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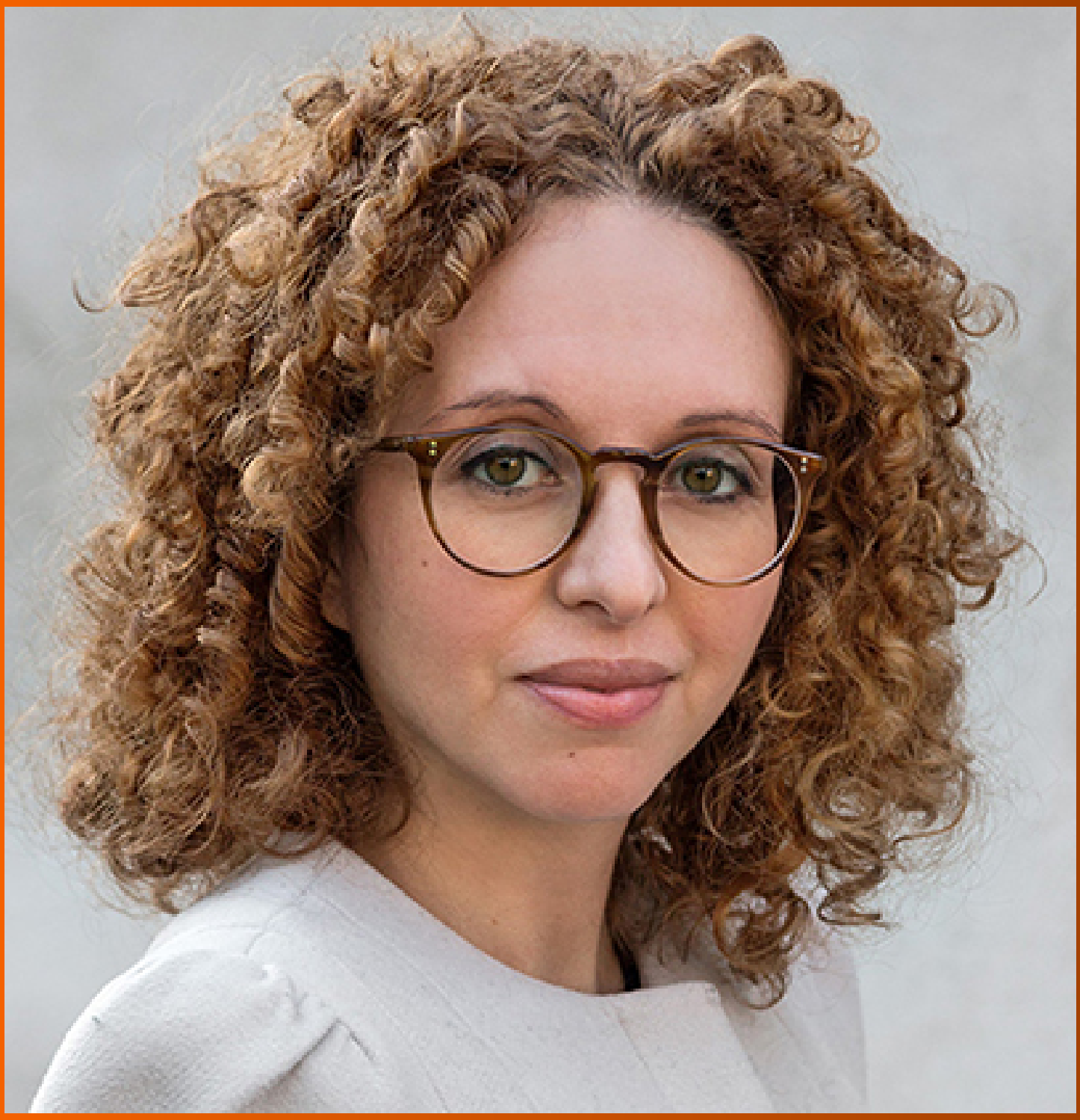

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REVIEW

Endoscopic transluminal drainage and necrosectomy for infected necrotizing pancreatitis: Progress and challenges

Yan Zeng, Jian Yang, Jun-Wen Zhang

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Yan Zeng, Department of Psychology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China

Jian Yang, Jun-Wen Zhang, Department of Gastroenterology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Corresponding author: Jian Yang, MD, PhD, Associate Chief Physician, Lecturer, Department of Gastroenterology, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing 400016, China. yangjian@hospital.cqmu.edu.cn

Abstract

Infected necrotizing pancreatitis (INP) represents a severe condition in patients with acute pancreatitis. Invasive interventions are recommended in symptomatic INP. Growing evidence has suggested interventional strategies of INP evolving from traditional surgery to minimally invasive step-up endoscopic procedures. However, there is still no standardized protocol for endoscopic interventions. Recently, various studies have been published about the endoscopic management of INP. This article reviews published articles and guidelines to present the progress and challenges of endoscopic transluminal drainage and necrosectomy in INP.

Key Words: Endoscopic; Drainage; Necrosectomy; Infected necrotizing pancreatitis; Progress; Challenge

Core Tip: Infected necrotizing pancreatitis (INP) is a severe condition in patients with acute pancreatitis. Endoscopic transluminal drainage and necrosectomy, especially endoscopic ultrasound-guided treatments, have become the mainstream minimally-invasive treatment for symptomatic INP. Growing evidence has proven progress in endoscopic transluminal interventions, while challenges and unsolved problems still need further investigation. Endoscopic transluminal interventions are neither omnipotent nor perfect. The predominant role of endoscopic treatment will be further developed with the advancements, standardization, and popularization of endoscopic techniques and devices in the near future.

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INTRODUCTION

Acute pancreatitis (AP) is one of the most common gastrointestinal (GI) discharge diagnoses and accounts for high medical costs, and its hospitalization rate has recently increased[1,2]. AP can be pathologically classified as interstitial edematous and necrotizing pancreatitis (NP)[3]. Infected NP (INP) is usually a result of fungal or bacterial infection of necrosis that occurs in approximately a third of patients with NP[3]. Infected necrosis leads to increased mortality in NP. In a systematic review and meta-analysis of 6970 patients, the mortality rates of infected necrosis with organ failure and sterile necrosis with organ failure have been reported to be 35.2% and 19.8%, respectively[4]. Therefore, effective interventions are needed in INP patients. Current treatment strategies consist of conservative therapy, endoscopic transluminal drainage and necrosectomy, percutaneous drainage and necrosectomy, minimally invasive surgery, and open necrosectomy[3,5-7]. Endoscopic transluminal drainage and necrosectomy are recommended as first-line therapy for patients with INP due to significantly reduced proinflammatory response, complications, hospitalization time and costs, new-onset multiple organ failure (MOF), and increased life quality of these patients[6,8,9]. Despite that growing evidence suggests interventional strategies of INP evolving from minimally invasive surgery to endoscopic therapy, a single treatment option may not suit all INP patients[10]. Meanwhile, other issues are still to be further investigated, such as standardizing endoscopic therapy[11], predicting and managing complications, and optimizing endoscopic drainage and debridement[12]. By comprehensively performing an electronic literature search of Medline/PubMed, Embase, *Reference Citation Analysis* (RCA, https://www.referencecitationanalysis.com/) databases, and Web of Science databases from inception to November 30, 2022, we have reviewed published articles and guidelines to present the progress and challenges of endoscopic transluminal drainage and necrosectomy for patients with INP.

CLASSIFICATION

Pancreatic parenchyma and peripancreatic tissue are most commonly involved in NP. Therefore, NP is classified into three types: Pancreatic parenchymal alone, peripancreatic necrosis alone, and a combination of the former two types[13]. NP may also be categorized as an acute necrotic collection (ANC) or walled-off necrosis (WON) based on the duration of the collection (≤ 4 wk or > 4 wk) and a well-defined encapsulation[14]. Four kinds of local complications caused by AP are classified by the revised Atlanta Classification, and acute peripancreatic fluid collection, ANC, pancreatic pseudocyst (PPC), and WON are included[15]. Sterile and infected types exist in PPC and WON[15]. Although a well-defined wall could be identified in PPC and WON by endoscopic ultrasound (EUS) or imaging examinations, their drainage effects are quite different[16].

ENDOSCOPIC TRANSLUMINAL DRAINAGE

Drainage and debridement of pancreatic necrosis are recommended for INP patients by multiple guidelines and consensus[5,17,18]. Endoscopic drainage, especially EUS-guided drainage, is a minimally invasive treatment for the drainage of pancreatic fluid collection (PFC)[19-21]. Compared with surgical cystogastrostomy, EUS-guided procedures demonstrates shorter hospital stay and lower mortality[19]. Although percutaneous drainage has proven efficient in INP[22,23], endoscopic drainage presents lower reintervention rates, shorter length of hospital stay, and decreased number of follow-up abdominal imaging than percutaneous drainage[24,25]. Thus, EUS-guided drainage has been recommended as the optimal drainage method for lesions near the stomach or duodenum (Table 1)[18].

Progress

Since the initially reported successful application of EUS-guided drainage in a patient with PPC[26], endoscopic transluminal drainage has proved effective and minimally invasive in treating INP. Moreover, indications for drainage have already evolved from a specific cystic diameter (> 6 cm) to the presence of INP-associated symptoms (abdominal pain, early satiety), lesion enlargement, and complications which include infection, hemorrhage, rupture, and obstruction[27,28]. Drainage options depend on various factors, including the patient's general condition; the size, number, and location of PFC; communication with the main pancreatic duct (PD); infection or other symptoms; and the expertise of

Table 1 Characteristics of endoscopic transluminal drainage and stents

	Recommendations and benefits	Areas of concern	Ref.
Recommending EUS guidance	Effective and minimally invasive; lower morbidity; reduced reinterventions; decreased follow-up imaging; shorter hospital stay	-	[18-21,24,25,66]
Indications for drainage	INP-associated symptoms and complications	Patients' general conditions and symptoms; PFC characteristics; endoscopic experience	[27-28]
Timing of intervention			
Early intervention (< 2 wk)	Not recommended; no superiority in complications	Increased mortality and invasive interventions	[5,45]
Early intervention (3–4 wk)	Safe and effective when identifying a partial collection	Increased mortality, endoscopic necrosectomy, and rescue surgery	[14,50,51]
Delayed intervention (> 4 wk)	Generally recommended; after INP encapsulation; excellent clinical success; reduced reinterventions and mortality	-	[17,45-49]
Stents			
DPPS	Affordable, safe, and easily accessible; recommended for little debris (≤ 10 %) or pure PPC	Stent occlusion; possible leakage; limited endoscopic access to the necrotic cavity	[18,28-30,54,57]
SEMS	Feasible; deployed when LAMS is unavailable	-	[32]
LAMS	Simpler procedure; higher technical and long-term success rates; less AD than DPPS; recommended for significant debris (≥ 30 %)	Higher cost; increased risks of pseudoaneurysm bleeding, delayed bleeding, perforation, and buried stent syndrome	[12,29,33,34,52-55,60-63]
Negative predictors for drainage effect	Male; MOF; extensive necrosis (≥ 150 mm); heterogeneity (necrosis ≥ 50%)	-	[35-37]
Improving drainage	Additional nasocystic drainage; multiple transluminal gateway technique; hybrid techniques	-	[28,31,38,39,42,43]
Technical aspects	Not always requiring fluoroscopy and LAMS dilation; novel techniques for complicated deployments; timely stent removal; endoscopic closure for patients with a poor situation or early needs for transoral feeding	Lack of standardized protocol	[11,12,17,61,62,68,69]

EUS: Endoscopic ultrasound; INP: Infected necrotizing pancreatitis; PPC: Pancreatic pseudocyst; PFC: Pancreatic fluid collection; DPPS: Double-pigtail plastic stents; SEMS: Self-expanding metal stents; LAMS: Lumen-apposing metal stents; AD: Adverse events; MOF: Multiple organ failure.

the endoscopists[27].

Stents commonly used in endoscopic transluminal drainage include double-pigtail plastic stents (DPPS), fully-covered self-expanding metal stents (SEMS), and fully-covered self-expanding lumen-apposing metal stents (LAMS)[29]. The initial application of DPPS in treating PPC was reported in 1989 [30]. DPPS is an affordable, safe, and easily accessible choice for INP drainage with satisfactory technical and clinical success rates (> 90%)[18]. Additional nasocystic drainage helps to reduce adverse events and increase drainage efficiency, thus significantly shortening the length of hospital stay for patients [31]. Therefore, nasocystic catheters are recommended by high evidence levels, especially in large or infected PPCs[18]. In addition, esophageal or biliary SEMS with a large diameter is reportedly feasible in treating large WON[32], and SEMS is usually used when LAMS is unavailable. With increasing applications, LAMS has proven the advantages of simplifying EUS-guided management with high technical and long-term success rates[33,34]. In addition to its safety and efficacy, the deployment of LAMS would facilitate subsequent endoscopic necrosectomy procedures, if necessary[34].

Since ineffective drainage is a significant cause of poor prognosis in INP patients, how could endoscopists predict the success of catheter drainage? Several studies have revealed that male, MOF, extensive pancreatic necrosis (≥ 150 mm), and heterogeneity of the collections (necrosis ≥ 50%) are negative predictors for the success of endoscopic drainage in INP[35-37]. Therefore, novel and effective drainage methods need to be introduced. Firstly, multiple transluminal gateway technique has been reported to improve drainage of sub-cavities and areas distant from the GI lumen in patients with multilocular or huge infected pancreatic collections[38,39]. Moreover, in addition to endoscopic transluminal drainage, percutaneous endoscopic step-up therapy also demonstrates an effective strategy for IPN[40]. The above research has also found that early organ failure and extensive pancreatic necrosis (> 50%) are independent predictors of mortality in this percutaneous procedure[40]. Moreover, although percutaneous drainage may not be suitable for young, active INP patients, it is more convenient for content analysis, flow monitoring, and catheter adjustment[41]. Therefore, for poor drainage, especially in WON patients, several hybrid techniques, including endoscopic drainage combined with percutaneous drainage or laparoscopic drainage, are also essential and practical solutions to complicated INP drainage[28,42,43].

Challenges

Timing of intervention: Although some experts believe that the conservative treatment of IPN with antibiotics could avoid invasive procedures, studies have revealed that an antibiotics-only protocol is a valid option only for hemodynamically stable and carefully selected patients[44]. Thus, invasive interventions are recommended for clinically suspected or proven INP by worldwide guidelines, including those from the American Gastroenterological Association, the European Society of Gastrointestinal Endoscopy (ESGE), and the Asian EUS group[5,17,18]. However, the choice of early or delayed intervention is still controversial for patients preparing for invasive intervention. The generally accepted recommendation for the first invasive interventions is at least 4 wk after pancreatitis until confirmation of INP encapsulation[17,45-47]. These delayed endoscopic interventions in INP demonstrates excellent clinical success, lower reintervention rates, and lower mortality[48,49]. At the same time, early drainage, whose efficacy, safety, and necessity of early drainage still need to be investigated, has received much attention recently. In exploring early drainage, one radical attempt is to perform drainage within 24 h after INP diagnosis. However, the results show no superiority of immediate drainage concerning complications, and these patients received more invasive interventions than those undergoing postponed drainage[45]. Therefore, due to increased morbidity and mortality, it is currently recommended that endoscopic interventions should be avoided in the early, acute period (< 2 wk)[5]. Endoscopic intervention in the third or fourth weeks of INP patients seems safe and effective when identifying a partial collection[14]. In contrast, other studies have revealed that early intervention would lead to increased mortality, more need for endoscopic necrosectomy, and rescue open necrosectomy[50,51]. Diverse studies have reached inconsistent conclusions about whether early intervention increases complications[50,51], which may be related to the patients' heterogeneity and sample sizes.

Endoscopists also have varied or even contrary opinions. Although early interventions do not apply to all INP patients, there must also be patients who need this procedure. Whether early interventions are performed depends on the patient's condition (such as infection and organ failure that need urgent interventions), the location and morphology of INP, the patient's tolerance for possible complications, and the operator's experience[50,51]. This process undoubtedly requires a comprehensive balance of advantages and disadvantages.

LAMS or DPPS: LAMS has received much attention since its application in the drainage of patients with INP[21,52], and research and debate on the merits of LAMS versus DPPs remains one of the hot issues. EUS-guided drainage with LAMS provides superior overall treatment efficacy with reduced numbers of interventional procedures[29]. Moreover, it demonstrates a lower adverse events rate than DPPS drainage for managing PFCs in a recent systematic review and meta-analysis comprising 1584 patients[53]. Thus, LAMS has been recommended by a multi-institutional consensus made by 22 experts as the standard procedure for WON drainage[12]. Most experts believe that metal stents with a large caliber should be considered for WON with significant debris (≥ 30 %), while DPPS may already be enough for WON with little debris (≤ 10 %) or pure PPC[54]. Although a large diameter (d = 15 mm) LAMS has been recommended for drainage in patients with WON[12,55], LAMS with a larger diameter (d = 20 mm) demonstrate comparable clinical outcomes with fewer subsequent endoscopic necrosectomy[56]. Meanwhile, previous studies have revealed that DPPS is cheap and easy to revise, while disadvantages and concerns include stent occlusion, possible leakage, and limited endoscopic access to the necrotic cavity[28,29,57]. Furthermore, there have been reports on novel devices and the double guidewire technique in EUS-guided DPPS drainage[58,59]. However, if multiple DPPS are introduced to maintain a large fistula for effective drainage, it would still lead to prolonged operation time, stent migration, and other complications[28].

Although clinically significant bleeding requiring endoscopic intervention has been less observed in large-caliber metal stents than in DPPS in some studies[55], contradictory conclusions from other studies have indicated more bleeding and endoscopic re-interventions in LAMS than in DPPS[60]. With the increasing applications of LAMS in endoscopic drainage, LAMS-related complications gradually attract general concerns, which include a higher risk of pseudoaneurysm bleeding, delayed bleeding, perforation, buried stent syndrome, and biliary stricture[52,60-63]. Endoscopists attempt to reduce LAMS-related adverse events by additionally placing DPPS through LAMS. However, a recent multicenter retrospective study revealed that deployment of DPS through LAMS had no significant effect on clinical outcomes, adverse events, or the need for re-interventions[64]. Thus, given the relatively higher cost[65], various possible complications, and the lack of significant differences with DPPS in outcomes, the non-clinical-trial application of SEMS and LAMS is not recommended for pancreatic PPC drainage by the Asian EUS group RAND/UCLA expert panel[18].

The results of studies on endoscopic drainage with LAMS are mixed. In some of the above studies, the size of the PFCs for drainage using LAMS tends to be larger[61], which seems to have a relatively higher risk of drainage-related complications. Moreover, the optimal stent for endoscopic drainage is determined by many factors, including the size of the PFCs, the proportion of solid necrosis, the patient's economic conditions, the therapeutic expectations of physicians and patients, and the endoscopic devices and operating experiences of the local medical center. Therefore, there is no best stent, only the most suitable stent for a specific patient. Furthermore, attention should be shifted to early

detection and effective treatment of these complications.

Technical aspects of endoscopic transluminal drainage: Although growing evidence has proven endoscopic transluminal drainage effective and minimally invasive in INP, endoscopic treatment has not been standardized yet[11], which is one of the fundamental reasons for the difference in clinical outcomes. As there are no multicenter randomized controlled trials (RCT) or guidelines for standard procedures of endoscopic interventions, the following hot issues will be emphatically discussed.

Is EUS guidance necessary? Although transmural drainage only *via* conventional endoscopy is technically available, previous studies have revealed its relatively low technical success rate with possible fatal bleeding[66]. Meanwhile, selected INP patients with bulging lesions without prominent portal hypertension may be more suitable for conventional endoscopic drainage without EUS guidance [67]. Therefore, EUS-guided drainage should be considered the first-line endoscopic drainage procedure when available.

Is fluoroscopy necessary? Fluoroscopy is recommended during EUS-guided PPC drainage by the Asian EUS group RAND/UCLA expert panel with low evidence level[18]. However, EUS-guided drainage can be completed without fluoroscopy[68]. Experienced endoscopists may choose to perform endoscopic drainage under EUS guidance alone to shorten the operation and reduce unnecessary radiation exposure for the physician and the patient.

How could endoscopists deal with complicated deployments of LAMS? Several novel techniques have been reported, among which the two-step puncture technique is recommended for IPN patients with massive solid necrosis and little fluid content, and the back-and-forth technique is intended for insufficient expansion of the distal flange[69].

Whether should LAMS be dilated after deployment? Some experts support dilation to increase rapid drainage, while others claim it is unnecessary and may cause increased dislodgment risks[12]. Although no consensus has been reached, dilation mostly depends on the endoscopists' subjective judgment of the intraoperative drainage effect and the content of PFCs[12].

When should the LAMS be removed? Literature on the removal timing of drainage stents is limited [70]. From the perspective of therapeutic purposes, stent removal should be considered when PPCs and WONs are entirely or at least mainly resolved[[68]. However, due to various complications that may occur during long-term placement[61,62], the recommended time of removal is 4 wk[17]. Recent research proposes an early removal of LAMS 3 wk after necrosectomy if WON resolution has been confirmed[71]. In some previous studies, the median indwelling time for LAMS is prolonged[33], but surprisingly, no significant increases in complications have been reported when even prolonged to 7.8 mo[68]. Another concern is that premature stent removal may lead to an increased recurrence of pancreatic collections[72]. Therefore, a long-term indwelling of transluminal DPPS is recommended in INP patients with disconnected PD syndrome by ESGE guidelines[17]. In addition, transpapillary PD stenting has proven improvements in treating IPN patients with PD disruption undergoing endoscopic transluminal drainage[73].

Is endoscopic closure necessary? Several studies have recommended metal clips or the over-the-scope clip for the endoscopic closing of gastroduodenal fistula after completing all endoscopic treatments and removing all stents[74]. Other experts may claim it is not necessary. Our experience is that endoscopic closure may not be essential for patients with satisfactory general conditions and relatively short disease duration. However, endoscopic closure should be performed for patients with the opposite situations or early needs for transoral feeding; otherwise, it may cause further infection, a long-lasting unhealed GI wall, and the recurrence of INP. Several combined techniques for managing other digestive fistulas may also be practical and feasible for a few complicated cases with poor efficiency by standard suture methods[75].

ENDOSCOPIC TRANSLUMINAL NECROSECTOMY

ANC occurs in most NP patients, and WON appears in more than half of them[76]. Previous studies have demonstrated that conservative management without necrosectomy could be a successful approach for 64% of patients with INP[77]. More than half of INP patients could be treated by catheter drainage alone and did not require necrosectomy procedures[20]. Moreover, endoscopic drainage with plastic double pigtail stents has been reported as sufficient in most PPC and WON, with or without infection[19]. However, there are significant differences in the pancreatic collections and drainage effect of varied INP patients. Although the natural resolution has been noted in more than one-half of WONs within 6 mo of onset[78], interventions should be considered when patients develop INP-associated fever, infection, abdominal pain, or GI obstruction[79]. Endoscopic transmural necrosectomy involves endoscopic access to the necrotic area and gradual removal of the necrotic tissue (Table 2)[80]. Endoscopic transmural necrosectomy is a natural orifice transluminal endoscopic surgery (NOTES) that combines endoscopic and surgical techniques[8,81,82].

Table 2 Characteristics of endoscopic transluminal necrosectomy

	Recommendations and benefits	Areas of concern	Ref.
Indications for necrosectomy	Unsolved INP-associated symptoms	Conservative management or endoscopic drainage alone is sufficient in selected patients	[77-80]
Endoscopic transluminal necrosectomy	First-line therapy; recommended endoscopic step-up approach; increased life quality; reduced proinflammatory response, complications, hospitalization time, costs, and new-onset multiple organ failure	One single treatment may not suit all INP patients; no superiority in reducing major complications or mortality when compared with the surgical step-up procedure	[6,8-10, 71,83-85]
Improve necrosectomy efficiency	A solid component is better assessed by EUS than by CT scanning	Lack of unified assessment protocol for necrosis proportion	[54]
Irrigation techniques	A three-step structured approach; saline, streptokinase, antibiotics, and hydrogen peroxide; reduced mortality and debridements	Lack of optimal procedure and concentration; prolonged stent retrieval; perforation caused by forced irrigation	[79,86-97]
Dedicated instruments	OTSG; PED; WAND; safe and effective; reduced interventions and hospital duration	Efficacy and indispensable safety; further research and popularization	[98-100]
Predictors for complications	Small size (≤ 7 cm) and delayed stent removal (≥ 4 w); PD disruption, abnormal vessels, and requirements of percutaneous drainage or hybrid techniques; elevated intracavitary amylase; exocrine insufficiency	Lack of prospective multicenter large-scale RCT	[37,106-109]
Managing complications	A novel algorithm for systematically managing hemorrhage events; LAMS with a larger diameter; mouthwash with chlorhexidine; suspension of PPI; timely follow-up and endoscopic management		[60,62, 63,74,79, 101-104]
MDT strategy	Individualized treatment; reduced mortality; improved clinical outcomes; optimal strategy for patients with high risks of potential complications	Lack of standardized endoscopic protocol; considerable variations among endoscopists	[11,79, 110-112]

EUS: Endoscopic ultrasound; INP: Infected necrotizing pancreatitis; OTSG: Over-the-scope grasper; PED: Powered endoscopic debridement system; WAND: Waterjet necrosectomy device; PD: Pancreatic duct; RCT: Randomized controlled trials; LAMS: Lumen-apposing metal stents; MDT: Multidisciplinary treatment.

Progress

Endoscopic transluminal necrosectomy demonstrates increased life quality of INP patients and significantly reduced proinflammatory response, complications, hospitalization time and costs, and new-onset multiple organ failure[6,71]. Therefore, it has become a first-line option for INP patients who require necrosectomy.

The endoscopic step-up approach refers to EUS-guided transluminal drainage followed by endoscopic necrosectomy if necessary. Although the conclusions of comparative studies on major complications and mortality of endoscopic transluminal and surgical step-up procedures are inconsistent, the rate of pancreatic fistulas and hospitalization time is lower in the endoscopy group in most studies[9,83]. Pancreatic fistula is one of the critical reasons for prolonged hospitalization, increased treatment costs, and reduced treatment experience and life quality in patients with INP. Therefore, endoscopic transluminal necrosectomy should be recommended as a first-line option for patients with debridement needs.

Challenges

Superior to surgical approaches or not: Endoscopic necrosectomy has often been compared with surgical approaches to answer whether it is superior to surgical techniques, but conclusions varied[6,9, 83]. The first-step comparison has been conducted in minimally invasive interventions and surgical open necrosectomy, and the following results are generally accepted. That is, minimally invasive approaches have replaced surgical open necrosectomy due to their advantages in the rate of the composite end point of major complications[7]. Moreover, minimally-invasive surgical and endoscopic necrosectomy demonstrated lower mortality than open necrosectomy in a pooled analysis of 1980 patients[84]. However, Comparing endoscopic step-up procedures to direct surgical necrosectomy may also lead to a bias in favor of endoscopic treatment[85].

Next, the second step compares two minimally invasive interventions, including the endoscopic transluminal and surgical step-up approaches. Reductions in the major complications, hospitalization time, and medical costs have been observed in the endoscopic transluminal step-up group in the TENSION trial, a randomized controlled, parallel-group superiority multicenter trial by the Dutch Pancreatitis Study Group[83]. Moreover, besides reduced major complications and therapeutic costs, increased life quality has also been revealed in the endoscopic transluminal approach when compared with minimally invasive surgery in INP patients[6]. In contrast, other studies have found that although

the rate of pancreatic fistulas and hospitalization time is lower in the endoscopic group, no superiority in reducing major complications or mortality has been noted in the endoscopic step-up approach (EUS-guided transluminal drainage followed by endoscopic necrosectomy if necessary) when comparing with the surgical step-up procedure (percutaneous catheter drainage followed by video-assisted retroperitoneal debridement if required)[9]. The reasons for the differences or even the contradictions of various studies may be related to the differences in the sample size, the INP lesions, the specific endoscopic procedures, and the experience and perioperative management in different medical centers. In general, minimally invasive necrosectomy is currently recommended, among which endoscopic necrosectomy may be a better first-step option. When it comes to a specific patient, it is necessary to consider all INP-related factors and the therapeutic experience of the local medical institution.

How to improve the efficiency: If endoscopic necrosectomy sessions can be effectively decreased, it will reduce the operation-related complications and costs, shorten the treatment process, and improve the overall experience. Therefore, it has always been a hot issue in INP treatment. Since the frequency of endoscopic necrosectomy is affected by the necrotic proportion in INP patients, assessing the necrosis proportion is the first problem. However, there is yet to be a unified assessment protocol[54]. Based on the current literature, the following drugs, devices, and techniques may help reduce endoscopic debridements.

Irrigation of the INP cavity is a commonly used procedure in INP patients undergoing invasive intervention. A three-step structured approach (debridement, necrosis extraction, and irrigation) has been developed and demonstrated fewer interventions[86]. Irrigation can be accomplished by a nasal catheter, a percutaneous catheter, or a combination[79]. Although percutaneous drainage has been considered one primary treatment for INP and helps most patients reduce open debridement in some studies, about one in five patients gets worse and requires open surgical intervention[87]. Furthermore, recent research has revealed that streptokinase irrigation through a percutaneous catheter helps reduce necrosectomy sessions and mortality in a step-up approach. Constant saline instillation *via* nasocystic catheter between each necrosectomy procedure has been reported effective for improving drainage and reducing debridement operations[88,89]. However, it still needs to be determined whether continuous or intermittent lavage is more suitable for the INP cavity[79]. In the meantime, complications have also been noticed, including forced irrigation-caused perforation, subsequent organ failure, and death[88]. Another study has introduced a vigorous irrigation technique to reduce mechanical debridement, and no mortalities or following surgical needs have been reported in these patients[90]. However, the reported mean time of stent retrieval seems prolonged than the recommended[90]. Moreover, aggressive lavage with large-volume warmed antibiotic solution has also been reported as an efficient alternative to saline irrigation, and reduced rates of adverse events and mortality have been noted in previous studies[91]. In addition, cessation of PPIs, local infusion of antibiotics, maximal fragmentation of necrotic tissue, and disruption of internal septate structures during the first necrosectomy can also improve drainage and reduce debridements[91-93].

In several previous studies, hydrogen peroxide has proven effective and safe in reducing debridements, even making external irrigation unnecessary in selected IPN patients[82,94]. Hydrogen peroxide has the advantage of healing INP by stimulating granulation and fibrosis, and foams produced by hydrogen peroxide in contact with organic tissue help remove the attached necrotic debris[95]. However, its operation time and treatment course to achieve equal clinical efficacy with routine debridement seem prolonged[96], and this technique's optimal procedure and concentration remain to be further studied[94]. Another recent single-center randomized pilot study has revealed that streptokinase irrigation in complicated INP cases demonstrates a lesser post-irrigation hospital stay and a reduced trend for mortality and necrosectomy sessions, while H_2O_2 irrigation may cause more bleedings, in contrast[97].

Besides, the optimal interval between each endoscopic necrosectomy remains unsettled. One possible reason may be the lack of data from large-scale multicenter RCTs. The current recommendation is 6.23 ± 4.71 d (range, 3-21 d), which is also based on endoscopists' experience[12]. Suppose the interval can be shortened, or even an endoscopic debridement is performed at the same time as the first drainage; in that case, it seems beneficial in shortening the overall treatment duration. Although studies have reported that simultaneous drainage and debridement in a small number of selected patients does not significantly increase the incidence of serious complications[90], most experts do not recommend such procedures[12].

Furthermore, endoscopic transluminal necrosectomy still lacks dedicated instruments. However, some innovations have emerged in recent years. A new grasping tool, the over-the-scope grasper (OTSG), has been reported to overcome the disadvantages of time-consuming endoscopic removals of necrotic debris[98]. OTSG can be attached to any standard gastroscope. Additionally, a novel powered endoscopic debridement system has been developed to achieve simultaneous resection and removal of solid debris. In recent research of a prospective, multicenter, international device trial, this system has revealed fewer interventions and shorter hospital duration in INP patients[99]. Thus, it seems to be a safe and effective dedicated instrument for WON. Another novel prototype of the waterjet necrosectomy device has also been designed and has already demonstrated effectiveness in fragmenting necrotic debris and avoiding trauma to healthy tissue in animal experiments[100]. The above-mentioned

two new devices are compatible with therapeutic endoscopes with at least a 3.2-mm and a 2.8-mm working channel, respectively[99,100].

Additionally, it seems lacking attractive to compare the advantages and disadvantages of traditional endoscopic necrosectomy devices, and related comparative trials of these devices barely exist. In all cases, any device or technique used in endoscopic procedures must balance necrosectomy's efficacy with safety.

Predicting and managing complications: Despite all the aforementioned advantages and the promising future of endoscopic interventions, various complications should be addressed. Moreover, the prediction and management of potential complications should also be emphasized.

Common complications of endoscopic interventions in INP include bleeding, infection, perforation, pneumoperitoneum, and stent migration[33,62,63,101]. Bleeding is a dangerous complication with serious, even deadly outcomes, and it can be classified into two types: Intraoperative and postoperative bleeding[102]. Intraoperative bleeding may occur near the fistula or inside the pancreatic collection. Common causes of bleeding include mechanical injuries and ruptures of pseudoaneurysm, collateral vessels, or other intracavitary blood vessels[60,102,103]. Timely and effective endoscopic management of these mild bleedings may not require interventional radiology-guided coil embolization or emergency surgery. Still, sometimes severe bleeding leads to the unfortunate outcome of the patient's death[60,62,63]. To date, the occurrence of bleeding has been presumed to be related to the type, size, and location of pancreatic collections; the type, diameter, and length of stents; varied intracavitary components; the time and protocol of endoscopic interventions; the experience of endoscopists; and the general health condition of the patient[62,102]. A novel algorithm has already been proposed for systematically managing hemorrhage events, which needs to be proven and refined in further RCT[102].

Moreover, infection often occurs in patients with poor drainage or a significant amount of solid necrosis. Using LAMS with a larger diameter, improving drainage efficiency, cooperating with antibiotics, and timely endoscopic debridement will help to improve or avoid severe infection in these patients[17,18,31,56,79]. Another human research has also demonstrated reduced intraabdominal infection by mouthwash with chlorhexidine and suspension of PPI before operation[74]. Stent migration needs to be paid enough attention to in patients using LAMS or SEMS. Endoscopic or imaging follow-up and timely removal of the stent will help reduce the occurrence of stent migration[71]. For long-term stent retention events caused by loss of follow-up or other reasons, most can also be solved by endoscopic interventions[104]. In addition, intraoperative perforation, pneumoperitoneum, and postoperative obstructive jaundice caused by stent compression could be reduced or timely treated to avoid fatal consequences in an experienced endoscopic center[16,105].

Furthermore, how to predict high-risk patients with these potential complications? Several predictors have been studied. A relatively small size (≤ 7 cm) and delayed removal of the stent (≥ 4 wk) have both been reported as effective predictors for delayed bleeding and buried stent syndrome[106]. Identifying intracavitary vessels during endoscopic interventions could also predict intraoperative bleeding, and patients with more transfusion requirements before interventions may require earlier radiological interventions[107]. Meanwhile, a predictive model for potential complications after LAMS deployment in INP patients has been reported. Higher risks for adverse events have already been identified in patients with preoperative evidence of PD disruption, abnormal vessels (perigastric varices and pseudoaneurysm), and requirements of percutaneous drainage or hybrid techniques[108]. Another research has also found that a significantly higher level of intracavitary amylase may indicate a higher risk of recurrence in INP patients[37]. In addition, long-term sequelae in patients undergoing endoscopic therapy include pancreatic endocrine insufficiency, exocrine insufficiency, and long-term opiate use. These long-term complications should not be overlooked. Previous research has revealed that patients with exocrine insufficiency may have a significantly poorer health-related quality of life [109]. These above studies help evaluate the potential risks and predict the prognosis before endoscopic interventions in INP patients. Further research will promote the continuous development of endoscopic interventional technology based on patient safety.

A multi-disciplinary treatment strategy: Despite all the progress of endoscopic transluminal interventions, INP remains a challenging and fatal condition. Due to lacking standardized endoscopic treatment protocol and considerable variations in the treatment selections among various endoscopists and medical centers[11], the short-term and long-term results of INP patients are affected by many factors. The optimal strategy varies in patients, especially those with high risks of potential complications. Moreover, not all patients with INP can be completely cured through endoscopic transluminal interventions alone. Thus it needs a multi-disciplinary treatment strategy in the whole clinical management of INP[110]. A multi-disciplinary team (MDT) consists of therapeutic endoscopists, gastroenterologists, anaesthesiologists, intensive care unit physicians, sonographers, interventional radiologists, and surgeons[111]. MDT aims to determine individualized treatment options for every INP patient, reduce mortality, improve clinical outcomes[79], and improve the risk-benefit ratio throughout the clinical treatment process. A staged, multi-disciplinary, minimally invasive "step-up" approach has already been proposed as an optimal treatment strategy for patients with INP, especially those with severe and complicated conditions[110-112].

LIMITATIONS

Increasing evidence has demonstrated promising benefits of endoscopic transluminal drainage and necrosectomy in patients with INP. Numerous experts and guidelines have also recommended endoscopic interventions as a first-line strategy. However, endoscopic transluminal interventions are neither omnipotent nor perfect. Moreover, endoscopic transluminal interventions represent only one invasive option for INP patients. It is also necessary to consider when and how to better connect with surgical treatment and other methods so that patients can obtain better overall therapeutic effects. In addition, there still lacks a standard protocol for endoscopic transluminal interventions, while surgical treatment of INP has already been standardized, in contrast[11].

Endoscopic transluminal drainage and necrosectomy are definitely hot in the field of INP therapy and advanced endoscopic techniques. However, differences and contradictions exist in the conclusions of various studies, which may be related to the sample size, the patients' heterogeneity, especially the varied ratios of patients with organ failure, and different proportions of patients with a significant amount of necrosis (≥ 50%)[113]. Further prospective multicenter large-scale RCTs are still needed for investigating the following contents: The standard protocol of endoscopic interventions, multi-disciplinary support strategies, accurate preoperative assessments (including necrosis proportion), optimal intervention time, predictors for perioperative complications, emergency treatment of severe complications, novel techniques and devices with improved efficiency, non-endoscopic supportive strategies [79], and predictors for short-term and long-term outcomes.

CONCLUSION

Endoscopic transluminal drainage and necrosectomy, especially EUS-guided treatments, have become the mainstream minimally-invasive treatment for symptomatic INP. A staged multi-disciplinary strategy may ensure an individualized treatment in appropriate patients. The optimal risk-benefit ratio of endoscopic transluminal interventions could be achieved by skilled endoscopists at the proper timing. Growing evidence has proven progress in endoscopic transluminal interventions, while challenges and unsolved problems still need further investigation. Furthermore, the predominant role of endoscopic treatment in INP will be further developed with advancements, standardization, and popularization in endoscopic techniques and devices in the near future.

FOOTNOTES

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Country/Territory of origin: China

ORCID number: Yan Zeng 0000-0003-4935-1306; Jian Yang 0000-0001-8170-0727; Jun-Wen Zhang 0000-0003-2911-598X.

Corresponding Author's Membership in Professional Societies: Chinese Society of Gastroenterology.

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