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Endoscopic Necrosectomy in Clinical Practice

Indications, Technical Issues, and Optimal Timing

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Introduction

Acute pancreatitis (AP) is the third leading cause of gastroenterology-related hospitalizations in the United States, accounting for approximately 280 000 admissions annually and more than US$2 billion in annual healthcare costs [1,2]. Despite advances in treatment algorithms over time, AP has an associated mortality rate of approximately 5%, with further increases to greater than 15% in those with severe AP in the presence of multiorgan failure [3]. Interstitial edematous pancreatitis accounts for the majority of AP cases; under 10% of AP patients develop necrotizing pancreatitis with the presence of pancreatic and/or peripancreatic tissue necrosis. While necrosis may be seen on imaging at presentation or early in the disease course, necrosis may slowly evolve over a number of days after the onset of symptoms, and lack of necrosis initially does not preclude its development thereafter [4,5]. If a concern exists for worsening clinical status days to weeks after prior imaging, consideration for repeat imaging to evaluate for complications including the presence of fluid and/or necrotic collections is advisable. The 2012 Revised Atlanta Classification guides the characterization of these local complications based on the presence or absence of tissue debris in the collection and on a time course after development to allow maturation of the collection with a well-defined wall [6]. There are four types of local collections associated with AP, including acute fluid collection (AFC), pancreatic pseudocyst (PP), acute necrotic collection (ANC), and walled-off necrosis (WON). AFCs develop early (under four weeks post AP episode) in interstitial edematous AP, contain only fluid without solid debris, classically appear homogeneous on cross-sectional contrast-enhanced imaging, and likely lack a well-defined wall or capsule. AFCs persisting beyond four weeks post AP are reclassified as PPs containing just fluid without solid debris and, importantly, having the presence of a clearly demarcated capsule. In contrast, collections in which solid debris is seen are classified as ANCs or WON depending on time course post AP and presence or absence of a clearly defined wall. ANCs develop within four weeks of necrotizing AP, contain both fluid and solid debris internally, and lack a clear wall. Once a wall has formed, again usually after four weeks, these are reclassified as WON. Superimposed infection may occur in approximately 40–70% of patients with necrotizing AP, with an associated drastic increase in mortality, from 15% in those with sterile necrosis to roughly 40% in those with infected necrosis [7]. Oftentimes, differentiation of AFC from ANC may be challenging early on as both may appear homogeneous with fluid consistency on imaging. Delaying subsequent follow-up imaging for one to two weeks if clinical status is stable is advisable to maximize the informative value of subsequent scans in differentiating AFC from ANC.

Most AFCs and ANCs will spontaneously resolve, with only a proportion persisting beyond four weeks and going on to develop a clearly defined capsule to become PP or WON. Interestingly, most ANCs will spontaneously resolve over time, and even in those who develop WON, approximately half will spontaneously resolve without intervention in a six-month period [8]. The critical juncture is to decide which patients with PP or WON require intervention, as intervention in AFC and ANC should be delayed until clear maturation of the wall is seen. The primary criterion for need to intervene is the presence of symptoms. Asymptomatic patients should be conservatively managed and observed regardless of collection size, while those who are symptomatic should be evaluated for potential intervention. Historically, open surgical intervention was the primary option especially for patients with large WON; however, patients often had prolonged hospitalizations with substantial morbidity and mortality

Clinical Pancreatology for Practising Gastroenterologists and Surgeons, Second Edition. Edited by J. Enrique Domínguez-Muñoz.

despite the most gifted of surgeons. Currently available approaches to drainage and debridement include endoscopic, percutaneous, surgical, and combination therapies. The decision to intervene should not be taken lightly. Some of the most common indications for intervention in PP or WON include obstruction of adjacent viscera (gastric outlet obstruction, pancreatobiliary obstruction), abdominal pain, nausea/vomiting or early satiety, infection, and rarely rupture or bleeding (usually handled surgically). Drainage should not be undertaken in AFC or ANC until there is a clearly matured wall, and percutaneous and surgical interventions should be delayed if possible for four weeks to enable adequate encapsulation as the success of endoscopic intervention is directly correlated with the degree of encapsulation, while early intervention (before four weeks) is associated with suboptimal outcomes [9,10].

Management of Symptomatic Pseudocysts

Endoscopic transmural drainage of PP was first described in 1985 and has subsequently evolved [11]. Endoscopic drainage has become the preferred standard of care for symptomatic PP. In a single-center, randomized prospective trial of 40 patients with PP by Varadarajulu et al. [12], endoscopic cystgastrostomy ($n = 20$) was equally technically effective as surgical cystgastrostomy ($n = 20$); endoscopic drainage was associated with the significant benefits of shortened length of hospital stay and lower associated hospital costs, with a greater than 50% reduction in both parameters in the endoscopic group. It is of critical importance to accurately differentiate between PP and WON as the subsequent management strategies are markedly different. At times, computed tomography (CT) may miss components of solid debris inside the collection, which may be seen on magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS). Additionally, EUS not only allows real-time assessment of a collection's characteristics but also has the ability to provide intervention if indicated. PPs should be distinguished from potential cystic neoplasms. Attention to a careful history regarding pancreatitis is helpful as a preceding history of pancreatitis increases the likelihood of the lesion being a PP whereas no history of pancreatitis favors the possibility of a cystic neoplasm. The approach to drainage of PPs will be dictated based on their size, location, anatomy, and any component of pancreatic ductal disruption that may be present. In the case of ductal disruptions, endoscopic retrograde cholangiopancreatography (ERCP) may be undertaken to enable transpapillary drainage to correct the underlying etiology in addition to other therapeutic modalities for PP drainage. The vast majority of these PPs are now drained transmurally, primarily under EUS guidance. This drainage can be done using plastic double-pigtail stents or lumen apposing metal stents (LAMS).

Management of Symptomatic Walled-off Necrosis

Indications and Timing for Intervention

Prior to undertaking drainage and debridement of WON, careful review in a multidisciplinary format is paramount. Regardless of the initial approach decided in an individual patient, appropriate interdisciplinary discussion is critical, with team approaches comprising gastroenterologists, interventional radiologists, pancreaticobiliary surgeons, and nutritionists. Regardless of the size of the collection, patients who are asymptomatic should not undergo interventions. This can only lead to complications. The indications for intervention on WON include symptoms of abdominal pain, nausea and vomiting, early satiety, and decreased oral intake; luminal obstruction including gastric outlet obstruction or pancreaticobiliary obstruction; or those with persistent infection despite broad-spectrum intravenous antibiotics. It is important to remember that empiric broad-spectrum intravenous antibiotics should be administered in patients with concern for infected necrosis prior to consideration for debridement. Conservative management with supportive care and intravenous antibiotics may frequently be able to effectively avoid the need for necrosectomy [13,14]. Historically, WON was managed surgically with multiple operative procedures required and associated significant morbidity. While endoscopic drainage of PP was first reported in 1985, endoscopic interventions for WON were not initially described until 1996, in which endoscopic drainage and debridement of necrosis was reported. Subsequently, Siefert and colleagues [15,16] in Germany reported endoscopic retroperitoneal necrosectomy in 2000. It cannot be stressed enough that endoscopic necrosectomy must be delayed until a clearly defined wall has developed, as rates of success for drainage and debridement are associated with the presence of a capsule, which traditionally is at approximately four weeks [17,18]. Besselink et al. [19] demonstrated in 53 patients with infected necrosis (83% with infected necrosis; 55% with preoperative organ failure) that there was a significant reduction in mortality with delayed surgical necrosectomy, the procedure having increasing benefit the further from date of initial admission (75% mortality if intervention at 1–14 days vs. 45% mortality at 15–29 days vs. 8% mortality at ≥30 days; $P < 0.001$).

Choosing the Best Interventional Option: the Step-up Approach

Historically, surgical debridement was the traditional management strategy for symptomatic necrosis with and without the presence of infection. This was done via an open approach with a wide drainage area and placement of multiple abdominal drains, usually with the need for repeat operative procedures over a prolonged period of time; reintervention rates from larger European and American series ranged from 30 to 70%, with associated morbidity and mortality estimated at 11–50% in some series [20–22]. In a series of 167 patients with necrotizing pancreatitis, 72% of whom had infected necrosis, surgical outcomes from a single-step debridement and closed packing technique was evaluated and showed a 12.6% risk of reoperation, 29.9% rate of subsequent requirement for percutaneous interventional radiology drainage, and overall operative mortality rate of 11.4%. Additional complications included postoperative pancreatic fistulas (41%), enteric fistulas (15%), endocrine pancreatic insufficiency (16%), and exocrine insufficiency (20%), while 57% required prolonged admission to the intensive care unit [21]. Though necessary to surgically intervene at times, the substantial associated morbidity and mortality served as the foundation to seek other interventional avenues to improve the overall outcomes.

Beyond open surgical debridement, multiple additional therapeutic interventional options exist for the treatment and management of pancreatic necrosis. These options include endoscopic intervention, percutaneous intervention, and minimally invasive surgical approaches including video-assisted retroperitoneal debridement (VARD). In the percutaneous approach, multiple large-bore catheters are placed into the collections under imaging guidance and the cavities are regularly flushed to promote liquefaction and drainage. Percutaneous approaches are relatively safe, with low complications and mortality, and may be used to guide additional necrosectomy subsequently by providing an access tract, as well as allowing patients who would otherwise not be candidates to undergo endoscopic or minimally invasive surgical approaches. Because percutaneous approaches are primarily a flush and drain approach, as opposed to direct debridement, this may limit their efficacy. In systematic reviews, the efficacy of percutaneous drainage is estimated to be 44–55% in treating necrosis and avoiding the need for subsequent surgery, making percutaneous drainage an attractive potential option either as a bridge to other interventional options in an unfit procedural candidate or as destination therapy in approximately half of patients [23,24].

As new approaches continue to evolve, there is increasingly more evidence to substantiate the use of endoscopic necrosectomy, laparoscopic transperitoneal or video-assisted retroperitoneal debridement, and percutaneous drainage. Cystgastrostomy with nasocystic irrigation for the treatment of WON was first reported in 1996, and transluminal direct endoscopic necrosectomy followed in 2000 [15,16]. Subsequently, there has been much work to further investigate the optimal management strategies and performance characteristics of each management strategy. Multiple initial studies demonstrated the efficacy of transgastric access into the retroperitoneum with debridement of necrotic tissue, followed by placement of stents into the collection to enable continued drainage [25–27]. The current standard of care when accessing these collections endoscopically is the use of EUS to confirm the location of the collection, characterize the collection, and ensure that there is no vascular structure in the interceding area between the puncture site and the collection [28].

Endoscopic transgastric necrosectomy was first compared to surgical necrosectomy in the randomized PENGUIN trial (Pancreatitis Endoscopic Transgastric vs. Primary Necrosectomy in Patients with Infected Necrosis) by Bakker et al. from the Dutch Pancreatitis Study Group, in which endoscopic necrosectomy led to a decreased proinflammatory response and was associated with a substantially reduced incidence of major complications or death (20% vs. 80%) [25]. In the PENGUIN trial, the endoscopic approach consisted of initial transgastric puncture followed by balloon dilation of the tract and subsequent drainage and necrosectomy, whereas the surgical approach first focused on VARD or laparoscopic debridement as opposed to open surgical necrosectomy if VARD was not possible. Subsequently, a step-up management approach was proposed that primarily aims at control of any subsequent infection and aims for minimally invasive management strategies as opposed to open necrosectomy, with a stepwise progression from percutaneous to endoscopic to VARD or laparoscopic drainage and debridement. The step-up approach was compared in the PANTER trial in which van Santvoort et al. [29] demonstrated a significant reduction in their primary composite end point of death or major complications in which this composite outcome was found in 40% of patients undergoing a minimally invasive step-up approach compared to 69% of those undergoing primary open necrosectomy [relative risk (RR) 0.57, 95% confidence interval (CI) 0.38–0.87; $P = 0.006$]. Interestingly, in this initial study, laparoscopic necrosectomy was not part of the algorithm, and in the step-up approach only a small proportion of patients underwent endoscopic necrosectomy whereas most underwent percutaneous drainage and then VARD.

These two large studies laid the foundation for hybrid management strategies in a multidisciplinary approach comprising gastroenterologists with therapeutic endoscopy training, interventional radiologists, and surgeons.

No particular size fits all, and the combination of multiple strategies may achieve the best outcomes in these oftentimes complex and very ill patients. More recently, there have been several large randomized trials and meta-analyses to investigate the nuances of the step-up approach and its efficacy. Hollemans et al. [30] recently reevaluated the patients initially presented in the PANTER trial with regard to their long-term outcomes and management; 73 of the initial 88 patients were still alive and able to be studied at a mean of 86 months post index admission, with a primary end point of death or major complications as well as long-term development of exocrine pancreatic insufficiency, endocrine insufficiency, and quality of life and pain scores. From index admission to long-term follow-up, there was a significantly higher rate of death or major complications in the open necrosectomy group compared with the surgical step-up approach group (73% vs. 44%; $P = 0.05$). Further, those undergoing open necrosectomy were more likely to have exocrine pancreatic insufficiency (56% vs. 29%; $P = 0.03$) and endocrine insufficiency (64% vs. 40%; $P = 0.05$), again demonstrating on a long-term basis the superiority of a surgical step-up approach compared to open necrosectomy.

Van Brunschot et al. [31] investigated EUS-guided transluminal drainage with endoscopic necrosectomy versus a surgical step-up approach in a multicenter randomized superiority trial involving 19 hospitals in the Netherlands. A total of 98 patients were enrolled and randomized, with no significant differences in mortality rates (18% in endoscopy vs. 13% in surgery), nor any significant differences in any other major complication, though there were lower rates of pancreatic fistula formation and length of stay in the endoscopy group. Bang et al. [32] conducted a single-center randomized trial of 66 patients with confirmed or suspected infected pancreatic necrosis requiring intervention with randomization to minimally invasive surgery (either laparoscopic or VARD) or endoscopic step-up approach including transluminal drainage with and without necrosectomy with a composite end point of major complications, including new-onset multiorgan failure, new-onset systemic dysfunction, enteral or pancreatocutaneous fistula, bleeding, perforation, or death. Of the patients undergoing the endoscopic approach, 11.8% reached the composite end point whereas 40.6% of patients undergoing surgical interventions reached the composite end point (RR 0.29, 95% CI 0.11–0.80; $P = 0.007$). There were no significant differences in mortality among groups but none of the patients undergoing endoscopic approaches developed fistula, while 28.1% of patients undergoing surgery developed fistulas ($P = 0.001$), with a significantly higher mean number of complications in the surgical group as well. The mean total cost was also significantly lower in the endoscopic group compared to the surgical group (US$75 830 vs. US$117 492; $P = 0.039$) [32]. Khan et al. [33] performed a meta-analysis evaluating the safety of endoscopic drainage versus minimally invasive surgical necrosectomy in the treatment of WON, in which two randomized controlled trials and four observational studies of 641 patients were included, with an overall 8.5% mortality rate in the endoscopic drainage group compared with a 14.2% mortality rate in the minimally invasive surgical necrosectomy group, with a pooled odds ratio (OR) of 0.59 favoring endoscopic drainage (95% CI 0.35–0.98). Further, rates of development of new major organ failure post intervention were 12% in the endoscopic group compared to 54% in the surgical group, with a pooled OR of 0.12 (95% CI 0.06–0.31) favoring endoscopic drainage, a lower overall adverse events rate favoring endoscopic drainage (pooled OR 0.25, 95% CI 0.10–0.67), as well as shorter length of stay in the endoscopic group with a pooled mean difference of –21.07 days (95% CI –36.97 to –5.18 days).

Methods of Endoscopic Necrosectomy and Stent Choice

Since their advent just a few years ago, LAMS have fundamentally altered the endoscopic management approach to both solid and cystic collections. These stents allow continued access with decreased risk of migration, can be easily and safely placed endoscopically, and enable drainage of larger amounts and sizes of tissue and allow direct endoscopic access into the collection for debridement. The endoscopic access options available to the endoscopist include placement of plastic stents or LAMS. Adler et al. [34] in a multicenter (four tertiary care centers across the United States) retrospective study of 80 patients with pancreatic fluid collections drained with LAMS showed that the overall technical success rate was 98.7% with no statistically significant difference in the technical success rate between the inpatient and outpatient groups, although there was a significantly lower number of procedures required for resolution in the inpatient group compared to the outpatient group (2.3 vs. 3.1; $P = 0.025$), as well as significantly lower adverse event rates in the inpatient versus the outpatient group ($P < 0.01$). While critically ill patients require inpatient hospitalization and management, this study demonstrates that those who have symptomatic collections who are otherwise stable may be able to be managed as outpatients in an ambulatory setting with close interval follow-up.

There have been multiple studies examining the use of LAMS or fully covered metal stents versus plastic stents in the management of WON. Abu Dayyeh et al. [35] performed a retrospective study of 94 patients with WON at the Mayo Clinic in which 36 patients underwent double-pigtail plastic stent placement and 58 patients underwent large-caliber fully covered self-expanding metal stent placement. There

was no significant difference in the resolution rates between the two groups, and interestingly of the 80% of patients successfully treated with endoscopic approaches alone without the need for percutaneous intervention, nearly half (49%) only required transmural drainage without subsequent necrosectomy. WON was significantly more likely to resolve without the need for endoscopic necrosectomy in the self-expandable metal stent group compared with the double-pigtail plastic stent group (60.4% vs. 30.8%; $P = 0.01$), which remained more likely after adjustment for patient age, size, and location of the necroma (OR 4.5, 95% CI 1.5–15.5). There was a clinically significant higher risk of bleeding requiring endoscopic intervention in the plastic stent group compared to the metal stent group (14% vs. 2%; $P = 0.02$). The results of LAMS in drainage remain somewhat mixed. Bang et al. [36] recently randomized 60 patients with WON to LAMS ($n = 31$) or plastic stent ($n = 29$) placement in which there was no significant difference in the total number of procedures performed (LAMS: median 2, range 2–7 vs. plastic: median 3, range 2–7). Unsurprisingly, procedure duration was significantly shorter using LAMS (15 vs. 40 minutes; $P < 0.001$); however, there were significantly higher stent-related adverse event rates with LAMS (32.3% vs. 6.9%; $P = 0.01$) and higher cost with LAMS (US$12 155 vs. US$6609; $P < 0.001$).

Importantly, one of the key factors in minimizing stent-related adverse events was performance of follow-up imaging and stent removal at three weeks post placement if the WON had resolved. This is especially important for preventing complications from collapse of the collection, with erosion of the posterior wall of the collection against the stent causing bleeding, which can be prevented by close interval imaging with removal of the stent on near collapse of the collection. Mohan et al. [37] performed a systematic review and meta-analysis examining LAMS and plastic stents in WON in which nine studies of 737 patients with LAMS were compared to six studies of 527 patients with plastic stents. The pooled clinical success rate showed no significant difference between LAMS (88.5%, 95% CI 82.5–92.6) and plastic stents (88.1%, 95% CI 80.5–93.0; $P = 0.93$). Further, there was no significant difference in the pooled rates of all adverse events (LAMS 11.2%, 95% CI 6.8–17.9 vs. plastic stents 15.9%, 95% CI 8.4–27.8; $P = 0.38$). The authors concluded that there were equal clinical outcomes and adverse events among both stent types, though significant heterogeneity was present in all included studies and end points.

Concurrently, in a multicenter, international, retrospective study of 189 patients at 14 centers with WON comparing LAMS and plastic stents, there was a significantly higher clinical success rate with use of LAMS (80.4% vs. 57.5%; $P = 0.001$) with similar rates of need for percutaneous drainage and a greater need for surgery in the plastic stent group. Of note, the rate of WON recurrence following initial clinical success was significantly greater in the plastic stent group compared to LAMS (22.9% vs. 5.6%; $p = 0.04$), with the conclusion that LAMS was associated with higher clinical success, short procedural time, decreased need for surgery, and decreased overall rate of recurrence [38]. Interestingly, in a cost-effectiveness analysis comparing LAMS with plastic stents for WON, LAMS were found to be more effective than plastic stents (92% vs. 84%), though LAMS were markedly more expensive ($US20 029 vs. $US15 941). This cost-effectiveness modeling favored LAMS, with an incremental cost-effectiveness ratio of $US49 214 in order to perform one additional successful drainage using LAMS compared to plastic stents, which was confirmed on sensitivity analyses [39].

Lastly, once endoscopic access into the collection has been obtained, there are multiple tools at the endoscopist's disposal to enable endoscopic debridement and necrosectomy. Some of the most common tools include use of rat-tooth forceps, snare, and Roth nets to remove pieces of debris. Biliary extraction baskets are also frequently used to this end point. There remains significant opportunities for innovation in this field as currently available tools are adapted to fit new indications and situations.

Conclusion

Patients with acute pancreatitis complicated by WON may be asymptomatic or may have significant symptoms with critical illness. Historically, these patients underwent open necrosectomy when they were symptomatic and critically ill, especially in the setting of concern for infected necrosis; however, this was associated with significant morbidity and mortality and overall poor outcomes long term. Over the past two decades, the pendulum has shifted, and there is now significant data to support the use of step-up approaches focusing on endoscopic and percutaneous drainage with avoidance of surgical debridement in the early stages and only using minimally invasive surgical options for treatment failures. As the ability to perform endoscopic access of these collections has improved, multiple tools have been added to the endoscopist's armamentarium to access and debride these lesions, with substantial data favoring the use of minimally invasive approaches. Most recently, the advent of LAMS has again markedly altered management strategies by enabling ongoing access to these collections with wider tracts and decreased risk of migration. Though LAMS are physically more costly than plastic stents, these costs are often mitigated by a variety of other factors, often favoring the use of LAMS as the preferable access option endoscopically. Finally, no matter what the interventional strategy, patients with WON have substantially benefited from multidisciplinary team management.

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