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Interventions for Necrotizing Pancreatitis

An Overview of Current Approaches

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Abstract and Introduction

Abstract

The management of necrotizing pancreatitis has undergone a paradigm shift toward minimally invasive techniques for necrosectomy, obviating the need for open necrosectomy in most cases. There is increasing evidence that minimally invasive approaches including a step-up approach that incorporates percutaneous catheter or endoscopic transluminal drainage, followed by video-assisted retroperitoneal or endoscopic debridement are associated with improved outcomes over traditional open necrosectomy for patients with infected necrosis. A recent international multidisciplinary consensus conference emphasized the superiority of minimally invasive approaches over standard surgical approaches. The success of these techniques depends on concerted efforts of a multidisciplinary team of interventional endoscopists, radiologists, intensivists and surgeons dedicated to the management of severe acute pancreatitis and its complications. This review provides an overview of minimally invasive techniques for management of necrotizing pancreatitis, including indications, timing, advantages and disadvantages.

Introduction

Acute pancreatitis (AP) is a dynamic inflammatory process involving the pancreas, peri-pancreatic tissues and less commonly remote organ systems. The incidence of acute pancreatitis is increasing globally[1] and the consequent increase in overall hospitalization has posed an enormous burden on healthcare utilization and costs.[2] In a recent study, pancreatitis was estimated to account for nearly 274,000 hospitalizations in the United States annually, making it the leading gastrointestinal discharge diagnosis.[3]

The most widely used definitions for acute pancreatitis are derived from clinically based Atlanta classification.[4] While seminal at the time of publication in 1993, the Atlanta criteria have undergone extensive revision by an international panel of experts from multiple disciplines, a summary of which has been recently published.[5] From a morphological point of view, AP is defined as either interstitial or necrotizing pancreatitis. Necrotizing pancreatitis 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 peri-pancreatic tissues (more commonly) or isolated peri-pancreatic tissue alone (least commonly). Isolated peri-pancreatic necrosis may be associated with improved long-term outcomes compared to pancreatic necrosis.[6,7] However, peri-pancreatic necrosis carries a worse prognosis than acute interstitial pancreatitis.[6–8] Both pancreatic and peri-pancreatic necrosis can be either sterile or infected.

From a clinical point of view, approximately 20% of patients with acute pancreatitis are classified as severe, based on presence of sustained organ failure or local complications such as necrosis.[9] 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.[10,11] 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.[12,13] Open surgical debridement is accompanied by significant risk of perioperative stress, organ failure, and long-term complications including external fistulas, diabetes, pancreatic exocrine insufficiency, and incisional hernias. 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 of the various minimally invasive modalities available for necrosectomy. Regardless of approach, 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.

Indications and Timing for Intervention

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, that is, in the first 4 weeks. Interventions should be considered later in course of sterile necrotizing pancreatitis only in the presence of disabling symptoms such as persistent pain requiring narcotics, in the presence of gastric outlet or biliary obstruction inability to eat and/or failure to thrive (continued systemic illness, anorexia and weight loss[13]). Currently there is a clear consensus that to optimize outcomes, interventions should be delayed until there is 'walled off' necrosis (WON), which can involve the pancreas itself, peri-pancreatic tissues, or both. WON (formerly known as organized necrosis) represents a well-demarcated collection of necrotic debris that replaces portions of the pancreas and/or peri-pancreatic tissues, especially the retroperitoneal fat.[14] Walled-off necrosis typically evolves four or more weeks after onset of AP. Larger size, extension into retroperitoneum, irregular wall definition and the presence of fat attenuation and debris enables CECT to distinguish WON from pseudocysts.[15] Asymptomatic WON does not mandate intervention regardless of the size and extension of the collection, and may resolve spontaneously over time. However, WON may become infected, obstruct or fistulize to adjacent anatomical structures, or can compress or erode into vasculature causing major hemorrhage, and can thus markedly impact the clinical course of patients with severe acute pancreatitis.[16] Interventions for pancreatic or peri-pancreatic necrosis within the first few weeks are generally associated with adverse outcomes and are typically reserved for infected necrosis in severely deteriorating patient. 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. Currently the consensus is that interventions for walled-off necrosis should be delayed as long as possible, preferably to at least 3–4 weeks after onset of disease, to allow liquefaction and encapsulation of necrotic collection.[17]

Diagnosis of Pancreatic, Peri-pancreatic and Infected Necrosis

CECT, MRI, magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) are potential modalities for imaging pancreatic necrosis. CECT remains the 'gold standard' for imaging in severe acute pancreatitis. CECT aids in the diagnosis of pancreatic parenchymal necrosis in determining the extent of necrosis and can identify local complications including venous thrombosis and pseudoaneurysm (Figures 1 & 2). Complete evolution of pancreatic necrosis may take up to 5 days. Hence CECT can underestimate or underdiagnose necrosis if performed before this interval.[9,18–20] Disadvantages of CECT include radiation exposure, especially with repeated imaging, and contrast-induced nephropathy.[17] 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.[21–23] Avoidance of radiation exposure, enhanced detection of non-liquid material in pancreatic and peri-pancreatic fluid collections, 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 (Figure 3).[24] 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.[17]

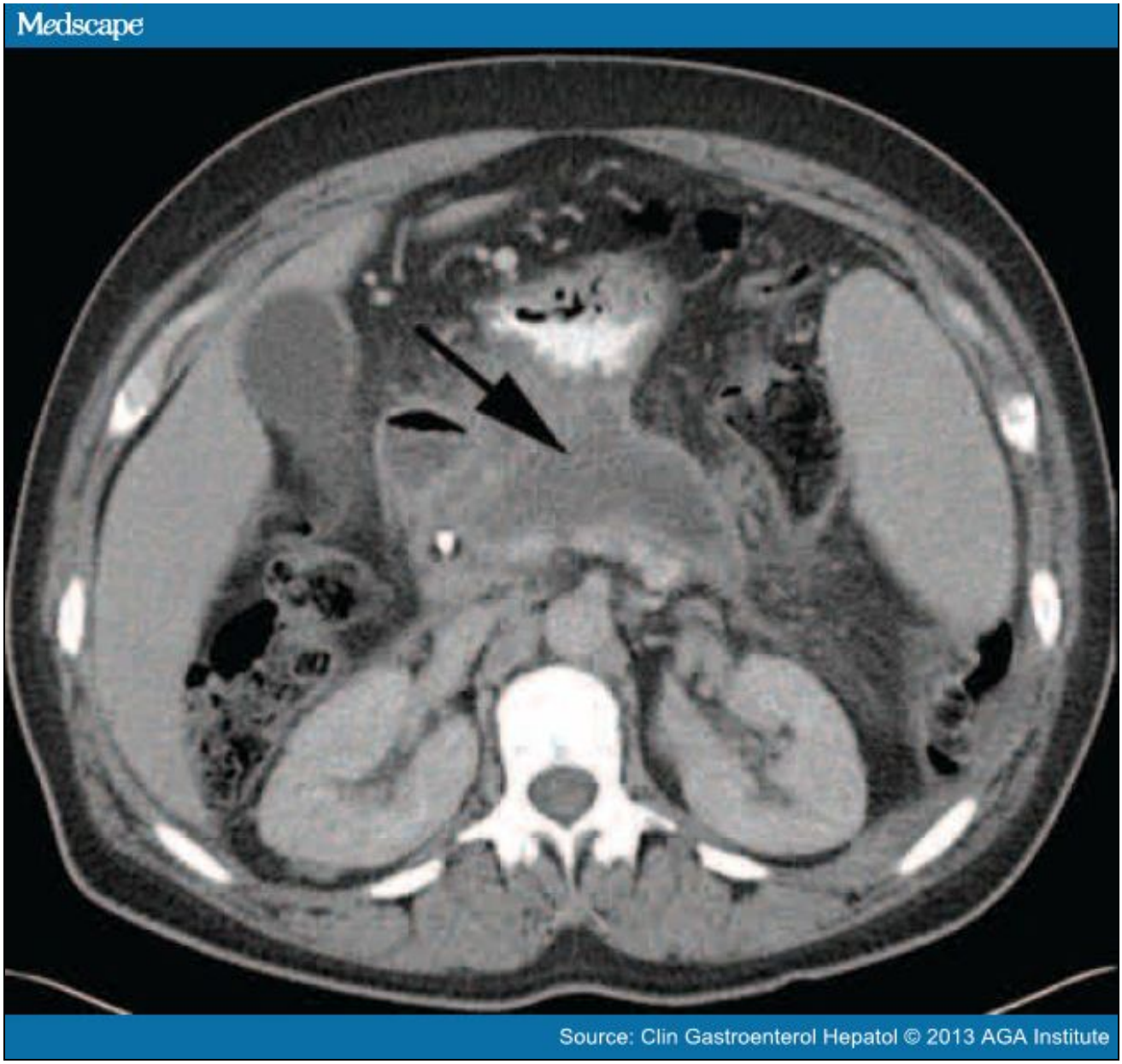

Figure 1.

Contrast-enhanced computed tomography (axial). Walled-off necrosis involving the pancreas is visible (arrow).

Figure 2.

Contrast-enhanced computed tomography (coronal). Walled-off necrosis involving peri-pancreatic tissue (extra-pancreatic) extending retroperitoneally deep into the pelvis (arrow) is visible (same patient as shown in Figure 1).

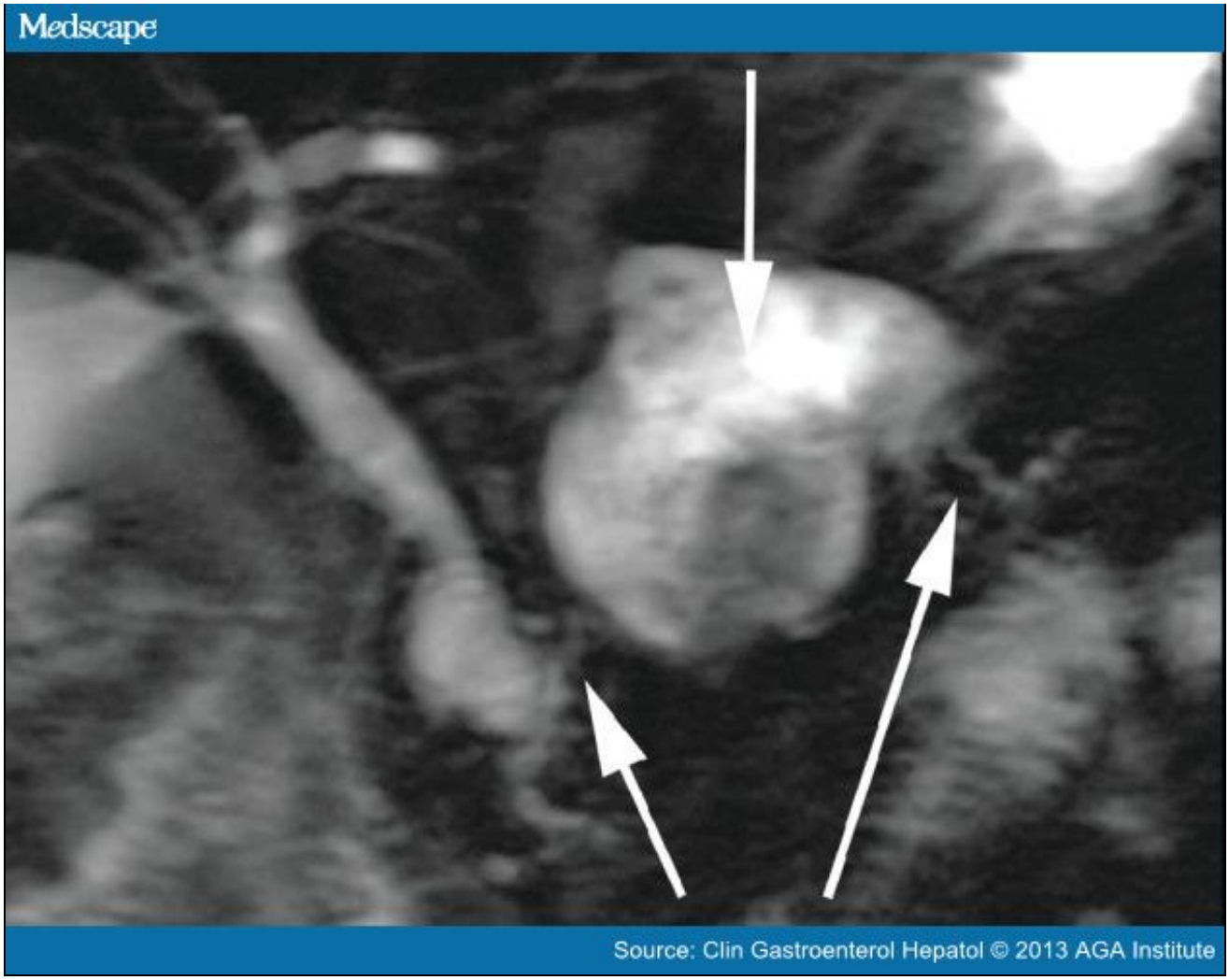

Figure 3.

MRI/magnetic resonance cholangiopancreatography showing walled-off necrosis of pancreatic body with disconnected pancreatic duct. Arrows from left to right: pancreatic duct in head; walled-off necrosis replacing body of pancreas and containing solid debris; pancreatic duct in tail draining into walled-off necrosis.

The peak incidence of infection of pancreatic or peri-pancreatic necrosis is between 2 and 4 weeks after presentation, but can occur at any time during the clinical course.[25] 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 peri-pancreatic or gas due to gas-forming organisms or fistulous communication with the stomach, small intestine or colon (with introduction of organisms and air) (Figure 4).[6] 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.[10,26] 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.[27,28] However, FNA has been demonstrated to have a false-negative rate of 10% or more[29] 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.[17] 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.[30] Currently, a possible remaining indication for diagnostic FNA in

necrotizing pancreatitis is to detect fungal superinfection when patient remains febrile despite ongoing treatment with broad spectrum antibiotics.[17]

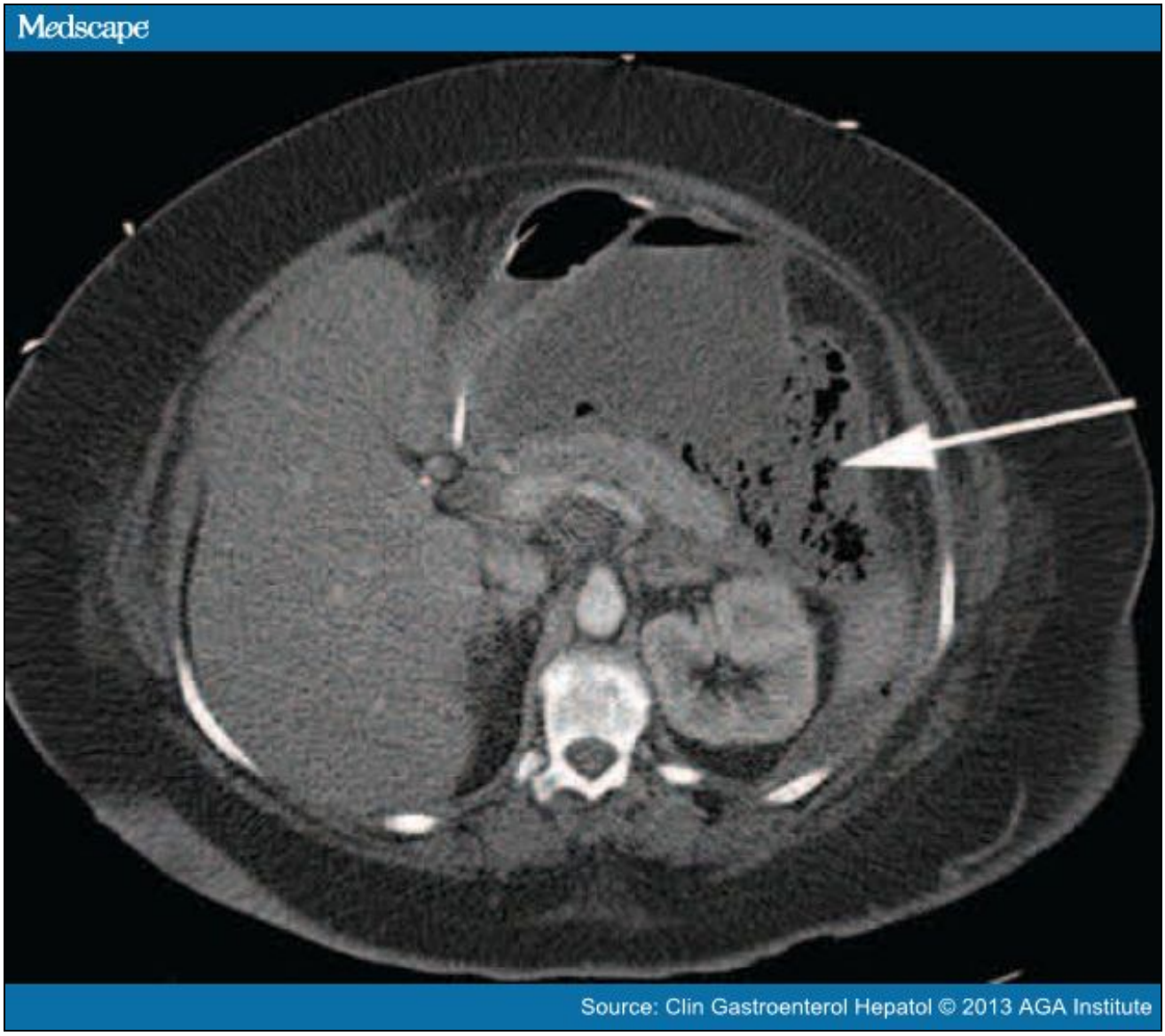

Figure 4.

Contrast-enhanced computed tomography showing infected peri-pancreatic necrosis. Obvious gas bubbles (arrow) can be seen. Note that pancreas itself is intact and without necrosis.

Minimally Invasive Approaches to Necrosectomy

The presence of infected necrosis has traditionally been thought to be an indication for debridement or necrosectomy.[9] Several studies have suggested the possibility of treatment of infected necrosis without formal drainage or necrosectomy – occasionally using antibiotics alone, or more commonly using selective percutaneous drainage.[31,32] A recent study by Garg *et al*.[33] described non-surgical treatment of infected necrosis by management in an ICU setting with sensitive antibiotics (third-generation cephalosporin with beta-lactamase inhibitors and carbapenems), aggressive nutritional support and judicious percutaneous intervention in the event of infected WON. Patients underwent surgical intervention only if they deteriorated in spite of the aggressive conservative management. They suggested significantly decreased need for hospitalization, duration of external drainage and number of radiological procedures, with a mortality that was comparable to surgery.[33] This concept of primary conservative management was further substantiated by two other

studies.[34,35] It is however unclear as to which patients could be safely and effectively managed without any form of necrosectomy.

Traditional approaches to debridement involve open surgery, either via an anterior transperitoneal approach or via retroperitoneal approach through a flank incision. 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), route (per oral, trans-papillary or transmural, percutaneous retroperitoneal, percutaneous transperitoneal, percutaneous transmural or other) according to a taxonomy developed by Windsor and colleagues.[36] Minimally invasive procedures are thought to induce less physiological stress as compared with open surgical debridement.[30,37]

Percutaneous Catheter Drainage

Percutaneous catheter drainage (PCD) of pancreatic and peri-pancreatic necrosis involves placement of single or multiple catheters that are subsequently upsized, irrigated and manipulated along with direct percutaneous necrosectomy (Figure 5).[17] Freeny *et al*.[38] 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. They reported a combined technique of PCD with active percutaneous necrosectomy that was achieved by placement of multiple large-bore catheters and vigorous irrigation. PCD was successful in postponing surgical intervention for a median of 4 weeks and in obviating the need for surgical necrosectomy in 47% of the patients.[38] Over the past two decades, PCD has been increasingly utilized to stabilize critical patients both as 'a bridge to surgery' and as sometimes as definitive therapy. The preferred route for PCD is via a flank approach through the retroperitoneum,[30,39] 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 retroperitoneal surgical video-assisted retroperitoneal necrosectomy (VARD) or sinus tract endoscopy.[37] The Dutch Pancreatitis group recently reported a nationwide multicenter prospective study primarily of patients with infected necrosis.[6] In that study, 63% (n = 130) of patients underwent PCD as a primary intervention. Of this group, 35% of patients recovered without additional necrosectomy.[6] 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. 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 can be treated with PCD alone.[40,41] The authors acknowledged the wide variation in techniques with only 5 of 11 studies employing the Seldinger technique. The size of the drains used varied from 8 to 28 Fr[40] and only one study undertook routine stepwise dilation for upsizing the drains.[35] Two prospective studies have suggested a more realistic primary success rate of PCD of 33% to 35%.[30,42]

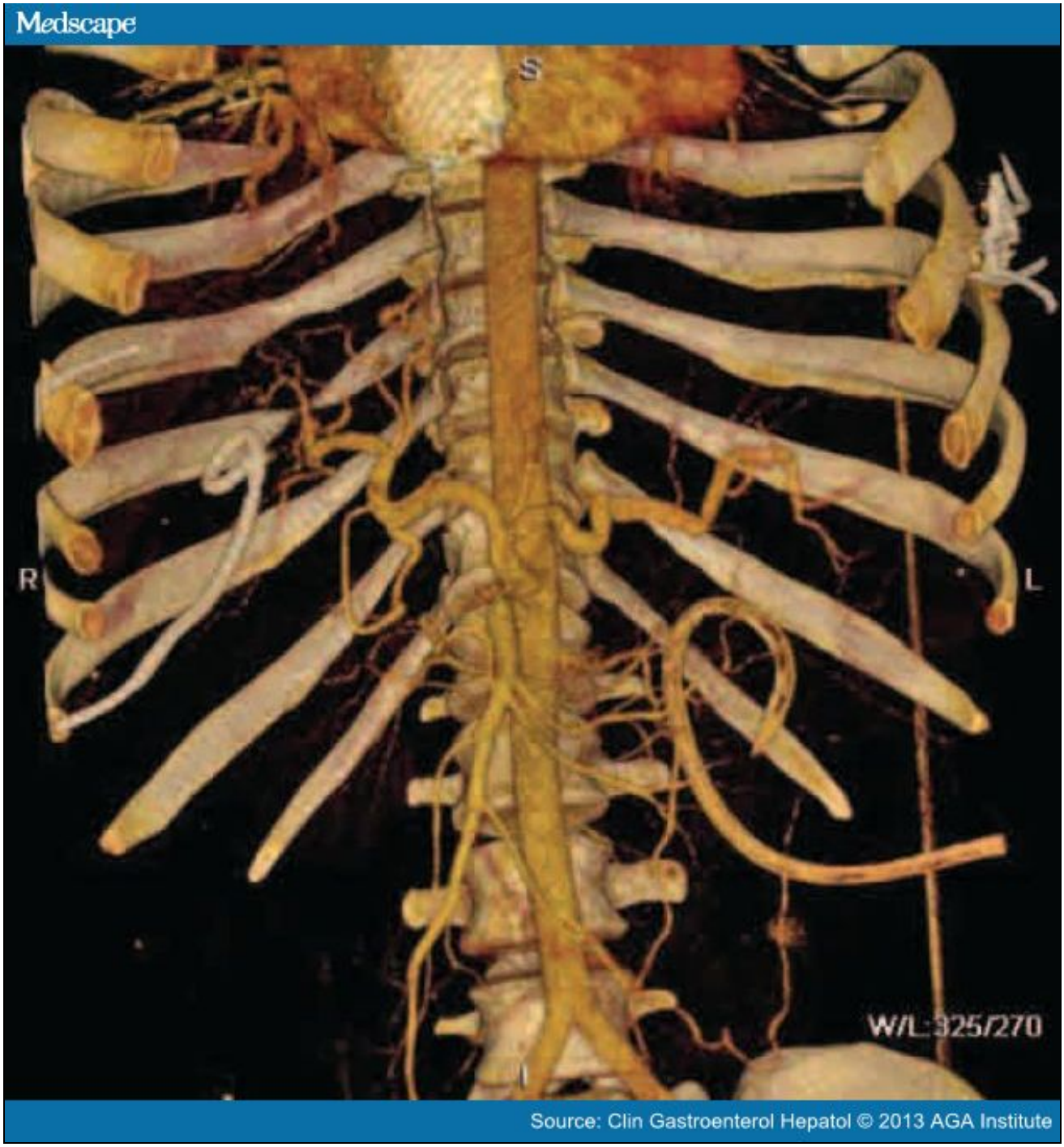

Figure 5.

Percutaneous catheter drainage. Computed tomography angiogram showing two percutaneous catheters placed to treat patient with infected peri-pancreatic necrosis that was poorly encapsulated and extending deep into left retroperitoneum and intraperitoneally under liver.

PCD is a relatively simple and well-established radiologic procedure.[30] It is beneficial especially as 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.[16] PCD is technically not adequate or feasible when retroperitoneal hemorrhage, bowel necrosis, duodenal/biliary obstruction further complicates necrotizing pancreatitis.[29] Persistent external fistulas occur in

up to 27% of patients.[17] Other drawbacks include limited ability to remove necrotic debris. Dilatation of the percutaneous tract up to 26 Fr and using grasping forceps to extract the debris has been described in a small series,[43] as has the use of assist devices such as stone retrieval baskets,[44] but these techniques are seldom performed in clinical practice. A dedicated team of radiologists willing to assiduously follow these patients, 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.[43,44]

Endoscopic Necrosectomy

Transluminal endoscopic necrosectomy represents a true natural orifice transluminal endoscopic surgical procedure. Endoscopic necrosectomy is increasingly gaining traction as primary therapy for infected pancreatic necrosis in carefully selected patients (Figures 6–12). Transmural drainage of chronic pancreatic pseudocyst is a well-established modality particularly when performed by experienced interventional endoscopists. However, the principal difference is that unlike with drainage of pseudocysts, endoscopic necrosectomy involves direct debridement of solid debris. The endoscopic approach to necrotizing pancreatitis also offers a method via transpapillary or internal cyst-enterostomy stenting to treat disconnected pancreatic duct that occurs as a result of dissolution of a major portion of the pancreas (Figure 3).

Figure 6.

Endoscopic ultrasound-guided drainage of infected walled-off necrosis. The needle can be seen traversing the gastric wall into solid necrotic debris in the lesser sac (same patient as in Figures 1 & 2).

Figure 7.

Fluoroscopic view showing endoscopic transgastric debridement through covered self-expanding metallic stent placed through cyst gastrostomy (same patient as in Figures 1 & 2).

Figure 8.

Endoscopic view of solid necrosis in lesser sac in patient undergoing direct endoscopic necrosectomy (same patient as in Figures 1 & 2).

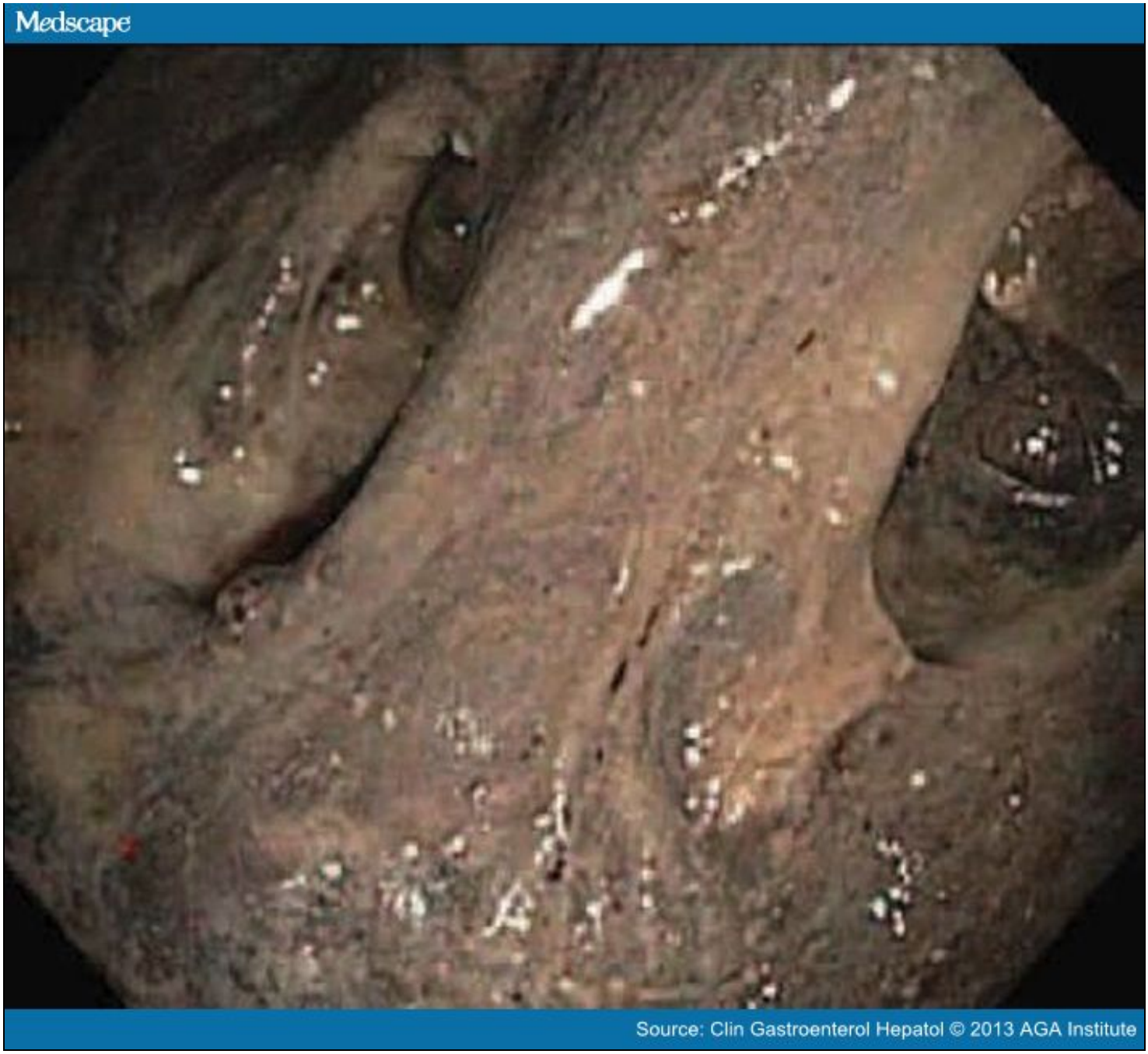

Figure 9.

Endoscopic view of obviously infected necrosis in lesser sac in patient undergoing direct endoscopic necrosectomy.

Figure 10.

Fragments of infected necrotic material extracted by direct endoscopic necrosectomy in piecemeal fashion.

Figure 11.

Single, very large piece of necrotic material extracted by direct endoscopic necrosectomy.

Figure 12.

Patient in prone position under general anesthesia showing left flank percutaneous catheter about to undergo minimally invasive retroperitoneal debridement via sinus tract endoscopy (same patient as in Figures 1 & 2).

Endoscopic drainage and lavage of WON was initially reported nearly two decades ago as an outgrowth of endoscopic pseudocyst drainage, combining cyst-enterostomy with nasocystic lavage to flush out necrotic debris.[45] Direct endoscopic necrosectomy (DEN) was first reported by Seifert and colleagues in 2000.[46] DEN involves creation of a cyst enterostomy, with large diameter (10–20 mm) balloon dilation, followed by direct entry of a forward viewing gastroscope into the necrotic cavity. Necrosectomy is performed under direct endoscopic vision using forceful irrigation, suction, snares, rat toothed–forceps, tripod retrieval, stone removal baskets and other endoscopic accessories.[46,47] Endoscopic necrosectomy is generally repeated until the necrotic cavity is thoroughly evacuated and healthy granulation tissue is evident. Several retrospective studies of DEN have been reported.

Some but not all involve selective use of adjunctive techniques such as nasocystic lavage or percutaneous catheter drainage (Figure 13). 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. At a mean follow-up 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.[46] An American multicenter study included 104 patients with symptomatic WON at six American centers undergoing endoscopic necrosectomy. A minority of patients had infected necrosis and this study included only patients selected as suitable for endoscopic necrosectomy, rather than as 'intent-to-treat.' Successful resolution was achieved in 91% of patients, with a mean duration of treatment of 4 months to achieve success. Two patients underwent operative drainage for persistent WON, one required surgery for massive bleeding on fistula tract dilation, and one died during the procedure presumably of an air embolus. This study by Gardner and colleagues confirmed DEN to be an efficacious and reproducible technique with an acceptable safety profile. Overall, endoscopic necrosectomy reports a 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 to 70% and a mortality from 0 to 15%.[17] As with all series of a single technique, case selection may be a primary determinant of outcome, allowing for limited direct comparisons with other approaches.

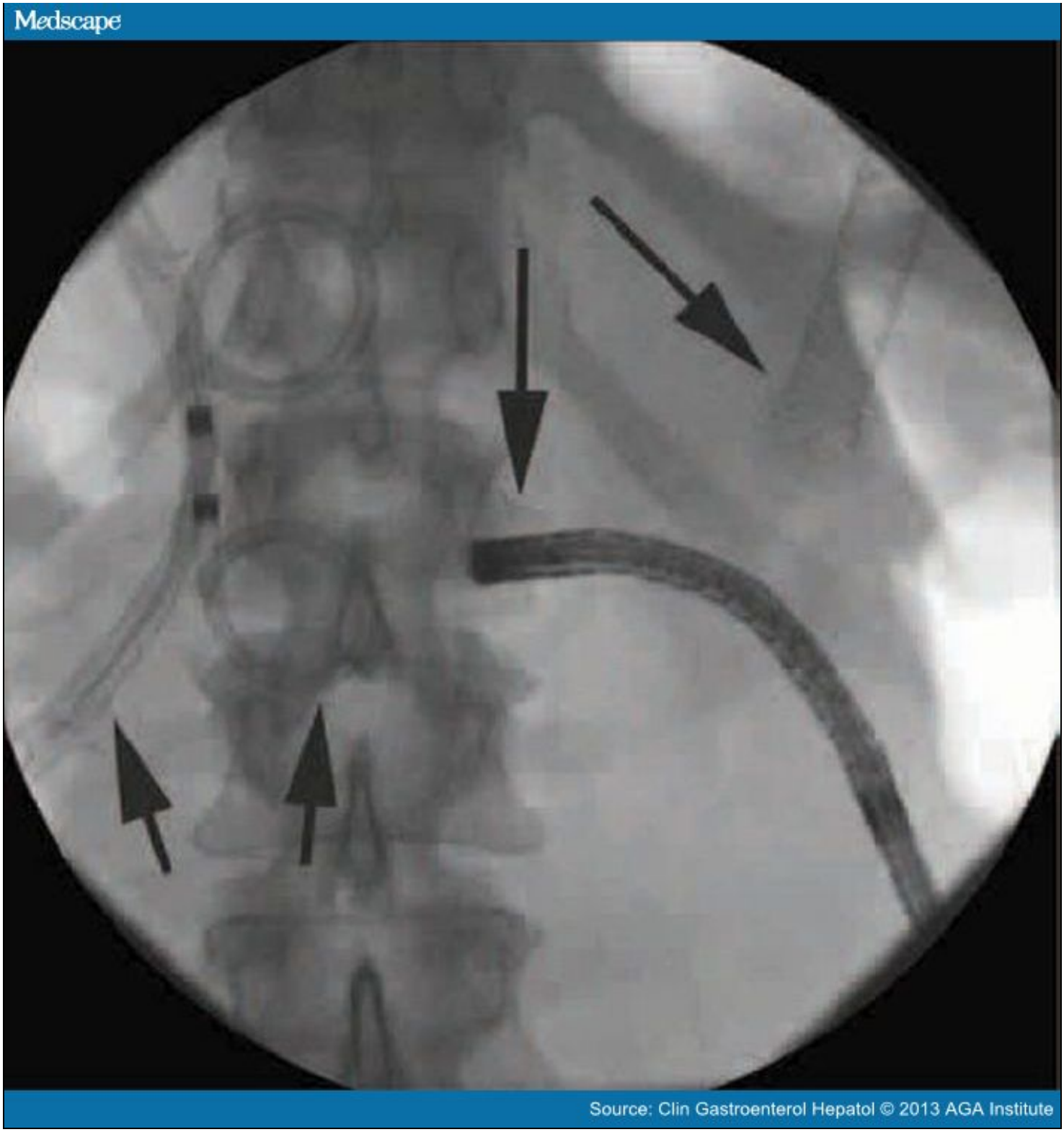

Figure 13.

Patient undergoing minimally invasive retroperitoneal debridement via sinus tract endoscopy after multi-gateway endoscopic drainage via cyst gastrostomy and cyst duodenostomy, plus biliary stenting. Arrows from left to right: biliary stents, cyst duodenostomy stent, endoscope passed from left flank tract through retroperitoneum into lesser sac; self-expanding metallic stent in cyst gastrostomy (same patient as in Figures 1 & 2).

The Dutch Pancreatitis Study Group recently reported the results of the first randomized control trial comparing

endoscopic transgastric necrosectomy (n = 10) and surgical necrosectomy (VARD or, if not feasible, open necrosectomy, n = 10) in infected necrotizing pancreatitis.[48] All patients underwent percutaneous catheter drainage, via a step-up approach, and if that failed, were randomized either to endoscopic necrosectomy or VARD. In this study entitled the 'PENGUIN' trial, investigators utilized a surrogate marker of post procedural serum interleukin (IL-6) as the primary outcome rather than clinical end points due to small sample size. 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, 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 multiorgan 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 physiologic stress. They also performed the endoscopic interventions 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,[48] but is almost universally utilized for endoscopic necrosectomy 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*.[49] recently described a multi-gateway approach that uses multiple transmural entry sites created under EUS guidance, to facilitate rapid drainage in large symptomatic WON (measuring >80 mm in diameter) (Figure 14). 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 in those not in close approximation to the lumen.[49] The Virginia Mason group has advocated another variation consisting of combining percutaneous large-bore drainage and debridement with internal transmural endoscopic drainage to blend the advantages of both techniques and in particular, to avoid external fistulas.[16,50] 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 percutaneous catheter drainage alone, suggesting significantly decreased hospitalization (26 days 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.[16] 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 cyst gastrostomy stents in place indefinitely. They also speculated that there was reduced risk of pseudoaneurysmal bleeding in the combined modality because of decreasing exposure of the retroperitoneal vasculature to pancreatic secretions and with smaller drains and fewer exchanges, and because of less mechanical trauma.[16,51] Multicenter randomized trials evaluating the efficacy of various combinations of techniques are awaited, but such combinations of techniques are increasingly used in clinical practice as they may reduce need for repetitive endoscopic interventions.

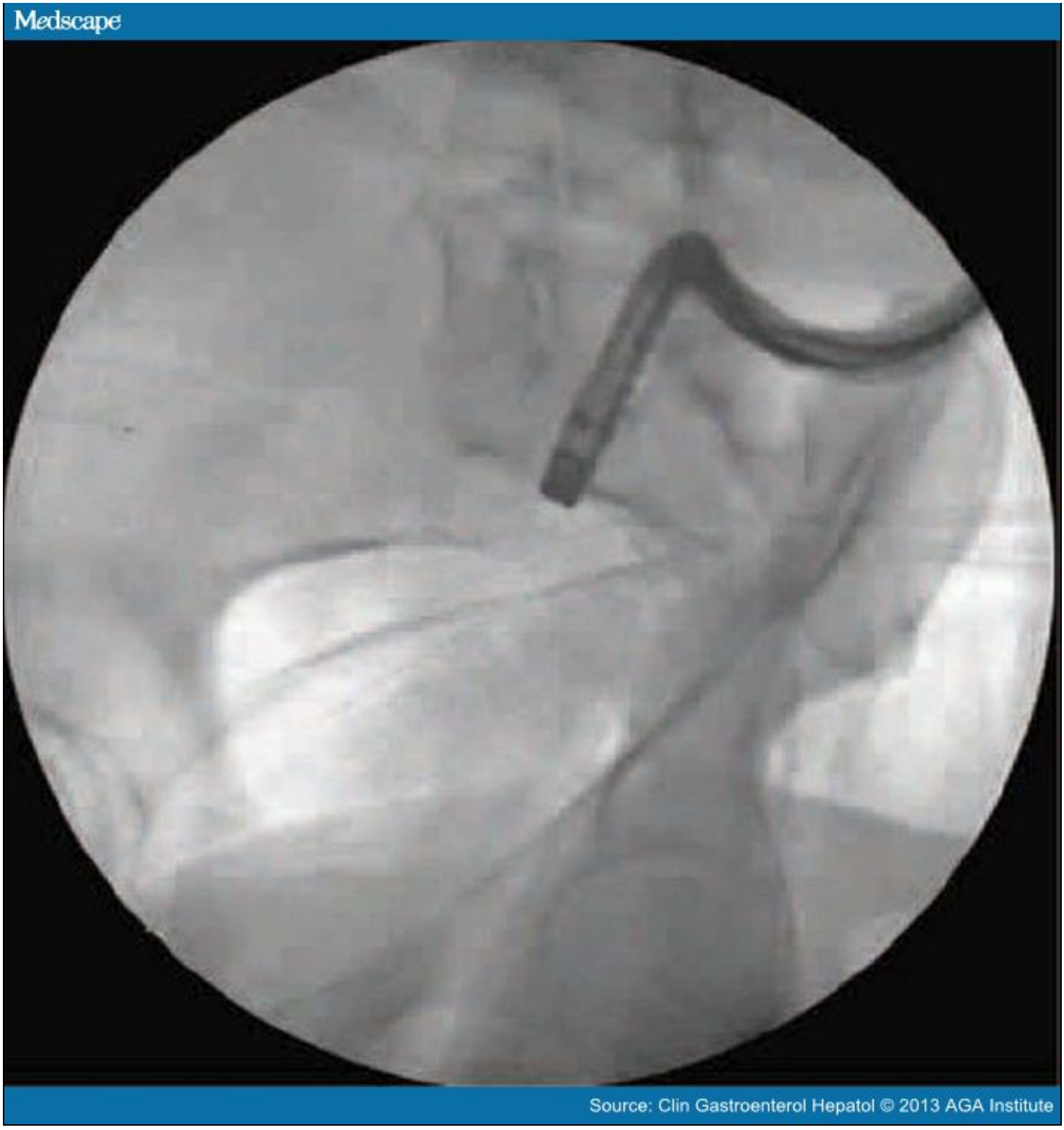

Figure 14.

Fluoroscopic view of sinus tract endoscopy via left flank percutaneous drain tract, showing that exploration and debridement is possible deep into retroperitoneum in left pelvis using this technique.

A recent systematic review of endoscopic necrosectomy pooling the results of 10 studies involving 260 patients (60% infected necrosis) showed a procedure-related morbidity in 27% of patients.[52] 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. Other serious and occasionally fatal

complications such as perforation and air embolism have been reported in series of endoscopic necrosectomy.[46,47] Carbon dioxide is increasingly used for insufflation during necrosectomy for many reasons, as it is thought to reduce risk of embolism,[46] and is currently approaching 'standard of care'.

Endoscopic visualization of the contact point with a collection and GI tract may be difficult. 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 toward reduced complications, likely because of enhanced visualization and transluminal targeting of the collection, and because of ability to identify and avoid vascular structures.[53,54]

Not all necrotic collections are amenable to 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, the use of substitute or adjuvant approaches needs to be considered.[15]

Several issues remain unresolved in DEN. Although the balloon size utilized to dilated the cyst enterostomy is correlated with the success of the procedure,[55] the ideal balloon size is yet to be determined. The reliability of transpapillary stenting in patients with a completely disrupted pancreatic duct to prevent or heal ductal disconnection is still unknown. Whether endoscopic necrosectomy should be performed in patients with sterile necrosis and when it should be performed are more controversial. In addition, the optimal schedule for endoscopic debridement, the completeness of required necrosectomy required once it is undertaken and how often to image the patient between necrosectomies are unknown. In addition, the optimal type (plastic, metal) and number or stents to use during endoscopic drainage are unknown. DEN is a time-consuming and labor-intensive process, which demands special commitment by the patient and the entire team of physicians. It is best to undertake these procedures either in the operating room or endoscopic suite in close proximity to the operating room. Since the training requirement and the learning curve is 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 cyst-enterostomy via a transgastric or retrogastric approach. 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. It may be most suitable for patients with well-organized necrosis who are scheduled to undergo simultaneous cholecystectomy late in the course of the disease.

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.[56] Bucher *et al*.[57] demonstrated the successful use of single-port laparoscopic necrosectomy in eight patients, with infected WON patients not responding to radiological drainage. The authors reported that the use of a single large-port laparoscopic trochar enabled good visualization for debridement and extraction. Only one patient needed a repeat minimally invasive necrosectomy. No peri-operative complications or postoperative morbidity was reported.[57] Parekh and colleagues reported on a series of 19 patients undergoing laparoscopic hand-assisted necrosectomy through a transperitoneal infracolic approach. 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 or bowel fistulae and a shorter hospital stay.[58] Fischer *et al*. described a novel laparoendoscopic rendezvous maneuver, which was successful in five out of six cases of symptomaticWON.[59] Overall, laparoscopic necrosectomy has a clinical success rate of 70–95%, morbidity of approximately 20% and mortality of 0–18%.[17]

There are theoretical advantages to each of the laparoscopic approaches. Laparoscopic debridement through a transgastric route via cyst enterostomy is less likely to injure major vessels and thus may avoid the associated risk of

visceral ischemia and bleeding.[60] 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.[61] Single large-port laparoscopic necrosectomy permits resection of a large amount of necrotic debris and may obviate the need for repeated interventions.[57] 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 that definitely warrants further refinement and investigation.

Minimally Invasive Retroperitoneal Approach

Once a radiological image-guided percutaneous tract is established by a retroperitoneal route, a wide array of minimally invasive techniques is available to perform necrosectomy. 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 (Figures 13–15). All variants of retroperitoneoscopy are collectively known as either sinus tract endoscopy[62–65] or video-assisted retroperitoneal debridement (VARD).[42,51,66] Sinus tract endoscopy involves intraoperative dilatation of the percutaneous drain tract followed by irrigation, lavage and suction using a nephroscope[64] or flexible endoscope (Figures 13–15). Gambiez *et al*.[63] 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. Carter *et al*.[64] used a nephroscope and long-grasping forceps for debridement and continuous irrigation after serial dilation to 30F tract under fluoroscopic guidance. Multiple sessions were needed to adequately evacuate all of the necrotic debris. Horvath *et al*.[66] 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. Debridement was achieved with hydro-dissection 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.[51] 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.

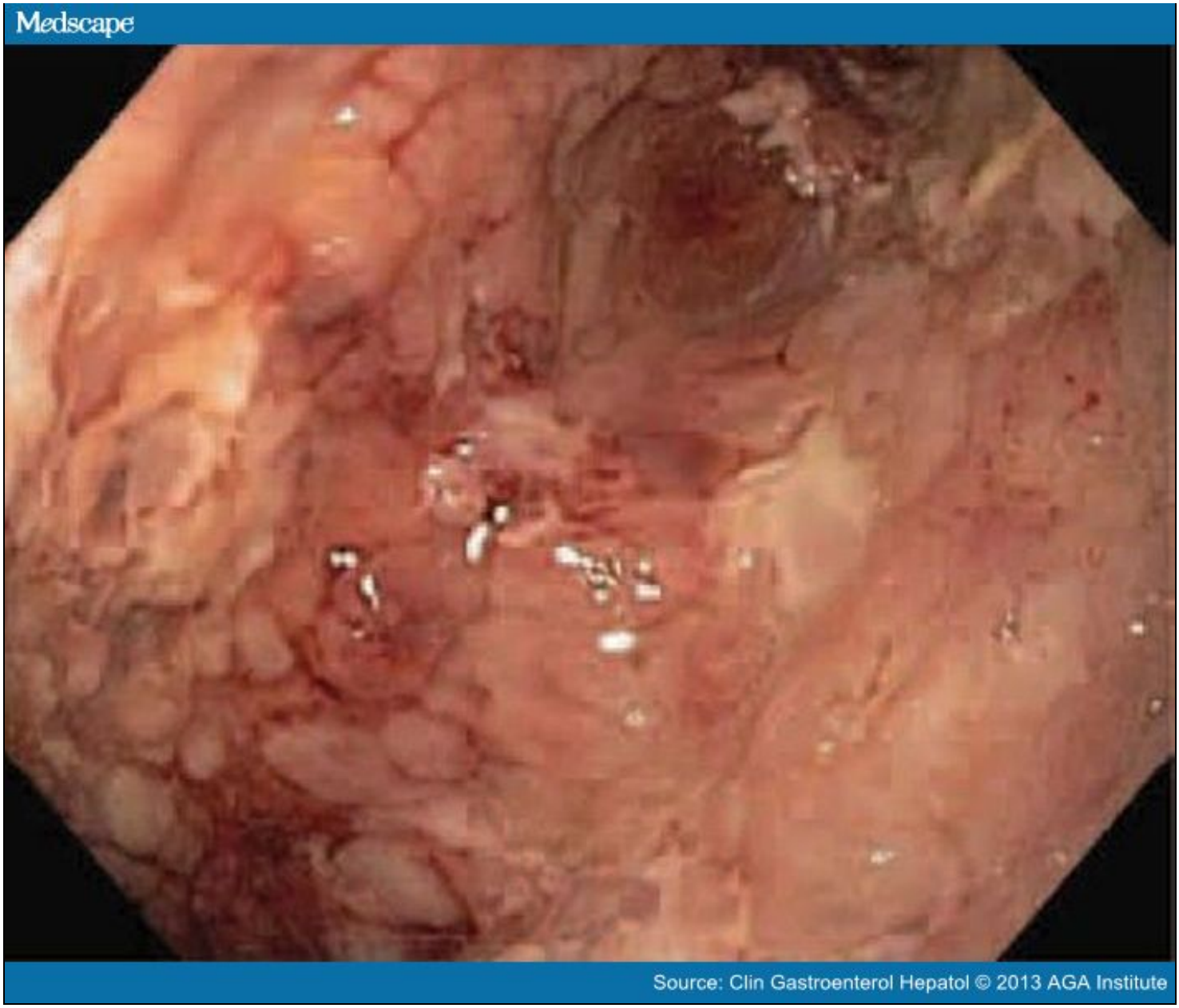

Figure 15.

Endoscopic view of cleaned cavity with healthy granulation tissue after combined direct endoscopic necrosectomy and sinus tract endoscopy (same patient as in Figures 1 & 2).

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.[62] A Taiwanese group recently proposed a 'delay until liquefaction' strategy wherein surgery was delayed until the retroperitoneal necrosis liquefied and reached the left flank. 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.[67] Other case series of minimally invasive retroperitoneal approaches have estimated peri-procedural complication rates to be less than 5%, median number of interventions to be less than 3% and mortality ranging from 0–20%.[17]

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.[30] Utilizing minimal incisions, surgeons have been able to perform large necrosectomies, resulting in shorter operating times and lesser need for repetitive procedures.[51] These techniques are particularly suitable for collections extending deep into the left side of the retroperitoneum that are partly liquefied.[68] Collectively, minimally invasive retroperitoneal debridement techniques have a clinical success rate of 60–84%, morbidity of up to 90% and mortality of 0–40%. As in all series, case selection and patient comorbidity are likely dominant factors in outcomes.[17]

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. Sinus-tract endoscopy involves the use of C-arm fluoroscopy and thereby, additional risks of radiation exposure and possible increased costs.[51] A reduction in mortality or reduction in hospital stay has not been clearly demonstrated for minimally invasive retroperitoneal techniques.[62]

Our approach for very extensive walled-off necroses, and especially those extending into the pelvis, has been to combine endoscopic necrosectomy via a transluminal approach with PCD, followed by minimally invasive retroperitoneal necrosectomy if that combination is insufficient (Figures 6–15). The retroperitoneal flexible endoscopic approach through the percutaneous tract is essentially identical to that performed via a transgastric route but with greater reach into the pelvis, and can be performed during the same anesthesia as the per-oral necrosectomy. In addition, the placement of the percutaneous retroperitoneal catheter allows the catheters to be flushed on the floor in between necrosectomy sessions.

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. The 'PANTER' trial involved 7 universities and 12 major teaching hospitals across the Netherlands.[30,69] 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 to undergo 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 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%) 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.[41] The same group has recently embarked on a nationwide randomized trial comparing the outcomes of the percutaneous and the endoscopic step-up approaches, with initial drainage and debridement as needed both performed by the same route as the initial drainage, that is, VARD or endoscopic necrosectomy (TENSION trial, registration number ISRCTN09186711[37]).

Expert Commentary and Five-year View

A small but significant number of patients with acute pancreatitis progress to severe disease including necrotizing pancreatitis. Infected necrosis can result in sepsis and single or multiple organ failure and death. Despite efforts to identify patients at risk, and significant improvements in the management of critically ill patients, necrosis and its consequent complications still remain the major cause of morbidity and mortality associated with acute pancreatitis. Over the past two decades, multiple alternative approaches to open surgery including percutaneous catheter drainage with minimally invasive variants of necrosectomy, endoscopic transluminal drainage with endoscopic necrosectomy, minimally invasive surgical approaches (including both laparoscopic transperitoneal and retroperitoneal) and various hybrid techniques involving multiple approaches (e.g., combined transluminal endoscopic and percutaneous catheter drainage) have been developed. Minimally invasive approaches have increasingly been shown to be associated with decreased patient morbidity and need for open surgery, now with level I evidence that a step-up approach involving PCD followed by VARD is superior to open surgery.[30] Results of a multidisciplinary consensus conference that included international experts from

multiple specialties has been recently published, representing the first contemporary consensus guidelines incorporating minimally invasive interventions for necrotizing pancreatitis.[17] The consensus committee, which was composed largely of surgeons as well as endoscopists, radiologists and medical pancreatologists, outlined indications for intervention in necrotizing pancreatitis. When intervention is indicated, they recommended a step-up approach utilizing percutaneous or endoscopic drainage followed by minimally invasive or endoscopic necrosectomy, with traditional open necrosectomy reserved as a second-line intervention for patients who fail minimally invasive approaches. Although the PENGUIN trial clearly demonstrated superiority of endoscopic necrosectomy over VARD in patients undergoing a step-up approach, the findings are limited by small numbers.[48] The Dutch Pancreatitis group is currently conducting a multicenter randomized controlled trial to compare the efficacy of a step-up approach using a purely endoscopic versus a percutaneous and minimally invasive surgical approach; the TENSION trial hopes to further our understanding regarding the optimal minimally invasive non-surgical approach for the management of infected necrosis.[37]

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 multi-disciplinary team consisting of specialists from surgery, interventional endoscopy, interventional radiology and critical care with expertise in necrotizing pancreatitis.

In the future, areas of further studies include improved ways for recognizing and predicting patients at risk for developing necrotizing pancreatitis, optimal early strategies to minimize risk of progression to necrosis, and identifying factors associated with development of infection and organ failure in patients who develop necrosis. On the technical front, refinements in endoscopic necrosectomy will likely include larger removable covered stents for cyst enterostomy 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 DEN 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.

Sidebar

Key Issues

- Interventions for necrotizing pancreatitis are increasingly focused on minimally invasive approaches rather than surgery.
- Per oral endoscopic and percutaneous catheter based approaches are both feasible methods for management of walled off necrosis when intervention is needed, and can be combined.
- Minimally invasive 'step up' approaches are associated with superior outcomes when compared to surgery in patients with infected necrosis.
- A multidisciplinary approach at a center with sufficient expertise in management of severe pancreatitis is imperative for successful management of necrotizing pancreatitis.

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Expert Rev Gastroenterol Hepatol. 2013;7(5):463-475.