Chapter

Endoscopic Management of Acute and Chronic Pancreatitis

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Abstract

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas, representing one of the most frequent causes of admission to hospital for gastrointestinal diseases in Western countries. Gallstones and alcohol play a fundamental role in the etiology of AP, but several other factors are involved, such as drugs, viruses, trauma, autoimmunity, anatomical anomalies. Chronic pancreatitis (CP) is a chronic inflammatory and fibrotic disease of the pancreas, in the pathogenesis of which both environmental factors, such as alcohol abuse and smoking, and genetic ones (SPINK1, CFTR, PRSS1 mutations) contribute. Endoscopic techniques are commonly used in the management of acute and chronic pancreatitis, allowing in many instances the avoidance of surgical intervention in acutely or chronically ill patients. This advantage is best represented by endoscopic removal of biliary stones in acute gallstone pancreatitis. Furthermore, also peripancreatic collections, such as pseudocyst or walled-off necrosis, can be managed endoscopically, ensuring a minimally invasive drainage. In CP endoscopy has a diagnostic role, especially in the early stages of the disease, but above all therapeutic, in the management of pancreatic duct strictures or stones. Other fields amenable to endoscopic intervention include treatment of potential causes of recurrent AP, such as sphincter of Oddi dysfunction and pancreas divisum.

Keywords: ERCP, EUS, walled-off necrosis, pseudocyst, acute pancreatitis, chronic pancreatitis

1. Introduction

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas that may involve peripancreatic tissues and/or other remote organs, as part of a systemic inflammatory syndrome. It represents one of the most common causes of hospitalization for gastroenterological disorders [1].

The course of AP can be variable, with most patients showing a mild self-limited disease, requiring only supportive treatment. However, some patients still have a severe course, with a mortality rate of 10–20% [2]. Even if many factors, as intensive care unit intervention and early recognition and treatment of complications, have reduced mortality from AP over the past 20 years, the management of this disease remains challenging.

Indication	Endoscopic therapy
Pain	
Pancreatic stone	ESWL, ERCP, per-oral pancreatoscopy (laser or electrohydraulic lithotripsy)
Pancreatic stricture	Stents (plastic or FCSEMS), EUS-guided drainage
Celiac plexus block	EUS-guided
Complication	
Biliary stricture	Stenting (multiple plastic stenting or FCSEMS)
Pseudocyst	Endoscopic drainage (EUS-guided, transpapillary, or combined)
Pancreatic duct leak	Transpapillary stenting
Vascular complications (gastric varices, pseudoaneurysm)	EUS-guided coil-glue, thrombin injection

ESWL, extracorporeal shock wave lithotripsy; ERCP, endoscopic retrograde cholangiopancreatography; FCSEMS, fully covered self-expandable metal stent; EUS, endoscopic ultrasonography.

Table 1.
Indications and endoscopic modalities in chronic pancreatitis.

The aims of endoscopy in AP include investigation and treatment of the causal factors and management of local complications, such as organized pancreatic necrosis, ductal disruption, and pseudocysts.

Chronic pancreatitis (CP) is a syndrome characterized by chronic progressive pancreatic inflammation, fibrosis, and scarring, resulting in damage and loss of exocrine (acinar), endocrine (islet cells), and ductal cells [3].

Pain is the predominant symptom observed during the course of CP. The etiopathogenesis of pain in CP is multifactorial and includes not only ductal hypertension due to obstruction of the pancreatic duct (PD) (calculi or stricture) but also neuropathy, peripheral sensibilization, and local or systemic complications (pseudocyst or distal biliary obstruction) [4]. Both pain intensity and frequency of pain attacks reduce quality of life in patients with CP.

Endoscopic therapy in painful CP is based on the rationale that pain is related to an overflow obstruction of the main pancreatic duct (strictures or pancreatic intraductal stones): the mainstay of endoscopic treatment includes decompression of pancreatic duct with stents (plastic or metal stent) in those with stricture(s), and fragmentation of pancreatic duct stone(s) using endoscopic retrograde cholangiopancreatography (ERCP) and/or in combination with extracorporeal shock wave lithotripsy (ESWL). This is the reason why only selected cases of patients with CP are amenable to endoscopic treatment.

Endoscopic ultrasonography (EUS) has emerged as a complementary endoscopic modality in the management of CP as well as associated complications like pseudocysts, refractory pain, and vascular complications (**Table 1**).

2. Acute pancreatitis

2.1 Endoscopic management of acute biliary pancreatitis

In Western countries, gallstone represents the first cause of AP, accounting for almost half of the cases, affecting middle-aged people, especially women [5].

The pathogenic mechanism by which gallstones determine AP is a temporary obstruction of the main pancreatic duct. Biliary AP should be suspected in presence of elevated liver function tests (LFTs) within 24–48 hours of the onset of symptoms, with alanine aminotransferase (ALT) >3× upper limit of normal having a 95% positive predictive value for AP. Nevertheless, its negative predictive value is only 50%. Aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin have both low sensitivity and negative predictive value [6].

Most patients with biliary AP have a mild-to-moderate disease course, benefiting from conservative management. The majority of common bile duct (CBD) stones causing biliary AP are small (≤5 mm), and their spontaneous passage into the duodenum occur in 80% of cases, with no need for endoscopic intervention. Magnetic resonance imaging (MRI) or EUS is requested to exclude the presence of CBD stones, prior to ERCP. While the utility of EUS in identifying the cause of AP after the acute attack is well established, data regarding the role of EUS during hospitalization for AP are limited. In presence of AP edema of the duodenal wall, pancreatic and peripancreatic inflammation, fluid or necrotic collections make difficult the study of pancreatic parenchyma, gallbladder, and biliary tree. Thus, EUS aimed to identification of small pancreatic cancer or early changes of chronic pancreatitis must be avoided. On the contrary, EUS could be useful in the diagnosis of choledocholithiasis due to its higher sensitivity compared to MRCP for small CBD stones (<5 mm). In those patients with AP and intermediate risk of CBD stones, EUS may avoid unnecessary ERCP [7, 8].

Guidelines recommend against urgent ERCP (within 48 hours) in AP, especially in case of severe disease, unless in presence of cholangitis or ongoing/worsening biliary obstruction. However, if choledocholithiasis is confirmed, ERCP with biliary sphincterotomy and stones extraction should be performed during the index hospitalization, in order to reduce the rate of readmission for a new episode of biliary AP. If CBD has been completely cleared from stones during ERCP, biliary stenting is not routinely indicated before cholecystectomy. In cases of acute suppurative cholangitis, when smaller contrast injection and shorter procedural time, due to bad clinical status of the patient, are required, placement of a biliary stent can ensure adequate drainage, waiting to be able to perform biliary stone extraction. In patients with large bile duct stones, endoscopic large balloon dilation after sphincterotomy is suggested [9].

In case of mild biliary AP, same-admission cholecystectomy or early cholecystectomy (within 2–4 weeks from the onset of AP) is recommended, to avoid recurrence of AP [10].

2.2 Endoscopic management of acute pancreatitis associated with congenital variants

2.2.1 Pancreas divisum

Pancreas divisum (PD) represents the most frequent congenital pancreatic malformation, resulting from a failure of the fusion between dorsal and ventral pancreatic ducts during the second month of fetal life, with preferential pancreatic juice outflow via the dorsal pancreatic duct through the minor papilla. PD is defined as complete if no communication between the ventral and dorsal ducts is visible, incomplete if communication remains. The prevalence of PD in caucasian population is about 5–10%, and more than 95% of these patients are asymptomatic, with incidental diagnosis on abdominal imaging [11].

PD has long been regarded as a predisposing factor to AP, but studies conducted on individuals with recurrent AP showed that the comparable AP incidence between

patients with PD and those with normal ductal anatomy. PD is, infact, a co-factor which in association with certain genetic mutations of serine protease inhibitor Kazal type 1 (SPINK1) gene, cystic fibrosis transmembrane conductance regulator (CFTR) gene, and chymotrypsin C (CTRC) gene increases the risk of AP [12]. Other additional factors that can determine AP in PD are the presence of stenosis of the minor papilla or santorinicele, which consists in cystic dilatation of the distal dorsal duct just proximal to the minor papilla [13].

ERCP is the gold standard for diagnosis of PD, but it is not used as a diagnostic method, given its invasiveness and the high accuracy of magnetic resonance pancreatography after secretin injection (s-MRCP) [14]. EUS shows also a high diagnostic accuracy for PD with a sensitivity of 87–95%, with absence of a "stack sign," i.e., the parallel alignment of distal CBD, ventral pancreatic duct and portal vein, presence of a "crossed duct sign," which is given by the crossing of dorsal pancreatic duct over the bile duct anteriorly and superiorly [15].

In asymptomatic patients with incidental diagnosis of PD therapeutic measures are not required, reserving them for those with recurrent attacks of AP, even if of mild entity, or those who had one attack of severe AP in absence of other identifiable causal factors. Also the presence of santorinicele with large main pancreatic duct could be an indication for treatment. Endoscopic therapy includes minor papilla endoscopic sphincterotomy (mPES) and minor papilla orifice balloon dilation. Given the high risk of post-ERCP AP associated with both these procedures, placement of a prophylactic temporary pancreatic stent is advisable [16].

2.2.2 Other congenital variants

Anomalous pancreatobiliary union (ABPU) affects 1.5–3% of individuals, and it consists in the union of the pancreatic and bile ducts outside the duodenal wall, resulting in a longer common channel (more than 15 mm proximal to the duodenum) that promotes reflux of bile and pancreatic juice into the alternative duct. Therefore, stones, protein plugs, or sphincter of Oddi dysfunction can cause temporary obstruction to pancreatic flow. All these factors determine an increase of pancreaticobiliary intraductal pressure, leading to AP [17]. AP is reported in 3–31% of APBU patients, and it is generally mild and self-limiting. Endoscopic sphincterotomy may decrease the risk of AP in these patients [18].

Choledochocele is a rare congenital or acquired condition, consisting in dilatation of the intraduodenal segment of the CBD. In these patients, AP occurs when the cystic dilatation or its content (sludge or stones) causes obstruction of the pancreatic duct outflow. Endoscopic sphincterotomy in order to unroof the choledochocele is recommended [19].

2.3 Endoscopic management of acute idiopathic pancreatitis

Recurrent AP is defined by the occurrence of two or more episodes of AP. Etiological diagnosis of AP is achieved in 70–90% of cases. Minimal diagnostic workup during a first episode of acute pancreatitis is suggested by guidelines and includes detailed personal history, family history, physical examination, laboratory tests (i.e. liver enzymes, calcium, and triglycerides), and transabdominal ultrasound (US) [20]. If etiology cannot be determined using this workup, AP is defined idiopathic, and this occurs in around 10–30% of cases [21].

There are several causes of AP that may be missed with this workup, and thus further diagnostic modalities, such as MRCP and computed tomography (CT), should be

considered to rule out the presence of ductal adenocarcinoma or intraductal papillary mucinous tumors, or autoimmune pancreatitis. EUS may identify an etiology in 61% idiopathic AP, mainly represented by microlithiasis or sludge [22]. Also early chronic pancreatitis could be diagnosed with EUS, as possible cause of recurrent AP. When no etiologic factors are identified, sphincter of Oddi dysfunction should be suspected. ERCP with sphincter of Oddi manometry is the gold standard diagnostic test, but it is associated with significant morbidity [23]. At present, ERCP with sphincterotomy represents the treatment of choice for patients with structural or functional stenosis of the sphincter of Oddi, with reports of 70–90% resolution of symptoms [24].

2.4 Endoscopic management of acute pancreatitis complications

2.4.1 Pancreatic fluid collections

Pancreatic fluid collections (PFCs) are a frequent complication of AP, and their correct classification is important to guide the management. In 2012, an international working group has modified the Atlanta classification for AP, introducing new terminology for PCFs, which are classified according to the time elapsed since the collection was formed and to the presence or absence of necrosis. Acute collections in the first 4 weeks are called acute necrotic collections (ANCs) if necrosis is present or acute peripancreatic fluid collections (APCs), in absence of necrosis. After 4 weeks, when a capsule develops, persistent acute peripancreatic fluid collections are called pseudocysts and acute necrotic collections are called walled-off necrosis (WON) (**Figure 1**) [25]. The majority of APC resolve spontaneously and only a 5–15% of them transform into pseudocyst. On the contrary, half of ANC become WON. 16–47% of pancreatic necrosis get infected [26, 27].

PFCs drainage is recommended in presence of symptoms and/or complications such as abdominal pain, gastrointestinal obstruction, vascular compression, biliary obstruction, or infection. Size alone is not an indication for treatment. Historically, drainage has been performed via surgical techniques. However, in the last decade,

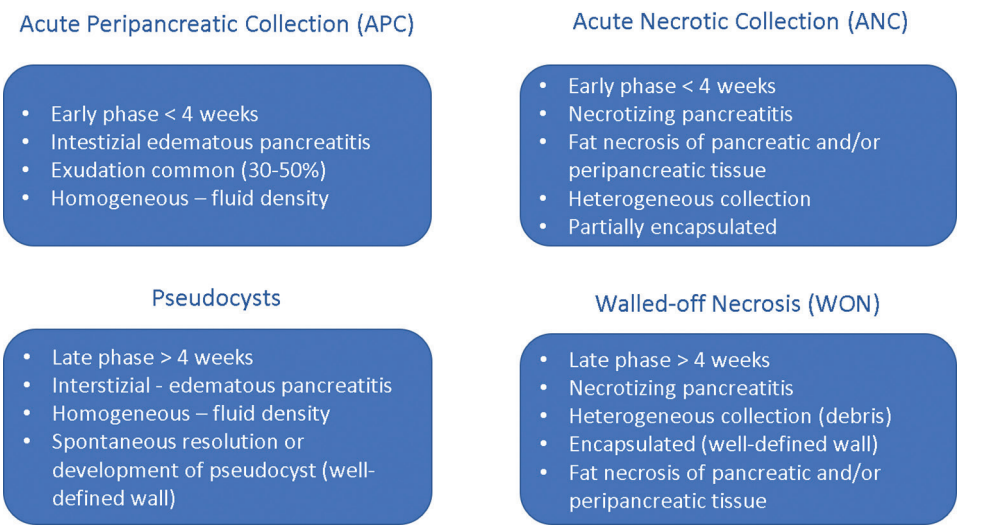

Figure 1.
Pancreatic fluid collections.

thanks to new and advanced endoscopic tools and expertise and consequent reduction in health care costs, minimally invasive endoscopic drainage has become the preferable approach [28].

The first conventional endoscopic transmural drainage of PFCs consisted of endoscopic visualization of PFC bulge in the gastric wall, creation of a fistulous tract between PCF and gastric lumen with a seldinger technique, insertion of a guidewire into the PFCs cavity, dilation of the tract, and, finally, deployment of one or more plastic stents to secure apposition of the lumens and continuous drainage [29]. A nasocystic catheter was generally performed to promote liquefaction of the debris and improve drainage. Infusion of hydrogen peroxide (H_2O_2) facilitated dislodgement and removal of necrotic debris. Adverse events, even if rare, such as bleeding, perforation, and self-limited pneumoperitoneum, have been reported [30]. To remedy the suboptimal drainage efficiency of plastic stents, especially in WON, covered biliary metal stents were used for this purpose. However, they were associated with complications, such as migration, erosions, or ulceration over gastric or retroperitoneal side and difficulty in performing necrosectomy [31].

Recently, a new dedicated bi-flanged lumen apposing metal stent (LAMS) has been introduced for EUS drainage of PFCs. LAMS has been specifically designed to create an anastomosis between the cyst cavity and the gut lumen. At first, the insertion of a guidewire inside the collection by a standard 19G FNA needle was necessary to release the stent. Subsequently, a new device in which the LAMS is equipped with an electrocautery-enhanced delivery system avoided the use of multiple accessories to achieve the drainage. Different diameters are available for these stents [32]. Published data report that, compared to plastic stents and fully covered metal biliary stents, LAMS determines an earlier resolution of PFCs. They are associated with increased costs and, in the first published series, with increased risk of adverse events, in particular pseudoaneurysm-related bleeding [33]. Recent studies have shown that earlier removal of LAMS, within 3 weeks from stent placement, significantly reduces the frequency of bleeding complications, with same rate of adverse events of plastic stents. Finally, recent scientific literature supports the use of LAMS for drainage of PFCs, mostly because they make possible to access the WOPN cavity with a standard gastroscope, after dilatation of the cysto-gastric tract with a balloon, to perform lavage and direct endoscopic necrosectomy (DEN) [34]. Hydrogen peroxide plus normal saline is used for the lavage of the cavity, and then necrotic debris is removed under direct vision using snares or baskets. Several sessions may be necessary to achieve complete DEN.

2.4.2 Disconnected pancreatic duct syndrome

In severe AP, necrosis of the pancreatic parenchyma may cause loss of integrity of the pancreatic duct, determining duct disruption, i.e., a partial interruption of the duct integrity, or its disconnection, i.e., a circumferential interruption of the duct. This leads to extraductal and extrapancreatic leakage, which can be complicated by recurrent PCFs and their possible infection, or pancreatic fistulas [35].

The diagnosis of disconnected pancreatic duct syndrome (DPDS) is usually delayed, given a lack of awareness on the topic, resulting in increased morbidity, cost of treatment, and duration of hospital stay. Surgery has been for long time the best approach for the management of DPDS, consisting of either resection or internal drainage procedures. Anyway, in the setting of a severe AP, surgery is often difficult due to presence of local inflammation and vascular alterations, as extensive venous collaterals consequent to splenic vein thrombosis [36]. With recent advancements, endoscopy offers new

minimally invasive therapeutic options for the management of DPDS. When a co-existent PFC is present, endoscopic approach consists of EUS-guided transmural drainage. In DPDS without a co-existing PFC, surgery is the best option as endoscopy cannot ensure internal drainage of the secretions of disconnected pancreas. Transpapillary drainage in patients with is effective only in patients with partial pancreatic duct disruption that can be bridged with the positioning of a stent. In complete disruption of pancreatic duct, bridging with pancreatic stent is often not feasible [37].

3. Chronic pancreatitis

3.1 Endoscopic diagnosis of chronic pancreatitis

Diagnosis of CP derives from a combination of clinical symptoms, as abdominal pain, malabsorption, diabetes mellitus, and pancreatic function tests, as fecal elastase and morphological pancreatic abnormalities, and as calcifications, atrophy, ductal dilatation or strictures, and pseudocysts. At advanced stages of the disease, when both symptoms and morphological alterations are present, reaching the diagnosis is generally easy. On the contrary, it is much more challenging in earlier stages, given both to the low sensitivity and specificity of usual diagnostic methods and to the absence of a widely shared definition of early CP. According to a recent consensus, the term "early" describes the disease state rather than the disease duration; thus, it refers to a condition in which features of advanced CP are lacking [38].

Imaging has a fundamental role in the diagnosis and therapeutic management of patients with CP, and the most frequently used imaging modalities for CP are EUS, ERCP, MRI, computed tomography (CT), and abdominal ultrasound (US). EUS and ERCP showed the highest sensitivity (81 and 82%, respectively) and specificity (90 and 94%, respectively) [39]. Nevertheless, guidelines recommend using US, CT, and MRI as first imaging diagnostic approach, due to their larger availability and noninvasiveness, reserving EUS only to cases in which cross-sectional imaging is not conclusive [40]. ERCP should be used for therapeutic purposes only.

EUS diagnosis of CP is based on the assessment of ductal and parenchymal morphologic features, which correspond to histopathological changes. They initially embraced 11 criteria, then become 9, which are summarized in **Table 2**. In the absence of any criteria, a diagnosis of chronic pancreatitis is unlikely, whereas when five or more criteria out of nine are present, chronic pancreatitis is likely [41].

Since the different pathological characteristics in CP have not the same importance in terms of diagnostic value, the "nine criteria classification," giving to each criterion the same relevance, has not a high diagnostic accuracy. Thus, another scheme,

Parenchymal abnormalities	Ductal abnormalities
Hyperechoic foci with and without shadows	Stones in the duct
Hyperechoic strands	Duct irregularity
Cysts	Main duct dilation
Honeycomb-like lobulation	Visible side branches
	Hyperechoic contours on the main duct

Table 2.
Nine classic criteria for establishing a diagnosis of chronic pancreatitis on EUS.

Major A criteria:
• Hyperechoic features with shadowing
• Main pancreatic duct calcifications
Major B criteria:
• Lobularity with honeycombing
Minor criteria
• Lobularity without honeycombing
• Hyperechoich features without shadowing
• Pseudocysts
• Stranding
• Irregular main pancreatic duct
• ≥ Dilated duct branches
• Main pancreatic duct dilation
• Hyperechoic main pancreatic duct wall

Table 3.
The Rosemont classification for endoscopic ultrasound-based criteria for the diagnosis of chronic pancreatitis.

named Rosemont classification, proposed by the International Consensus, divides parenchymal and ductal criteria in major and minor features. Major criteria for CP are hyperechoic foci with shadowing and main pancreatic duct (PD), calculi and lobularity with honeycombing. Minor criteria for CP are cysts, dilated ducts, irregular pancreatic duct contour, dilated side branches, hyperechoic duct wall, strands, non-shadowing hyperechoic foci, and lobularity with noncontiguous lobules (**Table 3**) [42]. Basing on these consensus criteria, the EUS diagnosis could be consistent with CP, suggestive of CP, indeterminate for CP or normal (**Table 4**).

3.2 Endoscopic management of obstructive pancreatic ductal stone

Pancreatic stones seem to arise either as direct and evenly calcified stones or as radiolucent protein plugs that may or may not become calcified during the course

Consistent with CP
A. 1 major A feature (+) ≥ 3 minor features
B. 1 major A feature (+) major B feature
C. 2 major A features
Suggestive of CP
A. 1 major A feature (+) <3 minor features
B. 1 major B feature (+) ≥3 minor features
C. ≥5 minor features (any)
Indeterminate for CP
A. 3 to 4 minor features, no major features
B. Major b features alone or with <3 minor features
Normal
≤ 2 minor features, no major features

Table 4.
EUS diagnosis of CP on the basis of consensus criteria.

of the disease [43]. The majority of pancreatic stones are calcified and radiopaque. Their prevalence increased with time and was detected in approximately 62% of patients with CP [44]. The best candidates for the successful treatment of painful CP are patients with solitary stones, with distal obstruction of the main pancreatic duct (located in the pancreatic head), and with a mean size of 10 mm and associated with strictures [4, 45].

ERCP and extraction are recommended for smaller (< 5 mm), nonimpacted stones of the main pancreatic duct [46]. ERCP can achieve main pancreatic duct drainage by sphincterotomy of the major and/or minor papilla, by short-term stent placement, or by pancreatic stone extraction using basket or balloon. Endoscopic therapy is also preferable in patients with risk factor (older age, co-morbidities) instead of surgery.

ESWL is recommended for fragmentation of large (> 5 mm), radiopaque stone(s) located preferentially in the pancreatic head [45]. For radiolucent calculi (difficult to target with X-ray), a nasopancreatic tube can be placed to facilitate targeting of the stones during ESWL [47].

Endoscopy alone allows stone extraction in a minority of CP patients (9–14%) [48, 49]; ESWL prior to endoscopy therapy allowed extraction of pancreatic stone in >80% of patients after failed stone extraction at primary endoscopy [48]. Pancreatic mechanical lithotripsy is burdened by major complications compared to biliary mechanical lithotripsy, and these included trapped or broken basket, traction wire fracture, and pancreatic ductal leak.

Pancreatic stone fragmentation after ESWL is obtained in 90% of patients (after multiple sessions) [50].

In a recent meta-analysis, ESWL alone allowed complete/partial main pancreatic duct clearance in 70%/22% of patients, respectively; pain was absent or mild–moderate during the 2 years following treatment in 52.7% and 33.4% of patients, respectively; quality of life improved in 88.2% of patients [51].

ESWL in not free from complications: most frequent is pancreatitis (up to 4.2%). The most severe complications are infection, acute stone incarceration in the papilla, bleeding, and perforation. Other minor adverse events reported are asymptomatic hyperamylasemia, hematuria, gastrointestinal mucosal injury, skin erythema, and tenderness in the region of contact with the shockwave head [52].

The systematically addition of endoscopic therapy after ESWL is not recommend by the European Society of Gastrointestinal Endoscopy (ESGE) [45]. Some studies and retrospective series reported similar decreases in main pancreatic duct diameter and no differences in pain resolution, instead of longer hospital stay and higher costs for patients who had ESWL combined with ERCP [53, 54].

Per-oral pancreatoscopy (POP)-assisted electrohydraulic lithotripsy (EHL) or laser lithotripsy (LL) is an emerging technology to fragment large intraductal stone(s). In a recent review and meta-analysis, technical success and overall fragmentation success were 91.2% and 85.5%, respectively [55]. Furthermore, stone fragmentation and ductal clearance could be achieved in 62% of patients in a single session; this suggests that POP may be an effective alternative to ESWL. Currently, with the newer version of cholangioscopes (SpyGlass-DS, Boston Scientific, Marlborough, MA), this technique will increase in the next few years.

The safety of POP-guided lithotripsy has been confirmed in two systematic reviews [55, 56]. The most common adverse events were post-ERCP pancreatitis (7%), pain (4.7%), perforation (4.3%), and hemorrhage (3.4%); overall, the incidence of adverse events was 11.2% with EHL and 13.1% with LL. Moreover, the technique has many advantages: it allows direct visualization of the stones (reducing ductal injury),

it can identify radiolucent stones, and it can confirm ductal clearance after lithotripsy [57]. However, the weaknesses of POP include need of expertise, additional costs, and need to dilated pancreatic duct (to allow insertion of pancreatoscope).

ESGE suggests to consider POP-guided lithotripsy when ESWL is not available or for stones that were not fragmented after adequately performed ESWL [45].

3.3 Endoscopic management of pancreatic stricture

Strictures of the main pancreatic duct may be a complication of a previously embedded stone or a consequence of acute inflammatory changes around the main pancreatic duct [58]. Strictures may be classified as either nondominant or dominant. Dominant main pancreatic duct strictures are defined by the presence of at least one of the following characteristics: 1) upstream main pancreatic duct dilatation (≥6 mm in diameter), 2) prevention of contrast medium outflow beside a 6-Fr catheter inserted upstream from the stricture, and/or 3) abdominal pain during continuous infusion of a nasopancreatic catheter inserted upstream from the stricture with 1 L saline for 12–24 h [45, 59].

Before endoscopic treatment of man pancreatic duct strictures, malignancy should be excluded, by cross-sectional imaging and cytology brushing (especially for patients without pancreatic calcification) [60].

Endoscopic management of pancreatic duct stricture includes pancreatic sphincterotomy, dilatation of the stricture using bougie, balloon or Soehendra stent retriever, followed by placement of one or multiple plastic stents [61]. Technical success is defined by stent insertion across a dominant main pancreatic duct stricture (or most proximal one in case of multiple strictures), and it aims to 1) decompress the main pancreatic duct and improve pain and 2) dilate the stricture(s). Less frequent indication includes facilitation of main pancreatic duct stone clearance in association with ESWL [62].

Dominant strictures are single in >80% of the patients, and insertion of single 10-Fr plastic stent can be used as the initial endoscopic therapy. In responders, endotherapy should be continued for at least 1 year before permanently removing the stent. Stent should be replaced if necessary (every 6 month or on demand), based on symptoms or signs of stent dysfunction [45].

Stricture resolution was achieved in 9–50% of patients [58, 63]; long-term pain relief is experienced by about two-thirds of patients (67.5%) after stenting. However, resolution of the stricture after stent removal was observed only in a minority of patients [64]. The follow-up after stent removal in most study was >24 months.

Refractory pancreatic duct stricture is defined as a symptomatic dominant stricture that persists or relapses after a single pancreatic stent placement indwelling for 1 year [45]. A substantial proportion of pancreatic duct stricture may not respond to conventional endoscopic therapy (single plastic stent). Treatment options for these strictures are multiple side-by-side plastic stents, self-expandable metal stents (SEMSs), or surgery. The use of multiple plastic stenting during multiple sessions of endotherapy allowed stricture resolution in 89.5% of patients and pain relief in 77.1% of patients after 9.5 years follow-up [65, 66].

More recently, the use of SEMS and biodegradable stents has been described for refractory pancreatic strictures. With respect to SEMS, only fully covered SEMS (FCSEMS) has provided acceptable results: pain improvement in 37–88% of patients (follow-up of 3–4 years) [67, 68]. However, there were no differences in pain relief between multiple plastic stenting and FCSEMS (84.2% vs. 85.2%). The main advantage of FCSEMS over multiple stenting is a lower number of endoscopic sessions [69].

Regarding complication with plastic stent, the most commonly reported in the short term were mild pancreatitis (severe pancreatitis was very rare) or worsening of pancreatic pain, followed by sepsis (2.6%), cholangitis (2.3%), and post-sphincterotomy bleeding (1.5%). During follow-up, distal (3.6%) or proximal (2.7%) stent migration and stent obstruction (almost all stent become obstructed for3 months) are reported. Furthermore, stent-induced ductal lesions were described in 18% of patients and mortality in 0.4% [45].

Adverse events reported with the use of FCSEMS include pain (7–20%), stent migration (15–46%), de novo strictures (16–27%), pancreatitis, cholestasis, and cholangitis [45, 70].

In symptomatic patients with main pancreatic duct obstruction and failure of conventional transpapillary drainage, endosonography-guided (EUS-guided) therapy can be a chance. The technic consists of puncturing the main pancreatic duct through duodenal or gastric wall, and a guidewire is inserted in the pancreatic duct to proceed with transpapillary (rendezvous technique) or transmural drainage using a stent [71]. This is a difficult technique that should be performed only in tertiary centers after multidisciplinary discussion [45]. In successful procedure, immediate pain relief has been reported in a majority of patients (50–100%); during long-term follow-up, pain relief was achieved in 70–90% of patients. In large series, failure of EUS-guided technique occurs approximately in 10% of cases and complications occur in about 10% that include severe pancreatitis, bleeding, hematoma, and perforation [72, 73]. Frequently (20–55%), stent migration or occlusion needs endoscopic reintervention.

3.4 Endoscopic management of chronic pancreatitis complications

3.4.1 Biliary stricture

Biliary strictures occur in about 10–15% of patients with CP [74]. Strictures can be asymptomatic or present with jaundice, cholangitis, choledocholithiasis, or asymptomatic elevation of ALP and/or bilirubin [75]. Before endoscopic treatment, malignancy should be reasonably excluded.

Biliary strictures related with CP are resistant to endoscopic treatment due to periductal fibrosis and calcification [74]. Endoscopic treatment consists of an ERCP with stent(s) placement to achieve biliary decompression. Only a small percentage of patients respond to a single plastic stent placement [76]. The suggested approach for benign biliary stricture consists of temporarily dilating the stricture using multiple side-by-side plastic stents (exchange every 3–6 months) or FCSEMS [77, 78]. Both approach provided similar results 2 years after stent removal (88% vs. 90.9%, respectively) and similar treatment-related morbidity [79]. Short biliary strictures respond better to endoscopic therapy [80], and severe CP and long length stricture are predictors for stricture recurrence [81]. After 1 year of unsuccessful endoscopy therapy, surgery should be considered.

3.4.2 Pseudocyst and pancreatic duct leak

Approximately one-third of patients with CP develop pancreatic pseudocyst (PPC) during the course of their disease, and less than 10% of these cases will resolve spontaneously [82]. PPCs should be differentiated from cystic neoplasm.

The indications for PPC drainage are the presence of symptoms (abdominal pain, gastric obstruction, early satiety, weight loss, and jaundice), progressively cyst

enlargement, or complications (infection, bleeding, rupture, and fistulization to adjacent hollow structures) [45, 83]. Asymptomatic pseudocysts can safely be kept under observation, provided they are carefully monitored and do not increase in size.

Endoscopic therapy of PPCs consists of transmural drainage (EUS-guided or conventional) with plastic or dedicated stents (PPCs ≥5 cm, no communication with pancreatic duct), endoscopic transpapillary drainage (PPC < 5 cm, communicating with pancreatic duct), or using a combination of these techniques [84]. Technical success is defined as insertion of the stent between the PPC and the digestive lumen [85]; instead clinical success is defined as disappearance of symptoms with resolution of the PPC or a decrease to less than 2 cm [86]. Compared with percutaneous drainage, endoscopic drainage is associated with higher clinical success rate, fewer reinterventions, shorter hospital stay, similar morbidity, and recurrence rate [87].

For an adequate treatment planning CT scan, MRI, EUS, and/or ERCP should be performed before PPC drainage to diagnose 1) the presence of necrotic debris inside the fluid collection (this may impede endoscopic drainage), 2) main pancreatic duct rupture (partial or complete), and 3) the presence of pseudoaneurysms close to the pseudocyst. If no ductal rupture is present, only transmural drainage can be performed; if partial ductal rupture is present, stent placement bridging the rupture is associated with the treatment success; if complete ductal rupture is present, long-term indwelling of transmural stents should be considered to avoid PPC recurrence [45, 88, 89]. Other technical aspects are underlined in Section 2.4.2.

3.4.3 Vascular complications

During CP progression, patients can develop, although rare, vascular complications that are difficult to treat and are responsible for significant morbidity and mortality. The CP-related vascular complications can be classified into arterial and venous (splanchnic thrombosis with splenic vein thrombosis) [90]. For the management of vascular complications, both surgical and nonsurgical interventions (endovascular, percutaneous, and endoscopic using EUS) are available. Nowadays, nonsurgical treatment options are the first-line therapy for these complications [90]. Obviously in this paragraph, we will focus on endoscopic technique.

Arterial complications are reported in 1.3–10% of patients with CP, and pseudoaneurysm is the most common arterial complications (approximately 70% of bleeding complications in CP, with a reported mortality rate of 15–50%) [91, 92]. They can be asymptomatic or present with hemorrhage due to rupture (hemosuccus pancreaticus, gastrointestinal bleeding, or intra-retroperitoneal hemorrhage), pain, or obstructive symptoms [92]. All pseudoaneurysms diagnosed on imaging require treatment irrespective of size as they have a high risk of rupture and life-threatening hemorrhage. The endoscopic approach is used for pseudoaneurysms detected on EUS. Hence, EUS-guided injection of the embolic agent (thrombin) is reserved for pseudoaneurysms arising from splenic and gastroduodenal arteries [90, 93].

The reported prevalence of venous thrombosis in patients with CP ranges from 3 to 41.7% with a pooled prevalence of 11.6%. Of the splanchnic veins, splenic vein thrombosis is the most common due to its proximity to the pancreas (prevalence ranging from 1.5 to 41.7%). Splenic vein thrombosis can extend to the portal vein in 1.5–4% of patients. Mesenteric venous thrombosis is uncommon and is reported in 0.8–1.1% of patients with CP [94]. In patients presenting with gastrointestinal variceal bleeding, endoscopic or surgical intervention of the gastroesophageal varices is required. Endoscopic therapy is preferred for patients without significant

pancreatic symptoms as they do not require surgery for CP [90]. Esophageal varices can be treated either with banding or sclerotherapy with conventional sclerosants. For gastric or fundal varices, these are not effective, and recent studies have reported reasonable success rates with cyanoacrylate glue injection [95].

4. Conclusions

Endotherapy is not only limited either to the diagnosis of AP and CP or to the management of biliary/pancreatic duct stones and strictures but also associated with the treatment of AP and CP complications.

The technological growth of endoscopy has made enormous progress, allowing a less invasive treatment of these pathologies. Obviously, to have a safe role and correct timing, discussions on treatments must be taken by a multidisciplinary group.

Conflict of interest

The authors declare no conflict of interest.

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