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Review

Endoscopic Therapy for Recurrent Acute Pancreatitis

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Abstract

Recurrent acute pancreatitis (RAP) is a clinical condition characterized by episodes of acute pancreatitis, occurring on more than one occasion. Pancreatitis generally recurs in a normal anatomical and functional gland. However, chronic disease at an early stage may be found either in the event of the first episode of pancreatitis or during follow-up. The etiology of RAP was identified in up to 70% of cases and the term "idiopathic" is used for the remaining cases. The most common cause include bile duct stone disease, sphincter of Oddi dysfunction, anatomical ductal variants interfering with pancreatic juice outflow, genetic mutations, obstruction of the main pancreatic duct or pancreaticobiliary junction, and alcohol consumption. Patients with RAP have limited treatment options available to manage their symptoms and prevent progression to chronic pancreatitis. Endoscopic therapy is widely used in clinical practice and has been found effective in cases with mechanical obstruction. The efficacy of which in patients with a history of RAP depends on two main

factors: the bouts of acute pancreatitis occurrence in normal pancreas or chronic pancreatitis, and whether a cause can be identified and removed. Occult bile stone disease and type I and II sphincters of Oddi dysfunction account for the majority of the cases of RAP. In these patients, when ductal dilation is documented, cholecystectomy, and eventually endoscopic biliary and/or pancreatic sphincterotomy are curative in most of the cases. However, recent concerns about the efficacy of endotherapy in the sphincter of Oddi dysfunction have been raised. Endotherapy should be discouraged when obstructive etiology is not confirmed, thus balancing the risk of complications and the unpredictable benefit of the intervention. Pancreatic endotherapy has been proven effective in the cases of recurrent pancreatitis caused by pancreatic ductal obstruction, independent from the cause of obstruction, in symptomatic pancreas divisum with dilated dorsal duct and in some cases of genetic mutations. However, data from meta-analysis studies report a wide variation in the response rate after minor papilla sphincterotomy.

Although endotherapy is currently been used in clinical practice in patients suffering from RAP by endoscopic retrograde cholangiopancreatography (ERCP), its real utility remains unclear. This is because several unknown factors may play a role in the occurrence of the disease, and data on follow-up are limited to a short period. Moreover, the majority of the studies that reported favorable outcomes after endotherapy are uncontrolled or retrospective. Although effective in symptom control, it is still not clear if endoscopic therapy can prevent the development of chronic pancreatitis in the long-term.

Keywords
Endoscopic; acute pancreatitis

1. Introduction

Recurrent acute pancreatitis (RAP) is a clinical condition characterized by recurring episodes of acute pancreatitis. Recently in an international state-of-the-science conference, recurrent acute pancreatitis was defined 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, separated by at least three months” [1].

Bouts of pancreatitis, in general, are mild or moderate, without local pancreatic or systemic complications, occurring in a normal morpho-functional gland. In some cases, minor ductal or parenchymal abnormalities are found. Whether these minimal lesions indicate chronic pancreatitis at an early stage with superimposed recurrent episodes of acute pancreatitis or are the consequence of repeated damage in an initially normal pancreas is still a diagnostic issue. Only limited data are available on the frequency and the progression toward chronic pancreatitis, which is reported in 4.0% – 32.3% of cases [2-6].

A meta-analysis has shown that 10% of patients after a single episode of acute pancreatitis and 6% with recurrent pancreatitis developed a chronic disease over the years [7]. In a follow-up study of 532 patients, the cumulative probability of developing chronic pancreatitis after the first attack

of acute pancreatitis was 13% over ten years and 16% over 20 years; the probability increased to 36% within two years, after the second attack [2].

Alcohol consumption, smoking, genetic mutations, and pancreas divisum are reported to promote the progression toward a chronic disease in patients with recurrent pancreatitis. Chronic pancreatitis was reported in about 80% of patients with concomitant history of alcohol consumption followed-up for 15 years [8]. In a population-based study, alcohol, bile stone, unknown causes, and smoking was found to induce chronic pancreatitis in 28%, 10%, 6%, and 1% of cases, respectively, in patients recruited over ten years and followed-up for a median of 40 months [5].

Whether a tendency toward chronic pancreatitis persists in pancreas divisum patients, even after successful treatment and its reason, remains an unresolved issue. Over five years, in 33 patients with RAP and pancreas divisum, endoscopic ultrasound findings were seen consistent with chronic pancreatitis with similar frequency in both, patients undergoing endoscopic therapy with symptom improvement (63.2%) as well as the observation group (57.1%). These data confirm that other factors rather than ductal abnormalities play a role in the evolution toward a chronic disease in these patients [9], and genetic mutations are supposed to play a significant role. In RAP patients with pancreas divisum, a higher incidence of cystic fibrosis transmembrane conductance regulator-gene (CFTR), cationic trypsinogen-gene (PRSS1), and serine protease inhibitor Kazal type 1-gene (SPINK1) mutations have been reported, suggesting that congenital anatomical variant genetic mutations may play a cumulative effect on the occurrence of recurrent pancreatitis and evolution toward chronic pancreatitis.

In a study, the pancreas divisum has been reported in 7% of subjects with normal gland, 7%, and 5% of patients suffering from alcohol-induced pancreatitis and idiopathic RAP, respectively. Among the latter group, 16%, 16%, and 47% of patients were found to have PRSS1-, SPINK1-, and CFTR-gene mutations, respectively ($P<0.0001$). The frequency of pancreas divisum was also found higher in patients with CFTR-gene mutations-associated pancreatitis, compared to idiopathic and alcoholic pancreatitis ($P<0.0001$) and SPINK1 and PRSS1 gene-mutations-associated pancreatitis ($P<0.02$) [10]. Another study showed that patients with pancreas divisum presenting with RAP had a higher frequency of SPINK1- and CFTR-gene mutations compared to healthy controls; these genetic mutations may serve as the sole-factor or a co-factor in causing pancreatitis. The frequency of SPINK1-gene mutations was similar in patients with pancreas divisum and recurrent pancreatitis (41.6%), as well as in those with recurrent pancreatitis without pancreas divisum (35.7%), and chronic pancreatitis (43.3%) [11]. In cases of non-alcoholic non-biliary (non-A non-B) RAP, the risk of developing chronic pancreatitis is variable, requiring further study. A long-term prospective study showed that 47% of patients with non-A non-B RAP over an 8-year follow-up developed chronic pancreatitis [12]. Overall, these data confirm that an underlying chronic pancreatic disease may render the treatment of acute pancreatitis ineffective in a high percentage of cases suffering from RAP.

2. Etiology of Recurrent Acute Pancreatitis

Several factors play an etiologic role in RAP and are best summarized under the TIGAR-O (toxic-metabolic, idiopathic, genetic, autoimmune, recurrent, obstructive and severe acute pancreatitis) classification [13]. If not treated, any cause of acute pancreatitis can lead to recurrent episodes.

These recurrent episodes after the first index episode have been reported to vary between 11% and 32% [4-16].

Pancreatic duct outflow obstruction is one of the most common causes of RAP because it induces transient or persistent intraductal hypertension. It may also occur when the obstruction involves the pancreaticobiliary junction reflux of bile into the main pancreatic duct. Obstruction can occur from common bile duct stone disease (including sludge and bile crystals), sphincter of Oddi dysfunction (SOD), anatomical variants of the pancreatic ductal system or pancreaticobiliary junction, choledochocele, and lesions of the main pancreatic duct, either benign or malignant.

Recognized genetic conditions associated with RAP are cystic fibrosis transmembrane conductance regulator-gene (CFTR-gene), cationic trypsinogen gene (PRSS1-gene), and serine protease inhibitor Kazal type I gene (SPINK1-gene) mutations [17-23]. These mutations are particularly frequent in patients with congenital abnormalities, such as pancreas divisum, and have also been reported to induce sphincter of Oddi dysfunction.

Mutations of CFTR-gene induce an abnormal viscous exocrine secretion that leads to persistent high intraductal pancreatic pressure. Over time, this condition leads to chronic pancreatitis and exocrine pancreatic insufficiency. Pancreatic insufficiency and pancreatic hyperenzymemia in a normal morphological gland are the most common finding; however, in some patients, RAP may be the only clinical sign.

Mutations in the cationic trypsinogen gene (PRSS1-gene) results in premature trypsin activation, thus making the pancreas unable to protect itself. The lack of this protective mechanism predisposes individuals from childhood to RAP (hereditary pancreatitis) and progression to chronic pancreatitis. Sphincter of Oddi dysfunction (SOD) may occur as the consequence of the chronic inflammation of the sphincter induced by the passage of activated trypsin through it over time, in the presence of a common biliopancreatic junction [22].

Serine protease inhibitor Kazal type I gene (SPINK1) has a protective effect on the pancreas because it serves as a feedback inhibitor of trypsin. SPINK 1-gene mutations render the pancreas to develop pancreatitis from other genetic or environmental factors. About 16%–23% of patients with idiopathic recurrent pancreatitis have shown SPINK1 mutations, compared to only about 2% of healthy controls [23].

Determining the causes of RAP is still a challenge. The etiology of RAP can be identified in the majority of patients. Despite the availability of advanced diagnostic technology, up to 30% of cases are unknown, and the term “idiopathic” is used. However, the number of cases diagnosed as “idiopathic” is decreasing as our understanding and diagnostic accuracy has improved.

The current standard diagnostic work-up includes magnetic resonance cholangiopancreatography after secretin stimulation (MRCP-S), endoscopic ultrasound investigation (EUS), testing for genetic and autoimmune pancreatitis, and evaluation of sphincter of Oddi motility. Bouts of the sphincter of Oddi manometry widely performed in the past by endoscopic retrograde cholangiopancreatography (ERCP) raised concerns about validated predictor of outcomes in SOD patients suffering from RAP [24, 25]. ERCP could also be performed for diagnostic purposes in selected cases. MRCP-S and EUS are complementary techniques that should be considered as the mainstay of the diagnostic work-up in RAP. They permit access to the morphology and kinetics of the pancreatic ductal system (MRCP-S) and the presence of morphological changes within the pancreatic parenchyma consistent with early-stage chronic pancreatitis (EUS). MRCP with secretin has been used as a non-invasive alternative to manometry

to identify sphincter of Oddi dysfunction. Three studies employed MRCP-S for the diagnosis of SOD. One found no differences between normal subjects and SOD patients [26], another found sensitivities of 37% and 62.5% and specificities of 85% and 85% in types II and III SOD [27], and the third found 57.1% sensitivity and 100% specificity for type I SOD in idiopathic pancreatitis [28].

In cases of idiopathic acute pancreatitis (IRAP) without evidence of abnormalities, botulin toxin (100 IU) injection into the Vater's papilla may help identify a possible sphincter malfunction and patients whose symptoms are most likely to improve after endoscopic sphincterotomy. In a study by Wehrmann and colleagues, benefit from endoscopic sphincterotomy was experienced by 91.6% of botulinum responders and 33% of non-responders [29]. Although promising, botulinum toxin injection remains an experimental treatment because only one study has been published, and a randomized controlled trial is essential to confirm these results.

In cases of IRAP of unknown etiology, pancreatic stenting has also attempted to predict the response of sphincter ablation. Small caliber pancreatic stent placement was tried on a few patients in two studies. Our group placed pancreatic 5 F and 7 F stents in patients unresponsive to empiric biliary sphincterotomy and found significant reductions in pancreatitis episodes in 50% of cases. In these patients, subsequent pancreatic sphincterotomy was successful [30]. In another randomized, prospective study, 34 patients with IRAP were enrolled for five years and randomized to treatment (19/34) or control (15/34); patients in the treatment group received pancreatic stents over 9 months, each stent left in place for three months. After a mean follow-up period of 33 months, a significantly lower incidence of RAP was reported in the stent group (11% vs. 53%, $p < 0.02$) [31]. Despite these promising results, there are insufficient data to consider the empirical main pancreatic ductal stenting as a potential diagnostic tool in IRAP. Moreover, placing a stent into a non-dilated pancreatic ductal system, even for a short duration, may cause ductal injury mimicking chronic pancreatitis. However, these changes tend to disappear once the stent is removed.

3. Endoscopic Treatment of Recurrent Acute Pancreatitis

In patients with RAP, there are limited treatment options to resolve the disease or prevent progression toward chronic pancreatitis. The efficacy of therapy depends on two main factors: whether the bouts of pancreatitis occur in normal pancreas or chronic pancreatitis, and whether the cause can be identified and removed. Identifying the cause, therefore, plays a pivotal role in achieving a cure for RAP.

Endotherapy by ERCP is an effective option but has a higher probability of success when a mechanical obstruction is found and can be resolved. The most reliable indicator of ductal obstruction is the dilation of either the biliary or pancreatic ductal system.

In RAP patients with CFTR-gene mutations, the presence of a dilated pancreatic duct may predict a beneficial effect of endoscopic pancreatic sphincterotomy. This intervention facilitates the outflow of particularly dense pancreatic juice and causes intraductal hypertension. However, there are conflicting data [32] and no prospective study has demonstrated that decompressive therapy can favorably alter the course of the disease.

Overall, in cases of IRAP, there is limited evidence of endotherapy effectively altering the natural history of the disease [33-35]. In a 7-year follow-up study, patients who underwent ES had a similar rate of attacks per year compared to controls on assessing the efficacy of endoscopic

sphincterotomy vs. conservative management in patients affected by IRAP, even if the bouts decreased significantly in both groups. Predictors during follow-up for recurrent attacks were gender (0.54 in females, p=0.045) and rate of attacks at baseline (ratio for doubling 1.2, p=0.025), but not endotherapy. In fact, endotherapy did not affect the clinical course of the disease in patients with a high burden of pancreatitis attacks. In addition, progression to chronic pancreatitis occurred more frequently in subjects who underwent endoscopic sphincterotomy (27%) than in those managed conservatively (8%) [33].

4. Endotherapy for Recurrent Acute Pancreatitis of Biliary Etiology

Gallstone disease is the most common condition associated with RAP in western countries, accounting for 10%–30% cases [36]. Rarely pancreatitis occurs as the consequence of an impacted stone. In most cases, it occurs as the consequence of transient edema of the pancreaticobiliary junction that induces hypertension or bile reflux into the pancreatic ductal system, even if the pressure in the main pancreatic duct is generally higher than in the common bile duct. If there is a common channel at the biliopancreatic junction, intra-pancreatic bile reflux is facilitated. Papillary orifice patency following the passage of stones may be another cause of pancreatitis.

Besides common bile duct stones, gallbladder sludge and bile salt crystals may induce acute pancreatitis. Crystals have been found in centrifuged bile aspirated from the duodenum or common bile duct in 36%–67% of patients. Occult gallstone disease is the most common cause of "idiopathic" recurrent pancreatitis, as confirmed by the successful outcomes of long-term ursodeoxycholic acid (UDCA) therapy, or cholecystectomy, or endoscopic biliary sphincterotomy in some patients with RAP of unknown etiology [30, 37].

RAP patients with signs suggesting a biliary cause, cholecystectomy and/or endoscopic biliary sphincterotomy represent the only effective therapies. Cholecystectomy is curative when gallbladder stones or sludge are detected; however, the clinical benefit for sludge is less evident. After cholecystectomy, common bile duct stones were found in 4%–24% of patients followed up for 15 years, while sludge formed in cases with sphincter of Oddi dysfunction led to bile outflow obstruction. In these patients, endoscopic biliary sphincterotomy remains the only effective treatment. In cases of IRAP without signs of biliary etiology, empirical cholecystectomy should be discouraged till all other potential causes have been sought and excluded.

5. Endotherapy for Recurrent Acute Pancreatitis Associated with Sphincter of Oddi Dysfunction

Sphincter of Oddi dysfunction (SOD) has been considered as a cause of RAP, recognized in 35%–65% of cases, and is probably another common cause of the idiopathic form [38-41]. However, concerns about this clinical entity have been raised, and sphincter manometry by ERCP has also not been validated as a predictor of outcomes in RAP [42, 43]. Whether the motility abnormality of the sphincter is a cause or an effect of repeated inflammation due to pancreatitis, needs to be still clarified.

SOD has been classified under three subtypes based on clinical and morphological parameters and manometric findings [44]. Type I refers to persistent increased basal pressure of the sphincter induced by a fibrotic process and is associated with biliary and/or pancreatic ductal dilation. Currently, it can be defined as sphincter stenosis and does not require a functional assessment of the sphincter [25]. Type II is characterized by dyskinesia of the sphincter, which refers to the

transient episodes of hypertonic sphincter or dysmotility. Currently, it should be called suspected functional sphincter disorder and may require a functional investigation of the sphincter [25]. Type III is associated with normal pancreaticobiliary morphology and no longer considered a definite entity but termed functional abdominal pain [25]. Episodes of RAP may occur in the presence of type I and II dysfunctions but not in type III dysfunction that is characterized by only pain without an increase in serum enzymes. Type III dysfunction does not exist as true pancreaticobiliary disease and, in general, does not respond to biliary and/or pancreatic sphincterotomy [42].

However, normal basal pressure from manometry does not exclude fluctuating dysfunction or the role of the sphincter in the recurrence of pancreatitis. Because of the lack of specific studies and conflicting data, it is still unclear whether biliary sludge/crystals or inflammation causes sphincter malfunction. Among subjects with choledocholithiasis, those having concomitant RAP were found to have significantly higher basal sphincter pressure and gradients between the common bile duct and duodenum, suggesting the possible role of SOD in pancreatitis [45].

Dysfunction can either affect the biliary or pancreatic segment of the sphincter or both. Manometric findings from previous data showed type I and II SOD involvement in the biliary or pancreatic sphincter in 65%–92% and 85%–100% of cases, and 58%–65% and 55%–67% of cases, respectively. In a series by Eversman et al. [46], among 123 patients with type II SOD, the dysfunction was diagnosed in 65% of cases. Elevated basal sphincter pressure was found in the pancreatic sphincter only, biliary sphincter only, or both, in 22%, 11%, and 32% of cases, respectively.

In RAP with documented SOD, endoscopic sphincterotomy is the current standard therapy that aims at reducing the resistance caused by the sphincter to the outflow of bile and/or pancreatic juice. However, abnormal manometry findings fail to predict the relief of symptoms after biliary and/or pancreatic sphincterotomy. Sphincterotomy may either ablate the biliary or the pancreatic segment of the sphincter of Oddi, or both (dual sphincterotomy). Overall, long-term clinical improvement is reported in 83%–100% of patients with type I SOD and in up to 79% of cases with type II SOD after sphincterotomy, depending on whether manometry or Secretin dynamic test at MRCP or EUS was abnormal. Compared to biliary sphincterotomy alone, dual sphincterotomy has shown better outcomes because of the high rate of consensual sphincter dysfunction in RAP. However, a randomized clinical trial comparing biliary with dual sphincterotomy in patients with RAP and pancreatic SOD showed a similar incidence of recurrent pancreatitis in the two groups (64.7% and 76.9%, respectively) during the post-sphincterotomy follow-up, with a higher recurrence rates during the first year of follow-up in patients randomized to dual sphincterotomy. This higher rate of recurrence could have been related to a cicatricial structure of the pancreatic segment of the sphincter [47]. Other studies reported controversial data about the efficacy of pancreatic sphincterotomy [48-50]. In patients with uncertain documentation of dysfunction, the risks and benefits of endoscopic sphincterotomy should be carefully weighed. Since SOD patients have an ERCP-related pancreatitis rate that is markedly higher compared to other disorders and the clinical efficacy of sphincterotomy may be uncertain. Endoscopic sphincterotomy may fail to prevent recurrence of pancreatitis for the following reasons: (1) Biliary sphincterotomy has been inadequate or re-stenosis has occurred. Sphincterotomy should be revised, if no ‘‘cutting space’’ remains, and balloon dilation should be considered. (2) Pancreatic sphincterotomy is not performed or pancreatic sphincter has residual/recurrent abnormal basal pressure. A persistent elevated basal pressure of the pancreatic sphincter has been reported in patients with recurrent

pancreatitis after biliary sphincterotomy. In one prospective study, persistent pancreatic sphincter hypertension was seen in 78% of patients [51]. In these patients, pancreatic sphincterotomy achieves symptomatic improvement in 60%–90% of cases [30, 51]. However, in a retrospective cohort study among 369 patients who underwent pancreatic sphincterotomy for RAP or pancreatic-type SOD, pancreatic orifice reintervention occurred in 41.7% of cases because of restenosis [52]. (3) Underlying chronic pancreatitis, even with an apparently normal pancreatogram. In patients with SPINK1 mutations, pancreatic sphincterotomy has been found associated with a poor symptomatic response [53].

Recently in the EPISOD multicenter prospective randomized (sphincterotomy vs. sham 2:1) study, doubts on the efficacy of endoscopic sphincterotomy on symptom control in SOD have been raised in patients with pain after cholecystectomy, over a follow-up up to five years. At 1-year follow-up, only 37% of patients in the sham treatment group and 23% in the sphincterotomy group reported successful outcomes. Among patients with pancreatic sphincter hypertension, 30% and 20% of those who had undergone dual sphincterotomy and biliary sphincterotomy alone, respectively, experienced a successful treatment [42]. At 5-year follow-up, success rates in patients in the sphincterotomy and sham arms were similar (40% vs. 42%, respectively). Overall, during the entire study, the success rate was 41% in patients underwent endoscopic sphincterotomy and 62% in patients with no active treatment at any time [50].

6. Endotherapy for Recurrent Acute Pancreatitis in Pancreas Divisum and other Anatomical Variants

Pancreas divisum is the most common variant of pancreatic ductal anatomy, occurring in up to 12% of individuals. Partial fusion of the ventral and dorsal ducts characterizes the incomplete (functional) pancreas divisum, in which the dorsal duct drains through the major papilla *via* a communicating branch of the ventral duct. This communicating branch is narrow, in most cases, and inadequate for draining the pancreatic secretion. Although one retrospective series found no correlation between pancreas divisum and RAP [54], this congenital variant is reported in about 20% of patients with RAP [55-58]. Several studies have suggested that a heterozygous defect in the CFTR gene may predispose pancreas divisum patients to RAP.

Endoscopic and surgical therapy are comparably effective in 70%–90% cases [57, 58]. Therefore, endoscopic therapy is currently preferred, even if a meta-analysis including 25 surgical and 31 endoscopic studies, showed better outcomes after surgery (success rate: 72% vs. 62.3; complication rate: 23.8% vs. 31.3%; re-intervention rate 14.4% vs. 28.3%) [59].

Dilation of the dorsal duct confirms the presence of some obstruction at the level of the minor papilla and suggests a positive outcome after sphincterotomy or stenting. It is still unclear whether endotherapy should be considered only in the presence of a dilated dorsal duct and if it can prevent the risk of progression toward chronic pancreatitis. In cases with a non-dilated dorsal duct, the MRCP-S test may help detect minor papilla malfunction and select the appropriate therapeutic strategy.

Endoscopic therapy includes minor papilla sphincterotomy or stenting, or dilation. In patients with dilated dorsal duct or abnormal function test and no ductal strictures upstream, the minor papilla, sphincterotomy, is preferred. Subsequently, a 2 or 4-week dorsal pancreatic duct stent placement is recommended to avoid cicatricial strictures and post-procedure pancreatitis. In cases

with dorsal duct stricture, minor papilla sphincterotomy must be associated with stricture dilation and/or stenting [9]. In cases without dorsal duct dilation or abnormalities and with a normal function test, the obstructive cause is not documented, and sphincterotomy not indicated. However, in some of these patients with frequent recurrence of RAP, dorsal pancreatic duct stent (no longer than three months) could help predict the beneficial role of minor papilla sphincterotomy. In the randomized controlled trial, evaluating endotherapy with dorsal duct stenting versus no therapy in pancreas divisum patients suffering from RAP of unknown etiology, the number of attacks of acute pancreatitis was significantly lower in the stent group compared with the control group [58].

If pancreatitis still recurs after sphincterotomy, pancreatic stenting may be useful with 5 F to 10 F stents depending on the dorsal duct dilation. On multivariate analysis, stenosis of the minor papilla sphincterotomy was the only predictive factor for increased risk of recurrent pancreatitis after initial therapy [60] reported to occur in 20%–30% of cases [61].

Studies so far showed an extensive rate of symptom resolution after endotherapy. In a meta-analysis including 23 studies with 874 patients, the rate of improvement after endoscopic therapy varied from 31% to 96%. On subgroup analysis, pooled success rates were 76% for RAP, 52.4% for chronic pancreatitis, and 48% for pancreatic-type pain [62]. In a follow-up study, the pancreas divisum with RAP and normal pancreatic results had better outcome rates after endoscopic therapy, compared to RAP and chronic pancreatitis or pain alone (53.2%, 18.2%, and 41.4%, respectively). The secondary success rates (additional therapeutic ERCPs) were 71.0%, 45.5%, and 55.2%, respectively (median follow-up, 43.0 months; range, 14–116 months) [63]. These findings suggest that pancreas divisum patients with RAP are the most likely to benefit from endotherapy.

Despite the reported efficacy of endotherapy, data are of limited value because most studies included uncontrolled retrospective series and not the genetic status of patients. Only one randomized controlled trial has been published: in the treatment group, 9 out of 10 patients (90%) had no further episodes of acute pancreatitis during a three-year follow-up, while 6 out of 9 patients (67%) who were randomized to no treatment had at least one episode [64]. The question of whether the tendency toward chronic pancreatitis persists in pancreas divisum patients, even after successful treatment, and its reason remain unclear [9].

A common abnormally long (>15 mm) pancreaticobiliary channel without sphincters separating the biliary and pancreatic ducts is a condition that facilitates free reflux of bile and pancreatic juice into the alternative duct and may induce RAP. This anatomical abnormality is frequently associated with choledochal cysts. In these patients, endoscopic biliary sphincter ablation prevents the bile from entering the pancreatic duct and reduces the intra-ampullary resistance to pancreatic juice flow, thus reducing the risk of recurrences of pancreatitis [65].

7. Endotherapy for Recurrent Acute Pancreatitis in Acquired Obstructive Conditions

Any acquired anatomical conditions that could cause outflow obstruction of pancreatic juices can induce episodes of RAP. Lesions of the main pancreatic duct, tumors of the Vater's papilla, intraductal papillary mucinous neoplasia (IPMN), and periampullary diverticula, may be benign and malignant strictures. Rare conditions associated with RAP are choledochocele and ampullary choledochal cysts.

Strictures of the main pancreatic duct are found in 5%–10% of patients with RAP [66]. They may be related to chronic pancreatitis, residual scars after an episode of severe acute pancreatitis, pancreatic trauma, or neoplastic condition. The differential diagnosis of the benign and malignant nature of the stricture is pivotal before planning any treatment. In the presence of segmental strictures, endoscopic ultrasound (EUS) offers the best sensitivity to identify pancreatic neoplasia or diagnose chronic and autoimmune pancreatitis-related ductal lesions. EUS also permits to obtain cytological samples by fine-needle aspiration. Diagnostic ERCP should be performed in selected cases, to perform wire-guided intra-ductal brush cytology, optical coherence tomography (OCT), confocal endomicroscopy or pancreatoscopy [67-71]. ERCP-guided stricture dilation and stenting may successfully treat benign strictures as well as to palliate malignant lesions unsuitable for curative surgery. Stenting of benign strictures should be planned for at least one year, with three-monthly stent exchange, using progressively larger plastic stents up to 10 F or multiple stents, to achieve persisting dilation and resolution of the obstructive symptoms. Self-expandable, fully covered metal stents (6 to 10 mm in diameter) should also be considered instead of multiple plastic stents [72].

In the case of ampullary adenoma or carcinoma confined within the muscularis mucosae excluding the biliary or pancreatic duct, endoscopic resection should be the preferred treatment. The lesion can be excised en-bloc or piecemeal by snare papillectomy. En-bloc resection is indicated when the neoplasia is confined within the ampulla. In these cases, there is no need to lift the mucosa because this maneuver of complete resection of the lesion may render it difficult. Piecemeal resection is performed when the lesion tends to extend around the papilla. In these conditions, lifting the mucosa from the submucosa permits a complete and safer resection of the adenomatous tissue.

Intraductal papillary mucinous neoplasia (IPMN) involving the main pancreatic duct causes recurrent pancreatitis because the abnormal mucin secretion produces a dense pancreatic juice leading to intraductal hypertension. Endoscopic biliary and pancreatic sphincterotomy facilitates the juice outflow through the papilla and may help prevent episodes of acute pancreatitis in patients on follow-up.

It is still debated whether periampullary diverticula are directly involved in the recurrence of pancreatitis. Although these diverticula are frequently found in both gallstone and recurrent pancreatitis in middle-aged subjects, its role in the occurrence of pancreatitis has yet to be proved.

Choledochocele is a congenital or acquired condition in which the intramural segment of the common bile duct is dilated and herniates into the duodenal lumen. Acute pancreatitis may thus develop when the cystic dilation or bile duct sludge or stones obstruct the pancreatic juice outflow. Endoscopically, the papilla shows a bulge into the duodenum, mainly involving the caruncula, and is soft when pressure is applied with the ERCP catheter. Besides, the endoscopic section by sphincterotomy or needle-knife is usually effective.

8. Conclusions

Although endotherapy by ERCP is currently used in clinical practice in patients suffering from RAP, its real utility remains unclear. This is because several unknown factors may play a role in the occurrence of the disease, and the data on follow-up are limited to a short period. Moreover, the majority of the studies that reported favorable outcomes after endotherapy are uncontrolled or

retrospective. Furthermore, although effective in symptom control, it is still unclear if endoscopic therapy can prevent the development of chronic pancreatitis in the long-term.

Endoscopic biliary sphincterotomy remains a valid option in case of RAP associated with gallstone disease, after removing the gallbladder by surgery and a dilated common bile duct is found or sludge/microlithiasis is confirmed by MRCP or EUS.

With regards to the treatment of RAP associated with some dysfunction of the sphincter of Oddi, biliary or dual sphincterotomy are generally successful in case of sphincter stenosis (type I SOD), while endotherapy should be reserved only for patients with dilated ducts indicating an obstructive condition in the presence of type II SOD. In cases without ductal dilation, a functional assessment of the sphincter function should be done to identify patients most likely to benefit from sphincterotomy. However, long-term results in controlled studies arose concerns about the limited efficacy of the sphincterotomy. Also, pancreatic sphincterotomy is associated with a high rate of recurrence of pancreatitis, likely because of recurrent stenosis.

In patients with IRAP and no evidence of obstructive conditions or sphincter of Oddi dysfunction, endotherapy should be discouraged in clinical practice. In these cases, botulinum toxin injection into the sphincter should be performed to guide the decision process, but limited data have been published. Pancreatic stenting can be another option; however, it should be performed only in prospective comparative trials.

In patients with RAP and pancreas divisum, endotherapy has provided conflicting results and seems to be unable to prevent the evolution toward chronic pancreatitis, even if effective, because of the high rate of genetic mutations occurring in this congenital anomaly. However, minor papilla sphincterotomy and/or stenting have proven effective in the presence of dorsal duct dilation, with the highest success rate reported for RAP patients. Again, controlled studies with an adequate follow-up period are lacking, and most of the data are from observational studies.

In the presence of RAP associated with acquired obstructive conditions, endotherapy is generally successful if the disease depends on intraductal hypertension and there is no chronic underlying disease.

In conclusion, the impact of endoscopic therapy on outcomes and the natural history of RAP continues to be elusive. Predictors of response and failure to achieve sustained improvement of symptoms need further investigation. In addition, patients undergoing endotherapy must be informed and aware of the risk of endotherapy-related complications and the uncertainty of the expected benefits.

Author Contributions

The authors contributed equally to this work.

Competing Interests

The authors have declared that no competing interests exist.

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