REVIEW ARTICLE

ERCP-Guided Endoscopic Therapy for Recurrent Acute Pancreatitis in Normal Pancreas and Chronic Pancreatitis

Pier Alberto Testoni[1], Sabrina Testoni[2]

[1]Division of Gastroenterology and Gastrointestinal Endoscopy Vita-Salute San Raffaele University Scientific Institute San Raffaele, Milan, Italy

[2]Endoscopic ultrasound and pancreaticobiliary endoscopy unit Scientific Institute San Raffaele, Milan, Italy

ABSTRACT

Recurrent acute pancreatitis is a clinical entity involving more than one episode of acute pancreatitis. Pancreatitis generally recurs in a subject with a normal anatomical and functional gland; however, either early or advanced chronic disease may be seen at the first episode of pancreatitis or during the follow-up. The etiology of recurrent acute pancreatitis can be identified in the majority of patients but, despite advanced diagnostic techniques, the causes still remain unknown in 10-30%: in these cases the term "idiopathic" is used. The efficacy of ERCP-guided endoscopic therapy in patients with RAP depends on two main factors: whether the acute pancreatitis involves a normal pancreas or is already in a setting of chronic pancreatitis, and whether a cause can be identified and removed. Occult common bile duct stone disease, sphincter of Oddi dysfunction, and pancreas divisum account for the majority of cases of recurrent acute pancreatitis, which can be successfully treated by endoscopic biliary and/or pancreatic sphincterotomy or minor papillary sphincterotomy, or stenting. However, in recent years concerns have been voiced about the efficacy of endo-therapy to treat sphincter of Oddi dysfunction and prevent the progression toward chronic pancreatitis in pancreas divisum. Trans-papillary endo-therapy has also proved effective for recurrent acute pancreatitis in patients with early or advanced chronic pancreatitis, and depending on pancreatic ductal obstruction or fluid collection; however, here again, despite symptom improvements, data on the impact of endo-therapy on the course of chronic pancreatitis remain uncertain.

INTRODUCTION

Recurrent acute pancreatitis (RAP) involves repeated episodes of acute pancreatitis, most of them of mild to moderate severity. An international state-of-the-science conference in 2018 defined RAP as "a syndrome of multiple distinct acute inflammatory responses originating within the pancreas in individuals with genetic, environmental, traumatic, morphologic, metabolic, biologic, and/or other risk factors who experienced two or more episodes of acute pancreatitis (AP), separated by at least 3 months" [1]. RAP may occur in a morphologically normal pancreas or in chronic pancreatitis (CP); RAP and CP may coexist or be completely independent. Moreover, when RAP occurs in a pancreas with minor ductal or parenchymal changes, it still an open question whether these changes are the consequence of repeated bouts of acute pancreatitis in an originally normal pancreas or are attributable to chronic pancreatitis at an early stage, with superimposed episodes of RAP.

The recurrence of acute pancreatitis after the first index episode can vary between 11% and 32% [2, 3, 4], and progression to CP in patients with RAP has been reported in 4.0-32.3% of cases [5, 6, 7, 8, 9]. A 2015 meta-analysis showed that after the first episode of acute pancreatitis 22% of patients presented at least one recurrence and 10% developed CP; among those with recurrences of pancreatitis, 36% developed chronic disease [10]. In a population-based study in 532 patients suffering from an initial episode of acute pancreatitis and followed up over 20 years, RAP occurred in 16.5%, CP developed in 13%

Received May 04th, 2020 - Accepted August 12th, 2020
Keywords Magnetic Resonance Cholangiopancreatography; Acute Pancreatitis; chronic pancreatitis; Endoscopic Retrograde Cholangiopancreatography
Abbreviations RAP Recurrent Acute Pancreatitis; CP Chronic Pancreatitis; AP Acute Pancreatitis; CFTR-Gene Cystic Fibrosis Transmembrane Conductance Regulator-Gene; SPINK1-gene Serine Protease Inhibitor Kazal Type I-gene; MRCP Magnetic Resonance Cholangio-Pancreatography; ERCP Endoscopic Retrograde Cholangiopancreatography; IRAP Idiopathic Recurrent Acute Pancreatitis; MPD Main Pancreatic Duct; CBD Common Bile Duct; SOD Sphincter of Oddi Dysfunction; UDCA Ursodeoxycholic Acid; EBS Endoscopic Biliary Sphincterotomy; EBPD Endoscopic Papillary Balloon Dilation; PEP Post-ERCP Pancreatitis; SOM Sphincter of Oddi Manometry; EPS Endoscopic Pancreatic Sphincterotomy; EPISOD Evaluating Predictors & Interventions in Sphincter of Oddi Dysfunction; OCT Optical Coherence Tomography; FCSEMS Fully Covered Self-Expandable Metal Stents; ESWL Extracorporeal Shock-Wave Lithotripsy; EUS Endoscopic Ultrasound; NAPS2 North American Pancreatitis Study 2
Correspondence Pier Alberto Testoni
Division of Gastroenterology and Gastrointestinal Endoscopy
Vita-Salute San Raffaele University
Scientific Institute San Raffaele,
Via Olgettina 60, 20132 Milan, Italy
Tel +39-2-26432756
Fax +39-2-26433491
E-mail testoni.pieralberto@hsr.it

over 10 years and in 16% over 20 years; the rate increased to 36% within two years from the second episode of pancreatitis [11].

Not all patients with RAP have the same risk of progression toward CP. Alcohol consumption; smoking and genetic mutations are very likely the most common factors associated with this. Heavy alcohol consumption has been reported to be associated with a 58% risk of RAP and a 41% risk of progression to CP; abstinence can reduce these risks to 20% and 13% [6]. Another study reported 80% of CP over a 15-year period in a series of patients with RAP and high alcohol consumption [12]. A population-based study in patients recruited over a 10-year period and followed up for a median of 40 months showed that alcohol, smoking, unknown causes, and bile stone disease were the causes of CP in respectively 28%, 1%, 10%, and 6% of cases [8]. Smoking is a significant dose-dependent risk factor for recurrence, but the benefits of smoking cessation have yet to be fully clarified [13].

Genetic mutations have long been recognized as associated with RAP and CP [14, 15, 16, 17, 18, 19, 20]. Genetic mutations in RAP patients involve the cystic fibrosis trans-membrane conductance regulator-gene (CFTR-gene), cationic trypsinogen gene (PRSS1-gene), and serine protease inhibitor Kazal type I gene (SPINK1-gene). These mutations are particularly frequent in patients with congenital abnormalities such as pancreas divisum, and may also induce sphincter of Oddi dysfunction. SPINK1-gene mutations have been reported in 16-23% of patients with apparent idiopathic RAP, compared with 2% in healthy controls [20]. Hereditary pancreatitis secondary to the PRSS1-gene mutation carries the greatest risk of progression to CP, with about 80% of carriers having at least one episode of acute pancreatitis and about 50% developing CP [21].

Gallstone disease, including occult (sludge, microlithiasis and bile crystal) or visible stones, accounts for up to one third of RAP cases [22]. However, as such it has a very low or no risk of progression to chronic disease if the recurrences of AP are prevented by removing the gallbladder or by endoscopic biliary sphincterotomy [23].

Even when alcohol, smoking, genetic and biliary factors are excluded, a substantial proportion of patients suffering from RAP of known or unknown etiology have an underlying chronic pancreatic disease that renders the therapies and changes of lifestyle ineffective, as documented in a long-term prospective study where 47% of patients with non-alcoholic and non-biliary RAP developed CP over an eight-year follow-up [24].

The causes of RAP can be identified in the majority of patients and are summarized in the TIGAR-O classification (toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, obstructive) - so called from the acronyms of the main predisposing risk factors [25]. In up to one third of cases the etiology remains unknown and these cases are termed "idiopathic" (IRAP). However, the percentage of "idiopathic" cases is decreasing as our diagnostic accuracy improves. Magnetic resonance cholangio-pancreatography, possibly with secretin stimulation (MRCP-S), endoscopic ultrasound (EUS), testing for genetic and autoimmune pancreatitis, investigation of sphincter of Oddi motility, or endoscopic retrograde cholangio-pancreatography (ERCP) in selected cases for advanced intra-ductal imaging increase the diagnostic yield in IRAP and reduce the cases of unknown etiology to approximately 10% [26].

ERCP-guided Endoscopic Treatment in Recurrent Acute Pancreatitis

Patients with RAP have few therapeutic options to abolish the recurrences or prevent progression to CP; the most important option involves ERCP. Its efficacy in RAP patients depends on two main variables: an underlying normal pancreas or CP and the identification of a mechanical cause that can be removed. A mechanical obstruction may also be involved in RAP associated with CFTR-gene mutation, because of the dense pancreatic juice that induces intraductal hypertension, and in patients with hereditary pancreatitis with a dilated main pancreatic duct (MPD). However, there are no prospective studies demonstrating that decompressive therapy favourably alters the course of these diseases. Progression toward CP was reported in 20-50% of cases of IRAP, independently from the efficacy of endoscopic interventions [22, 27, 28].

Fundamental tools in endoscopic therapy of RAP are sphincterotomy of the biliary and/or pancreatic segment of the sphincter of Oddi, or the minor papilla, and pancreatic stents inserted trans-papillary to dilate MPD dominant strictures, or drain the ductal system upstream of strictures or fluid collections.

Endoscopic Treatment of RAP in a Normal-Appearing Pancreas with a Non-Dilated Pancreatic Ductal System

When AP recurs in a normal-appearing pancreas with a non-dilated pancreatic ductal system, the etiology depends in most cases on common bile duct (CBD) stones (mainly sludge or bile crystals) and sphincter of Oddi dysfunction (SOD). The pancreaticobiliary ductal system may even be normal in IRAP.

RAP with Gallstone Disease

Gallstone disease is the most common condition associated with RAP in western countries and CBD stones have been found in 4-24% of patients after cholecystectomy; however, in most RAP cases the main etiologic role is played by microlithiasis, rather than true bile stones. Occult microlithiasis (stones ≤ 3 mm in diameter and biliary sludge) has been reported as the cause of IRAP in up to 73% of cases [29].

AP generally occurs as the consequence of transient papillary edema induced by the passage of sludge or small stones; ampullary obstruction may cause hypertension and/or bile reflux into the pancreatic ductal system, even though intra-ductal pressure within the pancreas

is generally higher than in the CBD in normal conditions. Bile reflux into the pancreatic ductal system is facilitated if there is a common channel at the bilio-pancreatic junction. With time, these repeated events may lead to SOD or stenosis.

In RAP and IRAP patients, bile crystals have been detected at microscopic examination of centrifuged bile aspirated from the duodenum or CBD in 36-67% of patients and was considered the primary cause of disease in 22% [30]. It is still not clear whether bile crystals alone can induce AP or might just indicate the presence of undetected stones; however, either long-term ursodeoxycholic acid (UDCA), or cholecystectomy, or endoscopic biliary sphincterotomy (EBS) may prevent further episodes of RAP in patients with no evidence of bile duct stones [29, 31].

Laparoscopic cholecystectomy is the intervention of choice in patients with RAP of biliary etiology; however, when no stones or sludge are found the indication for empirical cholecystectomy remains controversial, even if some experts recommend it in IRAP [32]. EBS is the intervention of choice in RAP patients with a history of gallstone disease, if pancreatitis recurs after cholecystectomy and in those unfit for cholecystectomy. In these latter patients, the presence of gallbladder has not been found to be a significant risk factor for complications after EBS, although it was hypothesized.

In the last few years, endoscopic papillary balloon dilation (EPBD) has been increasingly done as an alternative to EBS when CBD stones are found, because lower complication and stone recurrence rates have been reported with this technique, compared to EBS (5.3% *vs.* 17.3 %, p=0.009; 4.4% *vs.* 12.7 %; p=0.048, for biliary stones ≤ 8 mm) [33]. EPBD is not indicated when no CBD stones are found and when SOD is suspected, because it is non-curative; in these patients endoscopic sphincterotomy remains the procedure of choice. When doing EPBT for RAP of biliary etiology the reported advantages and possibly higher risk of post-ERCP pancreatitis (PEP) should be weighed up; however, the incidence of PEP did not differ after EPBT and EBS in most studies assessing this [33].

RAP with Sphincter of Oddi Dysfunction

SOD has been reported in 35-65% of cases with RAP and is probably the most common cause of IRAP [34, 35, 36, 37]. Patients with CBD stones suffering from RAP had significantly higher basal sphincter pressure gradients between the CBD and duodenum, suggesting a possible primary role of SOD in the pancreatitis [38]. However, in recent years concerns have been raised about the clinical importance of SOD and the efficacy of endoscopic therapy. SOD may depend on persistently increased basal sphincter pressure or dyskinesia and has been grouped in three types on the basis of clinical, morphological and functional parameters (sphincter of Oddi manometry – SOM) [39, 40, 41], but in the last few years type 3 dysfunction has no longer been considered a clinical entity.

Types 1 and 2 SOD are relevant in the etiology of RAP [39, 40]: type 1 SOD refers to a persistent obstruction to bile or pancreatic juice outflow and is associated with mild dilation of either the CBD or MPD, or both; type 2 SOD is very likely associated with sphincter motor dysfunction and not with ductal dilation. In type 1 SOD the diagnosis is based on clinical findings; for type 2 SOD the diagnosis is suspected and may require functional investigation of sphincter motility (secretin test or SOM) [42, 43]. However, normal basal sphincter pressure does not exclude a fluctuating dysfunction which may play a role in the recurrence of pancreatitis.

SOD can involve either the biliary or pancreatic segment of the sphincter, or both. Consensual involvement of the biliary and pancreatic segments is the most common condition; in a large series of patients diagnosed with type 2 SOD, respectively 22%, 11%, and 32% had elevated basal sphincter pressure in the pancreatic sphincter only, biliary sphincter only, or both [44].

Endoscopic sphincterotomy is currently the standard therapy for both type 1 and type 2 SOD with documented sphincter dysfunction; when the documentation of sphincter dysfunction is uncertain, endoscopic sphincterotomy should not be recommended and the risks and benefits of the intervention must be carefully weighed up, because outcomes are uncertain in these patients and there is a higher risk of post-ERCP pancreatitis than in patients with ductal stones.

In general, EBS is done first and achieves clinical improvement in 83-100% of patients with type 1 dysfunction and up to 80% of type 2 SOD patients with documented sphincter dysfunction. If acute pancreatitis still recurs, endoscopic pancreatic sphincterotomy (EPS) may be considered, proceeded or not by further functional testing. Pancreatic sphincter hypertension has been reported in up to 78% of patients [30] with unsuccessful EBS; EPS achieved symptomatic improvement in 60-90% of these cases [30, 31].

Dual sphincterotomy (consensual biliary and pancreatic sphincterotomy) has also been widely used to treat SOD, considering the high probability of consensual sphincter dysfunction. However, a randomized trial comparing biliary and dual sphincterotomy in patients with RAP and pancreatic SOD documented by manometry reported a similar incidence of RAP in the two groups (64.7% and 76.9%), with a tendency toward higher rates of recurrent pancreatitis during the first 12 months of follow-up in the group randomized to dual sphincterotomy [27]. These findings suggest that EPS may have been inadequate for normalizing pancreatic sphincter pressures, or else there was a high incidence of re-stenosis, or that SOD was just an epiphenomenon and not the primary cause of RAP in some patients. In a retrospective study including 369 patients who had undergone pancreatic sphincterotomy for RAP or pancreatic-type SOD, pancreatic orifice re-intervention was required in 41.7% because of re-stenosis [45]. The latter hypothesis is further borne out by the evidence that

EPS in patients with SPINK1 mutations and SOD gave a poor symptomatic response [46]. The search for genetic mutations and EUS may help identify a genetic etiology of RAP or pancreatic changes suggesting early-stage CP in cases with persistent RAP after successful pancreatic sphincterotomy.

However, a few years ago concerns were voiced about the clinical efficacy of endoscopic sphincterotomy for the treatment of SOD, in the EPISOD trial. This was a multicentre, long-term, prospective, randomized trial (sphincterotomy *vs*. sham 2:1) in patients with pain after cholecystectomy, with a five-year follow-up [47]. At one year outcomes were better in patients in the sham group (37%) than in those after sphincterotomy (23%); among patients with pancreatic sphincter hypertension, only 30% and 20% of those who underwent respectively dual and biliary sphincterotomy reported successful treatment. At five-year follow-up, success rates for the patients in the sphincterotomy and sham arms were similar (40% and 42%). Overall, during the entire study successful outcomes were reported in 41% of patients after endoscopic sphincterotomy and 62% of those who had no active treatment at any time [48].

Idiopathic Recurrent Acute Pancreatitis

In cases of IRAP, once one has excluded the possibility of unrecognized biliary and SOD etiology, there is limited evidence that endo-therapy can really alter the course of the disease [28, 31, 49, 50]. In a multicentre study with seven-year follow-up (the North American Pancreatitis Study 2 - NAPS2), among 50 patients suffering from IRAP those operated by endoscopic sphincterotomy had similar pancreatitis recurrence rates/year to those who had been managed conservatively, and progression to CP was more frequent in the former than the latter (27% *vs*. 8%). Predictors for recurrences of pancreatitis were female sex and number of attacks at baseline, but not endo-therapy [28].

In IRAP patients, when the etiology remains unknown despite advanced investigations (EUS, MRCP + secretin test or SOM, and genetic testing), botulin toxin injected into the papilla of Vater may help identify an unidentified sphincter malfunction. Botulin toxin is diluted in 4 mL of saline and injected on the four quadrants of the papilla, 5-10 mm distal from the papillary orifice; these precautions reduce the risk of transient pancreatic orifice obstruction. In 44-80% of cases botox injection can predict which patients are most likely to improve with EPS [51].

Pancreatic stent as an empirical test to predict the response to pancreatic sphincter ablation in IRAP patients has been tried only in two studies, with few patients. Our group has used pancreatic 5 F and 7 F stents, with significant reductions in pancreatitis episodes; in these cases EPS was successful [31]. In a prospective study by Jacob et al. in 2001, 34 IRAP patients were randomized to receive three pancreatic stents over nine months, each stent left in place for three months, and followed up for five years [52]. After mean follow-ups of respectively 33 and 35 months in the stent and control groups, the incidence of RAP was significantly lower in the stent group (11% *vs*. 53%).

These studies still confirm that in a subset of IRAP patients recurrences of pancreatitis depend on some intra-ductal hypertension, even if not documented. However, despite these promising results, there is still not enough literature data to consider empirical main pancreatic ductal stenting as a potential routine diagnostic tool in IRAP. Moreover, placing a stent in a non-dilated pancreatic ductal system, even for a short time, may cause ductal injury mimicking CP. However, these changes do tend to disappear once the stent is removed.

Since patients with IRAP strongly demand treatment and the outcomes of endoscopic biliary or dual sphincterotomy may be satisfactory even when a biliary or SOD etiology cannot be documented (87.5% success rate in our experience [31]), empiric sphincterotomy should be considered too but only after an informed discussion with the patient about the potential risks and unpredictable outcomes of this intervention.

An algorithm of endoscopic management of IRAP is reported in **Figure 1**.

Endoscopic treatment of RAP in patients with pancreas divisum and anomalous pancreaticobiliary junction

Pancreas divisum is the most common anatomical variant of the pancreas, seen in approximately 10% of the general population, but the reported rates vary worldwide from 2.7% to 22%, with the highest in the United States and Europe [53]. The incidence of this anatomical variant is higher (up to 20% of cases) in RAP patients than healthy subjects [54, 55, 56, 57, 58]. About 15% of pancreas divisum cases are of the incomplete type. The persistent intra-ductal hypertension caused by the inability to accommodate the pancreatic juice flow through the minor papilla when the gland is stimulated may lead to RAP in some patients, and over time to chronic obstructive pancreatitis.

Besides the obstructive etiology, genetic mutations also play a role in RAP and progression toward CP in pancreas divisum. A higher incidence of CFTR-gene and SPINK 1-gene mutations have been found in symptomatic patients with pancreas divisum, compared with those with idiopathic or alcoholic pancreatitis (p=0.0001) and healthy controls [59, 60].

Endoscopic therapy is indicated when there is a dilated dorsal duct or impaired juice outflow through the minor papilla (documented by a secretin test), when the pancreatic ductal system is not dilated. However, whether endo-therapy - even when effective on symptoms - can prevent the progression toward CP is still not settled.

Endoscopic therapy includes minor papilla sphincterotomy and/or stenting, or dilation.

After sphincterotomy, placement of a short-term dorsal pancreatic duct stent is recommended to avoid

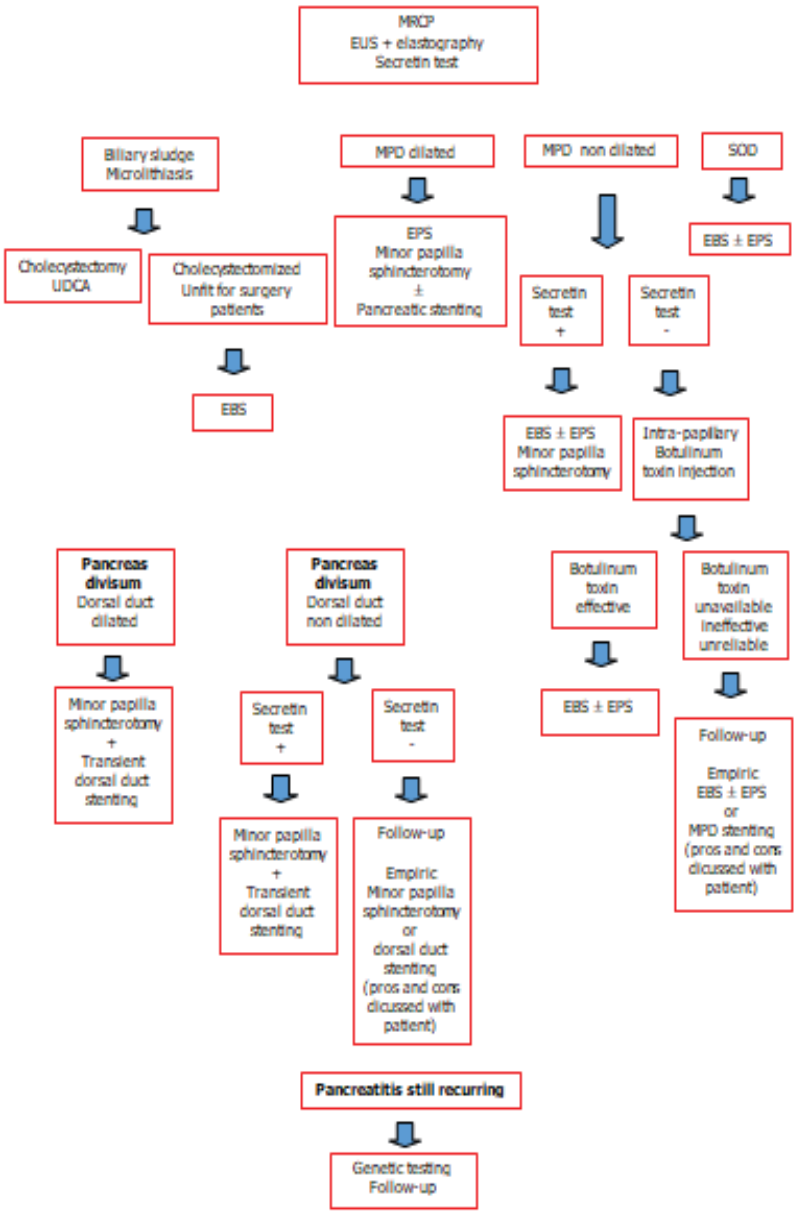

Figure 1. Recurrent acute pancreatitis Advanced diagnostic-therapeutic algorythm in normal anatomy and pancreas divisum.

MRCP Magnetic resonance cholangio-pancreatography; EUS Endoscopic ultrasound; UDCA Ursodeoxycholic acid; EBS endoscopic biliary sphincterotomy; EPS endoscopic pancreatic sphincterotomy; MPD main pancreatic duct; SOD Sphincter of Oddi dysfunction.

cicatricial strictures and post-ERCP pancreatitis. Stenosis of sphincterotomy occurs in 20-30% of cases and is the main cause of persistent recurrent episodes of pancreatitis after endo-therapy [58, 61]; in these cases, revision of the papillotomy or pancreatic stenting may be useful, with 7 F to 10 F stents depending on the dorsal duct dilation [62].

In patients without dorsal duct dilation and with a normal function test, the obstructive cause of RAP cannot be documented and sphincterotomy is not indicated. In these cases three-month dorsal duct stenting (repeated if effective) may identify some unrecognized minor papillary malfunction and help predict which patients could benefit from sphincterotomy. In the only randomized controlled trial comparing dorsal duct stenting with no therapy in pancreas divisum patients suffering from IRAP with a non-dilated dorsal duct, the rate of recurrent episodes of AP was significantly lower in the stent group than the control group [63].

Studies so far published report resolution of RAP and symptoms in 60-100% of patients after endo-therapy. However, most of them refer to uncontrolled retrospective series. Pancreas divisum with RAP gave better outcome rates than CP or pancreatic pain alone after either endoscopic therapy (53.2%, 18.2%, and 41.4% respectively) or additional therapeutic ERCPs (71.0%, 45.5%, and 55.2% respectively) over a median follow-up of 43 months [64]. 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 findings show that PD patients suffering from RAP are the most likely to benefit from endo-therapy [65]. Only one randomized controlled trial has been published on the efficacy of endo-therapy in RAP patients, but on a small number of patients: in the treatment group 9 out of 10 patients (90%) had no further episodes of RAP during a three-year follow-up, while 6 out

of 9 (67%) randomized to no treatment had at least one episode [66].

A still unsettled issue is whether a tendency towards CP persists in pancreas divisum patients, even after successful treatment, and if so, why. In our series of 33 pancreas divisum patients suffering from RAP followed up to five years EUS findings consistent with CP were seen in similar percentages of patients after endoscopic therapy and the observation group (63.2% and 57.1%), though the therapy improved symptoms and pancreatitis recurrences [62]. These results suggest that factors other than ductal abnormalities, such as underlying genetic mutations, may be involved in the development of a chronic disease in these patients.

Figure 1 shows an algorithm for endoscopic management of pancreas divisum patients.

A common pancreaticobiliary channel without sphincters separating the biliary and pancreatic ducts is another anatomical condition associated with RAP that can be treated endoscopically. The common channel facilitates the reflux of bile and pancreatic juice into the alternative duct. This abnormality is easily diagnosed by MRCP or ERCP, is frequently associated with choledocal cysts, and is thought to raise the risk of biliary tract malignancies. In patients with an abnormally long (>15 mm) common pancreaticobiliary channel EBS reduces the intra-ampullary resistance to pancreatic juice flow and the risk of recurrent pancreatitis [67]. However, the role of biliary sphincterotomy is not clear, because it is not effective when the anomalous junction extension goes beyond the endoscopic limit of sphincterotomy [68].

Endoscopic treatment of RAP caused by biliary and pancreatic parasites

A rare cause of ARP, usually limited to subtropical and tropical climates, is *Ascaris lumbricoides* in the biliary tree and/or pancreatic duct, where it obstructs the bile flow or pancreatic exocrine secretion. This parasite is transmitted by the feco-oral route; the egg hatches in the duodenum, and the larva penetrates the mucosa to enter the bloodstream. The larva reaches the lung alveolus and migrates to the oropharynx. Then it is swallowed and matures into an adult worm in the gastrointestinal system again, to feed off the host's food. Pancreaticobiliary ascariasis commonly occurs in subjects with a history of cholecystectomy and sphincterotomy. Ultrasonography of the biliary system is the investigation of choice to reveal the parasite in the pancreaticobiliary ductal system.

The treatment of these parasites is principally pharmacologic, but in cases with recurrent pancreatitis or cholangitis ERCP is used to decompress ducts obstructed by parasites, usually by biliary and/or pancreatic sphincterotomy and trawling with a balloon or basket catheter.

Endoscopic Treatment of RAP in Mild-Change Chronic Pancreatitis

RAP may occur in a patient with CP because of segmental MPD strictures, stenosis of the pancreatic sphincter, or pancreatic intra-ductal stones; all these conditions can lead to intra-ductal hypertension. The persistent intra-ductal hypertension favours the recurrences of AP and accelerates the progression toward more advanced CP and atrophy of the gland upstream of a stricture. Fluid may collect even in mild-change CP, as the consequence of an acute bout of pancreatitis, and can promote further episodes of pancreatitis, if not resolved.

Pancreatic sphincterotomy, dilation and stenting are the mainstay of endoscopic therapy and are currently considered the first-line strategy [69]. In CP with mild changes according to the Cambridge classification [70] and with no dominant MPD strictures, pancreatic sphincterotomy is indicated as a single therapeutic intervention, but there is little information on the outcomes. In two series of patients treated endoscopically for CP, mild changes were recorded in 14/40 and 26/398 cases, but outcomes were not reported [71, 72].

Fortunately there is ample data suggesting the effectiveness of pancreatic sphincterotomy in preventing pain and RAP for moderate to marked changes of chronic pancreatitis. Factors independently associated with successful long-term outcomes (≥ 2 years) after pancreatic sphincterotomy are the location of the obstruction in the head of the pancreas (the most robust predictor of a good outcome), a small number of RAP episodes before endoscopic therapy, short duration of disease, no dominant MPD stricture at initial endoscopic therapy, and complete intra-ductal stone clearance [73].

Pancreatic sphincterotomy can be either a dual-step procedure (biliary sphincterotomy followed by pancreatic sphincterotomy) or a single step (direct pancreatic sphincterotomy). Biliary sphincterotomy as a precursor to pancreatic sphincterotomy gives better visualization of the relevant anatomy prior to the sphincterotomy, and could theoretically make pancreatic sphincter section technically easier, allowing a more precise section; however, there are no data to support this hypothesis. More importantly, it has been reported that there is a lower risk of cholangitis with consensual biliary sphincterotomy [74, 75, 76].

Segmental strictures of the main pancreatic duct are found in 5-10% of patients with RAP superimposed on CP [77]. The differential diagnosis between the benign and malignant nature of the stricture is pivotal for planning treatment, which in most cases is endoscopic. EUS is the diagnostic procedure with the best sensitivity for identifying a pancreatic neoplasm in a subject with small lesions. ERCP can be used for diagnostic purposes only in selected cases, for guidewire-guided intra-ductal brush cytology, confocal endo-microscopy, or optical coherence tomography (OCT). OCT has been re-evaluated in the last few years after a period of neglect, in view of its good capacity to discriminate between early neoplastic and inflammatory changes in MPD strictures [78].

If there are dominant MPD strictures, defined by upstream MPD dilation 6 mm or more in diameter, trans-

papillary stenting is the intervention of choice. Stent insertion across the stricture decompresses the MPD and may permit persistent dilation of the stricture, if maintained for up to 24 months, with 3-/6-month stent exchange. In a meta-analysis of nine studies, pain relief and no recurrences of pancreatitis were reported in 51.5-80.2% of patients after long-term stenting [79].

Clinical outcomes after stenting are better when the MPD stricture is in the head of the pancreas. When there are multiple strictures stenting should be reserved for the dominant ones, most proximal to the papillary orifice. Insertion of a single 10-F plastic stent is the first step in the treatment of MPD strictures. Smaller-diameter stents may expose the patient to more frequent hospitalization for recurrent symptoms; in a retrospective study, CP patients fitted with stents ≤ 8.5-Fr were 3.2 times more likely to be hospitalized for abdominal pain than those who had received 10-Fr stents [80].

If there are very tight strictures mechanical or pneumatic dilation may be required to permit insertion of the plastic stent. Refractory strictures may be treated with multiple side-by-side plastic stents or fully covered self-expandable metal stents (FCSEMSs). The temporary insertion of multiple side-by-side plastic stents was reported to definitely resolve strictures in about 90% of patients, at 9.5-year follow-up [81, 82].

For refractory dominant strictures in the head of the pancreas an effective alternative to multiple plastic stents is the placement of 6-10 mm FCSEMSs. In a systematic review of four prospective series (total 61 patients), placement of a FCSEMS provided some pain relief in 85% of patients [83], and three more recent studies have reported pain improvement in 37-88% of patients during a 3-4 year follow-up [84, 85, 86].

Stents are generally changed every six months when there are no stent-related adverse events which are, however, infrequent with 10-F stents, or on demand; in fact, even if the stent tends to occlude in a very short time, the pancreatic juice outflow is maintained between the duct and stent wall. With the six-month stent change policy, sepsis of pancreatic origin was reported in about 5% of patients in four series, while in 12 series with stent changes scheduled at three months, there were no septic complications. With FCSEMSs, the reported mean stenting duration was 2-6 months, and stents were removed uneventfully in 98% of patients [73]. However, FCSEMSs can stay in place for longer than plastic stents.

In a recent pilot study, a biodegradable non-covered self-expandable stent was clinically successful in 53% of patients who had had no resolution of the stricture in at least six months after insertion of a plastic stent; adverse events were reported in 21% of patients [87].

We also inserted temporary FCSEMSs to remove stones up to 8 mm in size upstream of MPD strictures in the head of the pancreas, avoiding extracorporeal shock-wave lithotripsy (ESWL). A FCSEMS with a diameter adequate to allow extraction of a stone was used to dilate the MPD dowstream of the stone and permitted easy removal with a basket or balloon. Once the stone was removed the stent could have been left in place or replaced with a 10-F plastic stent, to treat the stricture **(Figure 2)**.

In CP, even with mild changes, fluid collections may occur as the consequence of an episode of superimposed AP with MPD disruption, or as a local complication related to intra-ductal hypertension. These rarely regress spontaneously when they are larger than 4 cm and located within the gland, and can themselves induce recurrent bouts of pancreatitis or a condition of smoldering pancreatitis. The

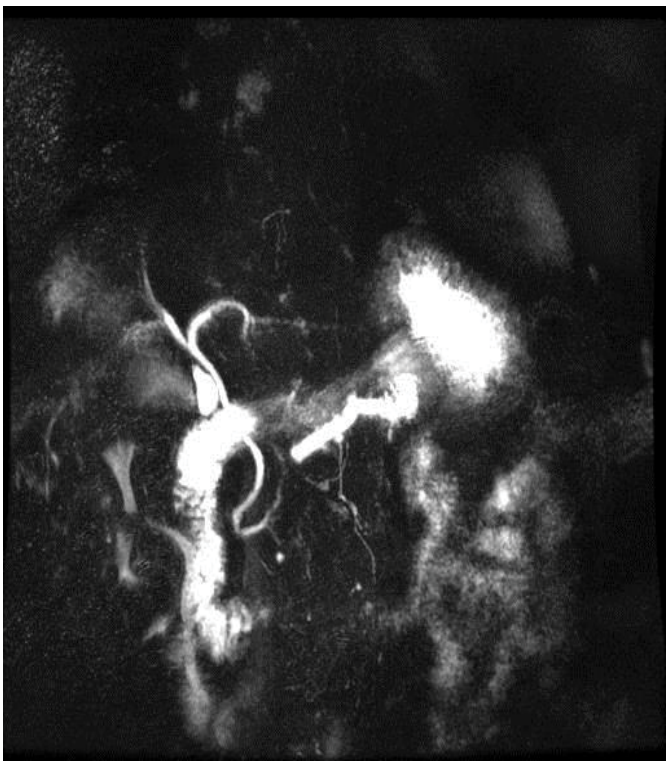

Figure 2. RAP in mild-change chronic pancreatitis with MPD stricture in the head of the gland and an 8-mm stone impacted upstream from the stricture. **2(a).** Pre-procedure MRCP-S imaging showing MPD stricture in the head of the pancreas with stone impacted and dilation of the upstream MPD.

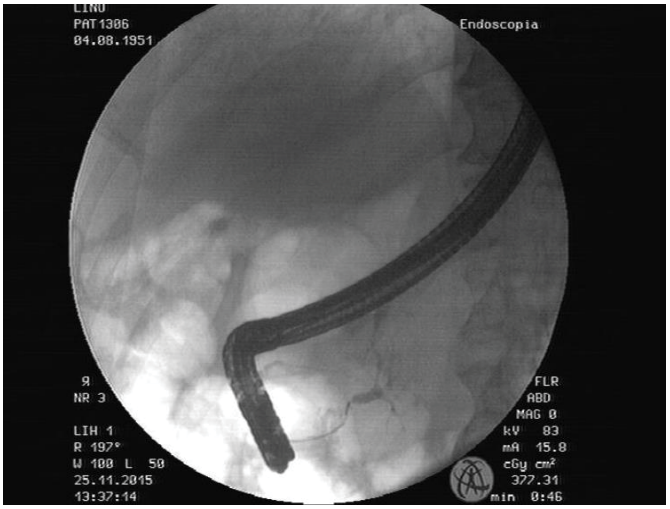

Figure 2(b). Injection of contrast medium confirms the presence of a tight, narrow dominant MPD stricture in the head of the gland, which prevents the progression of the contrast medium upstream in the ductal system.

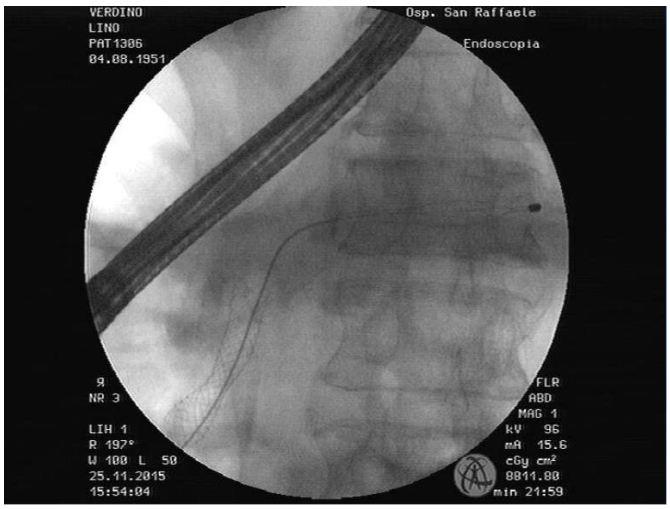

Figure 2 (c). Pancreatic sphincterotomy is done over a guidewire and the stricture is dilated, then a 10-mm FCSEMS is placed downstream of the impacted stone.

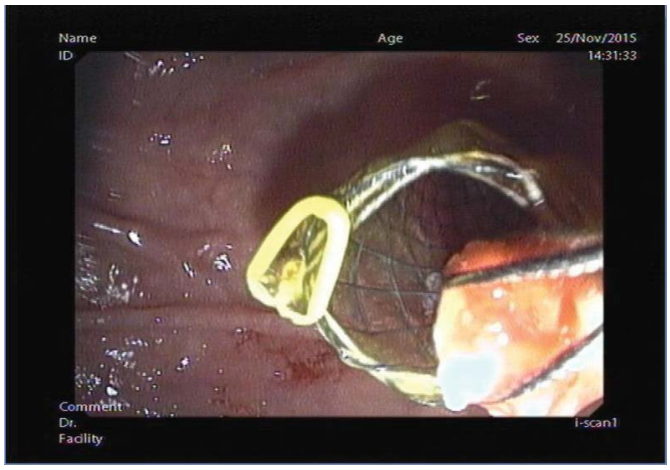

Figure 2 (d). The stone is removed by a basket through the FCSEMS.

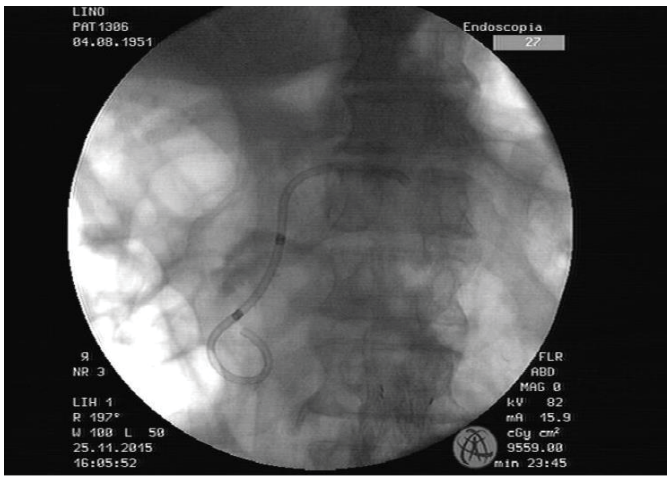

Figure 2 (e). The FCSEMS is removed and a double-pigtail 10-F stent is inserted and maintained for up to three months, with 10-F plastic straight stent exchanges scheduled up to 12-24 months.

persistence of the fluid depends on two factors: sustained intra-ductal hypertension and a communication between the pancreatic ductal system and the fluid.

In these patients, the only effective ERCP-guided intervention is trans-papillary stenting of the MPD or fluid collection, independently from MPD dilation or changes in severity, when there are small collections (≤ 50 mm) communicating with the MPD. If an ERCP-guided approach is considered, the strategy should be planned prior to the intervention with careful assessment of ductal morphology by magnetic resonance cholangio-pancreatography, enhanced with secretin when possible (MRCP-S).

Trans-papillary stenting of the MPD may be useful for fluid collections communicating with the ductal system, wherever they are within the pancreas. The stent inverts the pressure gradients between the ductal system and duodenum, promoting the spontaneous drainage of fluids from the cavity into the duodenum and may allow spontaneous resolution of the fluid collection. The stent can also be placed to bridge the communication and prevent the fluid entering the cavity, by mechanical action.

Trans-papillary drainage of a fluid collection by placing a stent in the cavity is more complicated and requires a visible communication between the MPD and the cavity when contrast is injected into the MPD, so a guidewire can be placed inside the cavity **(Figure 3)**. Inserting a stent across a MPD disruption is successful in 33-67% of patients [73]. This approach can be effective when the fluid collections are in the head or body of the pancreas, where a stent can be placed in the collection relatively easily through a trans-papillary approach. In this case, a plastic double-pigtail stent should be preferred to a straight one, because of the lower risk of displacement and parietal damage inside the cavity **(Figure 4)**.

Compared with EUS-guided trans-mural drainage, trans-papillary drainage achieves similar success with similar morbidity rates but fewer surgical complications.

CONCLUSION

The efficacy of endoscopic therapy in patients with a history of RAP depends on whether the AP recurs in a normal pancreas or in a setting of CP, and whether a cause can be identified and eliminated. In patients with normal-

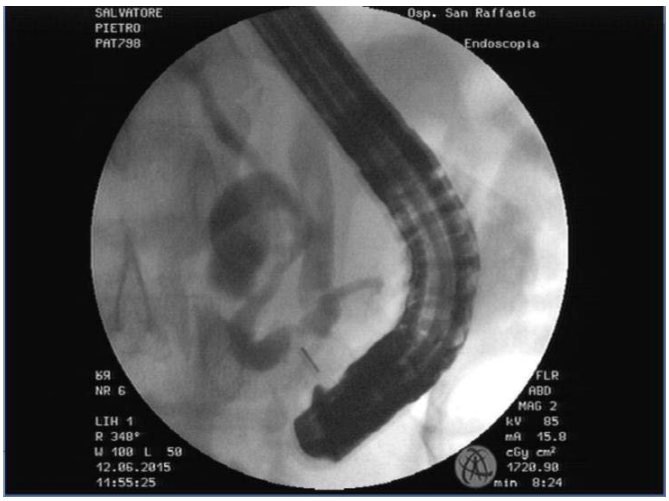

Figure 3. RAP associated with symptomatic acute fluid collection communicating with MPD in the body of the gland in mild-change chronic pancreatitis, maintaining recurrences of acute pancreatitis. **3(a).** ERCP shows a dilated MPD in the head of the pancreas and a fluid collection communicating with the MPD in the body of the pancreas.

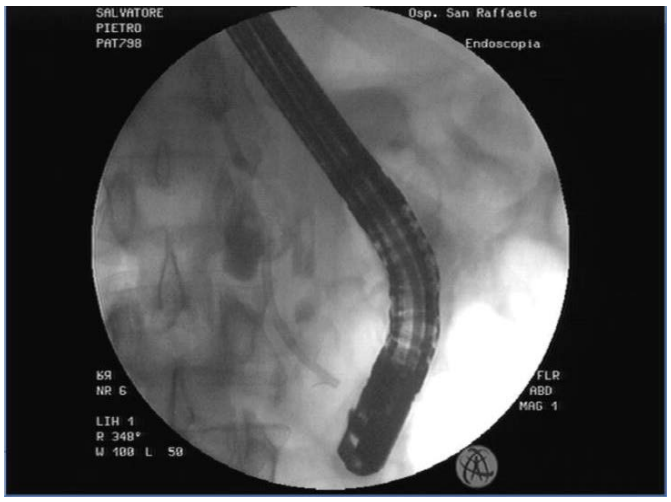

Figure 3 (b). A 10-F 5-cm-long pancreatic plastic stent is placed through the major papilla, but the angle of the MPD makes it impossible to reach the MPD-cavity communication and drain the fluid collection.

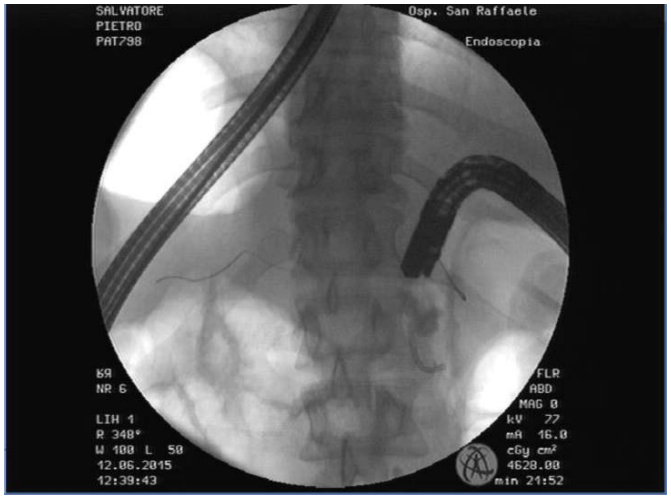

Figure 3 (c). A second 10-F 5-cm-long pancreatic plastic stent is then inserted into the MPD through the minor papilla, to bridge the communication between the MPD and the fluid collection.

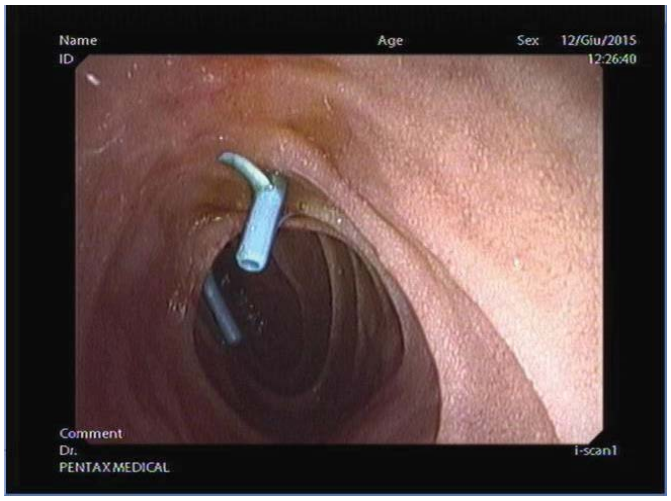

Figure 3 (d). Endoscopic view of the two stents inserted through the major and minor papillae.

appearing pancreas, the efficacy of endo-therapy remains elusive, because an underlying chronic disease cannot be excluded and there are as yet no long-term follow-up studies assessing the progression of the disease, independently from the therapeutic success of endo-therapy. This is particularly true for IRAP, in which endoscopic treatment is at best questionably beneficial and at worst unlikely to alter the natural history of the disease.

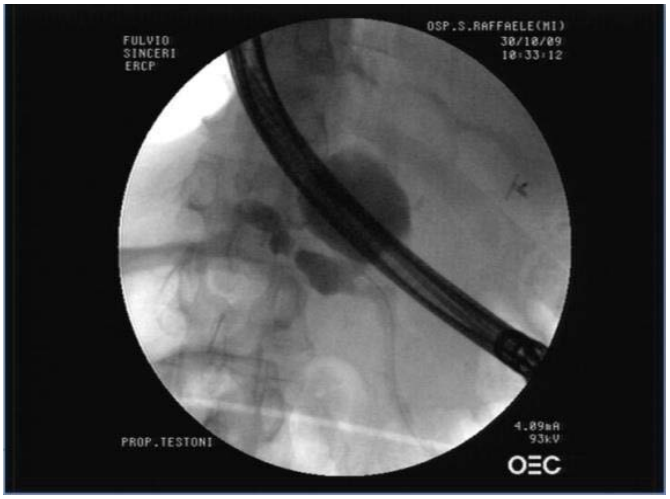

Figure 4. RAP with post-acute pancreatitis symptomatic fluid collection communicating with the MPD in mild-change chronic pancreatitis. **4(a).** ERCP imaging showing a visible communication between the fluid collection and a dilated MPD, in the body of the pancreas.

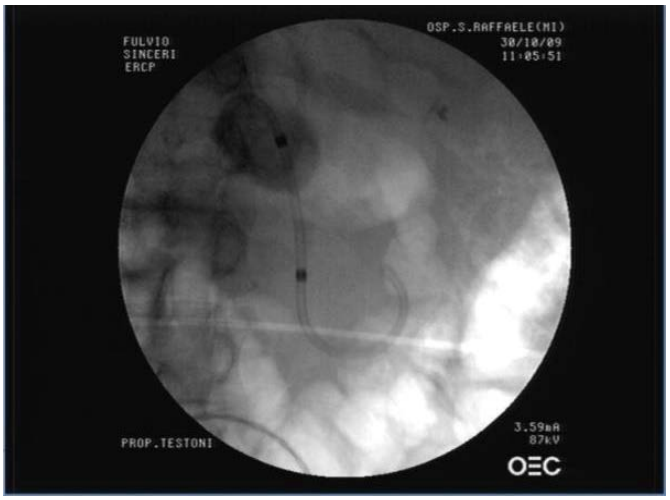

Figure 4 (b). Over a guidewire, a 10-F double-pigtail plastic stent in inserted into the fluid collection through the communication with the MPD, achieving drainage of the cavity and symptomatic improvement.

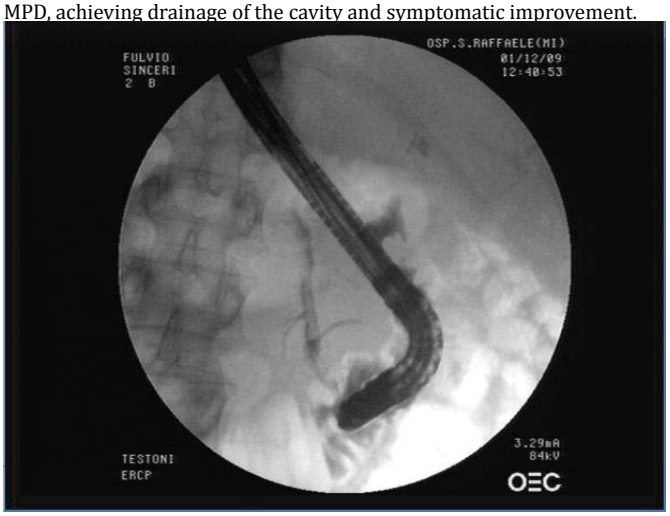

Figure 4 (c). One month later, the double-pigtail stent is removed; the fluid collection is no longer visible but there is still a communication between the MPD and the cavity.

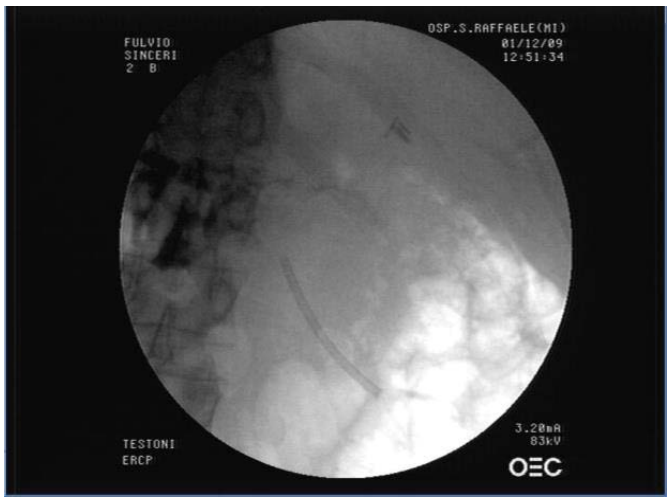

Figure 4 (d). A plastic 10-F stright pancreatic stent is placed to bridge the MPD-cavity communication and maintained for up to three months, to achieve complete closure of the communication.

Once a careful diagnostic algorithm identifies an obstructing etiology of RAP, ERCP is pivotal in the initial management of the disease or its cure. In RAP with biliary etiology, EBS and cholecystectomy have been reported as curative. In SOD-related RAP, dual sphincterotomy seems to have no added benefit compared with biliary sphincterotomy alone, although earlier studies suggested otherwise. In pancreas divisum-associated RAP, most studies have documented the efficacy of minor papilla sphincterotomy and endo-therapy; however, long-term prospective randomized controlled trials are lacking and the role of genetic mutations in the progression toward CP remains to be clarified.

In cases of RAP superimposed on CP with MPD obstruction and/or communication between the ductal system and fluid collection, trans-papillary stenting and drainage of fluid collections has proved effective, mainly for lesions in the head of the pancreas, and are currently widely used rather than more aggressive approaches.

Conflicts of Interest

All named authors hereby declare that they have no conflicts of interest to disclose.

REFERENCES

1. Guda NM, Muddana V, Whitcomb DC, Levy P, Garg P, Cote G, et al. Recurrent Acute Pancreatitis International State-of-the-Science Conference With Recommendations. Pancreas 2018; 47:653-666. [PMID: 29894415]

2. Zhang W, Shan HC, Gu Y. Recurrent acute pancreatitis and its relative factors. World J Gastroenterol 2005; 11:3002-3004. [PMID: 15902746]

3. Gullo L, Migliori M, Pezzilli R, Oláh A, Farkas G, Levy P, et al. An update on recurrent acute pancreatitis: data from five European countries. Am J Gastroenterol 2002; 97:1959-1962. [PMID: 12190160]

4. Gao YJ, Li YQ, Wang Q, Li SL, Li GQ, Ma J, et al. Analysis of the clinical features of recurrent acute pancreatitis in China. J Gastroenterol 2006; 41:681-685. [PMID: 16933006]

5. Machicado JD, Yadav D. Epidemiology of recurrent acute and chronic pancreatitis: similarities and differences. Dig Dis Sci 2017; 62:1683-1691. [PMID: 28281168]

6. Takeyama Y. Long-term prognosis of acute pancreatitis in Japan. Clin Gastroenterol Hepatol 2009; 7:S15-S17. [PMID: 19896091]

7. Nøjgaard C, Becker U, Matzen P, Andersen JR, Holst C, Bendtsen F. Progression from acute to chronic pancreatitis: prognostic factors, mortality, and natural course. Pancreas. 2011; 40:1195-1200. [PMID: 21926938]

8. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. Am J Gastroenterol 2012; 107:1096-1103. [PMID: 22613906]

9. Cavestro GM, Leandro G, Di Leo M, Zuppardo RA, Morrow OB, Notaristefano C, et al. A single-centre prospective, cohort study of the natural history of acute pancreatitis. Dig Liver Dis 2015; 47:205-210. [PMID: 25475611]

10. Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology 2015; 149:1490-1500. [PMID: 26299411]

11. Lankisch PG, Breuer N, Bruns A, Weber-Dany B, Lowenfels AB, Maisonneuve P. Natural history of acute pancreatitis: a long-term population-based study. Am J Gastroenterol 2009; 104:2797-2805. [PMID: 19603011]

12. Ammann RW, Muellhaupt B, Meyenberger C, Heitz PU. Alcoholic nonprogressive chronic pancreatitis: prospective long-term study of a large cohort with alcoholic acute pancreatitis (1976-1992). Pancreas 1994; 9:365-373. [PMID: 8022760]

13. Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med 2009; 169:1035-1045. [PMID: 19506173]

14. Cohn JA, Friedman KJ, Noone PG, Knowles MR, Silverman LM, Jowell PS. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Engl J Med 1998; 339:653-658. [PMID: 9725922]

15. Castellani C, Sgarbi D, Cavallini G, Di Francesco V, Bovo P, Frulloni L, et al. CFTR mutations and IVS8-5T prevalence in idiopathic chronic and acute recurrent pancreatitis. Gastroenterology 1998; 114:A445.

16. Choudari CP, Yu AC, Imperiale TF, Fogel EL, Sherman S, Lehman GA. Significance of heterozygous cystic fibrosis gene in idiopathic pancreatitis. Gastroenterology 1998; 114: A447.

17. LaRusch J, Whitcomb DC. Genetics of pancreatitis. Curr Opin Gastroenterol 2011; 27:467-474. [PMID: 21844754]

18. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996; 14:141-145. [PMID: 8841182]

19. Robechek PJ. Hereditary chronic relapsing pancreatitis. A clue to pancreatitis in general? Am J Surg 1967; 113:819-824. [PMID: 6023921]

20. Witt H, Luck W, Hennies HC, Classen M, Kage A, Lass U, et al. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. Nat Genet 2000; 25:213-216. [PMID: 10835640]

21. Rebours V, Boutron-Ruault MC, Schnee M, Férec C, Le Maréchal C, Hentic O, et al. The natural history of hereditary pancreatitis: a national series. Gut 2009; 58:97-103. [PMID: 18755888]

22. Garg PK, Tandon RK, Madan K. Is biliary microlithiasis a significant cause of idiopathic recurrent acute pancreatitis? A long-term follow-up study. Clin Gastroenterol Hepatol 2007; 5:75-79. [PMID: 16931169]

23. van Geenen EJM, van der Peet DL, Mulder CJJ, Cuesta MA, Bruno MJ. Recurrent acute biliary pancreatitis: the protective role of cholecystectomy and endoscopic sphincterotomy. Surg Endosc 2009; 23:950-956. [PMID: 19266236]

24. Ali UA, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol 2016; 14:738-746. [PMID: 26772149]

25. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 2001; 120:682-707. [PMID: 11179244]

26. Hallensleben ND, Umans DS, Bouwense SAW, Verdonk RC, Romkens TEH, Witteman BJ, et al. The diagnostic work-up and outcomes of 'presumed' idiopathic acute pancreatitis: A post-hoc analysis of a multicentre observational cohort. United European Gastroenterol J 2020; 8:340-350. [PMID: 32213015]

27. Coté GA, Imperiale TF, Schmidt SE, Fogel E, Lehman G, McHenry L, et al. Similar efficacies of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. Gastroenterology 2012; 143:1502-1509. [PMID: 22982183]

28. Das R, Clarke B, Tang G, Papachristou GI, David C, Whitcomb DC, et al. Endoscopic sphincterotomy (ES) may not alter the natural history of idiopathic recurrent acute pancreatitis (IRAP). Pancreatology 2016; 16:770-777. [PMID: 27450967]

29. Ros E, Navarro S, Bru C, Garcia-Pugés A, Valderrama R. Occult microlithiasis in 'idiopathic' acute pancreatitis: prevention of relapses by cholecystectomy or ursodeoxycholic acid therapy. Gastroenterology 1991; 101:1701-1709. [PMID: 1955135]

30. Kaw M, Brodmerkel GJ. ERCP, biliary crystal analysis, and sphincter of Oddi manometry in idiopathic recurrent pancreatitis. Gastrointest Endosc 2002; 55:157-162. [PMID: 11818915]

31. Testoni PA, Caporuscio S, Bagnolo F, Lella F. Idiopathic recurrent pancreatitis: long-term results after ERCP, endoscopic sphincterotomy, or ursodeoxycholic acid treatment. Am J Gastroenterol 2000; 95:1702-1707. [PMID: 10925971]

32. Levy MJ. The hunt for microlithiasis in idiopathic acute recurrent pancreatitis: should we abandon the search or intensify our efforts? Gastrointest Endosc 2002; 55:286-293.

33. Testoni PA, Mariani A, Aabakken L, Arvanitakis M, Bories E, Costamagna G, et al. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2016; 48:657-683. [PMID: 27299638]

34. Coyle WJ, Pineau BC, Tarnasky PR, Knapple WL, Aabakken L, Hoffman BJ, et al. Evaluation of unexplained acute and acute recurrent pancreatitis using endoscopic retrograde cholangiopancreatography, sphincter of Oddi manometry and endoscopic ultrasound. Endoscopy. 2002; 34:617-623. [PMID: 12173081]

35. Fazel A, Geenen JE, MoezArdalan K, Catalano MF. Intrapancreatic ductal pressure in sphincter of Oddi dysfunction. Pancreas 2005; 30:359-362. [PMID: 15841048]

36. Elta GH. Sphincter of Oddi dysfunction and bile duct microlithiasis in acute idiopathic pancreatitis. World J Gastroenterol 2008; 14:1023-1026. [PMID: 18286682]

37. Fischer M, Hassan A, Sipe BW, Fogel EL, McHenry L, Sherman S, et al. Endoscopic retrograde cholangiopancreatography and manometry findings in 1,241 idiopathic pancreatitis patients. Pancreatology 2010; 10:444-452. [PMID: 20720445]

38. Guelrud M, Mendoza S, Vicent S, Gomez M, Villalta B. Pressures in the sphincter of Oddi in patients with gallstones, common duct stones, and recurrent pancreatitis. J Clin Gastroenterol 1983; 5:37-41. [PMID: 6841947]

39. Yaghoobi M, Romagnuolo J. Sphincter of Oddi Dysfunction: Updates from the Recent Literature. Curr Gastroenterol Rep 2015; 17:31. [PMID: 26143628]

40. Wilcox CM. Sphincter of Oddi dysfunction Type III: New studies suggest new approaches are needed. World J Gastroenterol 2015; 21:5755-5761. [PMID: 26019439]

41. Hogan WJ, Sherman S, Pasricha P, Carr-Locke D. Sphincter of Oddi manometry. Gastrointest Endosc 1997; 45:342-348. [PMID: 9087852]

42. Pereira SP, Gillams A, Sgouros SN, Webster GJ, Hatfield AR. Prospective comparison of secretin-stimulated magnetic resonance cholangiopancreatography with manometry in the diagnosis of sphincter of Oddi dysfunction types II and III. Gut 2007; 56:809-813. [PMID: 17005767]

43. Testoni PA, Mariani A, Curioni S, Zanello A, Masci E. MRCP-secretin test-guided management of idiopathic recurrent pancreatitis: long-term outcomes. Gastrointest Endosc 2008; 67:1028-1034. [PMID: 18179795]

44. Eversman D, Fogel EL, Rusche M, Sherman S, Lehman GA. Frequency of abnormal pancreatic and biliary sphincter manometry compared with clinical suspicion of sphincter of Oddi dysfunction. Gastrointest Endosc 1999; 50:637-641. [PMID: 10536318]

45. Dufault DL, Elmunzer BJ, Cotton PB, Williams A, Cote GA. Adverse events and reinterventions following pancreatic endoscopic sphincterotomy. Pancreas 2018; 7:880-883. [PMID: 29912853]

46. Sun C, Liu MY, Liu XG, Hu LH, Xia T, Liao Z, et al. Serine protease inhibitor Kazal type 1 (SPINK1) c.194 + 2T>C mutation may predict long-term outcome of endoscopic treatments in idiopathic chronic pancreatitis. Medicine (Baltimore) 2015; 4:e2046. [PMID: 26632706]

47. Cotton PB, Durkalski V, Romagnuolo J, Pauls Q, Fogel E, Tarnasky P, et al. Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on pain-related disability following cholecystectomy: the EPISOD randomized clinical trial. JAMA 2014; 311: 2101-2109. [PMID: 24867013]

48. Cotton PB, Pauls Q, Keith J, Thornhill A, Drossman D, Williams A, et al. The EPISOD study: long-term outcomes. Gastrointest Endosc 2018; 87:205-210. [PMID: 28455162]

49. Somani P, Navaneethan U. Role of ERCP in Patients With Idiopathic Recurrent Acute Pancreatitis. Curr Treat Options Gastroenterol 2016; 14:327-339. [PMID: 27371265]

50. Guo A, Poneros JM. The Role of Endotherapy in Recurrent Acute Pancreatitis. Gastrointest Endosc Clin N Am 2018; 28:455-476. [PMID: 30241638]

51. Wehrmann T, Schmitt TH, Arndt A, Lembcke B, Caspary WF, Seifert H. Endoscopic injection of botulinum toxin in patients with recurrent acute pancreatitis due to pancreatic sphincter of Oddi dysfunction. Aliment Pharmacol Ther 2000; 14:1469-1477. [PMID: 11069318]

52. Jacob L, Geenen JE, Catalano MF, Geenen DJ. Prevention of pancreatitis in patients with idiopathic recurrent pancreatitis: a prospective nonblinded randomized study using endoscopic stents. Endoscopy 2001; 33:559-562. [PMID: 11473324]

53. Liao Z, Gao R, Wang W, Ye Z, Lai XW, Wang XT, et al. A systematic review on endoscopic detection rate, endotherapy, and surgery for pancreas divisum. Endoscopy 2009; 41:439-444. [PMID: 19337962]

54. Morgan DE, Logan K, Baron TH, Koehler RE, Smith JK. Pancreas divisum: implications for diagnostic and therapeutic pancreatography. AJR Am J Roentgenol 1999; 173:193-198. [PMID: 10397125]

55. Richter JM, Schapiro RH, Mulley AG, Warshaw AL. Association of pancreas divisum and pancreatitis, and its treatment by sphincteroplasty of the accessory ampulla. Gastroenterology 1981; 81:1104-1110. [PMID: 7286588]

56. Cotton PB. Congenital anomaly of pancreas divisum as cause of obstructive pain and pancreatitis. Gut 1980; 21:105-114. [PMID: 7380331]

57. Bernard JP, Sahel J, Giovannini M, Sarles H. Pancreas divisum is a probable cause of acute pancreatitis: a report of 137 cases. Pancreas 1990; 5:248-254. [PMID: 2343039]

58. Jagannath S, Garg PK. Recurrent acute pancreatitis: current concepts in the diagnosis and management. Curr Treat Options Gastro 2018; 16:449-465. [PMID: 30232693]

59. Bertin C, Pelletier AL, Vullierme MP, Bienvenu T, Rebours V, Hentic O, et al. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. Am J Gastroenterol 2012; 107:311-317. [PMID: 22158025]

60. Garg PK, Khajuria R, Kabra M, Shastri SS. Association of SPINK1 gene mutation and CFTR gene polymorphisms in patients with pancreas divisum presenting with idiopathic pancreatitis. Clin Gastroenterol. 2009; 43:848-852. [PMID: 19593166]

61. Tringali A, Voiosu T, Schepis T, Landi R, Perri V, Bove V, et al. Pancreas divisum and recurrent pancreatitis: long-term results of minor papilla sphincterotomy. Scand J Gastroenterol 2019; 54:359-364. [PMID: 30880501]

62. Mariani A, Di Leo M, Petrone MC, Arcidiacono PG, Giussani A, Zuppardo RA, et al. Outcome of endotherapy for pancreas divisum in patients with acute recurrent pancreatitis. World J Gastroenterol 2014; 20:17468-17475. [PMID: 25516660]

63. Lans JI, Geenen JE, Johanson JF, Hogan WJ. Endoscopic therapy in patients with pancreas divisum and acute pancreatitis: a prospective, randomized, controlled clinical trial. Gastrointest Endosc 1992; 38:430-434. [PMID: 1511816]

64. Borak GD, Romagnuolo J, Alsolaiman M, Holt EW, Cotton PB. Long-term clinical outcomes after endoscopic minor papilla therapy in symptomatic patients with pancreas divisum. Pancreas 2009; 38:903-906. [PMID: 19672208]

65. Michailidis L, Aslam B, Grigorian A, Mardini H. The efficacy of endoscopic therapy for pancreas divisum: a meta-analysis. Ann Gastroenterol 2017; 30:550-558. [PMID: 28845111]

66. Buxbaum J. The role of endoscopic retrograde cholangiopancreatography in patients with pancreatic disease. Gastroenterol Clin North Am 2012; 41:23-45.

67. Samavedy R, Sherman S, Lehman GA. Endoscopic therapy in anomalous pancreatobiliary duct junction. Gastrointest Endosc 1999; 50:623-627. [PMID: 10536316]

68. Dumonceau JM, Delhaye M, Tringali A, Dominguez-Munoz JE, Poley JW, Arvanitakis M, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline Endoscopy 2012; 44:784-796. [PMID: 22752888]

69. Sarner M, Cotton PB. Classification of pancreatitis. Gut 1984; 25: 756-759. [PMID: 6735257]

70. Hookey LC, RioTinto R, Delhaye M. Baize M, Le Moine O, Devière J. Risk factors for pancreatitis after pancreatic sphincterotomy: a review of 572 cases. Endoscopy 2006; 38:670-676. [PMID: 16810591]

71. Okolo PI, Pasricha PJ, Kalloo AN. What are the long-term results of endoscopic pancreatic sphincterotomy? Gastrointest Endosc 2000; 52:15-19. [PMID: 10882956]

72. Dumonceau JM, Delhaye M, Tringali A, Arvanitakis M, Sanchez-Yague A, Vaysse T, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Updated August 2018 Endoscopy 2019; 51:179-193. [PMID: 30654394]

73. Kozarek RA, Ball TJ, Patterson DJ, Brandabur JJ, Traverso LW, Raltz S. Endoscopic pancreatic duct sphincterotomy: indications, technique, and analysis of results. Gastrointest Endosc 1994; 40:592-598. [PMID: 7988825]

74. Cremer M, Devière J, Delhaye M, Baize M, Vandermeeren A. Stenting in severe chronic pancreatitis: results of medium-term follow-up in seventy-six patients. Endoscopy 1991; 23:171-176. [PMID: 1606413]

75. Buscaglia JM, Kalloo AN. Pancreatic sphincterotomy: technique, indications, and complications. World J Gastroenterol 2007; 13:4064-4071. [PMID: 17696223]

76. Levy MJ, Geenen JE. Idiopathic acute recurrent pancreatitis. Am J Gastroenterol 2001; 96:2540-55. [PMID: 11569674]

77. Tyberg A, Xu MM, Gaidhane M, Kahaleh M. Second generation optical coherence tomography: Preliminary experience in pancreatic and biliary strictures. Dig Liver Dis 2018; 50:1214-1217. [PMID: 29937365]

78. Jafri M, Javed S, Sachdev A Sadiq J, Lee D, Taur T, et al. Efficacy of endotherapy in the treatment of pain associated with chronic pancreatitis: a systematic review and meta-analysis. JOP 2017; 18:125-132. [PMID: 28966569]

79. Sauer BG, Gurka MJ, Ellen K, Shami VM, Kahaleh M. Effect of pancreatic duct stent diameter on hospitalization in chronic pancreatitis: does size matter? Pancreas 2009; 38:728-731. [PMID: 19657308]

80. Costamagna G, Bulajic M, Tringali A, Pandolfi M, Gabbrielli A, Spada C, et al. Multiple stenting of refractory pancreatic duct strictures in severe chronic pancreatitis: long-term results. Endoscopy 2006; 38:254-259. [PMID: 16528652]

81. Tringali A, Bove V, Vadalà di Prampero SF, Boškoski I, Familiari P, Perri V, et al. Long-term follow-up after multiple plastic stenting for refractory pancreatic duct strictures in chronic pancreatitis. Endoscopy 2019; 51:930-935. [PMID: 31378858]

82. Shen Y, Liu M, Chen M, Li Y, Lu Y, Zou X. Covered metal stent or multiple plastic stents for refractory pancreatic ductal strictures in chronic pancreatitis: a systematic review. Pancreatology 2014; 14:87-90. [PMID: 24650959]

83. Matsubara S, Sasahira N, Isayama H Takahara N, Mizuno S, Kogure H, et al. Prospective pilot study of fully covered self-expandable metal stents for refractory benign pancreatic duct strictures: long-term outcomes. Endosc Int Open 2016; 4:E1215-E1222. [PMID: 27853749]

84. Oh D, Lee JH, Song TJ, Park DH, Lee SK, Kim MH, et al. Long-term outcomes of 6-mm diameter fully covered self-expandable metal stents in benign refractory pancreatic ductal stricture. Dig Endosc 2018 30: 508-515. [PMID: 29453786]

85. Tringali A, Vadalà di Prampero SF, Landi R, Bove V, Familiari P, Hamanaka J, Attili F, Costamagna G. Fully covered self-expandable metal stents to dilate persistent pancreatic strictures in chronic pancreatitis: long-term follow-up from a prospective study. Gastrointest Endosc 2018; 88:939-946. [PMID: 30142349]

86. Cahen DL, van der Merwe SW, Laleman W, Poley JW, Bruno MJ. A biodegradable noncovered self-expandable stent to treat pancreatic duct strictures in chronic pancreatitis: a proof of principle. Gastrointest Endosc 2018; 87:486-491. [PMID: 28843580]

87. Tyberg A, Karia K, Gabr M, Desai A, Doshi R, Gaidhane M, et al. Management of pancreatic fluid collections: A comprehensive review of the literature. World J Gastroenterol 2016; 22:2256-2270. [PMID: 26900288]