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Endotherapy in Pancreatic Diseases

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Abstract

Interventional endoscopy is now considered an effective minimally invasive treatment modality for the management of pancreatic diseases. It is important for the clinician to know the indications and contraindications as well as the timing of various endoscopic interventions. This will help in its safe and effective use and consequently decrease morbidity and mortality from various pancreatic diseases. This review will provide a broad overview of the indications, techniques, and outcomes of pancreatic endotherapy.

Keywords

- pancreatitis
- endosonography
- endoscopic retrograde cholangiopancreatography
- stent

Background

Interventional endoscopy is now considered an effective minimally invasive treatment modality in the management of pancreatic diseases. This review will focus on the role of endotherapy in the management of acute pancreatitis and its complications, recurrent acute pancreatitis, chronic pancreatitis, pancreatic cancer, pancreatic neuroendocrine tumors, and cystic lesions of the pancreas.

Endotherapy in Acute Pancreatitis

The role of endotherapy when a patient initially presents with acute pancreatitis (AP) is mainly limited to two situations: first, patients with acute biliary pancreatitis (ABP) and, second, to place nasojejunal/nasogastric tube for nutritional support.

Acute Biliary Pancreatitis

The role and timing of Endoscopic retrograde cholangiopancreatography (ERCP) in ABP is still a topic of debate in absence of cholangitis.[1] ERCP in patients with ABP is usually performed in patients with cholangitis ($<$ 24 hours) or prolonged cholestasis (i.e., an elevated serum bilirubin level that fails to fall suggesting persistent biliary obstruction). The recently completed ABP: urgent ERCP with sphincterotomy versus Conservative treatment (APEC) trial randomized 230 patients with predicted severe ABP and the results of this study support a conservative strategy in patients with predicted severe ABP without cholangitis or persistent cholestasis.[2] EUS can help to confirm common bile duct stones before ERCP in absence of obvious signs of biliary obstruction and prevent unnecessary ERCP and consequent adverse events.[1]

Enteral Feeding

Early enteral feeding (preferably within 24–72 hours) for patients with severe acute pancreatitis is recommended in view of a significant reduction in infectious complications, mortality, and organ failure rates.[3] Nasogastric (NG) feeding appears to be as effective as nasojejunal (NJ) feeding.[3] A randomized controlled study has also suggested that NJ fluid resuscitation with oral rehydration solution is feasible and is equally efficacious in patients with acute pancreatitis as intravenous fluid resuscitation with ringer lactate.[4] NJ resuscitation also resulted in the early institution of enteral feeding. NJ feeding has also been shown to improve pain in

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patients with pancreatic fluid collections and thus obviate or delay drainage.[5]

Endotherapy in Local Complications of Acute Pancreatitis

There are a variety of local complications that can arise as a consequence of AP with defined nomenclature.[6] Based on the revised Atlanta classification, these include peri-pancreatic fluid collections (PFC), pancreatic and peripancreatic necrosis (sterile or infected), and pseudocyst and walled-off necrosis (WON; sterile or infected). Acute peri-pancreatic collections form early in the course of AP and usually resolve without any intervention. Intervention should be delayed as long as possible depending upon the clinical status of the patient to allow time (> 4 weeks) for encapsulation of collection (pseudocyst or WON).[7]

Endotherapy now provides an effective minimally invasive treatment modality for complications of AP with an approach to their management simplified in three steps: delay, drain and if necessary, debride.[8] Percutaneous drainage (PCD) can be utilized as a temporizing measure for source control in critically ill and septic patients prior to PFC maturation. Although there is recent data on the safety and efficacy of endoscopic transmural drainage in patients with partially enclosed PFC, PCD currently is used in the majority of patients with symptomatic pancreatic fluid collections without a well-defined wall.[9–11] Early endoscopic interventions might be performed in patients with partial or complete encapsulated PFC, but careful consideration should be given to endoscopic drainage in the very early stage (<2 weeks) due to limited safety data and absence of encapsulation.

The following section will focus on the role of endotherapy in the management of local complications, recognizing that PCD itself may be adequate in 23–55% of patients with infected or symptomatic necrotizing pancreatitis avoiding step up endoscopic or surgical therapy.[12]

Pseudocysts

Acute pseudocysts usually arise as a sequela of AP, require at least 4 weeks to encapsulate, and are devoid of significant solid debris. In some patients with significant early acute pancreatic necrosis (>30% necrosis), the peripancreatic and pancreatic necrosis may evolve into a collection that on computed tomography resembles a pseudocyst.[13] Also, over a period of time the solid necrotic content in WON may liquefy and the collection may resemble an acute pseudocyst.[14,15] Drainage of an acute pseudocyst is indicated if the patient is symptomatic or the pseudocyst is infected. Pseudocysts may be drained by trans papillary or transmural (through gastric/duodenal wall) route.[16]

Transpapillary Drainage

Transpapillary drainage alone with or without sphincterotomy can be attempted for smaller pseudocysts (less than 6 cm) when there is a communication of pseudocyst with the main pancreatic duct (PD).[17] Evidence from two studies does not support the use of combined transpapillary and transmural drainage in the management of pseudocyst as opposed to the transmural approach alone.[18,19] Yang et al[19] demonstrated that pancreatic duct stenting along with transmural drainage for pancreatic pseudocyst negatively affects the long-term resolution of PFC's. However, PD disruption was not characterized as partial or complete in this multicenter trial and only 36.2% of patients received bridging stents.[20] Transpapillary drainage alone of larger pseudocysts should be avoided as it is associated with increased risk of infection because of the limited ability of narrow caliber transpapillary stents to drain large PFC's. In this setting, use of nasopancreatic drain is preferred, as it is associated with lower risk of infection as compared with use of stent.[21] Any downstream stricture can lead to persistence of pseudocyst so bridging the duct disruption or stricture is considered the preferred approach because it restores ductal continuity and appears to be more effective.[22] 5 to 8.5 Fr size plastic stents can be used as per pancreatic duct diameter on pancreatogram and are usually left in place for 4–6 weeks.

Transmural Drainage

The transmural drainage involves the creation of a conduit between the gut and the collection (cystogastrostomy or cystoduodenostomy). It is performed by entering the collection using a needle without electrocautery or using an electrocautery device (e.g., needle knife, cystotome, cautery-enhanced lumen apposing metal stent [LAMS].[23] EUS is now the preferred modality for transluminal drainage, as it enables accurate visualization and puncture of PFC independent of the presence of endoscopically visible bulge, and the use of color Doppler during EUS avoids injury to intervening blood vessels. Two RCTs have shown improved outcomes with EUS guided approach as compared with blind endoscopic drainage.[24,25] EUS guided drainage with LAMS is preferred for drainage of larger PFC as well as collections with significant solid debris because their larger luminal diameter facilitates prompt drainage and longer patency of the stent.[26] However, their use in pseudocysts does not appear to be advantageous over plastic stents probably given the absence of solid debris resulting in effective drainage via plastic stents also. Therefore plastic stents may be preferred over LAMS in the management of patients with pancreatic pseudocysts as their use seems to be cost-effective.[27] Till date no randomized studies have addressed the optimal number of plastic stents that should be inserted for adequate drainage of an acute pseudocyst. It appears that placement of two plastic stents (7–10 F) may provide optimal drainage of an acute pseudocyst.[28]

While many studies do not differentiate between PFCs in describing treatment outcomes, a recent review reported a clinical success rate of 94% with endoscopic drainage of pseudocysts.[29] A cross-sectional imaging prior to drainage is recommended to delineate the detailed anatomy as well as to detect any vascular complication that may preclude transluminal drainage.[28]

Walled Off Necrosis

The landmark PANTER trial provided evidence about the superiority of minimally invasive step-up approach, where a percutaneous drain is initially inserted followed by a step up to endoscopic and/or minimally invasive surgery was compared with open surgical necrosectomy in patients of infected necrosis or WON.[30] Refractory abdominal pain, gastric outlet obstruction, or failure to thrive (i.e., continued systemic illness, anorexia, and weight loss) at 4 or more weeks after the onset of acute pancreatitis are indications for drainage of sterile WON. Three recent RCTs have reported better outcomes with an endoscopic approach in infected necrotizing pancreatitis.[31–33] However, the difference in the treatment approaches with regards to the type of stents used and variable use of co-interventions (e.g., percutaneous drainage and number of debridement procedures performed), might add heterogeneity to the results of these trials.

Current strategies for managing WON include placement of large diameter LAMS or Bi-flanged Metal Stents (BFMS) to provide efficient drainage of solid necrotic debris and facilitate direct endoscopic necrosectomy (DEN), if necessary (►**Fig. 1**). Three designs of metal stents are available, BFMS (Nagi, Taewoong, South Korea), LAMS (Spaxus, Taewoong, South Korea, and Axios, Boston Scientific, United States), and lumen apposing stents with cautery enhanced tip (Hot Spaxusand Hot Axios Boston Scientific). A multicenter study showed that in comparison to plastic stents, LAMS in WON is associated with higher clinical success, shorter procedure time, lower rate of recurrence, and lower need for surgery.[34] Studies from our center showed similar technical success, rates of WON resolution, and complications in patients treated with multiple plastic stents and LAMS. However, LAMS were associated with a significantly shorter time to resolution.[35] In RCT of 60 patients, Bang et al showed higher stent-related adverse events (bleeding, biliary stricture) with the use of LAMS than with double pigtail plastic stents with similar clinical success.[36] Therefore removal of LAMS is advised at 3–4 weeks after insertion with insertion of plastic stents in exchange in case of partial resolution of WON. DEN is not routinely performed and is reserved for those patients who fail to improve or demonstrate clinical deterioration in view of associated complications ranging from 3 to 35% (bleeding, air embolism, perforation), and 6–8% mortality.[8,37] The addition of a coaxial double pigtail stent inside a LAMS/BFMS may be associated with lower rates of SEMS migration.[28] The role of transpapillary drainage in patients with acute necrotizing pancreatitis is unclear and a recent review suggested that transpapillary pancreatic duct stenting could improve the results of endoscopic transmural drainage of WON.[38]

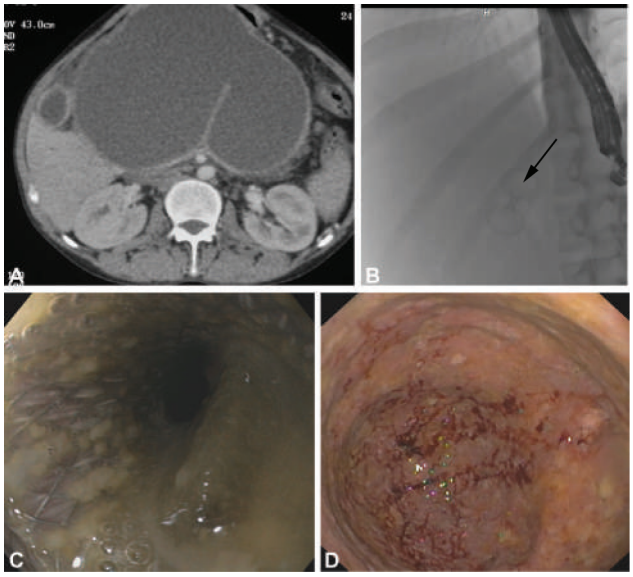

Fig. 1 (**A**) CT abdomen: Large WON. (**B**) EUS-guided drainage: a lumen apposing metal stent (Hot Axios) deployed. (**C**) Direct endoscopic necrosectomy (DEN): endoscope being negotiated into the WON cavity through the stent. (**D**) Post DEN: resolved WON with healthy granulation tissue in the cavity.

Disconnected Duct Syndrome

Disconnected duct syndrome (DDS) is a complication of necrotizing pancreatitis affecting ~30–50% of patients.[8] The leak of pancreatic juice from the remnant pancreas leads to recurrent PFC or refractory external pancreatic fistulae (EPF) and ductal hypertension in the disconnected segment results in recurrent abdominal pain/pancreatitis. Due to complete disruption in DDS, transpapillary drainage is usually considered to be ineffective as bridging with a pancreatic stent is often not feasible.[39] In the current endoscopic era, management of DDS has shifted from open surgery to minimally invasive endotherapy, though DDS is still more likely to require hybrid therapy, re-intervention, rescue surgery, and often results in a longer hospital stay.[40] Fluid collections with DDS are drained transmurally with plastic stents left in place indefinitely whereas external pancreatic fistulae with DDS usually require surgery or complex EUS guided interventions.[8,41]

Endotherapy in Recurrent Acute Pancreatitis

Recurrent acute pancreatitis (RAP) is defined as 2 or more episodes of acute pancreatitis with complete resolution of symptoms between episodes in patients with no evidence of chronic pancreatitis.[42] Recurrence occurs in 11–32% of patients with acute pancreatitis resulting in RAP.[43] Preventing recurrences is important because repeated episodes of AP can lead to chronic pancreatitis in almost one-third of patients.[42] Here, we will focus on the causes of RAP that can be treated endoscopically or endoscopy plays an important role in their management.

Biliary Etiology

Gall Stones

Indications of ERCP in gall stone-related pancreatitis have been discussed previously. EUS plays a very important role in the selection of patients for ERCP in cases of ABP that are at intermediate risk (abnormal LFTs and/or CBD dilation on Ultrasound) for persistent choledocholithiasis.[44]

Microlithiasis

Microlithiasis are gallstones < 3 mm in size and cannot be visualized on abdominal ultrasound. EUS offers the best modality to diagnose microliths with a sensitivity of 96%.[43] Laparoscopic cholecystectomy is an intervention of choice in these patients to prevent further episodes of AP. Endoscopic biliary sphincterotomy can be done if pancreatitis recurs after surgery and in those unfit for cholecystectomy.[45]

Tumors

Pancreatobiliary tumors are considered to be a less common but important cause of RAP and should be considered as a cause of AP in patients older than 50 years with no identifiable etiology. EUS is the most sensitive modality for diagnosing small peri-ampullary tumors, intraductal papillary mucinous neoplasm, and pancreatic tumors < 2 cm in size and should be part of the diagnostic algorithm for evaluation of idiopathic AP in the elderly.[43] EUS also permits obtaining cytological samples by fine-needle aspiration/biopsy. EUS plays an important role in staging ampullary lesions to determine the feasibility of endoscopic resection.

Choledochocele

A choledochocele is a cystic dilatation of the intraduodenal portion of the common bile duct which can present with RAP likely as a result of bile reflux into the pancreas. EUS can aid in accurate diagnosis and endoscopic sphincterotomy forms the current standard of treatment by unroofing the cyst and separating both biliary and pancreatic duct.[46]

Anomalous Pancreatobiliary Ductal Union (APBDU)

An elongated pancreatobiliary junction (common channel >1.5 cm) has also been associated with RAP. Pancreatitis in APBDU probably occurs due to bile reflux into the pancreatic duct. Treatment with sphincterotomy may prevent future episodes of AP but benefits are uncertain. Cholecystectomy is recommended in these patients owing to an increased risk of gallbladder cancer and frequent association with choledochal cyst.[44]

Pancreas Divisum

Pancreas divisum is the most common congenital anomaly of the pancreas and is seen in 5–14% of the general population. It results from failure of the dorsal and ventral pancreatic ducts to fuse during gestation.[43] The majority of patients with pancreas divisum are asymptomatic. Instead, only those with this anomaly and increased risk of pancreatitis due to coexisting disorder such as from genetic mutations (cystic fibrosis transmembrane conductance regulator), environmental exposures (alcohol, smoking), or associated morphologic abnormality such as a santorinicele, develop RAP.[44] In symptomatic patients with RAP, after a comprehensive evaluation, to rule out other causes of pancreatitis, endotherapy may be offered. ERCP with minor papilla sphincterotomy is the preferred endoscopic intervention to prevent recurrent attacks of AP.[47] After sphincterotomy, placement of a short-term dorsal PD stent is preferred to avoid the risk of pancreatitis and cicatricial strictures. The risk of post ERCP pancreatitis is greater in patients of pancreatic divisum without CP.[48] Evidence from most retrospective series report resolution of symptoms in 60–100% of patients post endotherapy.[45] A meta-analysis of 23 studies reported a pooled success rate of 67.5%; by subgroup, pooled success rates were 76% for RAP, 52.4% for CP, and 48% for pancreatic-type pain. These results show that endotherapy is most effective in patients of pancreatic divisum presenting with RAP.[49] A case series of seven patients from north India with RAP and pancreatic divisum reported long term symptomatic improvement after endoscopic papillotomy of minor papilla.[50]

Mariani et al analyzed 33 patients of RAP with pancreatic divisum with follow-up of up to 5 years and reported similar CP findings on EUS in patients post endotherapy and the observation group (63.2% and 57.1%). These results suggest a tendency to progress to CP persists even after successful endotherapy likely due to underlying genetic mutations in these patients.[51]

Sphincter of Oddi (SOD) Dysfunction

Type 1 and Type 2 SOD are relevant in the etiology of RAP. Type 1 SOD is associated with mild dilation of either CBD or PD or both due to persistent obstruction to bile or pancreatic outflow and diagnosed based on clinical findings. Type 2 SOD is associated with sphincter motor dysfunction without any ductal dilation and diagnosis requires secretin test or sphincter of Oddi manometry.[52] Involvement of both biliary and pancreatic sphincters is the most common form of involvement in SOD.[45] Endoscopic sphincterotomy is the first line of management in type 1 SOD and type 2 SOD with documented sphincter dysfunction. Biliary sphincterotomy can be attempted first with reported clinical improvement in 83–100% of patients with type 1 SOD and up to 80% in type 2 SOD with documented sphincter dysfunction. Endoscopic pancreatic sphincterotomy can be attempted if symptoms recur. A dual sphincterotomy is also an option but an RCT comparing biliary and dual sphincterotomy in patients with RAP and pancreatic SOD reported similar incidence in two groups with higher rates of RAP in the dual therapy group during the first 12 months period.[53] Short-term stenting or overnight nasopancreatic drainage is recommended to decrease the chances of pancreatitis following pancreatic sphincterotomy.[54] Re-stenosis requiring re-intervention is reported in 41.7% of patients in a retrospective analysis of 369 patients following pancreatic sphincterotomy for RAP or Pancreatic SOD.[55]

Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a rare cause of RAP (more common with type 2 than type 1). EUS can aid in its diagnosis via fine-needle biopsy.

Idiopathic Recurrent Acute Pancreatitis

No identifiable cause is found even after thorough laboratory evaluation, genetic tests, or imaging studies in 10–30% of patients with recurrent pancreatitis.[42] The diagnostic yield of EUS is 68–80% in patients with idiopathic pancreatitis with

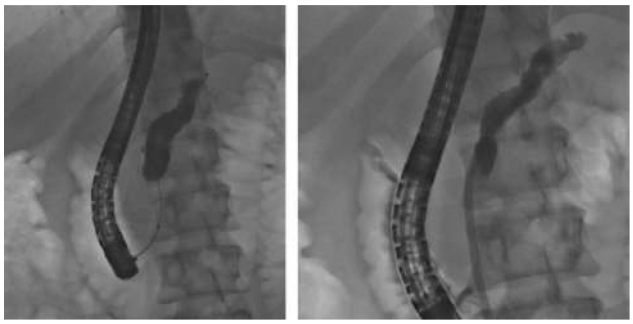

Fig. 2 (**A**) ERCP: Stricture in the head of the pancreas with an upstream dilated pancreatic duct. (**B**) Placement of a 10Fr plastic stent after dilatation of stricture with a balloon.

gall bladder in situ and a little lower in patients with the previous cholecystectomy.[56] Occult microlithiasis has been reported as the cause of Idiopathic RAP in up to 73% of cases.[45] EUS should be performed after the first episode of idiopathic pancreatitis, particularly if the patient has not undergone cholecystectomy or is > 40 years of age.[43,44,57]

Endotherapy in Chronic Pancreatitis

Pancreatic Ductal Endotherapy

PD strictures and/or stones in patients with chronic pancreatitis can result in recurrent abdominal pain by causing a ductal obstruction. Endoscopic therapy is usually considered as first-line therapy for interventional management of PD stricture and includes pancreatic sphincterotomy, followed by dilatation of stricture, extraction of pancreatic duct stones, and PD stent placement (►**Fig. 2**). Multiple options are available for dilatation of stricture, which includes balloon or Bougie dilators and Soehendra stent retriever or cystotome if the dilator cannot traverse the stricture

Fig. 3 Dilatation of the pancreatic duct stricture using the Soehendra stent retriever.

(►**Fig. 3**).[58,59] Plastic stents can be exchanged upon the recurrence of symptoms or on a scheduled basis. Single 10-Fr plastic stent across the dominant stricture is preferred to avoid multiple hospital admissions for pain as smaller stents are prone to occlusion. Multiple small studies have evaluated fully covered self-expandable metal stents (FCSEMS) for managing pancreatic duct strictures (►**Fig. 4**). A recent meta-analysis of ten studies with 163 patients reported a stricture resolution rate of 93% (95%CI 84–99%) with an overall rate of adverse events being 34.9% in patients with FCSEMS compared with a complication rate of 7.85% in patients with plastic stents.[60] Another meta-analysis comparing FCSEMS and multiple plastic stents in refractory PD stricture reported similar improvement in pain after stenting, risk of recurrence of pain after stent removal, and stricture resolution with a significantly higher risk of adverse events with FCSEMS.[61] Lack of long-term data and clinical experience of significantly high adverse events including development of new strictures warrants further evaluation and improvement in stent design before FCSEMS can be routinely recommended for pancreatic duct strictures.[58]

The number and location of ductal stricture are the major factors determining the success of pancreatic endotherapy. A single stricture in the head of the pancreas is an ideal candidate for pancreatic endotherapy compared with a patient with stricture in the tail of the pancreas or multiple ductal strictures. ERCP has a technical failure rate of 3–10% and the common reasons include failure of cannulation of the main pancreatic duct, tight non-negotiable strictures, pancreatic stones, or altered gastroduodenal anatomy (Whipple's procedure, Billroth II, Roux-en-Y gastric bypass). In such patients, EUS-guided PD drainage has evolved as a minimally invasive alternative to surgery.[58] EUS can facilitate a

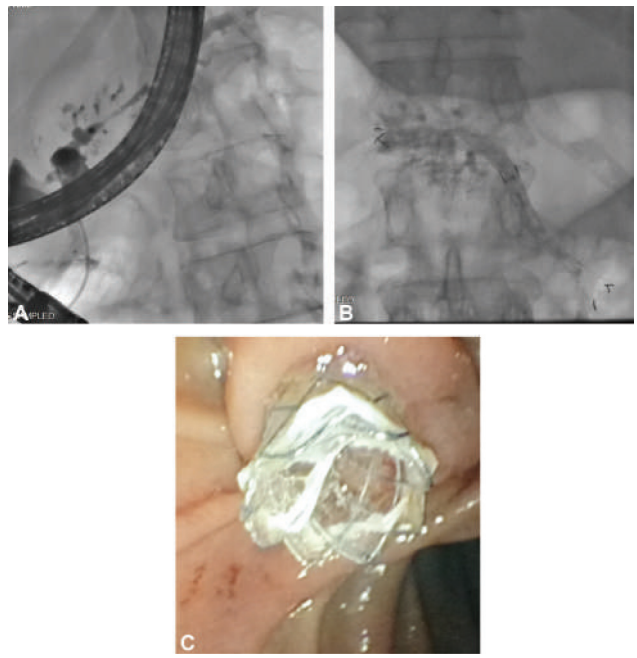

Fig. 4 (**A**) ERCP: Tight pancreatic duct stricture. (**B**) Placement of fully covered SEMS across the ductal stricture. (**C**) Fully covered SEMS across the papilla.

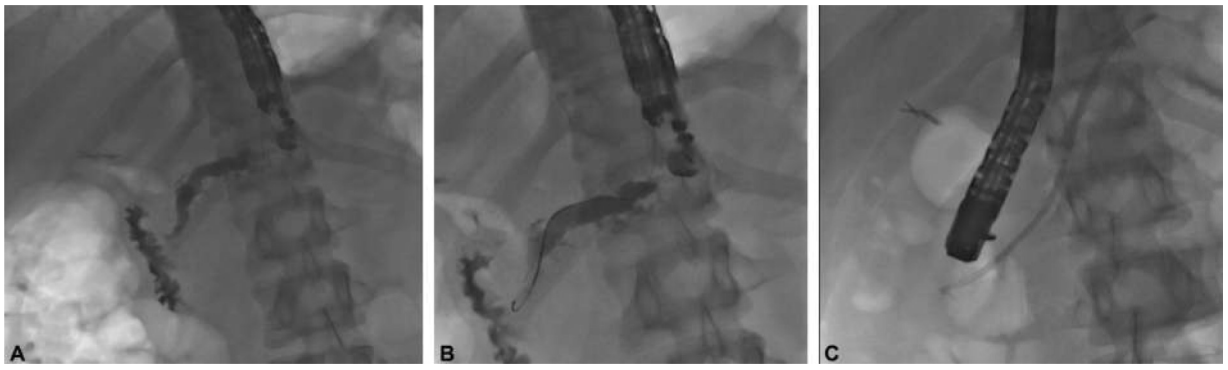

Fig. 5 (**A**) EUS-guided rendezvous: pancreatogram obtained after puncturing of the pancreatic duct. (**B**) Guidewire being negotiated across the stricture in the pancreatic duct. (**C**) A stent placed after exchanging the echoendoscope with a duodenoscope.

rendezvous procedure (►**Fig. 5**) or provide transgastric or transduodenal pancreatic duct stent placement.[58]

Pancreatic sphincterotomy and stone retrieval can rarely be achieved using standard biliary stone removal techniques, as the pancreatic duct stones are usually calcified and hard. Moreover, they are either usually impacted within side branches or are upstream to coexistent PD strictures making endoscopic removal difficult. Extracorporeal shockwave lithotripsy (ESWL) can be used to fragment stones prior to endoscopic removal and is usually recommended for clearance of radiopaque obstructive main pancreatic stones larger than 5 mm located in the head/body of the pancreas.[62] Factors predicting failure of ESWL include stone in the tail, extensive calculi throughout the pancreas, PD stricture, and early post-ESWL (<2 days) ERCP attempt. The overall complication rate with ESWL is around 6% and the most common complication is pancreatitis.[63] EHL (Electrohydraulic lithotripsy) and LL (Laser lithotripsy) under pancreatoscopic guidance has also been used to fragment and remove obstructing stones as rescue therapy or as first-line therapy when ESWL is not available.[64] A recent meta-analysis on the efficacy of peroral pancreatoscopy (POP) for pancreatic duct stones using these two techniques (Ten of included studies reported outcomes on POP using EHL and 8 studies reported outcomes on POP using LL) demonstrated technical and clinical success rates of 76.4% and 76.8% respectively with POP.[65] Therefore limited data suggest it to be viable and effective option for management of pancreatic duct calculi in chronic pancreatitis.[64]

Endotherapy is associated with higher clinical and technical success rates in patients with a single stricture, stone less than 1 cm in size, 3 or fewer stones in number, and disease limited to the head or proximal body of the pancreas.[58] Recent ESGE guidelines suggest endoscopic therapy and/or ESWL as the first-line therapy for painful uncomplicated chronic pancreatitis with an obstructed main PD in the head or body of the pancreas.[62]

Pseudocyst

The endoscopic approach for the management of pseudocyst associated with chronic pancreatitis is similar to that for acute pseudocyst discussed in the previous sections. However underlying ductal abnormalities may lead to recurrences if left untreated and downstream pancreatic ductal obstruction from stones or fibrotic strictures should be endoscopically managed to prevent recurrences. Pancreatic pseudocysts occurring at atypical locations such as in the kidneys, liver, and spleen can also be treated endoscopically.[66–68]

Celiac Plexus Block

EUS guided Celiac Plexus Block (CPB) involves the injection of an anesthetic with a steroid into the celiac plexus region or directly into the celiac ganglia. Higher clinical success rates were reported in a randomized study from India after EUS-CPB as compared with percutaneous CPB.[69] Despite being considered safe, the long-term efficacy and duration of pain relief following CPB are limited. Also, central sensitization in CP patients renders CPB less effective for pain control.[8]

Biliary Strictures

Recurrent inflammation and fibrotic process within the pancreatic head can encase the distal bile duct and result in the formation of a distal biliary stricture which can lead to cholangitis and secondary biliary cirrhosis. Pancreatic calcification in CP renders them more refractory to endoscopic therapy as compared with other benign biliary strictures.[70] Malignancy should always be excluded in this setting before planning any therapy. Persistent asymptomatic elevation of alkaline phosphatase or jaundice for more than 1 month should be taken as an indication of endoscopy therapy as edema or associated PFC's usually resolved in this time frame and waiting any longer will increase chances of secondary biliary cirrhosis which is relatively frequent.[62]

Balloon dilation and endoscopic guided insertion of multiple plastic stents or a fully covered self-expandable metal stent (SEMS) across the biliary stricture is the first line of treatment. An RCT in CP patients showed that six 10 Fr plastic stents placed sequentially in 2 sessions every 3 months (3 stents at a time) and a fully covered 10 mm SEMS provided similar success rates (88.0% versus 90.9%, respectively) at 2 years after stent removal (Stent duration 6 months) with similar treatment-related morbidity.[71] Plastic biliary stents are usually placed in a sequential manner in increasing

numbers over 1 year, with stent exchanges every 3–4 months. The scheduled duration of a metallic stent is usually kept as 6–12 months. A recent international multicenter study showed the placement of a single FCSEMS for 10–12 months results in good long-term results in patients with benign biliary strictures and with an acceptable safety profile even 5 years after stent placement.[72] Available data supports the use of fully covered SEMS as a first-line option over plastic stents. Failure of stricture to resolve after 12 months or three endoscopic procedures is considered an indication for surgery. The presence of associated inflammatory mass is an indication for early surgical referral.[73]

Pancreatic Duct Leaks

PD leaks may occur as a complication of pancreatitis (acute or chronic), trauma as well as after pancreatic surgery.[74] Indwelling surgical drains can control most PD leaks following pancreatic surgery. Many of these leaks will close over time, and endoscopic therapy is generally reserved for refractory or persistent PD leaks.[75]

In the setting of a large PFC, transmural drainage may be undertaken, with or without concomitant transpapillary therapy.[76] In the absence of any PFC, transpapillary PD stent placement to promote internal drainage is usually sufficient to heal the duct disruption.[77]

Endotherapy in Pancreatic Cancer

Obstructive Jaundice

ERCP-guided biliary drainage (BD) is considered the first line modality for palliation of malignant biliary obstruction. In addition to failed biliary cannulation, duodenal infiltration of pancreatic tumor can be encountered leading to failure of ERCP guided BD.[78] EUS-guided biliary drainage (EUS-BD) is now being utilized in the management of biliary obstruction with failed ERCP as an alternative to percutaneous transhepatic biliary drainage (PTBD). In a systematic review, EUS-BD had better clinical success (odds ratio, 0.45; $p = 0.02$), similar technical success (odds ratio, 1.78; $p = 0.25$) and lesser adverse events (odds ratio, 0.23; $p < 0.0001$) as compared with PTBD.[79] However, it is still unclear whether EUS-BD can adversely affect clinical outcomes, either oncologically or surgically in patients with resectable or borderline resectable cancers, and therefore the decision to proceed with EUS BD in such cases requires consultation among a multidisciplinary team.[80]

Gastric Outlet Obstruction

Gastric outlet obstruction (GOO) due to duodenal invasion by a pancreatic tumor can be seen in 15 to 20% of patients. Endoscopic placement of an uncovered SEMS is an effective method of palliation, with a more rapid return of oral intake but with an increased risk of occlusion and need for re-intervention as compared with bypass surgery. EUS guided gastroenterostomy (GE) whereby the stomach is anastomosed to the duodenum or jejunum using a LAMS is a newer nonsurgical intervention for the palliation of GOO. A retrospective cohort study from single-center analyzed patients with GOO who underwent EUS-GE or open gastrojejunostomy (OGJ) and reported reduced hospital costs, shorter hospital stay and quicker institution to the resumption of oral intake and chemotherapy with EUS-GE.[81]

Endoscopic-guided Radiofrequency Ablation

Endoscopic radiofrequency ablation (RFA) is a minimally invasive approach used for tumor ablation. Radiofrequency-induced hyperthermia causes coagulative necrosis of tumor tissue and a recent meta-analysis on the use of RFA for treatment of locally advanced unresectable pancreatic adenocarcinoma and other pancreatic tumors like neuroendocrine tumors has shown EUS-RFA to have high technical (100%) and clinical (91.5%) success rates.[82] Re-canalization of biliary or pancreatic duct obstruction by unresectable tumors using RFA with subsequent stent placement has been successfully achieved with reported prolonged stent patency.[83]

EUS-Guided Fine-Needle Tattooing

Preoperative EUS-guided fine-needle tattooing (EUS-FNT) helps in the accurate localization of pancreatic tumors during surgery and is being increasingly used for patients with lesions in the distal pancreas. A retrospective cohort study comparing EUS-FNT followed by laparoscopic distal pancreatectomy (LDP) and LDP alone reported that preoperative EUS-FNT was safe and feasible, with shorter operative time and led to R0 resection in all patients without any complications.[84]

EUS-guided Fiducial Placement

EUS guided fiducial placement is safe and effective in patients with borderline resectable, locally advanced, and metastatic pancreatic cancer patients who have been undergoing radiation therapy as it improves the accuracy of target delineation and reduced radiation exposure. Recent international guidelines on the management of pancreatic adenocarcinoma (NCCN version 1.2020) have recommended placement of 1–5 (preferably ≥ 3) gold fiducial markers preferentially by EUS in patients with localized pancreatic cancer (resectable, borderline, and locally advanced) for targeted radiotherapy.[85] New preloaded needles appear to reduce the procedure time along with the reduced risk of needle stick injuries compared to the traditional back-loaded needles.[86]

Role of Endotherapy in Management of Pancreatic Cystic Lesions

Pancreatic protocol CT and MRCP along with clinical context are usually sufficient for accurate diagnosis of pancreatic cystic lesions. EUS can be utilized as third line tool in remaining cases.[87] EUS FNA is not routinely recommended for pancreatic cystic lesions in view of low diagnostic yield and risk of tumor seeding which despite being rare is a

matter of serious concern. Therefore, EUS FNA should be done only when it could change management.[88] Analysis of molecular DNA markers and use of micro forceps biopsy devices for sampling are recent methods that have shown great promise in improving preoperative diagnostic yield of EUS FNA.[89]

Molecular DNA markers specific to the type of pancreatic cysts are evaluated which increases the diagnostic yield of the aspirated sample. The microforceps or through the needle biopsy device pass through standard 19 G EUS FNA needle to obtain targeted tissue samples under direct EUS vision. This method is feasible for even small pancreatic cysts irrespective of location. A meta-analysis of 8 studies (mostly restrospective and small sample size) comparing both these techniques with surgical pathology specimen as reference standard has shown that microforceps biopsies led to a high diagnostic yield (73%) and a high rate of correctly identifying cyst subtypes (70.7%).[90]

EUS guided pancreatic cystic ablation can be performed with alcohol-free chemoablation or radiofrequency. Typical indications for ablative therapy are not well defined but it can be considered for patients with branch duct IPMN and mucinous cystadenoma (2–6 cm) who are not candidates for surgery with good life expectancy or in patients refusing surgery.[91] Multi-agent chemoablation regimens containing both paclitaxel and gemcitabine have shown encouraging results with an overall complete response rate of 64% at 12 months.[92] A large prospective multicenter study analyzed outcomes of EUS-RFA in 17 patients of pancreatic cystic neoplasms (mean size 28 mm, range 9-60 mm). They reported a significant response rate of 71% (11 complete disappearances and 1 showing > 50% decrease in diameter) with all 12 mural nodules showing complete resolution.[93]

Role of Endotherapy in Management of pNET

Pancreatic NETs are rare, accounting < 2% of all pancreatic tumors, and are usually diagnosed incidentally. EUS guided ablation therapies are promising options for nonfunctioning NETs and insulinomas measuring < 2 cm.[93,94] Ablation can be achieved with alcohol or RFA. In the largest case series of 11 patients with 14 tumors (4 insulinomas and 10 nonfunctional tumors) by Park et al,[95] 7/13 patients had a complete response after 1 session and 2 patients with insulinomas became asymptomatic with alcohol ablation. The risk of pancreatitis can be minimized by avoiding excess ethanol injection and keeping the needle in tumor tissue. A prospective multicenter study evaluated EUS RFA in 14 NETs and reported a complete resolution rate of 86% at 1 year with delayed response in 3 patients possible due to stimulation of immune response by release of antigens from necrotic tissue.[93] Adequate prophylaxis (antibiotics and rectal NSAIDS) decreases post-procedure complication rates. RFA provides more controlled ablation as compared with alcohol and is therefore safer. However, long-term outcomes are still pending and also surveillance protocols after ablation are not well defined.[96]

Conclusions

Advancements in interventional techniques have put endoscopy at the forefront of the management of pancreatitis and its complications. The advent of interventional EUS has further expanded the scope and indications of pancreatic endotherapy along with considerable reductions in adverse events. The further development and refinement of EUS dedicated stents will expand the indications of pancreatic endotherapy.

Conflict of Interest
None declared.

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