic control, and bowel ischemia. Whenever an exploratory laparotomy is performed for the above indications, it is prudent not to explore the lesser sac because of the danger of introducing infection and bleeding complications (4).

## ETD AND NECROSECTOMY

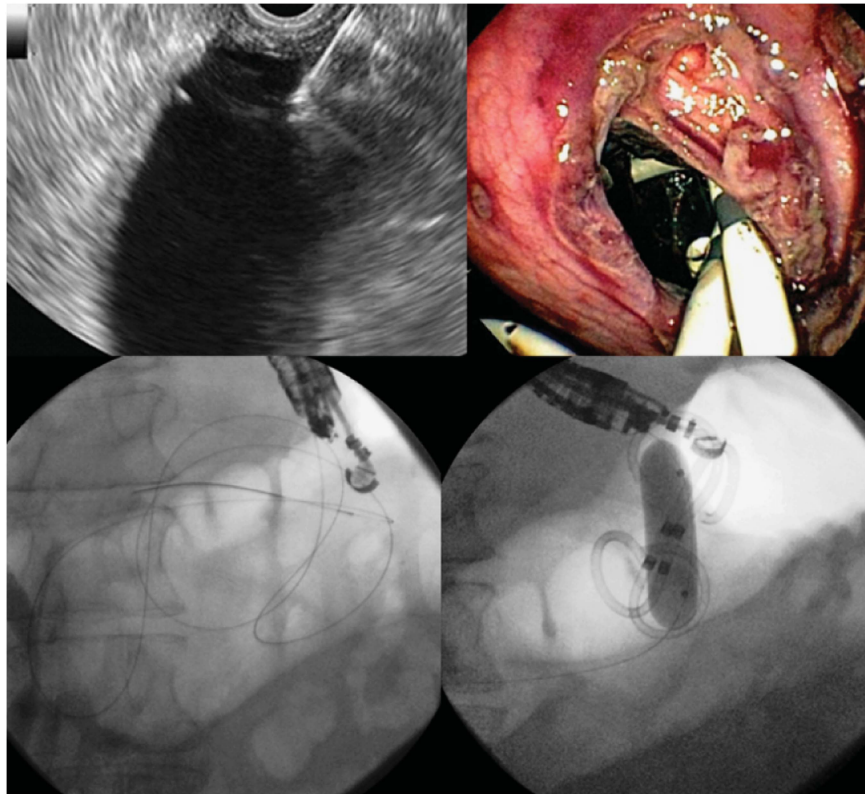
ETD and ETN for WON have evolved from the endoscopic drainage of pseudocysts. However, drainage alone of WON often proves inadequate such that direct endoscopic necrosectomy with mechanical debridement of solid debris is often required (12,20–22). Besides the ability to directly debride collections, endoscopic treatment of WON allows simultaneous treatment of disrupted pancreatic ducts via transpapillary or internal cystenterostomy stenting, removal of bile duct stones, and stenting for obstructive jaundice resulting from extrinsic or inflammatory strictures related to WON. ETN represents a true natural orifice transluminal endoscopic surgical procedure (Figures 2–9).

The first reported approach to endoscopic treatment of WON involved transmural drainage with irrigation through a nasocystic drain (12). A variant of that technique included placement of an irrigation catheter through a gastrostomy tube into the cystgastrostomy for irrigation (21). Despite these improvements, complications such as bleeding, infection besides failure to resolve the necrotic collection occurred with substantial frequency during primary drainage of WON (12). Simple drainage of WON, which have often been confused with pseudocysts, generally results in the conversion of a sterile collection to an infected one, often with significant complications, including infection and failure of resolution (22).

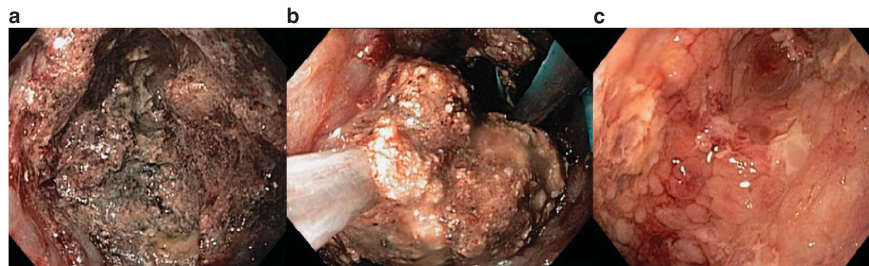
ETN was initially described in 2000 (13). The technique involved passing a peroral flexible endoscope transmurally into the necrotic cavity for debridement using a variety of devices. The site of transmural puncture for ETN was determined visually and fluoroscopically by an obvious bulge from the extrinsic compression of the necrotic collection abutting into the bowel lumen in about 50–60% of patients (4). The bulge is often absent with smaller collections, low serum albumin, and in patients with collections in or near the tail of the pancreas (23–25).

EUS allows visualization and puncture of the targeted collections independent of a visible bulge into the stomach, and color Doppler allows avoidance of vessels in the puncture tract (Figure 3). In two randomized trials involving drainage of pseudocysts, EUS was associated with higher technical success (95 vs. 33–66%) and a trend toward lower adverse event rates (0–4 vs. 13–15%) than conventional transmural endoscopic drainage (23,24). The success of EUS-guided drainage of pseudocysts has been extrapolated to the management of symptomatic and infected WON (12), and EUS is now nearly universally recommended for initial puncture and drainage (1–5).

Necrosis that is closely adhered to the posterior gastric wall or medial duodenal wall is considered ideal for endoscopic necrosectomy (26,27). Although a distance of 1 cm from the lumen to



**Figure 3.** Endoscopic ultrasound-guided access for endoscopic transmural drainage of infected walled-off necrosis, followed by placement of two double-pigtail 10F stents and large balloon dilation of cystgastrostomy.

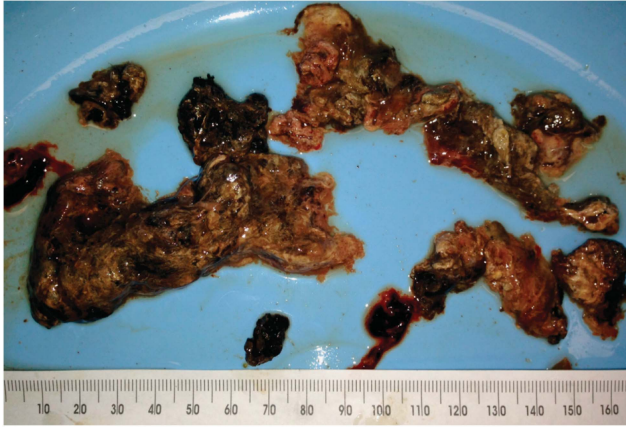


**Figure 4.** Sequence of endoscopic images showing endoscopic entry into (a) complex walled-off necrosis, (b) basket removal of necrotic material, and (c) clean cavity after repeated debridements.

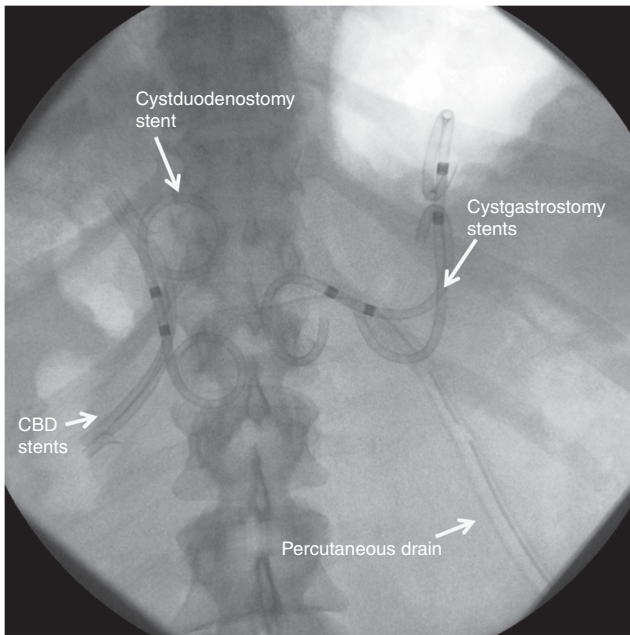
the collection has previously been considered the maximum safe distance, EUS allows distances of up to 2 cm to be traversed safely in some cases (26). Selection of a site some distance from the gastroesophageal junction has been preferred, as it allows straight positioning of the scope allowing easy entrance into the collection (28). However, the best point of entry into the cavity can vary markedly depending on the location of the collection, and it is best determined and performed via EUS.

If there are no contraindications such as bleeding diathesis, disrupted cystenterostomy tract, or patient instability, the goal is to dilate the tract to up to 15–20 mm at the time of the first

endoscopic drainage, followed by placement of multiple large-bore double-pigtail stents or of a single large-diameter fully covered metallic stent. Larger size of balloon dilation has been correlated with increased clinical success of necrosectomy (26). Transluminal necrosectomy can be performed at the index procedure, but it is usually best performed at repeat procedures as dictated by evolution of the cavity and clinical course after there has been time for decompression of purulent contents. For ETN, the cavity is entered with a forward-viewing endoscope, preferably with at least one double-pigtail stent left in place to maintain access and drainage, and the cavity irrigated and debrided of solid contents using



**Figure 5.** Large amount of necrotic material removed via endoscopic transluminal necrosectomy through cystgastrostomy and cystduodenostomy.



**Figure 6.** Fluoroscopic image of multifaceted endoscopic management of large infected walled-off necrosis involving pancreas and extending deep into the pelvis. Patient underwent biliary stenting for obstructive jaundice, endoscopic ultrasound-guided cystduodenostomy and cystgastrostomy, and left flank retroperitoneal percutaneous catheter drainage and lavage, with eventual necrosectomy via transluminal and sinus tract routes using flexible endoscopy.

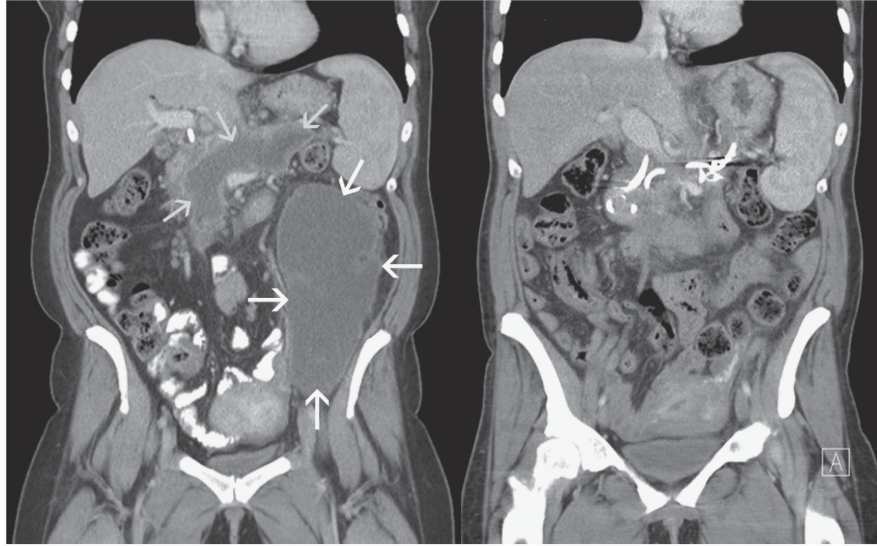
balloons, baskets, snares, nets, and/or a variety of other standard endoscopic accessory devices (29,30). Endoscopic debridement and lavage is usually repeated on a regular basis until the cavity is clean by endoscopic inspection and radiographic imaging, either CECT or magnetic resonance imaging. As many as 3–6 sessions may be necessary for complete debridement of the necrotic cavity, with or without nasocystic or percutaneous drain placement

to provide irrigation (4). Optimal timing, number, and completeness of endoscopic debridements are uncertain at present, as each procedure carries a risk of complications, particularly intracavitary bleeding and perforation.

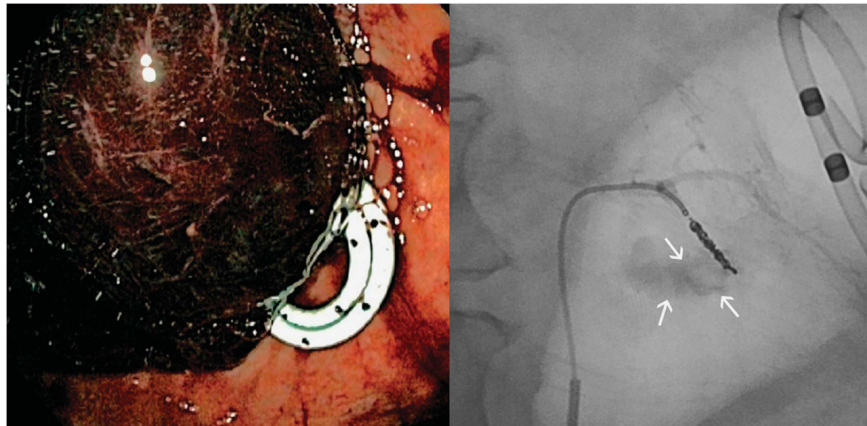
Special challenges to the success of endoscopic (and all other methods of) necrosectomy include poorly liquefied or demarcated collections and deep retroperitoneal extension into the pelvis. Most collections are retroperitoneal. Intraperitoneal extension, although uncommon, poses a particular risk of disseminating infection or perforation into the peritoneal cavity. Percutaneous catheter drainage (PCD) may be required as an adjunct or substitute in such cases, as well as in cases of deep retroperitoneal extension of WON. A retroperitoneal approach for percutaneous drainage is usually possible and always preferable (4).

### DISCONNECTED PANCREATIC DUCT SYNDROME

Disconnected pancreatic duct occurs in up to one-third or more of patients with necrotizing pancreatitis (4,5) and results from dissolution or debridement of a central portion of the pancreas, leaving viable secreting gland upstream of the cavity, and predisposing to recurrent pancreatitis, collections and fistulae (31) (Figure 9). External fistulae occur in over 25% of patients with WON treated with surgical or percutaneous methods owing to spontaneous or intervention-induced disconnected duct (4,5). Transpapillary stenting of the main pancreatic duct via ERCP into the cavity or across the disruption into the tail may resolve the disconnection. In a multicenter prospective study, 19 patients undergoing endoscopic transpapillary stenting for fistulae associated with necrotizing pancreatitis were compared with 16 patients undergoing conservative management, with similar rates of fistula closure (84 vs. 75%) but a shorter median time to closure (71 vs. 120 days) (32). Recurrence of pancreatic collections is relatively common after transpapillary stenting for disconnected duct (33). As a result, the most widely used approach is to leave cystenterostomy stents in place indefinitely to maintain patency of the internal fistula and divert pancreatic secretions back into the gastrointestinal lumen. Compared with removing cystenterostomy stents after successful endoscopic drainage of walled-off collections, leaving stents in place indefinitely has been shown in a randomized trial to result in a substantially reduced rate of recurrence of collections (0/15 vs. 5/13,  $P < 0.05$ ) (34). The safety of long-term indwelling transmural stents for disconnected pancreatic duct was confirmed by a recent retrospective study, in which 30 patients with transmural stents were followed up for an average of 20 months (35). Stent migration occurred in 5 (17%) patients, 4 of whom remained asymptomatic and 1 had recurrence of a pancreatic fluid collection. In selected refractory cases of disconnected duct with persistent fistulae or recurrent collections, internal drainage via EUS-guided pancreatoenterostomy or combined percutaneous and endoscopic internal drainage may be performed (36). If still refractory, further options include surgical diversion with a Roux-en-Y pancreaticojejunostomy or distal pancreatectomy with or without islet cell autotransplantation to preserve islet cell function (4).



**Figure 7.** Left: Patient with very large complex walled-off necrotic pancreatic (small arrows) and extrapancreatic (large arrows) collections. Right: Complete resolution of walled-off necrosis after treatment by endoscopic transluminal drainage via duodenum and stomach, percutaneous catheter lavage, and flexible endoscopic necrosectomy through transgastric, transduodenal, and sinus tract routes.

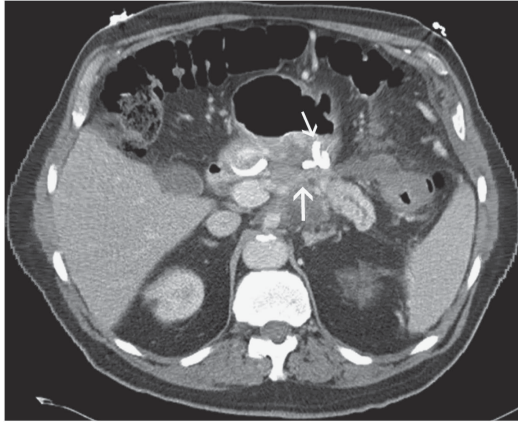


**Figure 8.** Massive bleeding from endoscopic cystgastrostomy (left) occurring 3 days after the procedure, when anticoagulation was instituted for deep vein thrombosis. Hemorrhage was refractory to endoscopic injection, coagulation, clipping, and placement of fully covered metallic esophageal stent, requiring angiographic coiling of left gastric artery (right).

### OUTCOMES OF ETD AND NECROSECTOMY

Published studies of ETD and necrosectomy for WON are summarized in **Table 2**. All are retrospective case series except for a single prospective randomized controlled trial. It must be emphasized that published series of ETN mostly represent highly selected cases that were felt to be suitable for endoscopic management, with varying degrees of extrapancreatic necrosis, liquefaction and encapsulation, and comorbidity, rendering comparisons with other techniques limited. In the only randomized comparative trial (PENGUIN study), the Dutch Pancreatitis Group compared direct endoscopic necrosectomy ( $n=10$ ) and surgical necrosectomy ( $n=10$ ) consisting of video-assisted retroperitoneal debridement (VARD) or, if not feasible, open necrosectomy

in patients with infected WON (37). All patients underwent a “step-up” approach, beginning with PCD, and if that failed randomization to either endoscopic necrosectomy or VARD was performed. Owing to the small sample size, the primary outcome was serum interleukin-6, a surrogate marker of systemic inflammatory response. Secondary outcomes included a composite clinical end point of death or major morbidity, including new-onset multiorgan failure, intra-abdominal hemorrhage, perforation of a visceral organ needing intervention, and enterocutaneous or pancreatic fistula. Interleukin-6 rose rapidly within the first 24 h after surgical necrosectomy, but it did not increase in the endoscopic group ( $P=0.004$ ). There were also strikingly improved clinical outcomes in the endoscopic group, with a significant reduction in



**Figure 9.** Contrast-enhanced computed tomography showing completely disconnected pancreatic duct, with a large gap separating the tail from the head (large arrow). The patient developed recurrent episodes of pancreatitis in remnant tail 1 year after successful endoscopic necrosectomy, despite leaving cystgastrostomy stents in place (small arrow), and eventually underwent distal pancreatectomy.

major complications (20% vs. 80%, risk difference 0.6,  $P=0.03$ ). New-onset multiorgan failure did not occur in the endoscopic group, and fewer patients developed external pancreatic fistulae, any of which were most likely the result of the initial percutaneous drainage. The authors attributed the superior outcome to less physiological stress resulting from the use of a natural orifice as an access route to the retroperitoneal cavity as compared with surgical dissection. Endoscopic interventions were conducted under moderate conscious sedation, obviating the need for general anesthesia. General anesthesia is known to provoke or prolong systemic inflammation in these critically ill patients (37), but it is frequently used for endoscopic necrosectomy in the United States and universally at our own center. For these reasons and the small size of the study, the promising results need to be replicated in larger trials before being generalized into routine clinical practice. Such a trial is underway in the Netherlands (the TENSION trial).

Factors that predict failure of endoscopic therapy have not been well studied. It has been suggested that the size of the necrotic cavity  $>15$  cm, deep retroperitoneal extension, presence of diabetes mellitus, and comorbid conditions are predictors for failure of endoscopic therapy (38). The presence of more extensive necrotic debris, severe duct disruption, or deep retroperitoneal extension of necrosis suggest the need for early aggressive adjuvant therapy such as PCD with or without sinus tract endoscopy or VARD in addition to or in lieu of endoscopic therapy (38).

### COMBINED APPROACHES

One of the major determinants for the feasibility of endoscopic necrosectomy is the location of the target collection. Central collections are almost always accessible, but left-sided and flank collections may not be amenable to transmural endoscopic man-

agement (4). In such cases, a variety of other minimally invasive retroperitoneal approaches, including PCD, minimally invasive retroperitoneal necrosectomy or sinus tract endoscopy using a flexible endoscope, and VARD procedure, may be either preferable or serve as adjuncts to endoscopic therapy.

In one center basing therapy primarily on percutaneous large-bore catheter drainage and debridement of WON, the systematic addition of ETD has been reported to improve outcomes compared with percutaneous management alone (39–41). Lavage through the percutaneous approach with egress through the transmural fistula theoretically facilitates more rapid debridement than either technique alone, and the internal drainage is intended to prevent external fistulae that are so prevalent after percutaneous management alone. In the first series of 15 patients undergoing such a combined approach for WON localized to the lesser sac (within 2 cm of the stomach or duodenum), 25 total endoscopies (4 for drain manipulation) were performed. Percutaneous drains were removed in 13/15 patients after a median follow-up of 189 days, with none of these patients developing chronic pancreaticocutaneous fistulae (39). The same group retrospectively compared the dual modality with PCD and lavage alone (41) and showed 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 purely PCD (41). The need for large-diameter balloon dilation and endoscopic debridement of the retroperitoneum was avoided, thus theoretically decreasing the risk of complications (39). Although promising, the combined technique based primarily on percutaneous necrosectomy may not be applicable to other centers with less dedicated and aggressive interventional radiologists. PCD is not an ideal primary approach for patients with WON directly behind the stomach or duodenum, which can be difficult to reach with PCD unless via an intercostal, transperitoneal, or transenteral route. The long duration of an indwelling PCD required for primary percutaneous therapy may be an impediment to the quality of life, especially after discharge from the hospital.

Other approaches to combined therapy involve selective use of the combination of ETD/ETN and PCD for patients with deep extrapancreatic collections, with adjunctive sinus tract endoscopy or minimally invasive retroperitoneal necrosectomy reserved for patients who fail to respond in a timely manner to the combination of endoscopic and percutaneous catheter-based therapies. Further data are needed to determine the optimal approach, but it clearly varies from patient to patient. In selected cases of well-demarcated WON, especially in patients who require cholecystectomy for gallbladder stones, a single laparoscopic procedure involving both a large-diameter stapled cystgastrostomy and cholecystectomy may be ideal (4). A suggested flow diagram for interventions in WON based on extensive ( $>100$  cases) multidisciplinary management of necrotizing pancreatitis at our center, which was focused on ETD/ETN when feasible, is shown in **Figure 10**.

**Table 2.** Outcome of endoscopic transluminal drainage and necrosectomy with or without adjunctive techniques

Author	Patients (n)	Infected (%)	Timing of intervention (mean/median days after presentation)	Modality	Mean number of repeat interventions	Overall success rate (%)
Baron <i>et al.</i> (12)	11	3 (27%)	50	Transmural stents+ nasocystic lavage± transpapillary stenting	2.7	9 (82%)
Seifert <i>et al.</i> (13)	3	1 (33%)	NA	ETN-first report	NA	3 (100%)
Park <i>et al.</i> (59)	9	9 (100%)	42	Transmural stents+ nasocystic lavage		8 (89%)
Seewald <i>et al.</i> (60)	13	13 (100%)	NA	ETN + transmural stents+ nasocystic lavage± transpapillary stenting	7	11 (85%)
Charnley <i>et al.</i> (61)	13	11 (85%)	27	ETN	4	9 (69%)
Voermans <i>et al.</i> (62)	25	19 (76%)	84	Transmural stents+ nasocystic lavage	2	23 (92%)
Papachristou <i>et al.</i> (38)	53	26 (49%)	49	Transmural stent±ETN± transpapillary stenting±PCD	3	43 (81%)
Escourrou <i>et al.</i> (63)	13	13 (100%)	28	PCD±ETN	1.8	13 (100%)
Hocke <i>et al.</i> (64)	30	30 (100%)	NA	ETN	2.7	27 (90%)
Matthew <i>et al.</i> (28)	6	6 (100%)	42	Transmural stents+ nasocystic lavage	0	6 (100%)
Schrover <i>et al.</i> (65)	8	8 (100%)	33	Transmural stents+ nasocystic lavage	4	6 (75%)
Seifert <i>et al.</i> (30)	93	50 (54%)	43	ETN	6.2	75 (81%)
Ross <i>et al.</i> (39)	15	9 (60%)	29	PCD±ETN	1.4	15 (100%)
Gardner <i>et al.</i> (29)	104	40 (39%)	63	ETN	3	95 (91)
Bakker <i>et al.</i> (37)	10	10 (100%)	59	PCD±ETN or VARD	3	10 (100)
Rische <i>et al.</i> (66)	31	24 (77%)	NA	ETN + transmural stents+ nasocystic lavage± transpapillary stenting	4	26 (83%)
Yasuda <i>et al.</i> (67)	57	57 (100%)	50	ETN + transmural stents + nasocystic lavage	5	43 (75%)

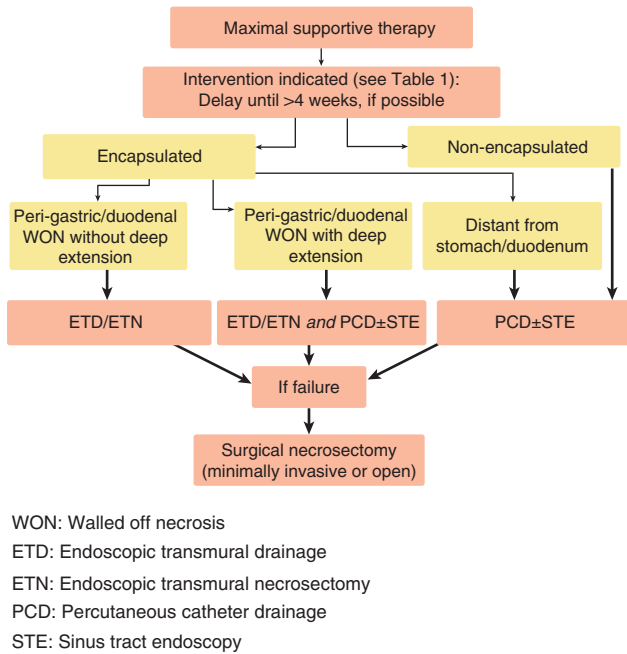
ETN, endoscopic transmural necrosectomy, PCD, percutaneous catheter drainage, VARD, video-assisted retroperitoneal debridement.

### NOVEL APPROACHES TO ETN

There are many variations in techniques and approaches for endoscopic necrosectomy. The multigateway approach uses more than one transmural entry site created under EUS guidance in order to facilitate rapid drainage in large (>80 mm) symptomatic WON (42). One tract may serve as a channel for irrigation, whereas the other acts as an egress conduit for drainage of necrotic contents and minimizes the probability of closed-space infection. Multiple gateways would theoretically reduce the number of sessions required for resolution (43). More than one ETD may not be feasible in smaller WON or in collections that are not in close approximation to the bowel lumen.

The use of covered self-expanding metal stents with a large internal diameter has been reported in drainage of pancreatic collections (44). The use of an esophageal metallic stent was first reported in a patient with infected necrosis who refused surgery

and failed four endoscopic sessions with plastic stents (45). Fully covered esophageal metallic stents were subsequently reported in 17 patients with infected WON, with an 83% success rate (46); the larger diameter of the stents (18 to 23 mm) may have resulted in fewer necrosectomy sessions and decreased time to resolution. Potential stent migration and uncertain cost-effectiveness preclude widespread adoption of fully covered esophageal stents in clinical practice. Recently, a single-step system for access and delivery of a specifically designed anastomotic fully covered stent with a maximum available inner diameter of 15 mm (Axios, XLumena, Mountain View, CA) is now approved by Food and Drug Administration but with limited availability in the United States (47). There is another fully covered self-expanding metal stent with an antimigration system specifically designed for cystenterostomy, but it is not currently available for use in the United States (Nagi stent, Taewoong Medical, Gyeonggi-do, Korea). Its use was



**Figure 10.** University of Minnesota flow chart for interventions in necrotizing pancreatitis. ETD, endoscopic transmural drainage; ETN, endoscopic transmural necrosectomy; PCD, percutaneous catheter drainage; STE, sinus tract endoscopy; WON, walled-off necrosis.

reported in a small pilot observational study of four patients with WON (48). The wide lumen of the stent (16 mm diameter) allowed the insertion of a small therapeutic gastroscope through the stent lumen for direct necrosectomy (48). Further studies with the use of lumen-apposing stents in endoscopic necrosectomy are awaited.

Novel methods of debridement are under continuous investigation. Hydrogen peroxide has been reported as a means of loosening the debris, although advantages and safety compared with conventional methods are unclear (49). The successful treatment of transgastroscopically accessible necrotic cavities by using an endoscopically placed vacuum sponge has been described in two patients; the authors observed spontaneous demarcation of necrotic tissue, which was automatically removed either by removal of the sponge or by suction (50). The use of Clutch Cutter (Fujifilm, Tokyo, Japan), a grasping type of scissors recently developed for endoscopic submucosal dissection using electro-surgical current, was recently reported in a case of WON in order to grasp, incise, and dissect large areas of necrotic tissue and provide hemostasis (51).

### STEP-UP APPROACH

The “step-up” approach involves minimally invasive techniques (PCD or ETD) to initially manage the infected necrosis, with definitive necrosectomy via VARD/ETN or open surgical approach postponed or avoided altogether depending on the

clinical course of the patient (4). Such an approach has been postulated to induce less physiological stress than open surgery or aggressive necrosectomy in already critically compromised patients (4,52–54). To assess whether the step-up approach is superior to open necrosectomy as first-line treatment, the Dutch Pancreatitis Study Group conducted a randomized controlled trial (PANTER trial) across 19 hospitals in the Netherlands (55). Patients with proven or suspected infected necrosis were randomly assigned to undergo either primary open necrosectomy with continuous postoperative lavage ( $n = 45$ ) or to undergo the step-up approach ( $n = 43$ ). Combined end points 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 multiorgan failure (12% vs. 40%), incisional hernia (7% vs. 24%), new-onset diabetes mellitus (16% vs. 38%), and pancreatic enzyme use (7% vs. 33%) and cost of care were all significantly lower in the ‘step-up’ group. Notably, 35% of patients in the step-up group did not need necrosectomy at all, with drainage alone sufficient to resolve the WON. The PANTER trial provides compelling evidence for a minimally invasive strategy for patients with suspected or confirmed infected necrosis and dispels the notion that direct mechanical necrosectomy is necessarily required for all WON (55). The same Dutch group has recently embarked on a nationwide randomized trial comparing the outcomes of a percutaneous with an endoscopically based ‘step-up’ approach, with debridement performed as needed by the same route as the initial drainage, i.e., VARD or endoscopic necrosectomy (TENSION trial, registration number ISRCTN09186711) (56). This important study will shed further light on the comparative effectiveness of endoscopic therapy for WON.

### COMPLICATIONS OF ENDOSCOPIC TRANSLUMINAL NECROSECTOMY

The complication rate of endoscopic necrosectomy in expert hands generally ranges from 15% to 30% (26) (Table 3). In a recent systematic review of 10 observational studies of >1,100 endoscopic necrosectomy procedures in 260 patients, procedure-related morbidity rate was 27% and all-cause mortality rate was 5% (57). The most common complication was bleeding, which may occur during access to the collection, particularly if a vessel is punctured during dilation of the transmural tract or during the direct debridement of the necrotic cavity (57) (Figure 8). Color flow Doppler in EUS-guided cystenterostomy allows identification and avoidance of vascular structures during access and is associated with a trend toward reduced risk of bleeding (23,24). Hemorrhage may also occur from retroperitoneal vessels such as the portal vein during the direct debridement of the necrotic material (57), representing a sometimes drastic complication that may require emergent angiography or even surgery.

Perforation with intra-peritoneal dissemination of infection may occur during initial cystenterostomy, repeated dilation of cystenterostomy, or disruption of the cavity wall during direct

**Table 3. Studies reporting complications and mortality**

Author	N	Number of days in hospital	Complications	Mortality (all cause)
Baron <i>et al.</i> (12)	11	14.9 (2–34)	Bleeding—5 Perforation—1 Infection—4	0
Seifert <i>et al.</i> (17)	3	NR	NR	0
Park <i>et al.</i> (59)	9	17	Bleeding—1	0
Seewald <i>et al.</i> (60)	13	NR	Bleeding—4	0
Charnley <i>et al.</i> (61)	13	NR	NR	2 (15%)
Voermans <i>et al.</i> (62)	25	5 (1–45)	Major bleeding—1 Minor bleeding—8 Perforation—1	0
Papachristou <i>et al.</i> (38)	53	13 (0–90)	Bleeding—9 Gallbladder puncture—1 Stent migration—2	3 (6%)
Escourrou <i>et al.</i> (63)	13	30 (8–60)	Bleeding—3 Infection—3	0
Hocke <i>et al.</i> (64)	30	NR	Bleeding, infection and fistula in 10%	2 (6.6%)
Matthew <i>et al.</i> (28)	6	16.5 (10–27)	None	0
Schrover <i>et al.</i> (65)	8	23 (13–41)	Bleeding—1 Pneumoperitoneum—1 (fatal)	1 (12.5%)
Seifert <i>et al.</i> (30)	93	46 (8–170)	Bleeding—13 Perforation—5 Fistula—2 Infection—1 Air embolism—2	7 (7.5%)
Ross <i>et al.</i> (39)	15	15.5 (1–80)	Infection—1	0
Gardner <i>et al.</i> (29)	104	12	Major bleeding—2 Minor bleeding—19 Retrogastric perforation—2 Pneumoperitoneum—3 Air embolism—1	2 (1.9%)
Bakker <i>et al.</i> (37)	10	45 (12–69)	Pancreatic fistula—1 Others—1	1 (10%)
Rische <i>et al.</i> (66)	31	44 (11–109)	Perforation of colon—2 Stent dislocation to jejunum—1 Major bleeding—1 (fatal)	3 (9.6%)
Yasuda <i>et al.</i> (67)	57	21 (10–101)	Major bleeding—5 Perforation—3 Air embolism—1	6 (11%)

NR, not reported.

necrosectomy. In the largest series of single-modality ETN for WON, perforation was reported in five patients, all of whom were managed nonoperatively (29). Providing enteral nutrition via a gastrostomy tube with jejunal extension, as required in many ill patients with WON, may be technically challenging and lead to dehiscence or perforation of the gastrostomy tract during repeated endoscopic procedures unless the stomach is fixed to the abdominal wall using T-fasteners or a novel endoscopic suturing technique

(58). Infection (especially of remaining necrotic material) has been reported and is particularly common when WON is mistaken for a pseudocyst and treated with simple drainage. Broad-spectrum antibiotics are generally given peri-procedurally, although efficacy is uncertain. Severe and sometimes fatal air embolism has been reported, likely from dissection of insufflated air through exposed retroperitoneal veins (29,30). Carbon dioxide is now very strongly recommended for insufflation during necrosectomy, as

it theoretically minimizes the chance of air embolism (29). Other reported complications include gallbladder puncture, migration of stents into the cavity, fistula to bowel or other structures, and bowel obstruction or ischemia (38). It is critical for endoscopists to recognize these potentially life-threatening complications and have appropriate collaboration with interventional radiology and surgery.

### CURRENT CHALLENGES AND FUTURE DIRECTIONS

Although ETD and necrosectomy are now well-established modalities for the management of WON, there are many remaining questions and controversies. It is still not known whether EUS is necessary in every initial cavity puncture and cystenterostomy (26). The best method of sedation—monitored anesthesia care vs. general anesthesia with endotracheal intubation—is not established. It is not known whether the optimal strategy involves a “step-up” approach with initial drainage followed by on-demand necrosectomies only if there is lack of resolution, vs. scheduled necrosectomies. It is also unclear whether necrosectomy, once started, needs to be carried to completion in every case or what is the optimal interval between sessions. Major technical impediments currently include a lack of dedicated instruments available for necrosectomy, many of which are borrowed from other endoscopic applications; limited ability to fix the bowel to the cavity wall with staples or sutures; and uncertain ability to avoid vessels and other vital structures within the necrotic cavity. Although larger balloon dilation is correlated with increased success of necrosectomy, the ideal size for balloon and fistula tract is yet to be determined (26). The optimal stent for cystenterostomies remains unsettled, although the trend seems to be toward increasingly large self-expanding tissue-apposition-type expandable removable stents. Long-term efficacy of transpapillary and/or prolonged transmural stenting in patients with disrupted or disconnected pancreatic ducts is still unclear. Limitations of endoscopic necrosectomy in large WON and especially those with deep retroperitoneal extension are not well defined, as are predictors of failure of ETN. The role for adjunctive or alternative techniques such as PCD and minimally invasive retroperitoneal techniques needs to be further elucidated. Further studies are needed to determine predictors of poor outcome, including comorbidities, immobilization, and poor nutritional status. Finally, the extent of technical mastery and understanding of necrotizing pancreatitis required to safely and effectively perform endoscopic management of necrotizing pancreatitis remains to be determined.

### CONCLUSIONS

A subset of patients with AP progresses to necrotizing pancreatitis and thus is prone to organ failure, infection, and other local complications. In specialized centers, the primary methods for management of necrotic collections have undergone a paradigm shift away from open surgical necrosectomy and toward minimally invasive techniques, with therapeutic endoscopists having an increasingly central role. A major multicenter trial has clearly

demonstrated the superiority of a ‘step-up’ approach combining PCD and VARD over open surgical necrosectomy, thus establishing the preference for minimally invasive techniques. Several multicenter series have confirmed the feasibility and safety of endoscopic transluminal necrosectomy in carefully selected patients and when performed by experienced interventional endoscopists. A small randomized trial has suggested the superiority of endoscopic over surgical necrosectomy, although a further multicenter trial is underway. It should be emphasized that no single approach can be applied to all patients with necrotizing pancreatitis, and thus the optimal method should be tailored to the individual patient. PCD and minimally invasive retroperitoneal necrosectomy techniques remain an essential adjunct to, or substitute for, endoscopic management of WON in a substantial number of situations. Given the complexity and risk associated with endoscopic management of necrotizing pancreatitis, specific understanding of necrotizing pancreatitis, training in pancreatic endotherapeutic techniques, and multidisciplinary management of patients in conjunction with intensivists, surgeons, and interventional radiologists is essential to optimize outcomes.

### CONFLICT OF INTEREST

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