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SPECIAL SECTION: PANCREATITIS

Endoscopic intervention in pancreatitis: perspectives from a gastroenterologist

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Abstract
The last decade has seen a dramatic paradigm shift for the treatment of pancreatitis and its related complications away from surgery to minimally invasive endoscopic approaches. In this review, we provide an overview of the indications, techniques and outcomes of endoscopic interventions in the management of acute and chronic pancreatitis. Emphasis is placed on drainage of pancreatic pseudocysts and treatment of pain in chronic pancreatitis.

Keywords Pancreas · Pancreatitis · Pancreatic pseudocyst · Endoscopy

Background

The last decade has seen a dramatic paradigm shift for the treatment of pancreatitis and its related complications. Technological advancements in endoscopic ultrasound (EUS) guidance and development of specialized stents have expanded the indications and possibilities of interventional endoscopy [1]. Interventional endoscopic techniques now provide an effective minimally invasive treatment option for complications of acute and chronic pancreatitis. The aim of this article is to provide an overview of the indications, techniques and outcomes of endoscopic interventions in acute and chronic pancreatitis.

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Acute pancreatitis

Pancreatic fluid collections

Classification and indications for drainage

Pancreatic fluid collections (PFC) can arise as a complication of pancreatitis. Accurate classification of these collections is important given differences in management and outcomes. Based on the revised Atlanta classification [2], PFCs are divided based on duration (> 4 weeks from onset of pancreatitis) and presence of necrosis into four main types (Table 1). While the majority of peri-pancreatic fluid collections resolve spontaneously [3], approximately 10% of pseudocysts and 21% of walled-off necrosis (WON) require intervention [4, 5]. Given risks associated with drainage, interventions to drain pancreatic pseudocysts or WON are reserved for patients with symptoms secondary to pain, infection, obstruction and/or bleeding [2, 6–8].

Principles of management

The approach to PFC management can be summarized in three steps: delay, drain and if necessary, debride. Intervention for a pancreatic pseudocysts or WON should be delayed as long as clinically possible in order to allow time for a granulation tissue wall to form around the collection (> 4 weeks). A prospective multicenter study of 242 patients found that delayed PFC intervention decreased mortality (0–14 days: 56%; 14–29 days: 26%; and > 29 days: 15%;

Table 1 Pancreatic fluid collections

Duration	Fluid collection	Management
< 4 weeks	Acute peri-Pancreatic fluid collection(s)	Expectant
> 4 weeks	Pancreatic pseudocyst(s)	Endoscopic transmural drainage
< 4 weeks	Acute necrotic collection	Expectant
> 4 weeks	Walled-off necrosis	Endoscopic transmural drainage ± Endoscopic necrosectomy

$P < 0.001$) [9] Imaging should be obtained prior to drainage to determine the quantity of debris within the PFC and evaluate for conditions that mimic a PFC, such as pancreatic cystic neoplasms [10]. If the patient is septic and source control is required prior to PFC maturation, percutaneous catheter insertion can be utilized as a temporizing measure. The following section will focus on endoscopic approaches to PFC management, recognizing that percutaneous catheter drainage alone will be sufficient treatment in 23 to 55% of patients with infected and/or symptomatic necrotizing pancreatitis without the need for step up endoscopic or surgical therapy [11–15].

Organized PFCs can be drained via transpapillary and transmural techniques. Endoscopic transmural drainage is more common and requires the creation of a conduit between the gut and the collection (cyst-gastrostomy or cyst-duodenostomy). Transpapillary drainage involves of endoscopic retrograde cholangiopancreatography (ERCP) with placement of a pancreatic stent. Endoscopic necrosectomy involves the additional steps of entering the cavity with a gastroscope and mechanically debriding the necrotic content. Transpapillary and transmural drainage may be used as stand-alone interventions or in combination. EUS is now considered standard for initial transluminal drainage, as it enables visualization and puncture of targeted collections independent of a visible bulge, and color Doppler allows avoidance of interposed blood vessels. Two RCTs have shown improved outcomes with EUS guided when compared with endoscopic drainage [16, 17].

Endoscopic intervention for pancreatic pseudocysts compared to WON has higher treatment success and a lower rate of recurrence [18, 19]. While many studies do not differentiate between PFCs in describing treatment outcomes, a recent review found that endoscopic drainage of pseudocysts was clinically successful in 94% of cases. [20].

The rise of minimally invasive techniques

Minimally invasive endoscopic techniques have replaced open surgery for management of symptomatic PFCs. RCTs have shown no difference in clinical success rates between surgical and endoscopic therapies but additional benefits of endoscopic therapy include shorter hospital length of stay, reduced costs, and improved quality of life [11, 21–23]. Recent RCTs are summarized in Table 2.

The landmark PANTER [11] [The Minimally Invasive Step Up Approach versus Maximal Necrosectomy in Patients with Acute Necrotising] trial established the minimally invasive 'step-up' approach, where a percutaneous drain is initially inserted followed by a step up to endoscopic and/or minimally invasive surgery as needed, as superior to open surgical necrosectomy for symptomatic and/or infected necrotizing pancreatitis or WON. Three subsequent RCTs have shown the superiority of the endoscopic approach for treatment of infected necrotizing pancreatitis (Table 2). While the MISER [23] trial showed reduced rates of a primary composite outcome in the endoscopic arm, the TENSION [22] trial demonstrated no significant difference between endoscopic and minimally invasive surgery. There was a difference in the treatment approaches with regards to the type of stents used and there was variable use of co-interventions which can impact the outcome of treatment (e.g. use of percutaneous drains and number of debridement procedures performed), which may explain the differing conclusions between the two studies.

Recently published long-term follow-up from the PANTER trial has further established the superiority of the minimally invasive step-up approach. [11] There was no difference in the need for reintervention between the step-up and open necrosectomy arms over 86 months. Additionally, patients in the step-up arm had lower rates of incisional hernias, pancreatic exocrine insufficiency and diabetes.

In a pooled analysis of 1980 patients with necrotizing pancreatitis from several RCTs, mortality was significantly reduced among critically ill patients with necrotizing pancreatitis undergoing minimally invasive surgical or endoscopic intervention when compared with open surgical necrosectomy. [24].

Transluminal endoscopic drainage and necrosectomy

Plastic stents (PS) were traditionally used for drainage of PFCs. However, the overall treatment success of PS is suboptimal for drainage of WON compared to pseudocysts due to the increased risk of stent obstruction. Lumen-apposing metal stents (LAMS) have a larger diameter which allows for improved drainage and direct endoscopic necrosectomy (DEN), as they have a unique "dumbbell" design to prevent stent migration.

An international multicenter study showed that LAMS were associated with higher clinical success, shorter procedure time, lower need for surgery, and lower recurrence when compared to PS in WON [25]. Conversely, a recent

Table 2 Randomized controlled trials comparing endoscopy and minimally invasive surgery for the treatment of walled-off necrosis

Trial, Author (year)	Number of Patients	Primary Outcome	Secondary Outcome	Limitations
PENGUIN Trial Bakker et al. (2012)	Endoscopy ($N=10$) Surgical ($N=10$)	Reduced postprocedural IL-6 levels in endoscopy group ($P=0.004$)	Reduced composite clinical endpoint of major complications (new-onset MOF, intra-abdominal bleeding, ECF, or pancreatic fistula) or death ($P=0.03$) in endoscopy group	Primary endpoint utilizing IL-6 represents a surrogate measure of severity Small sample size
TENSION Trial Van Brunschot et al. (2018)	Endoscopy ($N=51$) Surgical ($N=47$)	No difference in composite endpoint of major complications (new-onset OF, bleeding, perforation of a visceral organ requiring intervention, ECF, incisional hernia) or death between groups	Reduced rate of pancreatic fistulas ($P=0.0011$) and hospital stay ($P=0.014$) in endoscopy group	Use of composite outcome that includes variables of lesser clinical impact and frequency 1/3 of patients in endoscopy group underwent additional percutaneous drainage
MISER Trial Bang et al. (2019)	Endoscopy ($N=34$) Surgical ($N=32$)	Reduced composite outcome (new-onset MOF, new-onset systemic dysfunction, enteral or pancreatic-cutaneous fistula, bleeding and perforation of a visceral organ) or death in endoscopy group ($P=0.007$)	Improved physical health scores for QOL at 3 months ($P=0.039$) and reduced total cost ($P=0.039$) in endoscopy group	Use of composite outcome that includes variables of lesser clinical impact Single-center trial conducted at a tertiary referral center, heterogeneity in the type of endoprosthesis used

MOF multiple organ failure, *ECF* enterocutaneous fistulae, *DM* diabetes mellitus, *OF* organ failure

RCT of 60 patients that compared LAMS with PS showed no difference in clinical success, with higher stent related adverse events (bleeding, biliary stricture) of 32.3% and 6.9% with the use of LAMS than with double pigtail PS, respectively [26]. Based on these results, removal of LAMS at 3–4 weeks is advised. In cases of partial WON resolution, LAMS should be exchanged for PS, which can remain in situ indefinitely to mitigate the risk of developing disconnected duct syndrome (DDS). LAMS are also associated with higher average cost per patient [27].

Direct endoscopic necrosectomy (DEN) can be avoided in 20–40% of patients who demonstrate successful resolution of WON with metal stents [28, 29]. In cases that do not respond to initial drainage, studies have shown DEN to have an approximate 80% success rate, with complications ranging from 3 to 35% (bleeding, air embolism, perforation), and 6-8% mortality. [27–31].

Previous studies showed the use of hydrogen peroxide as an adjunct to DEN to facilitate the chemical dissolution of solid necrotic collections. [32, 33] DEN should thus be limited to patients who have failed to improve after appropriate transluminal drainage with the goal of clinical symptom resolution.

Interventions for other complications of necrotizing pancreatitis

Fistulae

An external pancreatic fistula is defined as the output of any measurable volume of fluid (from a percutaneous drain, percutaneous drain tract, or surgical wound) with an increased fluid amylase concentration ≥ 3 times the serum value [8]. Initial management is conservative unless sepsis is present. Transpapillary stenting can be considered when fistulae are associated with partial pancreatic duct disruption and PFCs < 5 cm, but success rate is 9% to 69%. [30, 31, 34] In the only study comparing transpapillary stenting and conservative management, there was no difference in the rates of external pancreatic fistula closure, although median time to closure was faster after stenting (71 vs. 120 days, $P=0.13$) [30]. Some centers perform imaging to assess integrity of the main pancreatic duct (MPD) by CE-CT, MRCP with secretin, and/or ERCP before stent removal. [8].

Disconnected duct syndrome

Disconnected duct syndrome (DDS) is a complication of necrotizing pancreatitis that affects 30-50% of patients [6, 30]. DDS involves complete transection of the main pancreatic duct by central necrosis, resulting in discontinuity between viable secreting pancreatic tissue upstream and the

gastrointestinal tract. [35] DDS management has shifted from open surgical to endoscopic management, though DDS is still more likely to require hybrid therapy, reintervention, rescue surgery, and longer hospital stay. [36] Fluid collections resulting from DDS are drained transmurally with PS left in place indefinitely. An RCT [37] and large retrospective study [36] have demonstrated long-term indwelling PS decrease the rate of PFC recurrence, while subsequent studies have confirmed their safety. [38–40].

Biliary pancreatitis

The role and timing of intervention for acute biliary pancreatitis remains controversial. Based on national guidelines and meta-analyses two points are clear: (1) ERCP/Endoscopic sphincterotomy does not have a clear advantage in patients with predicted mild acute biliary pancreatitis and (2) Coexisting cholangitis is an indication for emergency ERCP/Endoscopic sphincterotomy (within 24 h of admission). However, there is no consensus for the indications and timing ERCP in predicted severe acute biliary pancreatitis. [41] The recently completed APEC trial from the Netherlands randomized 230 patients with predicted severe acute biliary pancreatitis to early ERCP (in first 24 h) or conservative treatment with ERCP performed only if patients developed cholangitis or persistent cholestasis [42]. Early ERCP was not associated with a change in outcomes including mortality, new-onset organ failure, or pancreatic necrosis.

Chronic pancreatitis

Pain

Chronic pancreatitis (CP) is a progressive and irreversible fibroinflammatory disease of the pancreas. Over 80% of patients with CP suffer from abdominal pain during the course of their disease. [43] The constant pain of CP is debilitating and associated with lower quality of life and higher disability when compared to intermittent pain. [44, 45] The goal of all therapy in CP is pain relief, the first step of which is conservative therapy (e.g., cessation of alcohol use and smoking, dietary changes, non-opioid analgesics). [46] If pain persists, subsequent interventional endoscopy or surgery is recommended for drainage of the obstructed main pancreatic duct due to calculi and/or strictures.

The selection of patients for endoscopic versus surgery are largely based on symptoms, morphological features, patients preference and provider expertise [47]. An endoscopy-first approach is only used in patients with evidence of pancreatic duct obstruction due to the presence of stricture(s) and/or stone(s) often manifested by a dilated ducts (≥5 mm).Endoscopy is associated with higher technical and clinical success rates in patients who have a single stricture, stone < 1 cm in size, 3 or fewer stones and disease limited to the head or proximal body of the pancreas [48]. A surgery-first approach is used in patients with small or large duct disease and should be preferred in patients who have multiple strictures, a significant stone burden throughout the pancreas, or an inflammatory head mass where cancer cannot be confidently excluded.

Due to its less invasive nature, an endotherapy-first approach is widely practiced. In the largest prospective cohort study of endoscopic therapy in CP of 1018 patients, endoscopic ductal decompression therapy offered pain relief in two-thirds of patients when used as the sole treatment modality, while one-fourth of the patients had to undergo surgery. [49] Two RCTs have compared surgery and endotherapy in the treatment of pain secondary to CP [50, 51] Both trials were small, but both showed superiority of surgical treatment over endotherapy [52, 53]. The benefits of surgical therapy include more effective pain relief, higher technical success rate, fewer number of total procedures, higher quality of life, no increase in hospital stay, morbidity or mortality, no difference in pancreatic function, and no recurrent obstruction. Five-year follow-up of the Cahen study showed that 47% of patients who underwent endotherapy required subsequent surgery, which was less effective. [54] It should be noted that there were many limitations to these RCTs that have been discussed in detail elsewhere [32, 55].

Despite data supporting the superiority of surgery over endotherapy, guidelines are contradictory. Per German S-3 guidelines [56] "as the most effective long-term form of pain therapy for CP, surgery should be performed (level of evidence grade 1a, recommendation grade A, consensus). In contrast, recent ESGE guidelines [47] suggest "endoscopic therapy and/or extracorporeal shockwave lithotripsy (ESWL) as the first-line therapy for painful uncomplicated chronic pancreatitis (CP) with an obstructed main pancreatic duct in the head/body of the pancreas." (Weak recommendation, low quality evidence). The ongoing ESCAPE [57] trial is comparing early surgery and current step-up practice with conservative management followed by surgery for CP in regard to pain control, pancreatic function, and quality of life.

In terms of adjunctive treatment modality, ESWL has traditionally been the preferred method for fragmentation of large stones in the pancreatic head or body in the presence/absence of strictures. An RCT comparing ESWL alone with ESWL combined with endoscopic drainage of the MPD in patients with painful calcific CP showed similar pain relief rates. [58] However, combining endoscopy with ESWL was found to triple the cost of patient care.

Limitations to ESWL include the costs, the need for multiple sessions, and the need of a non-gastroenterologist (usually an urologist in the U.S. as ESWL is not FDA approved for pancreatic stone dissolution) to perform lithotripsy [59]. ERCP with per-oral pancreatoscopy guided intraductal lithotripsy can aid stone fragmentation and removal while treating strictures using dilators and stents during the same procedure, potentially obviating the need for ESWL. Limited data has suggested that more than half of patients can achieve ductal clearance in a single session [59, 60] Clinical success rates using this approach vary from 50-80%. [61–63] Controlled trials are needed to further evaluate the role of intraductal lithotripsy on pain in CP.

Celiac plexus block

Celiac Plexus Block (CPB) involves injection of anesthetic with a steroid into the celiac plexus region or directly into the celiac ganglia during EUS. CPB was historically performed using the percutaneous approach. An RCT from India showed higher clinical success rates of EUS-CPB when compared to percutaneous CPB [64]. One reason for the difference may be the significant anatomical variation of the celiac trunk which requires that percutaneous approach be performed under CT guidance as opposed to blind or fluoroscopic needle insertion. [65] Although the technique is considered to be safe [66], the long-term efficacy and duration of pain relief of CPB is limited. A systematic review of earlier RCTs reported that 51% of patients achieve temporary pain relief lasting from a few weeks to a few months, rending EUS-CPB ineffective as a single method of chronic pain control in CP. [67] An important limitation of earlier RCTs was the inclusion of many patients who may not have had CP due to non-definitive definitions of the disease. Attempts to improve the efficacy of EUS have been unsuccessful. There have been no differences found with bilateral versus unilateral injection [68]. Higher injection volumes have been shown in a cadaveric study to result in more diffuse percolation of anesthetic and steroid across the plexus and ganglia [69]; however, this has not been evaluated in a controlled study. A rigorously conducted, single center RCT of 40 CP patients comparing EUS-CPB using bupivacaine only to EUS-CPB using bupivacaine and triamcinolone, found similar and suboptimal rates of pain control between the two groups (intention to treat analysis: 14% vs. 16% for controls) [70]. This RCT was terminated early due to futility. An editorial [71] accompanying this RCT belied the fact that there has been a sham-controlled trial of EUS-CPB which renders assessment of this procedure for pain relief difficult to interpret since pain relief rates in the sham arm of interventional studies can be as high as 70%. [72] CPB may also be less effective in CP patients with central sensitization.

Conclusion

Advancements in interventional techniques have put endoscopy at the forefront of management of complications of AP and CP. This review aimed to provide radiologists with an adequate familiarity with these procedures, including their rates of clinical and technical success, outcomes, and limitations. Future research should aim to improve the care of AP and CP by identifying which subgroups of patients will respond best to a minimally invasive endotherapy-first approach.

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